STUDIES ON THE INFLUENCE OF COMPOSITION AND PROCESSING ON THE MECHANICAL PROPERTIES OF PELLETS AND COMPACTED PELLETS

Abraham Bahre Bashaiwoldu

A thesis submitted for the Degree of Doctor of Philosophy to the Faculty of Medicine, University of London

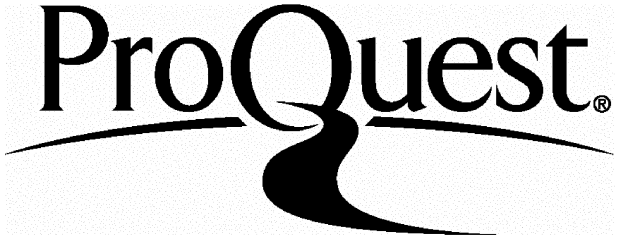
AUGUST - 2002

Department of Pharmaceutics

School of Pharmacy

University of London

29-39 Brunswick Square, London WC1N 1AX, UK



ABSTRACT

A study on the influence of formulation and processing factors on the mechanical properties of pellets produced by extrusion and spheronization has been conducted. Microcrystalline cellulose (MCC) was mixed with lactose or glyceryl monostearate (GMS) in different proportions. Similarly, mixtures of water with ethanol or glycerol were used as liquid binders. Based on the different rate of moisture removal, and means of heat and mass transfer, four different drying techniques namely: hot-air oven drying, freeze-drying, fluid-bed drying, as well as desiccation with silica-gel were used in the production of pellets. In addition, pellets containing model drug (paracetamol) and having different mechanical properties were prepared and coated with an aqueous dispersion of ethyl cellulose (Surelease®).

A range of properties from a simple fracture load to detailed load/displacement curves were used to characterize the pellets in terms of their tensile strength, deformability, linear strain elastic modulus and shear strength. Additionally, dynamic mechanical analysis (DMA) established the viscoelastic properties of uncoated and coated pellets. A non-contact laser profilometer was also used to quantify the permanent structural change of the pellets after compaction. The Heckel plot, Kawakita compressibility constant, pressure/displacement and logarithm of pressure/density profiles were employed to study the compaction mechanism of the pellets. Compacted pellets were investigated in terms of their strength and volumetric elastic recovery.

Statistical analysis established that freeze-drying, fluid-bed drying, and rapid evaporation of ethanol produced porous pellets which were weak, deformable, less strainable and resulted in rigid compacts. The strength and nonconnective nature of MCC was modulated by the incorporation of lactose, GMS, or glycerol. The brittle fracture, as indicated by Weibull modulus, of the lactose-rich pellets created new surfaces to form stronger compacts. Improvement in the deformability of the pellets with the addition of GMS, produced strong tablets with the lowest surface roughness. The increase in phase angle, determined by DMA, highlighted the increase in the viscous nature of the pellets as a result of coating.

ACKNOWLEDGMENTS

I wish to express my sincere gratitude to Professor John Michael Newton, my supervisor, who shared his expertise of many years with me and led my project without sparing his effort and time. Working with him was truly inspiring and outmost fascinating. My specially thank is due for his guidance along the winding paths of science, always patient and supportive, always there offering words of wisdom and encouragement.

I extend my deepest thanks to my second supervisor Dr. Fridrun Podczeck for her guidance, suggestions and providing facilities. Her warm support, encouragement and advise had been invaluable during all stages of this work.

My indebtedness to others in the school of pharmacy is very great: Mr. Keith Barnes in department of pharmaceutics, Mr. David McCarthy from SEM, Jason, Tes and Ann in Multi Media and all my colleagues in the department and school for their warm friendship.

I express my deepest gratitude to Mr. Osman Saleh and Beraki Ghebre-Selassie for their reference, encouragement and their confidence on my capability. I also thank all my Zero-School mates, teachers and guardians for inspiring me to this modest level of achievement.

At last, but not least, my warm thanks are due to my family, particularly my mother (Militeyey), my uncle (Yemane), my brothers and sisters especially Mahari, Tesfamicael, Nighisti, Akberet and all other family members and friends for their encouragement and support.

This study was financed by the University of Asmara. The Italian cooperation and, through them, the World Heath Organization (WHO) are acknowledged for funding my study.

Dedicated to my dearest sister, Yirga-alem,

Father, and a friend Efrem.

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GENERAL INTRODUCTION

1.1 MECHANICAL PROPERTIES OF PHARMACEUTICALS

1.1.1 MECHANICAL PROPERTIES AND MEASURING TECHNIQUES

The mechanical property of a pharmaceutical powder compact is a complex function of the properties of the materials which constitute the compact and the dynamic process to which the individual particles are subjected. The process includes compression, shearing and tension in a complex unknown manner and the response of the particles may include deformation and/or fracture. Thus, it is important to select a procedure that results in compacts of required properties and to identity a standard procedure that enables the indication of the compactibility of different materials of known properties. On the other hand, if the properties of a compacted specimen are going to be used to predict the mechanical properties of pharmaceutical materials, a procedure should be chosen which produces equivalent test compacts free of macroscopic and microscopic flaws which would distort the test results.

According to York (1992), there is no any single method of material characterization technique which can adequately point out the ability of the material to form tablets and hence a range of properties, which include the physicochemical and physicomechnical properties of the powder, have to be studied. He suggested the assessment of mechanical strength, tableting indices, and determination of mechanical moduli and constants, which include fracture mechanics and single crystal analysis. Rowe and Roberts (1996) indicated that in order to predict the compaction behaviour of a material, it is essential that methods be derived to measure the Young's modulus of elasticity, hardness and/or yields stress of plastic materials, and critical stress intensity factor (K_{IC}) for powder materials. Hiestand (1996), however, suggested that the measurement of tensile strength and indentation hardness from which bond index (BI) is derived as well as measurement of brittle fracture index (BFI) would be enough. These properties and their measuring techniques can be summarized as follows.

Tensile Strength: is the property of a material to resist failure from tensile stress. Pharmaceutical compacts may be subjected to tension directly by axial pulling or indirectly. Due to their brittle or semi-brittle nature, they easily fail in tension. This makes it the most

commonly used technique. Tensile strength is the inherent property of the material. In the characterization of pharmaceutical compacts, it is achieved by the application of diametral compression (Fell and Newton,1970a), direct axial pulling (Nystrom et al. 1978) or flexure testing (eg. David and Augsburger, 1974; Stanley and Newton, 1980).

Young's Modulus of Elasticity is the ratio of a stress to the relative strain in an elastic region of the material and measures the stiffness or rigidity of the material. It is related to interatomic or intermolecular bonding energy for inorganic and organic solids respectively. Young's Modulus of materials can be determined by many techniques several of which have been used in the study of pharmaceutical materials, namely flexure testing using both four- (Mashadi and Newton, 1987a,b) and three-point beam bending (Roberts et al.1993) and compression testing (Kerridge and Newton, 1986), and indentation testing (Ridgway et al.1970; Hiestand et al. 1971).

Hardness and/or Yield Stress are measures of the resistance of a material to deformation. Yield stress can be measured directly form a stress/strain curves obtained during compression, while hardness is measured by an indenter where a spherical ball is pressed under a load into the surface of the compact and involves measuring the recovered depth of indentation. This test may be static (Ridgway et al. 1970; Duncan-Hewitt and Weatherly, 1989) or dynamic involving a pendulum (Hiestand et al. 1971)

Critical Stress Intensity Factor:- The stress intensity factor, K_I, describes the state of stress around an unstable crack or flaw in a material and the critical value, K_{IC}, is an indication of the stress required to produce catastrophic propagation of the crack. It is thus a measure of resistance of a material to cracking. Critical Stress Intensity Factor measuring methods involve specimens containing induced notches and/or cracks and for pharmaceutical materials the methods include diametral compression (Roberts and Rowe, 1989), double torsion technique (Mashadi and Newton, 1987a,b) and three- or four- point beam bending (Fig-1.1) (Mashadi and Newton, 1987a, b; York et al. 1990; Roberts et al. 1993) which have different mode of crack propagation and are determined by equation 1 and 2 respectively.

Not only are there different means of characterizing pharmaceutical compacts, but within one technique there could be many varying factors. The rate of stress application is the most

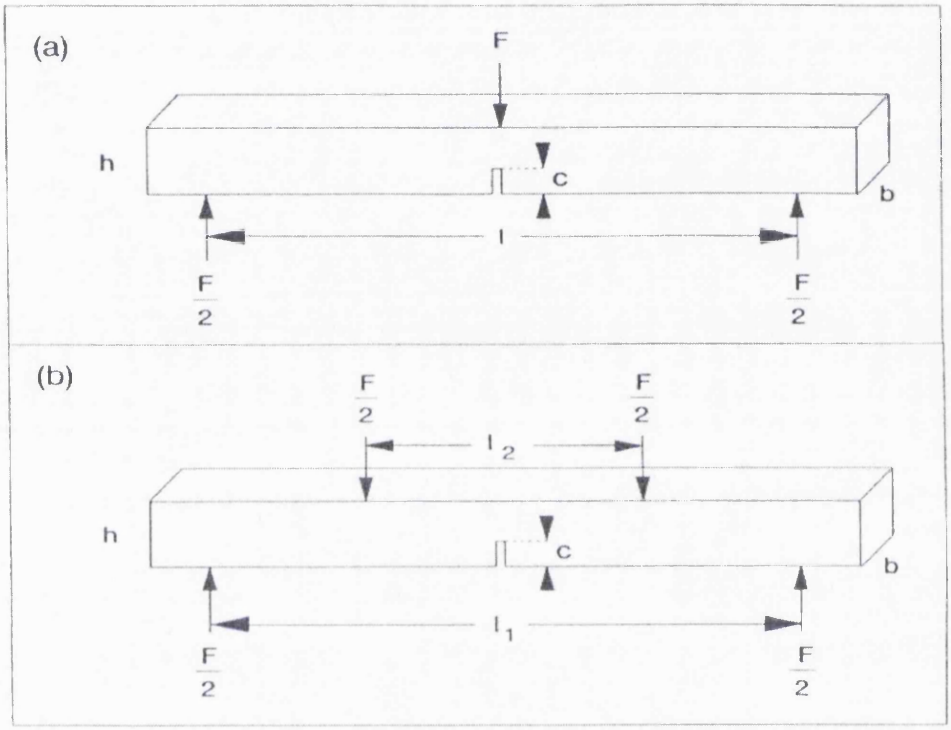


Fig-1.1 Geometries for (a) three-point and (b) four-point single-edge notched beam: F, applied load; h, beam thickness; b, beam width; l and a, distances between loading points as shown; c, crack length (taken from Rowe and Roberts, 1996)

$$K_{IC} = \gamma \frac{3Fc^{1/2}l}{2bh^2} \qquad \text{.....(1)}$$

$$K_{IC} = \gamma \frac{3Fc^{1/2}(l_1 - l_2)}{2bh^2} \qquad \text{.....(2)}$$

where, γ is a function of c/h

important of which for time dependent changes in the properties of the materials (viscoelasticity) are a common occurrence in pharmaceutical materials. The effect of compaction rate, during preparation, upon the mechanical strength of tablets has been investigated by several workers. An increase in compaction rate was shown by Seitz and Flessland (1965) to cause a decrease in breaking strength. David and Augsberger (1977) reported that with increasing compaction rate, there was a decrease in strength for plastically deforming materials but that there was no change in tensile strength of tablets produced at differing compaction rates for brittle materials. Pitt et al. (1987) reported a significant decrease in the strength of aspirin tablets with a 10 fold punch velocity increase in the region where tableting machines operate while at lower compaction rates even the effect of 100 fold was not significant. They indicated the potential effect of the punch velocity on the scale-up processes. Although the effect of strain rate has not been identified in the elastic modulus of pharmaceuticals (Pitt et al. 1987), its effect on yield stress of plastically deformable materials was evident. Roberts and Rowe (1986) findings of increase in yield pressure of Avicel as a function of punch velocity can be mentioned.

The rheological behaviour of ideal solids is mathematically described by Hooke's law, which states that the strain of a sample is directly proportional to the stress applied, unless elastic limit is exceeded. The proportionality constant is referred to as Young's modulus of elasticity. For ideal liquids, Newton proposed that the applied stress is proportional to the rate of strain (the velocity gradient), the proportionality constant being referred to as the viscosity. Thus, the response of ideal liquids to an applied stress is time dependent, i.e. dependant on the rate of strain and not the strain itself.

Many pharmaceutical and polymer systems exhibit behaviour that combines both elastic (solid) and viscous (liquid) properties, in which the applied stress is proportional to both the resultant strain and rate of strain. Such systems are termed viscoelastic. They are commonly characterised by the non constant but continued deformation as a function of time during a constant stress, a phenomena referred as creep, and the storage of some energy which is used for delayed recovery of the structure from the stress induced deformation.

Even though the conventional techniques, mentioned earlier, are used to determine the mechanical properties of pharmaceuticals by a variety of mechanisms, each results in

irreversible damage to the structure of the compact. Consequently, limited information can be learned about the viscoelastic properties of the specimen. Rippie and Danielson (1981) and Danielson et al. (1983) demonstrated the viscoelasticity of some pharmaceuticals by measuring the stress-relaxation phenomena during the unloading and post-compression periods in the die of a rotary tablet press. These authors postulated viscoelastic parameters that can provide insight into kinetically controlled changes in structure.

Dynamic mechanical analysis (DMA) has emerged as one of the most powerful tools available for the study of the viscoelastic properties of materials. In a dynamic mechanical test it is the sample stiffness and energy loss that are being measured. The sample stiffness will depend on its modulus of elasticity. And the modulus measured itself will depend upon the choice of geometry and mode of strain, Young's for tension, compression and bending, shear for torsion. The modulus is defined as the stress per unit area divided by the strain resulting form the applied pressure. Therefore, it is a measure of material's resistance to deformation, the higher the modulus the more rigid the material is. This definition, however, does not take time into account. For materials that exhibit time-independent deformation, for example ceramics at room temperature, any measurement of strain will lead to constant value of modulus. However, for materials that exhibit time dependent deformation, such as polymers, the quoted modulus must include a time to be valid. Here is where dynamic mechanical testing offers a powerful advantage by measuring the time dependent loss or storage of energy simultaneously.

Dynamic mechanical analysis is a versatile technique that may be used to simultaneously characterise both the rheological and thermal properties of polymeric system of pharmaceutical and biomedical significance. (Jones, 1999) has reviewed its importance in determining: 1. Quantitative modulus, i.e. storage and loss moduli; 2. Glass transitions (primary, secondary etc.); 3. Rate and extent of polymeric curing; 4. Quantification of gelation, eg. Sol-gel transitions; 5. Damping properties, i.e. characterisation of the ratio of loss to storage moduli at defined temperatures; 6. Polymer morphology/compactibility; and 7. Interactions between polymeric components or between drug molecules and polymeric constituents of pharmaceutical and biomedical systems.

In pharmaceutical powder compacts, however, not many published works are available.

Maarschalk et al. (1996) employed DMA in assessing the consolidation and relaxation behaviour of a 'viscoelastic' powder (pregelatinized, spray dried potato starch) compressed at different speeds. It was observed that the material becomes more rigid and more elastic with increasing deformation rates. Compaction of the materials at low speed resulted in the formation of tablets with low porosity. This effect is caused by the dominant viscous component, which results in irreversible deformation. The ratio of moduli (the damping), however, was almost constant due to the simultaneous increase in storage and loss modulus. In a latter work Maarschalk et al. (1997) found a decrease in the elastic modulus with the decrease in the difference of experimental temperature to that of glass transition temperature of the material as well as with the increase in strain rate of the test.

1.1.2 RATIONAL OF MEASURING MECHANICAL PROPERTIES

During formulation and production of pharmaceutical compacts, the mechanical properties of the compacted specimens are assessed for different reasons. Newton et al. (1992a) summarized them into three points:-

FIRST *there is a need to standardize the mechanical properties of the final product to ensure that the compacts can withstand mechanical stresses during handling.*

A compact must possess sufficient strength to withstand the rugose mechanical treatment during production and further processing such as coating and packaging. It should retain its structural integrity without uncontrolled changes during transportation and yet must disintegrate in the required period of time or meet the dissolution specifications to maximise absorption of the active ingredients into the bloodstream. That is why determination of the mechanical strength of pharmaceutical tablets dates back to late 1930s. In those days, a rule of thumb was used to describe a tablet to be of proper strength if it was firm enough to break with a sharp snap when it was held between the 2^{nd} and 3^{rd} fingers and using the thumb as the fulcrum, yet did not break when it falls on the floor (Rudnic and Schwartz, 1990). Currently the diametrical compression test (Fell and Newton, 1970a) has become one of the routine procedures.

SECONDLY *for the evaluation of the mechanical properties of the compact might be an interesting alternative to provide the mechanical properties of the solid material.*

The vast majority of pharmaceutical drugs and excipients exist as crystalline and/or amorphous powders mainly due to the way they are prepared. These powders are heterogeneous system consisting of solid particulate material intermixed with air that can exist both between and inside the particles. Due to their small dimensions and irregular shapes it is difficult to stress the individual particles in a uniform controlled manner and measure the dimensional changes and fracture. Moreover in its bulk, powder flows like a liquid to dissipate the stress in unconfined condition, while the particles deforms or fracture during compaction in a confined space. This makes the characterization of pharmaceutical powders, as they are received, more complicated. It is for this reason, therefore, that testing are undertaken on specimens formed from the powder with the assumption that the properties of the specimens will be indicative of that of the constituting materials (Newton et al. 1992a). For illustration, the works of some researchers in an attempt to assign some values to the mechanical properties of pharmaceutical powders can be mentioned.

After studying the indentation hardness (Hiestand et al. 1971) and tensile strength of square compacts (Hiestand and Peot, 1974), Hiestand and Smith (1984) were able to propose the bonding indices of various pharmaceutical powders as a ratio of the latter to the former. The values for the "Worst-Case" bonding index (BI_w), where the dwell time at maximum penetration of the indenter in measuring compact hardness is less than a millisecond have been observed to be within the range of 0.001 to 0.04 (Hiestand, 1989). The values for the "Best-Case" bonding index (BI_b) , where the dwell time at maximum penetration of indenter is 30 minutes (Heistand, 1989), were also observed to be within the ranges of 0.002 to 0.14. They indicated the importance of characterization of pharmaceutical powders using these indices in conjunction with the brittle fracture index (BFI) (i. e. the ratio of the tensile strength of a compact with and without a hole in the centre) in evaluating different pharmaceutical materials and similar materials available from more than one source.

Moreover, mechanical properties of some powders (eg. Avicel PH-101 and lactose monohydrate) were reported by determining the properties of compacts at different porosities

and extrapolating the results to zero porosity. Bassam et al. (1990), found the Young's modulus of Avicel PH-101 of 50 μm mean particle size and alpha-lactose monohydrate of 63 μm mean particle size to be 9.2 and 3.2 GPa respectively. York (1978) determined yield stress of Avicel PH-101 and alpha-lactose monohydrate to be 46 and 183 MPa respectively. The critical stress intensity factor of Avicel PH-101 of 50 μm particle size was determined to be 0.99 $MPam^{1/2}$ (York et al. 1990), and that of alpha lactose monohydrate of 20 μm mean particle size was 0.35 $MPam^{1/2}$ (Roberts et al. 1993). A similar technique was used to differentiate four grades of microcrystalline cellulose products by determination of their critical stress intensity factor (Podczeck and Newton, 1992a) and Young's modulus (Podczeck and Newton, 1992b).

THIRDLY *to assess the ability of the powder to compact into coherent specimens, i.e. to estimate the compactibility of pharmaceutical powders.*

The impracticality of measuring the properties of individual pharmaceutical powder particles, from which compacts are made, is a major obstacle to obtain an accurate description of tableting performance of the powder. To tackle this challenge pharmaceutical researchers have tried to obtain information from the properties of the compact that would possibly indicate the processing performance of the material. To this end, two separate attempt to predict the compactibility of pharmaceutical powders can be mention.

Roberts and Rowe (1987) and Rowe (2001), predicted the compaction mechanism of pharmaceutical powders based on the knowledge of Young's modulus of elasticity, yield stress, hardness, and strain rate sensitivity (SRS) of the their compacts. Table-1.1 shows the relationship between material properties predicted from their compacts and compaction behaviour of the materials.

They also claimed that their approach combined with further measurements on critical stress intensity factor enabled the prediction of critical particle sizes, d_{crit} (to account for particle size effects), which could enable prediction of the compaction mechanism of any material of known particle size.

Py MPa	S.R.S %	H MPa	E GPa	$\frac{H}{P_y}$	Description	Consolidation mechanism	Example
>400	0	>1000	>15	2.2	Hard, Brittle	Fragmentation	Inorganic minerals eg. $CaCo_3$, $MgCo_3$
150-400	<10	500-1500	>70	3.5	Hard, Brittle	Plastic flow at contact points	Metals: eg. Iron, Copper
60-200	<10	160-600	5-15	2.4	Moderate hard, Brittle	Fragmentation, some plastic flow at contact points	Paracitamol*
60-200	20-60	160-600	5-15	2.4-2.8	Moderate hard, Brittle, ductile	Fragmentation, some plastic flow at contact points	Lactose*
60-200	>60	160-600	5-15	3.0	Moderate hard Ductile	Less fragmentation, more plastic flow	Manitol, Sucrose
40-80	20-60	160-600	5-15	3.5	Soft, Ductile	Plastic flow, little or no fragmentation	Microcrystalline cellulose*, Sodium chloride
40-80	>60	50-150	2-5	2.5-3.0	Soft Ductile, Elastic	plastic, elastic flow	Maize starch, PVC/PVA
<40	>60	<50	<2	1.5-2.0	Highly Viscoelastic	Total plastic	PTFE

Table-1: The relationship between the properties of the materials and their compaction mechanism, where Py, is yield stress, H is hardness, E-elastic modulus, and S.R.S, stands for Strain Rate Sensitivity (Adapted from Robets and Rowe (1987)

N. B.:- (*)- indicates three of the four powder particles employed in this project

In another work Hiestand (1989) reported that the tableting indices, worst-bonding index (BI_w), best-bonding index (BI_b), and brittle-fracture-index (BFI) provide a quantitative evaluation of the tableting performance of a powder or powder mixture. He claimed that these techniques detect mechanical property differences between lots that meet all chemical specifications, and they permit a rational approach to the selection of excipients. According to him, the higher the bonding index, the stronger a tablet more likely to be, the higher the brittle-fracture-index, the weaker the tablet. Hypothetical illustrations of potential benefits from having a quantitative evaluation of tableting properties has been given in Hiestand (1989). He reported that tablets can be made from powders having low bonding index values, but are soft and excessively friable. The acceptable value, however, he suggested is not independent of the brittleness. Usually if the final formulation has a brittle fracture index (BFI) value below 0.2, it indicates a formulation that would not give fracture problems. Nevertheless, he concluded if the bonding index value is too low, e.g., 0.001, a slightly lower BFI value would provide a better margin of tableting safety. This information could be especially desirable, Hiestand (1996) indicated, when the dosage is high and the volume of excipients must be kept very small.

The aforementioned works on prediction of compactability of pharmaceutical powders are mostly limited to specific materials and from specific sources. The success of the postulated technique seems yet to be assessed in a wider scope. The extensive researches performed in an attempt to characterize pharmaceutical materials form the properties of their compacts seems to have a reasonable results in an attempt to differentiate various materials and similar materials form different sources. However, there still remains some discrepancies in the reported results.

1.1.3 DISCREPANCIES

The Young's modulus of Avicel PH 101 was reported to be 6.25 GPa (Church and Kennerley, 1983), 7.4 GPa (Roberts et al. 1991), and 10.3 GPa (BinBaie et al. 1996). Increase in Young's modulus of lactose monohydrate from 6.44GPa to 6.66 GPa was also noted with increase in particle size fraction from 5-11 to 11-19 μm (BinBaie et al. 1996). Moreover, Rowe and Roberts (1996) reported that the Young's modulus values determined by diametral compression of a variety of materials were lower than those measured by the other techniques. The critical stress intensity factor (K_{IC}) of Sorbitol instant was reported to be 6.98

$MPm^{1/2}$ (BinBaie et al. 1996) while Mashadi and Newton (1987a) found it to be 4.5 $MPm^{1/2}$. The K_{IC} value of Avicel PH-101 obtained by double torsion technique was also found to be higher than that of beam bending method (Mashadi, 1988). The tensile strength of Avicel PH 101 was reported to be 18 MPa (Church and Kennerley, 1983) while BinBaie et al. (1996) found it to be 30 MPa as they used different modes of fracture. Thus, it is not possible to quote definite values for the materials' properties. There still seem to be variations in value which may be due to several factors.

One of the main source of errors could be the inability to produce non porous materials and the need to extrapolate the finding from different porosities to zero porosity using empirical equation and curve-fitting function, hence only valid for the conditions assumed. A list of many empirical equation which relate the Young's modulus with porosity, and the condition upon which those equations are applicable are presented in Mashadi (1988).

Another factor could be the variation in sensitivity of the materials to the different techniques due to their intrinsic material properties such as melting point, particle shape and size, molecular weight and structure. The previously mentioned particle size effect of lactose monohydrate can be one example. Although Mashadi (1988) tried to use materials from a homologous series, having closely related molecular weight and melting point, he observed an increase in the K_{IC} value with increase in melting point of the materials. Moreover, it could be due to the material batch variation as suggested by Bassam et al. (1988).

Furthermore, the variation in the specimen preparation, their inhomogeneity based on the direction from which they are compacted and tested (Newton et al. 1992a), their suitability for the different techniques in terms of dimensions and compaction techniques as well as variation in the occurrence and distribution of flaws and defects, could be the reasons for these discrepancies in the reported material properties. Thus, when reporting the values of the mechanical characteristics of pharmaceutical materials, there is a need to identify the original particle size of the material and the method of producing the test specimens. Moreover, the technique utilized to test the specimen should be noted as variation in the techniques provides different results, and yet it is possible to test a specimen by different techniques as is summarized earlier.

Having pharmaceutical powders with well defined characteristics and reasonable compactibility does not guarantee the ability to produce compacts of uniform size and drug distribution. That is because bulk properties of powders, such as flowability and uniform mixing without segregation can not be guaranteed. Therefore, the production and characterization of intermediate specimen, such as spherical granules, may be desirable.

1.2 AGGLOMERATES AND THEIR MECHANICAL PROPERTIES

1.2.1 GRANULES

Pharmaceutical granules were described by Alderborn and Wikberg (1996) as a cluster of discrete particles for the size and shape characteristics of the primary particles are unchanged and definable. This description implies that the primary particles have not yielded or fractured during the granulation procedures considered, for the stress applied to them was relatively low in the conventional wet granulation process. However, the particles are subjected to considerable stress during dry granulation (slugging) (Khan and Musikabhumma, 1981) and during extrusion and spheronization (Reynold, 1970). In such cases it is difficult to identify the primary particles and the granule can be considered as the smallest unit. Granulation of pharmaceuticals is done for many reasons, some of which are: to improve the flow properties and compression characteristics of the mix, to prevent segregation of constituents, to reduce dust, to densify the material, to facilitate metering of volumetric dispensing, and to increase uniformity of drug distribution in the product .

It is difficult to characterize pharmaceutical granules in terms of their mechanical properties mainly due to their irregular shapes. This means that controlled and reproducible stress distribution, and thereby the calculation of a mechanical modulus of a single granule is difficult to achieve. Yet, researchers tried to characterize granule strength mainly by friability test (eg. Khan and Musikabhumma, 1981), compression test (eg. Jarosz and Parrott, 1983) and confined uniaxial compression test (Adams et al. 1994).

Often the force needed to fracture granules varies considerably. The difference in breaking forces and variations in the number of fragments for a certain granulation are probably the results of variations in the stress distribution during testing and in the intra- and inter-granular strength distribution (Ahuja, 1977). The deformability of granules was also related to the

slope of a force/displacement curve produced during the diametral compression test (eg. Shotton and Edwards, 1974; Wikberg and Alderborn, 1992).

The reported finding on factors affecting mechanical strength of granules are: type and amount of binder (eg. Jarosz, and Parrot, 1983; Cutt et al. 1986; Wells and Walker, 1983) process variables (eg. Hunter and Ganderton, 1973; Khan and Musikabhumma, 1981) particle size of primary particles (Shotton and and Ganderton, 1961; Rumpf, 1962) as well as porosity (Rumpf, 1962; Wikberg and Alderborn, 1991).

Rumpf (1962) illustrated the effect of particle size and porosity on the tensile strength of aggregates of monodispersed spheres by developing an empirical equation:

$$\sigma = \frac{9(1-\varepsilon)kH}{8\pi d^2} \qquad \text{.....(3)}$$

where, σ is tensile strength of aggregate (N/m^2); ε is porosity of aggregate; k is a coordination number, i.e., number of contact points for one sphere; H is bonding force at a point of contact (N); and d is the diameter of primary spheres (m)

The deformability of the granules was also observed to be affected by the type of binders and granulation process (Shotton and Edwards, 1974), and porosity (Wikberg and Alderborn, 1992). With a decrease in granule porosity, there was a trend for the slope of the force-displacement profile to increase (Wikberg and Alderborn, 1992). This indicates, they argued, that with the reduction of granule porosity, the granules are less prone to change their structure, i. e. to deform and/or densify before fracturing.

The effects of the granule mechanical properties on the properties of their compacts were also studied. Wikberg and Alderborn (1990a,b) noted that the weaker lactose granules, had a higher degree of fragmentation and produced stronger tablets. The increase in deformability of granules was also reported to improve the strength of the tablets due to the higher axial to radial stress transmission (Shotton and Edwards, 1974).

1.2.2 THE FRIABILITY OF AGGLOMERATES

Particle breakage can be distinguished as attrition, fracture, abrasion, and chipping. Small scale damage due to normal forces is called attrition; large-scale catastrophic damage is called fracture. Small scale incidental damage due to tangential force that results in polishing of the granule is called abrasion. If each impact causes a substantial tangential force on the granule and results in local damage to the particles' surface, the breakage is called chipping (Beekman, 2000).

In most cases the abrasion and attrition of agglomerates can be measured as a weight loss during friability test (eg. Ghebre-Sellassie et al. 1985; Wan and Jeyabalam, 1987; Millili and Schwartz, 1990; Kleinebudde, 1994a; Varshosaz et al. 1997). It may be a more realistic indication of the wear if the technique used simulates the environment that agglomerates may be exposed to. To develop a method for determination of agglomerate friability Schultz and Kleinebudde (1995) used an open system with an air stream to simulate a fluid bed process and studied the effects of air-flow, sample weight, and fluidising time on pellet friability. They concluded that air-flow had a great influence, fluidising time had a small influence and sample size demonstrated a negative influence on friability. Alternatively, agglomerates may be placed in a friabilator with or without abrasive of different nature. For instance, Millilil and Schwartz (1990) used 200 (4mm) glass beads with their 10g pellets as abrasive, Khan and Musikabhumma (1983) used polythene spheres, while Wan and Jeyabalam (1987) used steel balls. The standardization of the technique seems important for one can simply note the effect of the density of the abrasives on the process.

The procedure of fraibility test seems to constitute two separate techniques (i.e. abrasion and dropping) as it is separately presented in Japan Industrial Standards (JIS_Z8841). Chuichi (1993) reported the need of standardizing the strength of granules and agglomerates as well as the endorsement of three standard procedures as Japanese Industrial standards (JIS_Z8841) "Granules and Agglomerates-Test Methods for Strength" in 1993. These standards include, 'Test methods for granules and agglomerates tumbler, drop, and crush strengths'. Tumbler Strength Test Method is used to express the resistance of agglomerates to breakage by abrasion. The tumbling speed should be such that the 400 ml test samples within the drum may be subjected well to abrasion with the inner walls of drum or with each other without

subjection to any strong actions such as drop impact. The drum is stopped immediately after it has attained a total of 200 revolutions. The weight loss is calculated as a percentage after hand sieving the agglomerates through a sieve aperture of about a fifth of their original diameter. Likewise, in the Drop Strength Test Method a 400 ml test sample is made to fall down along a 2000 mm vessel into a copper receptacle. After the operation has been repeated five times, loss in weight is calculated in a similar manner.

Beekman (2000) used a Repeated Impact Machine (R.I.M.) to assess the attrition tendencies of the granules. By placing about 300 granules in a small sample box where the granules were made to impact with the top and bottom wall of the box in a controlled way as 50 to 60 Hertz frequency is applied to shake the box. Impact velocity was controlled accurately between 4 and 10 metres per second. He determined the threshold impact velocity below which, no damage to the granules occurred. The damage rate that was observed above the threshold velocity for fluid bed granules was proportional to the impact velocity squared and linearly proportional to the granule diameter. From the collision sounds generated by a single granule, he was able to analyse the granule impact condition one-dimensionally. He used computer simulation to obtain a thorough understanding of three-dimensional motion of the granules in the test. Finally, he claimed to have been able to discriminate the different attrition mechanisms, namely attrition by erosion and attrition by fatigue.

1.2.3 THE STRENGTH OF AGGLOMERATES

According to the concept of fracture mechanics, if the stress on a specimen is continuously increased, at some point the structure of the specimen fails because of crack propagation. The inherent ability of the specimen to resist this fracture is called strength (mechanical strength). Thus, strength is a measure of the ease of crack initiation and propagation. Fracture, upon which the exerted force is commonly used to explain the mechanical strength, can be broadly classified into two types: ductile and brittle. The difference between the two types is largely related to the strain at which fracture occurs. Brittle fracture result from rapid propagation of a crack under an applied stress with little or no deformation of the material before fracture, while considerable plastic deformation occurs before separation in a ductile fracture. However, most actual fractures involve both modes of failure though they are usually dominated by either.

Many researchers used the load that causes failure to express the mechanical strength of agglomerates. The value they obtain depends on the dimensions of the specimen and their orientation between the upper and lower loading points with respect to their shapes. However, determination of the stress that causes tensile failure is a more convenient procedure for most materials are weakest in tension (Newton et al. 1996) and it is an inherent property of the agglomerates and theoretically depends only on the stress distribution inside the agglomerate during loading (Podczeck, 1998a).

> *Tensile strength is defined as the unidirectional, maximum tensile force per unit of the plane cross-sectional area of the bulk material at right-angle to the direction of the tension when a locally constant, purely tensile stress prevails in the fracture cross-section of the material regarded as a continuum* (Schubert et al. 1975).

The strength of agglomerates can not be defined sufficiently by one single characteristic parameter only (Schubert, 1975). He suggested that it is necessary to know at least both the tensile strength and shear strength. Salako et al. (1998) determined the tensile and shear strengths to characterize their hard and soft pellets. Moreover, the measurement of the critical stress intensity factor (K_{IC}) was found to be useful in characterizing granule strength (Mullier et al. 1991) for most pharmaceutical are brittle in nature. They varied the tensile strength of their sand granules by using various concentration of PVP as binder solution and they were able to characterize them using critical stress intensity factor.

1.2.4 MEASUREMENT OF AGGLOMERATE STRENGTH

A comprehensive strength test which consists crushing the pellets between flat parallel plates by which the load at failure is registered is a widely used procedure. For instance, Jarosz and Parrott (1983) used this technique in their study on the strength of granules. They reported the difficulty in identifying the load at which a granule failure occurs. Wikberg and Alderborn (1992) used the same technique but stopped the crushing machine when they noted at least a 30% drop in the force. In the Standards-G001 (Granules and Agglomerates Crushing Strength Test Method of the Association of Powder Process Industry and Engineering Japan (APPIE), however, the maximum load value at which a test sample is broken completely is taken as a crushing strength, without consideration of some fluctuation

resulting from the breakage of small projection or change in the internal structure of agglomerates (Chuichi, 1993). Nevertheless, these techniques do not take into account either the mode of failure or the dimension of the granules.

To overcome this discrepancy many researchers first determine the crushing load then they convert it to tensile strength using some empirical formulae or formulae having theoretical and practical bases. In their kinetic studies of compaction processes of granules of calcium carbonate and microcrystalline cellulose, Kuno and Okada (1982) determined the strength of an agglomerate, σ_f, as a function of crushing load, F_0, using the following equation:

$$\sigma_f \approx \frac{4F_0}{\pi D^2} \qquad \text{.....(4)}$$

where D is the agglomerate diameter.

Horisawa et al. (1995) used the same equation to study the effect of the physico-chemical properties of various polymer binders on the strength of agglomerates. Silkong et al. (1990) employed a different equation (equation-5) as given by Hiramatsu and Oka (1966), to assess the breakage behavior of fine particles of brittle minerals and coal in a size range of 88 μm to 1 μm. They calculated the stress σ_f, required to initiate fracture in a spherical particles of radius R from the crushing load, F_o from:

$$\sigma_f \approx \frac{0.7F_0}{\pi R^2} \qquad \text{.....(5)}$$

Shipway and Hutchings (1993) presented a theoretical and experimental study of the fracture of a single brittle glass spheres by uniaxial compression between opposed platens. They proved that the above equation which was used by previous investigators to estimate the maximum internal tensile stress from the load, provides a useful approximation only under certain conditions, and more generally leads to significant error. They suggested an equation (equation-6) by which determination of the tensile strength of spherical samples was possible.

$$\sigma_f \approx \frac{0.4F_0}{\pi R^2} \qquad \text{.....(6)}$$

An alternative way of determining the strength of agglomerates is using a confined uniaxial

compression test (Adams et al. 1994). In this type of technique, average single agglomerate strength is inferred from the behavior of the whole bed under compression which is achieved experimentally using a piston and a cylinder. In this model (equation-7), the pressure-volume relationship is used to determine the strength of the agglomerate.

$$\ln P = \ln(\frac{\tau'_0}{\alpha'}) + \alpha'\varepsilon + \ln[1 - \exp^{-\alpha'\varepsilon}] \qquad .....(7)$$

where P is the compaction pressure, τ'_0 is the average strength of the granules, α' is the parameter related to the coefficient of friction and ϵ is related to the strain of the compact formed. To determine the average strength of the granules, the porosity of the compacts formed must be reduced considerably. At a large values of the applied strain, the third term in the right hand side of the equation becomes very small and can be neglected, and the value of the granule strength can be calculated form the linear relationship between the ln P and ϵ.

In a confined uniaxial compaction test, a local crack opening within a single agglomerate resulting from the major principal stress acting in the axial direction would be constrained by the radial principal stress induced by neighbouring agglomerates (Adams et al. 1994). Thus, the particle would be constrained to fail in oblique shear. Hence, the strength of agglomerated determined from this equation provides the shear strength of the granules. Salako et al. (1998) used this technique to determine the shear strength of their soft and hard pellets.

1.2.5 WEIBULL-ANALYSIS

Tensile strength results are characterized by a comparatively large variability between individual measurements, no mater how carefully the test specimen are prepared or the test conditions are controlled (Newton and Stanley, 1974). This variability is an inherent feature of a material which cannot deform plastically under increasing stress (i.e. brittle material). Griffith's theory considers the presence of flaws on the surface of the granules, at the most unstable of which fracture occurs by crack extension due to a concentration of the applied stress at the apex of the flaw (Podczeck, 1998a). The fracture behaviour of brittle materials is, thus, governed by the flaw distribution within the materials and the variability in strength of a set of normally identical specimens is a direct consequence of the random nature of this

distribution (Stanley and Newton, 1977) .

Therefore, a statistical treatment is essential for a full characterization of the mechanical strength of pharmaceutical compacts. The Weibull-distribution (Weibull, 1951) offers a valid mathematical model of this particular form of variability (Stanley and Newton, 1977). Weibull (1951) considered the system to be represented by links in a chain, from which he deduced the probability of the failure of the chain based upon the preposition that the chain as a whole fails if any of its links fail. In the application of this technique for characterization of the strength variability of pharmaceutical compacts Newton and Stanley, (1974) suggested two principal assumption: (i) that the material is isotropic and contains a statistically uniform distribution of flaws and (ii) that once a crack has initiated from a flaw it will propagate without further increase in load, resulting in fracture.

In equation-8, the Weibull-modulus, m, is a measure of the variability of the failure properties of a batch and is indirectly proportional to the range of flaw sizes present in the brittle specimens. The smaller the value of m, the more brittle is the compact. The value of the Weibull-constant, $X_{o,}$ is a characteristic strength value of the compact and quantifies the stress for 63.2% probability of failure. A further constant, X_u, is introduced to account for deviations from a perfect brittleness (Erck, 1994). The Weibull-function for the probability of failure, P(x), thus takes the following form:

$$P(x) = 1 - \exp^{\frac{-[(x-x_u)^m]}{x_o}} \qquad \text{.....(8)}$$

In a further experiments with lactose monohydrate powder compacts of different size, Stanley and Newton (1977) found the dependence of mean fracture stress and Weibull modulus on the dimensions of the compacts. Their results suggest that there may be some difference in both strength and strength variability of powder compacts of different size due to a dependence of the details of the compaction process on the dimensions of the compact. They expressed their finding using the following equation.

$$\frac{\sigma_{fA}}{\sigma_{fB}} = \left(\frac{V_B}{V_A}\right)^{1/m} \qquad \text{.....(9)}$$

This indicates an important feature that is the mean fracture stress of a batch is a characteristics of the specimen and not of the material alone and it is a size dependent quantity. The larger a specimen the more likely it will contain a flaw of a given severity and consequently the smaller will be the mean fracture stress of a batch of such specimens.

1.2.6 THE STRAIN OF AGGLOMERATES

In many cases, even the knowledge of tensile and shear strength alone is not sufficient to understand the mechanical properties of agglomerates. One more criterion which is often needed for evaluation is the strain behaviour of the agglomerates. This is commonly expressed in terms of elastic/plastic deformability of the agglomerates. Wikberg and Alderborn (1992) related the deformability of their granules to the linear portion of the inverse of the slope of the force/displacement profile produced during the diametral compression test (from 1N up to the breaking force).

Another criterion is the determination of the linear strain of pellets (Dyer et al. 1994). The ratio or percentage decrease in the unidirectional dimension of the pellet along the direction of the force is determined before the pellet fails during the diametral compression test. Kuno and Okada (1982) explained this phenomena as a linear shrinkage. Moreover, they tried to determine the " Deformation modulus", d_g of the granules using the shrinkage value from:

$$d_g = \frac{S_g}{D} \qquad \text{.....(10)}$$

where, S_g is the linear shrinkage, which is the decrease in the diameter of the particle along the load direction until it breaks, and D is for the diameter.

The elastic modulus of the pellets was also expressed as a ratio of the crushing load to their linear strain calculated from the force/displacement profile during diametral compression test (Dyer et al. 1994).

1.2.7 VISCOELASTIC PROPERTIES: DYNAMIC MECHANICAL ANALYSIS

Dynamic mechanical testers apply a small sinusoidal stress or strain to a sample and measure the resulting strain or stress response. Due to the time-dependent properties of viscoelastic materials the resultant response is out-of-phase with the applied stimulus. The observed

complex modulus, G**, is defined as the instantaneous ratio of stress/strain (σ_0/γ_0). To understand the deformation mechanics occurring in the material this is resolved into an in-phase or elastic response, being recoverable stored energy and out-of-phase or imaginary or viscous response, this being proportional to the irrecoverable or dissipated energy. The angle, δ, is the measured phase lag between the applied stimulus and the response (Fig-1.3). Tan δ is given by the ratio of loss to storage modulus and is proportional to the ratio of energy dissipated/energy stored (equation 11-14). This is called the loss tangent or damping factor. Radebaugh and Simonelli (1983) and Jones (1999) have presented the mathematical description of the dynamic experiment under strains within a sample's range of linear viscoelasticity. The complex modulus, G**, was defined as a vectorial sum of the storage (real or elastic) modulus , G', which represents the energy stored per cycle within the sample (i.e. the 'solid' response), and the loss (imaginary or viscous) modulus, G", which represent the energy dissipated per cycle within the sample (i.e. the 'liquid' response):

$$G^{**} = (\sigma_0/\gamma_0)\cos\delta + i\,(\sigma_0/\gamma_0)\sin\delta \qquad .....(11)$$

where $G' = (\sigma_0/\gamma_0)\cos\delta$ .....(12)

and $G'' = (\sigma_0/\gamma_0)\sin\delta$ .....(13)

Thus, $\tan\delta = G''/G'$ .....(14)

A typical DMA (eg. DMA7, Perking Elmer Corp., High Wycombe, UK), is made up of four major components (Fig-1.2): a precise linear high force motor, a central core rod and measuring system assembly, a high sensitivity displacement detector (LVDT), and fast-response furnace. The measuring systems are attached to the lowest end of the core rod. The LVDT is the detection system of the DMA and it accurately tracks any changes in the sample thickness. The LVDT provides high sensitivity as well as broad dynamic range to accommodate a variety of sample sizes and geometries. The linear force motor provides a precise control of all forces applied to the sample. The DMA has also an attached furnace that permits the application of different temperature programmes.

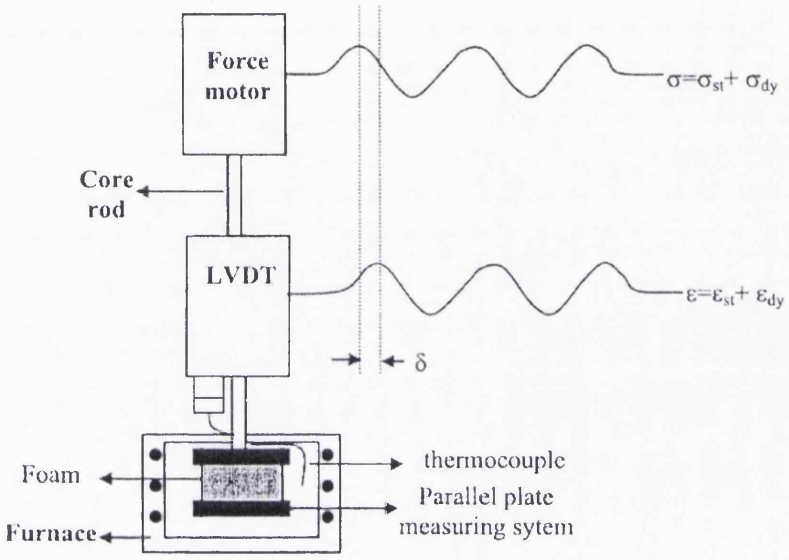


Fig-1.2:- Schematic representation of the DMA 7

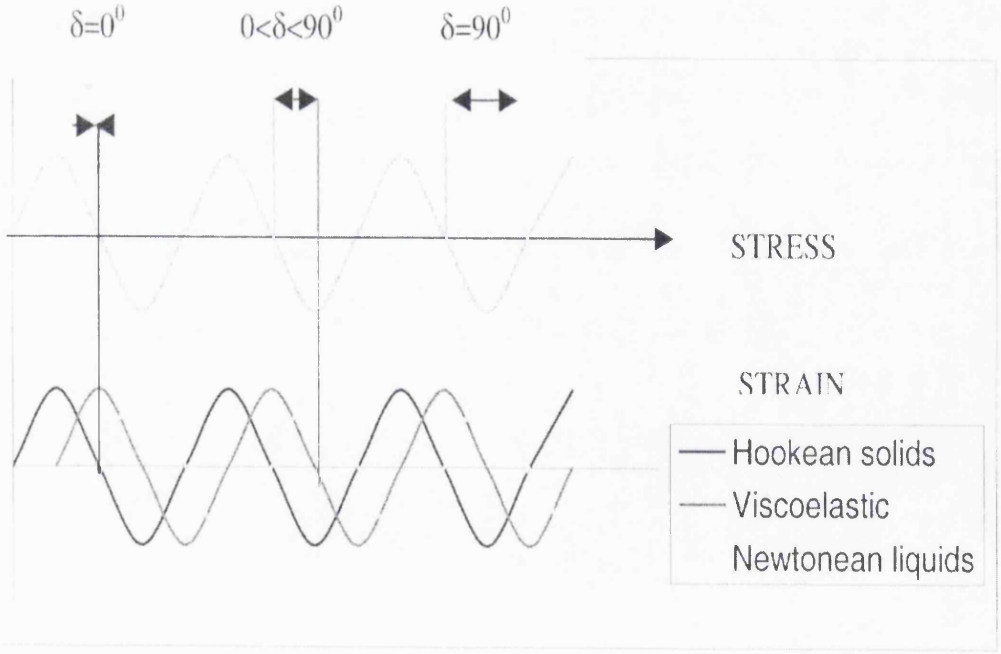


Fig-1.3:- The stress and strain relationship of elastic (Hookean solids), viscous (Newtonean liquids), and viscoelastic materials.

1.3 PELLETS AND THEIR PROGRESS

1.3.1 INTRODUCTION

Pharmaceutical pellets can be defined as small and spherical agglomerates containing drugs and excipients (Reynold, 1970). Their size is commonly expressed as a ranges of diameters between 0.5-2.0 mm. These entities have been named differently in many pharmaceutical publications, for instance, beads, agglomerates, pellets, spheroids, microspheres, and spherical granules (Celik, 1994). Moreover, they are also termed "marumes", particularly in Japanese literatures, a term which stems from the registered trade name of the original Japanese spheroniser, the Marumerizer.

Although various industries have routinely utilized pelletization processes to manufacture particles of defined sizes and shapes, it was only in the middle of last century, in response to a desire to sustain release of drugs over extended periods of time, that the pharmaceutical industries developed a keen interest in the technology (Ghebre-Sellassie, 1989). That is because pellets can be used in the modification of drug release by their preparation in the form of drug reservoir enclosed in a polymer coating as used by Chang and Rudnic (1991), Bechard and Leroux (1992), Bansale et al. (1993), and Beckert et al. (1996) or as release retarding matrices by incorporating hydrophobic substances such as wax (eg. Shaefer et al. 1990; Thomsen et al. 1993, 1994; Adeyeye and Price, 1994).

Earlier products were produced by coating sugar and starch pellets, obtained from the confectionary industry with low doses of drug (Newton, 2000). This was noted in the first publication by Cimicata (1951) who presented a detailed description on the manufacturing and polishing process of the seeds. The process utilized standard coating pans and involved successive layering of powder and binder on sugar granules until spherical seeds of the desired size were obtained. This process was refined and perfected by Smith Kline & French (SKF) who also launched a spray congealing process, where a drug is allowed to melt, disperse, or dissolve in hot melts of gums, waxes, or fatty acids, and is sprayed into an air chamber where temperature is below the melting points of the formulation components, to provide, under appropriate processing conditions, spherical congealed pellets (Ghebre-

Sellassie (1989). Newton (2000) indicated that SKF's production of the spansusles in 1960s, provided a good example of their potential as controlled release products.

The introduction of a Marumerizer, first patented in Japan, enabled the production of pellets that contained a higher drug concentration (Conine and Hadley, 1970). It also offered accurate control dosage, higher speed of production, and choice of batch or continuous flow production (Woodruff and Nuessle, 1972). The process involves extrusion of a wet mass of a mixture of active ingredients and excipients to provide cylindrical segments or extrudates followed by spheronization of the extrudates in the marumerizer or spheronizer (Conine and Hadley, 1970). Following these early 1970s publications (eg.Reynolds, 1970; Conine and Hadley, 1970; Woodruff and Nuessle, 1972; Jalal et al. 1972; Malinowski and Smith, 1974) the processing and formulation factors that affect the production and application of pharmaceutical pellets has been the subject of extensive researches.

The most widely used pelletization processes is extrusion/spheronization (Reynolds, 1970; Conine and Hadley, 1970; Newton, 1994,1996; Vervaet et al. 1995). Other processes which have limited applications are solution/suspension layering (Jones, 1994), powder layering (Niskanen et al. 1990), and melt pelletization (Shaefer et al. 1990).

A pan, perforated drum or fluid beds are usually utilized to prepare pellets by liquid layering, a process similar to coating process. Beside to their advantage of utilizing a single piece of equipment, Newton (1999) noted that this process is ideal for relatively low drug levels, offering rapidity and the ability to process with a range of solvents and coating solutions. The pellet making process using a regular powder layering method is very difficult for uniformity is seldom achievable. Nevertheless, there are several reports of successful pellet preparation by such a system as rotary processor (Niskanen et al. 1990). Shaefer et al. (1990) have presented a detailed account of melt pelletization in which solid of lower melting points are agglomerated at elevated temperature and cooled to room temperature to provide pellets.

Other processes with limited application in the development of pharmaceutical pelletization products were summarized by Ghebre-Sellassie (1989) as: (i) globulatioin : a process of spray drying or spray congealing of suspensions to form spherical pellets; (ii) balling, where finely divided particles are converted, upon the addition of appropriate quantities of liquid, to

spherical particles by a continuous rolling or tumbling motion; and (iii) compression, in which mixtures or blends of active ingredients and excipients are compacted under pressure to generate pellets of defined shape and size. In fact, pellets produced by compression are nothing but small tablets that are approximately spherical in shape.

1.3.2 RATIONAL FOR PELLETIZATION

Pellets are of great interest to the pharmaceutical industry for a variety of reasons. In processing, their spherical shape renders a free flowing property to alleviate material handling problems and are easily mixed when combination product is desired (Conine and Hadley, 1970). They are ideal for coating process, providing the minimum surface area to volume ratio and a smooth surface texture allowing the uniform application of coating (Reynold, 1970). The single most important factor is, however, their utilization in the production of controlled-drug-release dosage forms by coating them with films of different composition (Yuen et al. 1993) and thickness (Zang et al. 1991). Moreover, site specific delivers such as intestine (Watanabe et al. 1990; Beckert et al. 1996) and colon (eg. Siew et al. 1999; Basit, 2000) delivery is possible with suitable polymer coatings.

Pellets also provide the pharmaceutical scientist with tremendous flexibility during the designing and development of oral dosage forms. For instance, pellets composed of different drug entities can be blended and formulated in a single dosage form (Conine and Hadley, 1970). Such an approach has numerous advantages. It allows the combined delivery of two or more drugs that may not be chemically compatible, at different sites within the gastrointestinal tract. It also permits the combination of pellets of different release rates of the same drug in single dosage form (eg. Follonier and Doelker, 1992; Melia et al. 1994).

The advantages of pellets over granules as an intermediate products were also noted by Jalal et al. (1972) in terms of flowability, denser packing, uniform size, and rapid drying time in their basic formula. Their flow rate increased from 38 to 102%, and provided a narrower particle size distribution and much less fines, and dried in a shorter (1/3) time compared to granules prepared by the conventional wet granulation process. The smooth surfaced spherical pellets renders a better packing by sliding over each other during a die or capsule filling (Reynolds, 1970). This provides a uniform and reproducible fill weights in dies or capsules, provided that the size and densities of the pellets are similar.

From pharmacological point of view, as a high degree of dispersion is achieved in the digestive tract, the risks of local irritation (Sarisuta and Punpreuk, 1994) or sudden dose dumping (Follonier and Doelker, 1992) can be minimised. Moreover, the evacuations through the pylorus spreads over a long period of time ensuring improved predictability and less dependence on the state of nutrition (Chetty and Dangor, 1994; Sandberg et al. 1988). The enhancement in the bioavilability of the drugs is also one of the marked therapeutic advantages of multiparticulate formulations. Houghton et al. (1984) reported that administration of ketoprofen in a once-a-day sustained-release pellet formulation containing 200mg drug produced similar minimum plasma ketoprofen concentrations to those achieved by dosing ketoprofen capsules (50mg) every 6 hours and markedly higher minimum plasma ketoprofen concentrations than that produced by ketoprofen capsules (100mg) every 12 hours. Furthermore, Bechagaard and Nielson (1978) and Bechagaard and Ladefoged (1978) have reviewed the pharmacological advantage of multi unit over single unit dosage form.

1.4 FORMULATION OF PELLETS

1.4.1 MICROCRYSTALLINE CELLULOSE

The most common tablet excipients such as fine powdered or granular cellulose (Lindner and Kleinebudde, 1994), lactose or dicalcium phosphate dihydrate (DCP) (Schwartz et al. 1994), starch or modified starch (O'Connor et al. 1984), sucrose powder (Conine and Hadley, 1970) were not able to produce pellets on their own, without addition of binders, by the process of extrusion and spheronization.

The basis for most pharmaceutical formulations is, therefore, the inclusion of microcrystalline cellulose, a spheronization enhancer. For instance, sucrose powder or lactose had to be mixed with 20% and 30% w/w MCC respectively to form pellets (Conine and Hadley, 1970), while Schwartz et al. (1994) reported the need of more than 20% w/w MCC for the production of dicalcium phosphate dihydrate (DCP) pellets. This substance not only enhance plasticity on the formulation, but also impart binding properties that are essential for pellet strength and integrity. MCC is the only excipient which could form pellets by itself (Conine and Hadley, 1970; Schwartz et al. 1994).

The inherent plasticity (Rees and Rue, 1978), and the capacity to hold water within its structures (Newton, 1994) could be the reasons for the suitable consistency of MCC in the process of extrusion and spheronization. MCC appears to have virtually unique properties in holding water within itself with sufficient affinity so that it is not pushed out by the forces of the process (Fielden et al. 1989; Newton, 1996). This important water retention property enables the extrusion process to have a steady state force (Harrison, 1982). Moreover, the extrudates can have a uniform water content that improve their plasticity to easily round up to spheres in the spheroniser in addition to its effect as a lubricant in the walls of the die. The content of most reported pellets produced by extrusion and spheronization is MCC, for it is only in the presence of MCC that they become amendable to the spheronization process (O'Connor and Schwartz, 1989). Robustness of formulations containing MCC was proven by their less water sensitivity (Bains et al. 1991). The greater the proportion of MCC, they observed, the less critical the quantity of water becomes in the consistency of the formulation. The proportion of MCC in a pellet formulation suitable for spheronization is determined by the physicochemical properties of both the active ingredient and other excipients incorporated, hence varies with the composition of the formulation. Conine and Hadley (1970) indicated the possibility of sphere preparation with 90-95% active ingredients, thus making it possible to prepare filled capsules of spherical particles at high dose level. The practical limit for good quality round spheres is, however, 80% w/w drug (Newton, 1994). Low proportions of active (below 10%) should present not too many problems, Newton (1994) recommended, and the inclusion up to 50% of MCC could be appropriate.

One of the variables which influences the quality of spherical granules prepared by extrusion/spheronization is the grade and type of commercially available MCC. The same grade is often available from more than one manufacturer, as in the case of Avicel PH101, Emcocel, and MG 100, which are different brands of the same grade. A manufacturer usually supplies grandes with a variety of particle sizes and water contents, eg., Avicel PH101, 102, 103, and 105, as well as colloidal grades containing sodium carboxymethyl cellulose. When mixed with lactose and water these different grades of MCC showed different rheological properties, when assessed by capillary rheometry (Raines et al. 1989). They found that, to obtain the same die wall shear stress for the three brands of MCC, different quantity of water were required. Moreover, they reported that for any given change in water content the three

brands of MCC showed different changes in die wall shear stresses. Newton et al. (1992b) demonstrated how these differences were carried over into the spheronisation process.

In a process of compacting pellets to form tablets, MCC pellets were found to be not compressible (Schwartz et al. 1994), exhibited elastic deformation (Maganti and Celik, 1993), and could not form compacts of reasonable strength (Schwartz et al. 1994; Maganti and Celik, 1993) mainly due to excessive volumetric elastic recovery (Maganti and Celik, 1993) and being too hard to consolidate by deformation and fracturing (Schwartz et al. 1994). For this reason, Schwartz et al. (1994) incorporated other excipients in the formulation, while Maganti and Celik (1993) added exterinal excipients such as soy polysaccharide and pregelatinized starch. The incorporation of binders such as starch paste, and PVP with the active drug was also suggested by Conine and Hadley (1970).

1.4.2 GLYCERYL MONOSTEARATE

Thomsen et al. (1993) used glyceryl monostearate 8.5% w/w in their prolonged release matrix pellets preparation by melt pelletization. In another work Thomsen et al. (1994) studied 12 meltable substances with respect to their ability to form prolonged release pellets in a melt pelletization process using a laboratory scale high shear mixer. They found that only few substances were able to pelletize a formulation with 12.5% m/m paracetamol and 87.5%m/m calcium hydrogen phosphate, while most of the substances did not demonstrate applicability as binders. However, glyceryl monostearate appeared to be the most suitable substance. It was observed that the presence of glyceryl monostearate in a binder combination enabled the pelletization process to proceed in a controlled, and regular way, while the presence of more hydrophobic substances such as microcrystalline wax in the binder mixture ensured constitutive prolonging of the drug release.

In their development and in vitro evaluation of a multi-particulate matrix controlled release formulation of theophylline Peh and Yuen (1995) produced pellet matrix using microcrystalline cellulose and glycerol monostearate. When microcrystalline cellulose was used alone, the drug release was not sufficiently sustained and was essentially completed within 6 hours. However, incorporation of glyceryl monostearate significantly retarded the rate of drug release. Hence, it was possible to modify in a predictable manner by varying the amount of glyceryl monostearate and microcrystalline cellulose mixture.

The ability of glyceryl monostearate to retard the rate of drug release from the pellets may be attributed to its lipophilic property. Incorporation of the glyceryl monostearate caused an increase in the lipophilicity of the pellet matrix, leading to the decrease in the effective interfacial area between the drug and dissolution medium, resulting in a reduction of wetability (Peh and Yuen, 1995). Consequently, there is a slower rate of water penetration and dissolution of the drug within the pellets and hence a slower rate of drug release is obtained.

The ability of glyceryl monostearate to modify the rate of drug release does not only mean to retard or delay the release of drugs. It could also be used to enhance the drug release rate of pharmaceuticals containing hydrophobic materials. Adeyeye and Price (1994) observed that pellet formulations containing waxes such as paraffin or ceresin wax without modifiers exhibited very slow dissolution profiles and incomplete drug release. The addition of modifiers such as glyceryl monostearate, however, greatly increased the dissolution rate. This could be due to the presence of hydroxy groups in the structure of glyceryl monostearate that may have provided relatively hydrophilic pathway for water molecules to access the drug and increase the rate of dissolution.

In all the aforementioned references, the incorporation of glyceryl monostearate to the formulation was in its molten state or it was immediately heated to above its melting point in the mixture to melt. For instance, in the preparation of their pellets Peh and Yuen (1995) first dispersed the glyceryl monostearate in a sufficient quantity of hot distilled water heated to approximately 80^0C. Then theophylline was added with constant stirring until a slurry was formed. The hot slurry was immediately mixed and blended with microcrystalline cellulose in the Kenwood planetary mixer for 10 min. The wet powder mass was then extruded and spheronized. Thomsen et al. (1993, 1994) also used melt pelletization technique to produce their pellets. However, Pinto et al. (1993) and Lundqvist et al. (1997) directly blended glyceryl monostearate powder with microcrystalline cellulose and other materials and extruded it directly after adding sufficient amount of water.

The use of water and microcrystalline cellulose appears critical to a successful extrusion and spheronzation process, yet recent experiments have shown that under certain circumstances microcrystalline cellulose can be replaced with glyceryl monostearate Newton (2000). In their

study on the feasibility of formulating ranitidine into pellets with a range of alternative excipients in place of microcrystalline cellulose, Basit et al. (1999) were able to produce ranitidine pellets with barium sulfate and glyceryl monostearate in place of MCC. Their pellets exhibited the necessary physical and mechanical characteristics required of oral dosage forms and for further pharmaceutical processing such as film coating.

1.4.3 LACTOSE

Incorporation of lactose at different weight by weight percentage in MCC/water mixture during the production of pellets is a common practice. For instance, 10% w/w (Maganti and Çelik, 1993), 67.5 % w/w (Schwartz et al. 1994), 20% or 80% w/w (Wang et al. 1995), 80% w/w (Dyer et al. 1994) lactose was blended with MCC for the production of pellets. The most extensive research on the effect of addition of lactose to MCC in the production of pellets by extrusion and spheronization processes was performed by Harrison, 1982, Harrison et al. (1985a and 1985b), Fielden 1987 and Fielden et al. (1989, 1992a). By using a ram extruder, Harrison et al. (1985a) demonstrated that steady-state flow could not be achieved when only lactose was extruded. Additionally, they demonstrated the reduced sensitivity of MCC to small changes in moisture, as determined by the force required to induce plug flow in a cylinder. When comparing MCC with a MCC/lactose blend and 100% lactose, they found that, with lactose, small changes in moisture caused large changes in force, whereas with MCC, large changes in moisture were required to have a similar effects on the force.

The inclusion of lactose in a microcrystalline cellulose/water formulation reduces the prevalence of surface roughness of the extrudate which could affect its subsequent processing (Harrison et al. 1985b). This was thought to be by reducing the deformability of microcrystalline cellulose and strengthening the extrudate surface. They reported the occurrence of surface roughness in all MCC extrudates at all die diameters and at all moisture contents greater than 51% w/w, but for MCC/lactose mix it occurred only at the widest die diameter, at the highest ram speed, and at its highest moisture content only.

Fielden et al. (1989) observed that the particle size of the lactose was an important factor in the extrusion process, extrudate properties and pellet properties when MCC/lactose/water mixture at 5: 5:6 ratio were used in the production of pellets by extrusion and spheronization. The use of a coarse grade lactose (mean size 117μm) gave rise to surface roughness and

shark-skinning, over a much wider range of extrusion conditions than if a grade of smaller particle size (18μm) was used. This was due to forced flow conditions in the die resulted from high extrusion force generation and nonuniform water distribution. They also observed the modification of the rheological properties of MCC/lactose/water mass with the change of the lactose particle size. At low shear rates, the die-wall shear stress was lower in the mixture containing coarse, but at higher shear rates the flow curves of the two formulations were the same. This indicated that the mixture containing coarse lactose was more shear-rate dependent, and that at high shear rates the rheological properties were equivalent to those of the mixture containing fine lactose in steady-state flow. Fielden et al. (1989) further associated this observation with the migration of the water through the powder. The larger particle size lactose appeared to allow greater water movement at low shear rates, the water seemed to have moved to the surface of the extrudate and reduced die wall shear stress as a lubricant.

Spheronization of the two formulations resulted in the production of spheroids of very different particle sizes (Fielden et al. 1992a). The smaller particle size fraction of lactose produced spheres which were approximately 1 mm in diameter and were able to reside on the plate for up to 10 minutes with no serious agglomeration. The larger particle size lactose formulation provided a product which had extensive growth of granules (3 mm) and a greater size distribution before it reached 10 minutes. A similar observation in increase in pellet size with increase of lactose particle size was also made by Wang et al. (1993).

1.4.4 LIQUID BINDERS

The commonly used liquid binder for the production of MCC pellets is water. The plasticity of this wet mass is vital on the production of pellets by the extrusion and spheronization method (Conine and Hardley, 1970). The property of this mixture can be modified by addition of adhesive or capillary type binders (Reynold, 1970) and emulsifying agents (Newton, 2000). Some researchers also tried to modify the characteristics of the wet mass by changing the composition of the binding liquid. Fore instance, water/ethanol mixure in different proportions were used to produce pellets of different properties (eg. Goodhart et al. 1973; Millili and Schwartz, 1990; Johannson et al. 1995; Johansson and Alderborn, 1996). However, no report has so far been published on the production of pellets without water.

The presence of water is an essential feature of formulations containing MCC for the preparation of spherical granules by the process of extrusion and spheronization. Tomer and Newton (1999) indicated the function of water as a two fold: to increase the plasticity of the mixture and to act as a lubricant at the wall of the die during extrusion process. Hence, MCC formulations which have insufficient water will not be extruded, will not deform and may even fail to cohere in the spheroniser. On the other hand, formulations containing moisture more than a certain limit, will agglomerate during spheronization. Bains et al. (1991) assessed the influence of water content on the ability of the mixture of a range proportions of barium sulphate and MCC to form spherical granules by extrusion spheronization. They found that below 2500 N of extrusion force, the extrudate was too wet and agglomerated, while above 10,000 N the product was too dry and failed to round or cohere. Fielden et al. (1993) noted the agglomeration of MCC/coarse lactose extrudate at moisture content of 37.5%w/w, but was not apparent at reduced moisture content of 33.5%w/w.

Pinto et al. (1993) identified water content as the most important variable in their factorial designed experiment to identify the formulation and processing factors that influence the property of the spherical granules. However, the sensitivity of formulations to water varies. Bains et al. (1991) noticed a decrease in sensitivity of the formulation with increase in the percentage of MCC in their MCC and barium sulphate pellets. Harrison et al. (1987) had also observed the decrease in moisture sensitivity of the wet mass during extrusion process with the increase of MCC proportion in the MCC/lactose mixture.

1.5 PREPARATION OF PELLET BY EXTRUSION AND SPHERONIZATION

1.5.1 MIXING

In an attempt to make an isotropic compact from more than one pharmaceutical powders, the crucial challenge is to have a uniform mutual distribution of the different powder particles. This could only be achieved during the dry powder mixing. For producing such a homogeneous powder mixture the autoadhesion forces between the particles of each single powder component must be overcome, i.e. the adhesion force between particles of either component must be greater than the autoadhesion forces (Podczeck, 1998a). In this way one component will be evenly distributed over the surface of the other component. This distribution process can, however, be disturbed by inherent particle properties such as size and size distribution, shape, surface energy and surface roughness. For instance, to determine

how the efficiency of mixing was affected by shape of particles Wong and Pilpel (1990a) mixed calcium carbonate and lactose of different particle shapes and measured the time required to achieve the acceptable standard deviation of mixing. They reported that the time needed increased with the irregularity of the particles of both components. Moreover the mixing procedure had a tremendous effect, hence the mixer type, mixing time and rate should be standardized.

In terms of conventional granulation, the work involved in incorporation of the fluid can also have a critical effect on the product. That is mainly due to its binding effect as well as the distribution of soluble ingredients in the wet mass. Newton (1996) indicated that the efforts made in producing the mixture depends on the subsequent processing of the mass. High-intensity mixing was found to be essential to distribute the water through the mass by Lovgren and Lundberg (1989) for their subsequently lower shear and compression forces (screen extruder) application to extrude the wet mass. For high compression, high shear extrusion using a ram with a long die, however, Fielden et al. (1993) found that the simple planetary mixers to be adequate.

The effects of wet massing process variables, such as kneading time and amount of granulation liquid, on conventional tablet granules has been reviewed by Kristensen and Schaefer (1987). However, the effect of wet massing stage on pellet properties has not been subjected to extensive study, although attempts were made to evaluate the rheological properties of wet mass to the quality of extrudate and their effect in the subsequent processes and pellet properties (eg. Harrison et al. 1985a, 1985b; Fielden et al. 1993; Chohan and Newton, 1996). From the works of these authors it is possible to established the fact that under-wet-mixing may lead to variability in the plasticity of the mass and therefore to an extrudate of variable quality, while over-wet-mixing may give rise to a soft mass with altered rheological properties and agglomeration of pellets during spheronization.

In the production of a wet powder mass for extrusion and spheronization, different types of mixers are used. The most commonly used batch-type mixer is a planetary mixer (eg. Fielden 1987; Pinto, 1992). Helen and Yliruusi (1993) and Helen et al. (1993a, b) used a continuous method, where powder fed from hopper was dispersed into small particles in the centre of a turbine to meet with the pumped and finely dispersed liquid mist for granulation.

1.5.2 EXTRUSION

Extrusion is the process in which a mass is forced through a restricted cross section, die or orifice, to densify and form a spaghetti-like or rigid cylindrical segments (Reynold, 1970). There are various types of equipment which can undertake this process. They may be classified according to the die design and the feed mechanism which transports the material to the die region (Rowe, 1985; Fielden and Newton, 1992; Vervaet et al. 1995).

Hicks and Freese (1989) and Fielden and Newton (1992) have reviewed the advantages and disadvantages of the different types of extruders and their application in plastic and ruber, ceramics, food, nuclear and pharmaceutical industries. Moreover comparison between gravity fed extruder and twin screw extruder (Baert et al. 1993) and the comparison of ram and cylinder extruders in the extrusion of MCC, lactose and water mixture has been discussed by (Fielden et al. 1992b). In a screw extruder, the exertion of a high pressure on the material generates excessive friction and heat as the wet mass passes between the screw and barrel (Fielden et al. 1992b). Moreover, their low length-to-radius ratio of the die holes can also result in low compaction in the extrudate and distortion of the surface finish, knowing as shark-skinning (Harrison, 1982).

The instrumentation of these extruders had attracted the attention of researchers to help in an in-process control and to correlate the quality of the final product to the extrusion force recorded. To this end, Elbers et al. (1992) and Baert and Down (1994) tried to show that the screw extruders could be instrumented to measure the power consumption or the extrusion force. They reported a decreased in power consumption with increase in fluid content in the formulation and related it with the plasticity of the wet mass. However, the most suitable equipment which allows a critical in-process control of parameters such as temperature, force, rate of extrusion, and size of extrudate is the ram extruder (Fielden and Newton, 1992).

Ram extrusion system provides the only accurate measurement of the extrusion pressure as all other systems measure average pressure across a series of holes (Newton, 1996). In this system, the cross-head may be driven down at various constant rates, and its displacement can be monitored by an attached time or displacement transducer. Output from this and the load cell is fed into an X-Y chart recorder or computer. This arrangement enables the force acting on the material during extrusion to be recorded as a function of the displacement of

the piston, and a force-displacement profile is produced. Harrison (1982) noted three distinct stages on the force/displacement profile recorded as compression, steady state flow and forced flow stages.

Harrison et al. (1985a) applied these stages in characterization the extrusion of wet powder mass made up of MCC and water at various ratio; MCC, lactose, and water at 5:5:6 ratio, as well as lactose and water at 8:2 ratio. They observed a decrease in the compression stage with the increase of moisture content in MCC and water mixture, while no effect was observed in MCC, lactose and water mixture with change in moisture content. They concluded that with the increase of moisture content, the plasticity and compressibility of the wet MCC powder mass increase significantly to result in flow before all the interparticulate voidage had been eliminated. They noted that the steady-state flow was possible with the MCC and MCC and lactose mixture, but not with lactose only. Furthermore, the extent of the steady state flow stage of the MCC/lactose mixture was moisture content and extrusion rate, but not die diameter dependent. Finally, they recommended that formulations and extrusion procedure should be optimized to minimise the compression stage and extend the steady state flow stage to increase the throughput.

A ram extruder has been used to characterize the rheological properties of wet powder (eg. Harrison et al. 1987), and the uniformity of water distribution during the extrusion process (Fielden et al. 1989). Conine and Hadley (1970) suggested that if regular spherical granules are to be formed by the process of extrusion and spheronization, the extrudate produced must be able to break into short segments that are sufficiently plastic to be rounded by spheronization. Harrison et al. (1987) attempted to determine rheological parameters to characterize the plasticity exhibited by microcrystalline cellulous alone or in combination with the water soluble diluent, lactose, when mixed together with a suitable quantity of water. Although exact rheological parameters could not be obtained due to die wall slip and complex changes associated with the convergence of flow into the die, a method was developed that enabled both a qualitative and quantitative assessment of extrusion of wet powder mass. They were able to derive a shear rate/die wall shear stress profiles by utilizing dies of a range of length to radius ratios versus the extrusion force at different position of the piston through the barrel. This was later applied by Fielden (1987) to investigate the effects of lactose particle size on the extrusion of MCC, lactose and water mixture. Raines et al.

(1989) further applied it to show that different sources of microcrystalline cellulose, when incorporated into a standard formulation with a given quantity of water, provide distinctly different rheograms. For a given die and shear stress, different quantities of water was required to achieve the same rate of shear for these different grades of microcrystalline cellulose.

The examination of extrudate quality in terms of surface nature, consistency of moisture distribution, and mechanical property could indicate its capacity to be rounded in a spheronizer. An extrudate must have a smooth surface finish. Surface imperfections causes breakage into irregular lengths on subsequent processing. In spheronization, this results in poorly shaped spheroids and a wide size distribution. Harrison (1982), Harrison et al. (1985b) and Fielden (1987) observed three different types of extrudate surfaces; smooth, rough and sharkskinned. The later two can be mentioned as defects. A sharkskinned extrudate has a characteristic ridge-like spiral structure running transversely to the flow direction (Fielden and Newton, 1992). Extreme sharkskinning can result in complete fragmentation of the extrudate on a spheronizer.

The development of such defects depends on the constituents of the formulation, the design of the extruder and its operation conditions (Newton, 1999). For the mixture of MCC, water, and lactose Harrison et al. (1985b) and Fielden (1987) observed increase in surface defect of the extrudate, essentially with the decrease in die length to radius ratio (mainly when the die length is equal or less than the diameter). Other factors they observed were those which can affect the balance of the tension in the outer surface of the extrudate and the forces required to maintain the cylindrical shape of the extrudate. They numerated the factors as (i) high ram speed, which can result in higher wall shear stress in the die (Harrison et al. 1987), thus increasing the outer radial surface tension; and (ii) moisture content, which results in a reduction in the forces required to maintain the smooth surface. They summed up their reports by noting that sharkskinning can be avoided by reducing the wall shear stress within the die by decreasing the ram speed or increasing the number of holes in the die, and reducing the deformability of the extrudate by decreasing the moisture content, or changing the formulation in terms of the solid components.

The effects of the amount of liquid on the rheological property of the wet powder mass (Harrison et al. 1985a) and its lubricating ability in the die wall (Pinto et al. 1993) was reported. Harrison (1982) discussed the slip-stick mechanism that occurs during extrusion and related it to the thin lubricating layer that was formed at capillary wall during extrusion of a wet powder mass. He elaborated that at zero thickness of the lubricant in the die there was a condition of stick, where the material on the die wall was static, while at maximal thickness, a condition of maximal slip occurred. The condition of stick would create tension in the material as it exits the die and thus cause the surface defect of the extrudates. This depended on the amount of lubricant (binding liquid) in the formulation. Moreover, self lubricating materials, such as glyceryl mono-stearate were observed to improve the surface nature of the extrudate (Pinto, 1992). Thus, the optimum plasticity of the wet powder mass for extrusion should be sought within a thorough consideration of the formulation factors (liquid and solid components) to produce extrudates of better surface quality although the degree of surface roughness which can be tolerated has not been yet quantified (Newton, 1999).

The extrudate should also retain a certain degree of rigidity so that to retain the shape imposed by the die (Reynold, 1970). Nevertheless, it should have an optimum rigidity and plasticity to be cut to short lengths to form short cylinders which are subsequently rounded by rolling in the spheronizer. If the segment will not break up, but are sufficiently plastic to form spheres, the size of the spheres may be larger than desired. Extrudate which will break up but is not sufficiently plastic, produces short cylinders rather than spheres (Conine and Hadley, 1970). Thus, formulae with optimum mechanical properties are required for good extrudate characteristics, but these do not necessarily produce good spheres, and the composition may have to be modified between the two processing stages, namely extrusion and spheronization (Reynold, 1970).

1.5.3 SPHERONIZATION

In this stage, the extrudate is placed on to a horizontally spinning plate and forced against the wall due to the centrifugal force. They are transported to the periphery of the plate where their residual momentum causes them to rise up the stationary wall and then to fall within or over the mass of the pellets as their momentum is dissipated (Reynold, 1970). They then are broken up into smaller cylindrical segments which are rolled again into a spherical shape

(Conine and Hadley, 1970). Chapman (1985) observed the various stages of shape changes which took place during spheronization by taking samples for analysis at fixed time points. Similarly, Fielden (1987) made the observation by using high speed flash photography by linking the stroboscopic flash to a high speed motorised shutter. With the combination of these techniques they proposed that the extrudates were first broken into short lengths which were 1.5 to 2 times their diameter. These were rounded at the ends and persuaded to shorten, apparently by compression, to form structures wider at the ends than the central portion "dumbbells". The central portion was then filled to form an ellipse, which gradually rounded to the spherical form. Baert and Remon (1993) suggested that another pellet-forming mechanism to account for the occurrence of spherical agglomerates with hollow centres. In this mechanism a twisting of the cylinder occurs after the formation of cylinders with rounded edges, finally resulting in the breaking of the cylinder into two distinct parts. Both parts have a round and a flat side. Due to the rotational and the frictional forces involved in the spheronization process the edges of the flat side fold together, they assumed, to form the cavity observed in certain pellets.

These changes are induced by the motion of the material relative to the plate, the wall and between the granules themselves. The design of the surface of the plate, mainly at the edge, appears to have an important function in terms of the chopping of the extrudate into appropriate length. Too sharp edge can considerably over-cut the cylinders and reduce them to fragments that can fail between the edges of the plate and the wall of the spheroniser. The plates have two different types of geometry of grooves (Rowe, 1985), cross-hatch geometry where the grooves form right angles and radial geometry where a radial pattern is used. Newton et al. (1995b) found that using a cross-hatch or radial-cut plane in a 20.3 cm spheronizer, produced slightly different pellets. This reiterates the importance of the depth and serration of the plate as noted by (Reynold, 1970). However Newton (1994) reminds that there is a lack of detailed published evidence linking the design of the plate and their performance.

Newton (1996) noted the importance of identifying some critical extrusion process features before trying to relate the spheronization process with the product quality. For example, he stated that studies with screen extruders do not necessarily give the same results as those involving extrusion through dies of greater length. In general systems using screen extruders

give a product which is far more sensitive to spheronization conditions than those that involve consolidation of the wet mass. The factor of outmost importance for the formation of the spheroids are, however, the consistency of the formulation in terms of coherency and inherent or induced plasticity (Conine and Hadley, 1970), as well as the quantity of the binding liquid and its distribution in the formulation as extensively reviewed by (O'connor and Schwartz, 1989; Newton 1994, 1996; Erkoboni, 1997).

The biggest variation, in the literatures, is as to how to assess the performance of the spheronizer, Hellen et al. (1993b), Wang et al. (1993) and Newton et al. (1995b) used the shape of the produced pellets, while Malinowski and Smith (1975), Hasznos et al (1992), and Hellen et al. (1993a) used the size and size distribution of the produced pellets, while Bataille et al. (1993) used the porosity, average pore size, pellet strength and surface conditions. Bulk density, flow rate, and friability of the dried pellets were also observed by Malinowski and Smith (1975) to assess the effectiveness of the spheronization conditions. Although the performance of the spheronizer depends on the plasticity of the wet mass (Conine and Hadley 1970; Reynold, 1970), and other factors such as extrudate diameter and length (Helen et al. 1992), extrudate surface quality (Harrison, 1985b), the moisture content and surface wetting of the pellets (Fielden et al. 1993), the spheronization process can also have a profound effect on the quality of the pellets produced.

Three operational processing variables, namely residence time, load and the speed of the plate were observed to have a significant effect on the properties of the produced pellets. Residence time of spheronization influenced the properties of pellets in different ways. However, this must be seen in conjunction with the speed of the plate, for less time may be enough to round the pellets at higher speed. With increase in residence time, improvement in 'hardness' (Bataille et al. 1993), increase in lower sieve size (Jalal et al. 1972; Helen et al. 1993b), improvement in shape (Helen and Yliruusi, 1993) narrowing of particle size distribution (Bianchini et al. 1992), increase in bulk and tapped density (Conine and Hadley, 1970; Helen et al. 1993b) were some of the reported findings. However, Woodruff and Nuessle (1972) observed no effect of spheronization time on the shape of their pellets containing sucrose, lactose, microcrystalline cellulose (Avicel PH 101), mineral oil, and water, while Wang et al. (1993) reported an increase in diameter of the pellets only up to a certain time above which small pellets were formed.

An optimum plate load was found for a 20.3cm plate spheronizer by Newton et al. (1995b) to produce pellets of better shape. They noted that too low quantity provided insufficient particle-particle interaction, whereas too high load produced insufficient plate-particle interaction. Hasznos et al. (1992) reported an increase in mean diameter of the pellets with increase in the load of the spheronizer indicating agglomeration of the pellets due to higher interaction with larger load. Helen et and Yliruusi (1993) reported the reduction in size and narrowing size distribution of the pellets with an increase in load of the spheronizer, which was accompanied with the increase in bulk and tapped density (Helen et al. 1993b). Barrau et al. (1993) reported that, although increasing the load decreased the elongation ratio and hence the sphericity, it increased the proportion in the modal size fraction and produced 'hard' and smoother pellets.

An increase in spheronization speed were reported to induce a decrease in the porosity and the average pore diameter with an increase in pellet strength and smoother surface condition (Bataille et al. 1993). Moreover increase in bulk and tapped density (Conine and Hadley, 1970; Helen et al. 1993b), improvement in roundness and size uniformity (Woodruff and Nuessle, 1972) were among other reported observation with the increase of the plate speed. Nevertheless, Newton et al. (1995a) argued that there was an optimum speed for a plate of 20.3 cm diameter upon which pellets of improved sphericity could be produced. If the speed was too low, they indicated, rounding was poor due to insufficient particle-particle interaction. If the speed was too high, the pellets broke. Nevertheless, no rotational speed is important without noting the diameter of the friction plate, for the peripheral part of the plate, which has a higher linear velocity is the position upon which the pellets roll. Based on this notion, Newton et al. (1995a) performed experimental examinations using consistent extrudates with a spheronizer of different plate dimensions. They indicated that it was possible to calculate the optimum speed of one plate size from the speed of another size by considering the linear velocity at the plate periphery. They demonstrated the optimum speed of the 100 cm plate form studies with the standard 20.3 cm plate as could for that of a 68.6 cm plate.

1.5.4 DRYING

A satisfactory pellet formation process by extrusion and spheronization occurs as a consequence of several carefully optimised processing stages that include drying. Drying is

commonly defined as the removal of a liquid by the application of heat, and is accomplished by the transfer of vapour into unsaturated phase, although some nonthermal methods (eg. desiccation with moisture removing material) also occur. Drying is used in pharmaceutical manufacturing as a unit process mainly to enhance the stability of the final products for it reduces the chemical reactivity of the constituents. Drying processes may be classified based on either the method of heat transfer (conduction, convection, radiation or in their combinations) or the method of solid handling.

In convection heating, the carrier gas for the evaporated moisture is preheated before passing over or through the material, and drying conditions can be readily controlled by the temperature and humidity of the warm gas. If the material to be dried is very thin or very wet, conductive heating may be employed. All the heat passes through the material from hot surfaces supporting or confirming the material, so the material temperature is higher than in convective drying. Drying by conduction is superficially different from drying by convection. In conduction, the wet solid is placed in a vessel which is heated from the outside and provided with a vent through which the vapour can be removed. In the convection case, however, hot gas is blown over the surface of the wet solid and this provides both the source of heat and the means for removal of the vapour.

In the solid handling method, the major criterion is the presence or absence of agitation of the material to be dried. A system in which there is no agitation of the materials or no relative movement among the solid particles being dried is called static-bed drying system. This constitutes tray or oven drying, freeze drying and desiccation with silica-gel among others. In a dynamic system such as fluid-bed drying, however, the solid particles are continually caught up in eddies and fall back in a random motion.

Most of the studies undertaken on the drying process of pellets had totally or partially MCC as a structure forming material (eg. Bataille et al. 1993; Kleinebudde 1994a; Dyer et al. 1994; Habib and Shangraw, 1997; Berggren and Alderborn, 2001a,b). As a fibrous material MCC can hold water by physically entrapping it in fine capillaries and internal pores. Moisture movement can therefore be slow during the drying process for the liquid has to diffuse through structural obstacles caused by molecular configuration. Different drying techniques

use different heat and mass transfer mechanisms to over come this obstacles, which can have some effects on the properties of the final products.

In the production of pellets, many researchers used different drying techniques, such as open atmosphere (eg. Johansson et al. 1995), conventional hot air oven (eg. Jalal et al 1972; Ahange et al. 1990) and fluid bed drier (eg. Harrison, 1982; Fielden, 1987; Pinto, 1992). Moreover, the drying time was variable. For instance, in their work to compare the effect of spheronisation technique (pan versus marumerizer) on drug release from uncoated beads Ahange et al. (1990) used the conventional hot air oven drying method at 40-45^{0}C for 20 hours, while Bataille et al. (1993) and Jalal et al. (1972) used the same technique for only 12 hours and 6 hours respectively to dry their pellets and obtain 1.0-1.5% w/w final moisture content in the case of the latter.

In an attempt to understand the effect of the different drying techniques on the quality of the produced pellets, comparison was made between fluid bed drier and tray (Dyer et al. 1994); between fluid-bed, oven and freeze driers (Kleinebudde, 1994a); and drying by microwave versus oven drying (Bataille et al. 1993). Moreover, pellets were dried at different rates by a specially constructed convective drier (Berggren and Alderborn, 2001b). The effects of these techniques on the strength (Bataille et al. 1993), diametral crushing strength and elasticity (Dyer et al. 1994), surface characteristics (Bataille et al. 1993; Dyer et al. 1994), in-vitro drug release (Dyer et al. 1994; Kleinebudde, 1994b), friability (Kleinebudde, 1994a), porosity (Bataille et al. 1993; Kleinebudde, 1994a; Berggren and Alderborn, 2001a,b), shrinkage/contraction and liquid saturation (Kleinebudde, 1994a, Berggren and Alderborn, 2001a,b) of the pellets was thoroughly studied. The migration and crystallization of soluble materials during drying (Dyer et al. 1994), the mechanism of heat generation and transfer (Bataille et al. 1993), the rate of moisture removal and contraction forces (Kleinebudde, 1994a; Berggren and Alderborn, 2001a,b), were noted as some of the main reasons for the observed drying effects.

Scott et al. (1963) noted some distinctive advantages of fluid-bed drying over conventional tray drying for lactose and magnesium tri-silicate granules. They reported that fluid-bed drying technique was at least 15 times faster than tray drying procedure. The contact between solid and drying gas in fluid-bed drying is far better than in any other type of drier because

the agitation of the particles almost eliminates the stagnant gas film around them and the gas itself is mixed thoroughly during its passage through the bed. Consequently the mass and heat transfer coefficients were higher. Kleinebudde (1994a) studied the effects of fluid-bed, oven and freeze drying techniques on the porosity, friability and liquid saturations as well as shrinking properties of his microcrystalline cellulose and low substituted hydroxypropyl cellulose pellets. He noted the variation in the size, apparent density, and mechanical stability of pellets dried by the different techniques. Image analysis showed an identical shrinking phenomena when the pellets were dried by fluid-bed or in oven, while freeze-drying suppressed shrinking to produce pellets of comparable size distribution to those of wet pellets.

Dyer et al. (1994) made a thorough investigation on the effect of two drying techniques on the mechanical, skeletal and drug release properties of ibuprofen/MCC or lactose/MCC (80:20) pellets. They reported that the main differentiating factor between oven and fluid bed drying methods was the rate of water removal from the product. Those pellets dried by fluid-bed technique achieved the desired moisture content much more quickly due to the rapid evaporation of water as a result of the turbulent motion of fluidized particles. Water removal from tray dried material was, however, slow due to the static nature of the bed. As to the effect of drying on migration of the soluble drug, they observed that the rapid water removal minimized the migration of solute particles within the spheres. The tray dried entities were more likely to exhibit solute migration during the lengthy drying process as they observed it in a faster drug release pattern and impaired surface quality as the solute migrated to the surface.

Recently, Berggren and Alderborn (2001a) studied the drying behaviour of microcrystalline cellulose pellets prepared by water and water/ethanol mixture. They observed variations in the pellet size, weight, and porosity with time, which indicated different rate of contraction and densification during drying to produce pellets of different properties based on the agglomeration liquids used. In a further study, Berggren and Alderborn (2001b) illustrated the effects of different drying rates on the porosity, deformability, and compactability of the microcrystalline cellulose pellets agglomerated by different ethanol/water proportions. The drying technique they employed was a specially constructed convective drier and by varying

the drying temperature and air flow rate, they subjected each batch of pellets to seven different drying rates.

1.5.5 COATING OF PELLETS

There are numerous reasons for which film coatings are applied to pellet formulations, for example, controlled release, taste masking, improved stability, elegance, and mechanical integrity (Porter, 1982). Polymers used in the film-coating fall into two broad groups based on either cellulosic or acrylic polymers (McGinity, 1989; Cole et al. 1995) which are commonly formulated into aqueous colloidal dispersions and organic solutions respectively. The high cost of solvents, higher price of solvent recovery system, strict air quality controls, and potential toxicity and explosiveness are the main disadvantages of the organic solvents based coating processes (Chang et al. 1987). This was resolved with the advent of aqueous polymer latexes and pseudo latexes in 1970s, which improved the lengthy processing time (due to high heat of vaporization), higher viscosities and lower polymer content of aqueous systems (Fukumori, 1994).

The individual polymeric particles in the dispersion have to be fused to form a continuous film for an efficient application to controlled-release pharmaceutical dosage forms. The theories that describe the mechanism of film formation from such aqueous polymeric dispersions have been reviewed by (Lahmann and Steuernage, 1989). Moreover, the polymeric particles have to be mechanically deformable to form films under specified conditions. This is achieved at softening temperature (Yang and Ghebre-Sellassie, 1990) which corresponds to a sharp increase in polymer chain mobility (Okhamafe and York, 1988), hence viscous flow, which eliminates the boundaries between adjacent polymer particles to complete coalescence (Porter, 1989). In addition to the possible incomplete fusion of the colloidal particles during coating process (Chang and Rudnic, 1991), the residual internal stresses within the film coating created by shrinkage of the film upon solvent evaporation and the differences in the thermal expansions of the coating and the substrate, can produce flaws and cracks in the film coating (Rowe, 1981a). Moreover the drastic shape and density change as well as the friction and impact of the die and punch surfaces during tableting of coated pellets could compromise the integrity of the coat, hence the controlled drug release property. Thus, the mechanical properties of the polymeric film and its response

to stresses of different type must be studied to determine its ability to remain intact during the life time of the product.

The mechanical properties of ethyl cellulose film cast were studied in terms of tensile strength (Arwidsson and Johansson, 1991; Narisawa et al. 1994) brittleness, puncture strength and elongation (Bodmeier and Paeratakul, 1994). Moreover, (Narisawa et al. 1994) performed in vitro dissolution test of ethyl cellulose film coated theophylline beads with abrasives (polystyrene beads) that could generate mechanical destruction or induce erosion of the film by frictional force. They were able to determine the ability of the film to withstand the mechanical stresses by quantifying the rate of drug release. Most studies on compaction of pellets coated with ethyl cellulose revealed a damage to the coating film with a loss of the sustained release properties (eg. Chang and Rudnic, 1991; Bansal et al. 1993; Sarisuta and Punpreuk, 1994; Maganti and Celik, 1994). This was attributed to the very brittle and weak with low puncture strength and elongation (i.e <5%) property of the film (Bodmeier and Paeratakul, 1994). Moreover, the damage in the coating film during tableting of coated pellets was related to the variation in mechanical properties between the coat and the core pellets (Aulton et al. 1994) as well as the size of the pellets (Ragnarsson et al. 1987; Ragnarsson and Johannson, 1988; Bechard and Leroux, 1992). This instigates the assessment of the properties of the core pellets in relation to the film.

The correlation of the mechanical properties of the pellets to that of polymeric-coat determined from the free film is, however, difficult. For this reason, (Ghaly and Ruiz, 1996; Wang et al. 1996, 1997) incorporated the polymeric dispersion in the binding liquid and tried to study the change in the mechanical properties of their compacts. Nevertheless, it was again impossible to extrapolate the property of a film coated pellet form the employment of the polymer dispersion as a liquid binder. Therefor, a detailed study of the mechanical properties of the core pellets versus the properties of the coated pellets seems to be an alternative approach to provide an insight into how the final coating system will behave.

1.6 STRUCTURAL CHARACTERIZATION OF PELLETS

1.6.1. SIZE AND SIZE DISTRIBUTION

The relation between the size of the pellets and their mechanical strength could be learnt from the strength measuring equations reviewed on (section 1.2.4). Furthermore, narrow pellet size distribution is important for (i) the uniformity of coating thickness; (ii) reduction in segregation which could result in non-uniform die or capsule fill, and (iii) to facilitate blending of pellets of different batch or content when required. Ragnarsson and Johansson (1988) observed that the rate of drug release in their multiple unit preparations was influenced by particle size of the coated core material. In an effort to examine the effect of particle size on film coating process Iley (1991) observed a decrease in thickness of coating material with decrease in particle size (700μm to 1000μm) due to increase in surface area and derived a theoretical equation to relate the particle size and coating thickness of the spheroids. Johansson and Alderborn (1998) studied the effects of MCC pellets size (agglomerated by ethanol/water 70/30) on the mechanism of compaction and the strength of their compacts. They reported that the tensile strength of compacts was independent of the original pellet size at applied pressure of 80MPa. At 160 MPa, however, the tablets made from the larger pellets were significantly stronger. Their reasons were three fold based on the difference in: contact area that lead to force concentration, inter-granular space, and intra-granular porosity. They reported that the porosity changed the pellets densification process. Morever, the process of removing air from the space between pellets was independent of the original pellet size although the larger pellets were deformed to a higher degree during compression.

The size of pellets can be readily expressed in terms of their mean diameter, for they are nearly spherical in shape. However, it is inconvenient and impractical to measure the diameters of every individual pellet and from different direction. Thus, microscopy or sieve analysis is used from which the mean diameter and size distribution is estimated.

The employment of sieve analysis for the characterization of pellets size and size distribution is a common practice for it provides the advantage of inexpensive, simple and rapid process with little variation among operators. However, the blinding of the screen and inability of the sieves to detect variation in the shape of the particles, which allows thin although longer particles to pass are some of the shortcoming of the practice. In a more extensive evaluation

Fonner et al.(1966) studied the effect of loading, shaker speed, and time of sieving process on the data obtained for the particle size distribution of model granules.

Many researcher (eg. Lundqvist et al. 1997) sieved their pellets according to the British Standard. The retained pellets in the successive sieves were weighed. The data was plotted in either the cumulative percentage over or under weight versus an average pellet size retained in each set. From the resulted sigmoidal curve, interquartile range (the size difference between the 75^{th} percentile and 25^{th} percentile) were determined to indicate the size distribution while the 50^{th} percentile was expressed as the median pellet size. Vertommen and Kinget (1997) used the same technique of sieve analysis but analysed their data using a log-normal frequency distribution, where the logarithm of the mean pellet size in each sieve was plotted against the cumulative percent frequency on a probability scale. Using a linear regression they determined the geometric mean diameter on a weight basis, which is the pellet size at 50% on the probability scale. They illustrated the size distribution by determining the difference in sizes between the pellet size at 84% and 16% (geometrical standard deviation) on the probability scale.

Helen et al. (1993a) employed an optical microscope in conjunction with image analyser to study the number average size and size distribution of their pellets. They determined the mean pellet diameter from the projected perimeter or area diameters as well as from the average of 32 distances between two tangent lines on opposite sides of the pellets, which is commonly known as Feret diameter. Moreover Fielden et al. (1993) used both techniques. The batch weight and number size distribution which were obtained by sieving and by image analysis respectively, and from these, they determined the weight and number median diameters.

1.6.2 THE SHAPE OF PELLET

In all the strength measuring techniques discussed on (section 1.2.4), it was assumed that the shape of the agglomerates were spherical. Thus, determination of the shape of the pellets or investigation on the deviation of their shape from a sphere is important to validate this assumption. Chopra et al. (2001) produced pellets of different shapes by modifying the processing parameters of standardised pellet formulations. The different pellet fractions were then characterised for their size, surface and density properties employing a series of established techniques in order to identify the most appropriate methods of characterisation

and interrelationship between these properties. Their results showed that preparing pellets of graded difference in shape from the same powder blend can result in changes of other important pellet properties such as surface roughness, surface area and pellet dimensions.

Several two-dimensional shape characterizing techniques have been used to express the deviation of pellets from sphericity. One of the most commonly used techniques (eg. York, 1992) is aspect ratio, i. e. the ratio between the longest calliper distance and the calliper distance perpendicular to it. However, a circle, a square or other polygonally symmetric shapes will all have an aspect ratio of 1.0, because in these examples length and breadth are equal. Some other popular techniques are the elongation ratio, a ration between the length and width, (eg. Barrau et al. 1993), and circularity, i.e. the ratio of the area of te pellets to the area of a circle having the same perimeter, (eg. Helen and Yliruusi, 1993).

Chapman et al. (1988) developed a method to characterize the roundness of pellets in terms of the theoretical angle necessary to tilt a plane such that the particle would roll, the "one plane critical stability (OPCS)". This method was based on the determination of the centre of gravity of the pellet from a digitized image of the coordinates of its outline and computing the angle necessary to incline a plane such that the centre of gravity moves outside the boundary of the pellet. Fielden (1987) employed this technique to assess the sphericity of pellets. Small changes in roundness could be differentiated using OPCS, but each pellet has to be analysed individually and there is a need of special computer system.

Podczeck and Newton (1994) derived a shape factor, e_r, a two terms expression, which describes the deviation of a shape from a perfect circle, being very sensitive towards an ellipse. Based on a two-dimensional image analysis, and a term describing the irregularity of the surface of a circle, e_r is expressed as a ratio of the theoretical and measured values of the perimeter, equation (15).

$$e_r = \frac{2\pi r_e}{P_m} - \sqrt{l - \left(\frac{b}{l}\right)^2} \qquad \text{.....(15)}$$

where, r_e is a mean radius calculated from the centre of gravity to the perimeter in different directions (eg. 36 measurements 10^0 apart) using the image analyser, P_m being the measured perimeter, l and b are the length and breadth of an ellipse.

The technique was sensitivity on differentiating a set of model shapes, such as circular, square, triangular, diamond, rectangular, stars and flowers of different points and petals (Podczeck and Newton, 1994). Moreover in another work Podczeck and Newton (1995), were able to develop a three dimensional shape factor, e_{c3}, by measuring the shape factor at a perpendicular angle. This technique gives an assessment of the deviation from the spherical shape as well as the extent of the surface roughness.

In an experiment on nine batches of pellets Podczeck et al. (1995) illustrated the advantage of the e_{c3} over the other techniques in identifying sphericity and surface roughness of pellets. They illustrated the ability of the techniques on differentiating the shape of four nearly spherical pellet batches employing analysis of variance (ANOVA) to test for the significance. They found that none of the batches were differentiated by aspect ratio, e_r was able to differentiate one, while e_{c3} differentiated three of the four batches.

Eriksson et al. (1997) performed a comparison on the sensitivity of elongation ratio, aspect ratio, one-plane critical stability (OPCS), and shape factor, e_r, in detecting the sphericity difference between their five pellet batches produced by extrusion and spheronization and a smooth surfaced spherical steel ball bearings. They reported that the elongation and aspect ratio methods were poor in distinguishing the shape variation between pellets of the same batch as well as between the batches. OPCS and the shape factor, e_r, were, however, able to distinguish the variations between and within the batches. Furthermore, they indicated that only the values obtained from the shape factor, e_r, approach were normally distributed, and their results could be investigated using statistical analysis which assumes a normal distribution.

1.6.3 DENSITY AND POROSITY

Density is universally defined as weight per unit volume, the difficulty arises when one attempts to determine the volume of particles, granules or pellets containing microscopic cracks, internal pores, and capillary spaces. For convenience, three types of densities may be defined, the true, granular, and bulk densities.

The true density, ρ_t, is that of actual solid material, exclusive of the voids and inter-particle pores larger than molecular or atomic dimensions in the crystal lattices. In B. S. 2955:1958 it is define as "apparently particle density" due to the difficulty of measuring the true density.

It may be determined by air pycnometer as used by (eg. Wilkberg and Alderborn, 1990a, 1991, 1992; Johansson et al. 1995; Johansson and Alderborn, 1996), and helium pycnometer as used by (eg. Kleinebudde, 1994a,b). Since helium is not adsorbed by any material and penetrates into the smallest pores and crevices, it is generally conceded that the helium method gives the closest approximation to the true density when no internal pores occur.

The granule density or effective granule density, ρ_g, includes the true density of the materials and the internal pores (open and closed pores). This may be determined by liquid displacement method when the material is insoluble. Mercury is commonly used since it fills the void spaces but fails to penetrate into the pores. The effective granule density was measured using mercury pycnometer by Wilkberg and Alderborn (1990a, 1991, 1992), Johansson et al. (1995) and Johansson and Alderborn, (1996) among others. In such technique the pellets are immersed in mercury and the volume displaced is used to determine the effective pellets volume from which the effective density is determined. Selkirk and Ganderton (1970), Bataille et al. (1993) and Kleinebudde (1994a,b) used mercury intrusion porosimetry, where pressure is applied to exclude the open pores of a limited size from the volume of the pellets. The volume of the open pores below that limit, the volume of the pellets together with their closed pores gives the effective pellet volume, and from a knowledge of the weight, the effective pellet density is obtained. The internal pores or intra-granular porosity, ϵ_{intra}, can be determined from:

$$\varepsilon_{intra} = \frac{\rho_t - \rho_g}{\rho_t} = 1 - \frac{\rho_g}{\rho_t} \qquad \text{.....(16)}$$

Bulk density, ρ_b, is defined as the mass of pellets divided by the bulk volume, which is measured by a standard measuring cylinder. The intergranular porosity or void is the relative volume of intergranular voids to the bulk volume of the pellets, exclusive of the internal pores. The intergranular space or porosity is computed from a knowledge of the bulk density and the granular density and is expressed by the equation:

$$\varepsilon_{inter} = \frac{\rho_g - \rho_b}{\rho_g} = 1 - \frac{\rho_b}{\rho_g} \qquad \text{.....(17)}$$

1.6.4 SURFACE AREA AND PORE SIZE DISTRIBUTION

The measurement of surface area and pore size distributions may be performed in several different ways. Gas adsorption is the most widely used and accurate method for total surface area measurements and pore size within the approximate range of 0.4 to 200 nm diameter (Gregg and Sing, 1982). This method provides very high resolution data and wider applicability. The method may be defined simply as the physical characterization of material structures using a process where inert gas molecules of known size are condensed (or adsorbed) on the sample surfaces. The quantity of gas condensed and the resultant sample pressure are recorded and used for subsequent calculation. This data, when measured at a constant temperature, allows an isotherm to be constructed. Isotherm data is then subjected to a variety of calculation models to obtain surface area and pore size distribution results.

The BET theory (owes its name to its creators: Brunauer, Emmett and Teller in1938), for example, is one model used for the determination of the sample specific surface area. It gives rise to a simple equation (equation-8) that permits calculation of monolayer capacity from an adsorption isotherm using only mass of a sample as the dependent input. Because of its simplicity, ease of use, general applicability, yielding of highly reproducible results and general acceptance BET surface area is now a standard measuring technique.

$$\frac{P}{V_{ADS}(P_0 - P)} = \frac{C-1}{V_m C} \times \frac{P}{P_0} + \frac{1}{V_m C} \qquad \text{.....(18)}$$

where V_{ADS} is volume adsorbed, V_m is monolayer volume, C is adsorption energy constant, P is sample pressure, and P_0 is saturation vapour pressure of adsorbate.

With increase in pressure multi layers of adsorbate molecules will be built upon the surface and all the 'open' pores will be completely filled with close packed molecules or liquefied gas. If gas is then removed from the sample, in doses of know volume, the gas pressure obviously starts to fall. At specific pressures pores of definite diameters start to empty in a way related by the Kelvin Equation (equation-19). Large pores emptying at first at relatively higher pressure followed by ever smaller ones.

$$R_K = \frac{2\gamma V}{RT} \times \frac{COS\theta}{LN(P/P_0)} \qquad \text{.....(19)}$$

where: R_K = Kelvin radius (pore radius), θ is contact angle, V is Molar volume, P is adsorbate pressure, P_0 is saturation pressure, and γ is surface tension.

A study of volume of gas evolved versus pressure is then used to determine the volume or size distribution of the pores based on some models, for example, BJH (Barrett, Joyner, Halenda) model (equation-20).

$$\Delta V/\Delta R = R_K \qquad \text{.....(20)}$$

where ΔV is the change in volume desorbed, ΔR is the change in calculated pore size, and R_K is Kelvin radius or calculated pore size.

1.7 COMPACTION OF PELLETS

1.7.1 INTRODUCTION

The lower production cost, higher production rate, and less sensitivity to tampering (eg. Tyleno® and Sudafed-12) (Çelik, 1994), less risk of adhering to oesophagus during swallowing (Marvola et al. 1983), better patient compliance (Bodmeier, 1997) have made the design and development of pellets in the form of compressed tablets increasingly important rather than filling them into hard gelatine capsules. Moreover their advantage over tableting powders include reduction in dust problems (Conine and Hardly, 1970) and may possibly render an opportunity to examine the change in size, shape and density after compaction. Fore instance, Aulton et al. (1994) examined the integrity of their pellets after recovering them from disintegration tubes by filtration and allowing them to dry under ambient temperature and humidity. Johansson and Alderborn (1996) were also able to examine the change in deformation and densification of their pellets after retrieving them from the highly lubricated compacts which reduced bonding between pellets.

Pellet compacts need to have an optimum strength to withstand the mechanical shocks encountered in their production, packaging, shipping and dispensing. Compacts made with MCC pellets prepared with water were noted to be very weak in strength (eg. Millili and

Schwartz, 1990; Schwartz et al. 1994; Wang et al. 1995; Salako et al. 1998). In an attempt to improve the consolidating factors, MCC was mixed with different excipients in making pellets (eg. Schwartz et al. 1994; Wang et al. 1995) and ethanol was added as binding solvent (Millili and Schwartz, 1990; Johansson et al. 1995). Moreover, coarse and fine excipients were also compressed with the pellets (eg. Bechard and Leroux, 1992; Torrado and Augsburger, 1994).

Another challenge is to retain the controlled release profile of the coated pellets after compaction. The polymer coating must be able to withstand the compression force, and accommodate the structural change by deformation instead of rupturing. A 7%w/w of the aqueouse colloidal ethyl cellulose dispersion, Surelease®, was observed to rupture on compression (eg. Chang and Rudnic, 1991; Bansale et al. 1993), and addition of different plasticizers were not enough for the film to deform and resist rupture (Sarisuta and Punpreuk, 1994). A thorough study on the mechanical properties of these ethyl cellulose film cast from the plasticized pseudo-latexes, Aquacoat® and Surelease® by Bodmeier and Paeratakule (1994) confirmed their brittleness and weakness with low values for puncture strength and elongation. Another possible reason given by Chang and Rudnic (1991) was the incomplete fusion of the colloidal particles. Thus, polymers with a better flexibility (eg. Eudragit NE 30 D and plasticized Eudragit RS/RL 30D) can resist damage during compression due to their enough plasticity to deform with change in shape of the pellets without rupture (Lahmann and Steuernag, 1989). Furthermore, to prevent a direct contact of coated pellets, some pharmaceutical excipients (eg. Bechard and Leroux, 1992; Aulton et al. 1994) and deformable placebo pellets (eg. Pinto, 1992; Lundquvist et al. 1997) were used as cushioning materials during compression. Thus, the type and amount of coating agent, selection of the external additives, and the rate and magnitude of the pressure applied must be considered carefully to maintain the desired drug release properties of the subunits.

To avoid such a problem, formulation scientists must have a comprehensive knowledge of how that formulation will behave during tableting, as well as how the other material and/or process-related parameters will affect the performance of that formulation as a drug delivery system. Despite the significant amount of work that has been performed in the field of tableting of aggregates, the actual process of compression of pharmaceutical aggregates is still not fully understood (Çelik, 1994). A conceptually oriented view of the compression

process and a more in-depth understanding of the relative importance of relevant parameters are needed in order to predict more accurately the tableting behaviour and its optimisation.

1.7.2 COMPACTION MECHANISM

It is appropriate, at the outset to define the word "compaction" in the context in which it is used in this work for mostly it is used synonymously with consolidation (eg. Alderborn and Nystrom, 1996). Marshal (1986) defined "compaction" as the compression and consolidation of two phases (particulate solid-gas) system due to applied force. Compression is reduction in bulk volume of the solid material as a result of elimination of the gaseous phase, while consolidation being an increase in the mechanical strength of the material resulting from particle-particle interaction. In this work, this definitions have been adopted.

Many equations have been proposed to characterize the compaction process, however, their applicability is over a limited range of applied force or for only a few types of materials (Celik and Marshall, 1989). After a thorough review, Celik (1994) pointed out the absence of a universal relationship due to the complexity of the system, and suggested for the use of more than one data evaluation techniques inorder to increase the validity of the conclusions drawn. Most of the reviews or reported pharmaceutical application of these equations are based on the compaction of powders (eg. Paronen and Ilkka, 1996). Based on these limited references, it would be convenient at this stage to classify the compaction data analysis techniques into three groups: (i) those techniques used to measure compression, (ii) techniques used to measure consolidation, and (iii) those used to measure decompression.

1.7.2.1 COMPRESSION

Compression is a reduction in bulk volume of materials as a result of closer re-packing. Commonly this is thought as to have occurred as a consequence of decrease in porosity due to compression force resulted from a two-step process (1) the filling of large spaces by inter particulate slippage and (2) the filling of small voids by deformation or fragmentation at higher loads. However, a more complex sequence of events occur during compression. It may involve four steps, which starts by initial re-packing of the particles followed by elastic deformation until the elastic limit is reached. Then plastic deformation and/or brittle fracture dominate until all voids are virtually eliminated. Finally, compression of the solid crystal lattice may occur.

From a review of the literature Marshall (1986) concluded that attempts that has been made to derive equations for the first three stages, are of limited value. Because in practice, the stages are not totally sequential owing to transmitted force variation, and they may also occur simultaneously in different regions of the same tablet. A number of mathematical equations, many of which are empirical in nature, have been developed to determine compressibility. Among others, the determination of the percentage of porosity or the degree of the volume reduction due to an applied pressure is commonly utilised (equation 21 and 22):

$$E\% = 100(1 - \frac{V_t}{V_c}) \qquad \text{.....(21)}$$

where V_t is the true volume of the material and V_c is the compact volume at a given pressure. Assuming radial wall expansion during compaction is negligible, this equation can be written in the form of:

$$E\% = 100(1 - \frac{H_t}{H_c}) \qquad \text{.....(22)}$$

where H_t is the theoretical true thickness of the compact at zero porosity and H_c is the compact thickness at a given pressure (corrected for punch deformation). This method was utilised by Maganti and Celik (1993, 1994) to compare the compressibility of MCC powder with the compressibility of uncoated MCC pellets. They observed that MCC powder exhibited a higher initial porosity change at lower pressure than that of uncoated MCC pellets. They also used this method to study the compression behaviour of uncoated and Surelease® coated MCC pellets.

Another equation that has received considerable attention in the field of powder compaction was developed by Kawakita (1956) as cited by Kawakita and Ludde (1970/1971). It is expressed as:

$$C = \frac{(V_i - V_p)}{V_i} = \frac{abP_a}{(1 + bP_a)} \qquad \text{.....(23)}$$

where C is the degree of volume reduction, V_i the initial apparent Volume, V_p the powder volume under applied pressure P_a, and both a and b are constants that can be calculated from P_a/C versus P_a plot. The constant "a" does not correlated to any property of the material being

compacted, while the constant "b", the coefficient of compression, is related to the plasticity of the material (Kawakita and Ludde, 1970/1971). The applicability of Kawakita equation, however, was reported to be limited by Ramberger and Burger (1985). They reported that using this method, the compaction process could be described only up to a certain pressure, above which the equation was no longer linear.

Johansson and Alderborn (1996) studied the degree of compression (i.e. a derived expression for the percentage of the decrease of the height of the pellet- bed in the die to the original bed height) of their pellets having different porosity with the increase of compaction pressure. They found that the compressibility of their pellets was a function of the porosity and the strength of the compacts was related to the compressibility of the pellets. Similarly, Nicklasson et al. (1999a&b) and Nicklasson and Alderborn (1999) used the same technique in studying the tableting behaviour of pellets of a series of porosities composed of MCC/dicalcium phosphate dihydrate and the tableting behaviour of MCC pellets with the incorporation of soft material (polyethylene glycol) respectively. Additionally, Berggren and Alderborn (2001b) used the Kawakita constant, "b", to characterize the deformability of their MCC pellets dried at different rates.

The most commonly used equation in pharmaceutical compaction studies was developed by Heckel (1961a,b), who considered that the reduction in voidage obeys a first order kinetics with applied pressure (equation-24):-

$$\ln\left(\frac{1}{1-\rho_r}\right) = KP_a + A \qquad \text{.....(24)}$$

where ρ_r is the relative density of the compact, and K and A are constants that can be determined from the slope and intercept of the extrapolated linear region of the plot respectively. The constant A is a function of the initial compact volume and can be related to the densification during die filling and particle rearrangement. K is related inversely to the ability of a material to deform plastically under pressure or to the mean yield pressure of the material (Hersey et al. 1973). This value has been shown to be particle size independent for plastically deforming materials such as sodium chloride and Avicel PH 101 (Hersey et al. 1973), but lactose and calcium carbonate which deform by particle fragmentation showed an increase in the mean yield pressure value with a reduction in particle size (York, 1978).

The relationship between pressure and porosity in the Heckel plot may be established by simply measuring the applied compressional force, F, and the movements of the punch during compression cycle and translating this data into values of P (applied pressure) and E (porosity). For cylindrical tablets, P is given by

$$P = \frac{4F}{\pi D^2} \qquad \text{.....(25)}$$

where D is the tablet diameter. Similarly values of E can be calculated at any stage from:

$$E\% = 100(1 - \frac{4W}{\rho_t \pi D^2 H}) \qquad \text{.....(26)}$$

where W is the weight of the tableting mass, ρ_t is its true density, and H is the thickness of the tablet at the point (obtained from the relative punch displacement). The effects of experimental variables on the Heckel plot have been studied extensively. The effects of compression time (Rue and Rees, 1978), the state and type of lubricant, die size, mode of die filling, technique used to measure compact dimensions (York, 1979), the die wall friction (Ragnarsson and Sjogren, 1985), particle shape (Wong and Pilpel, 1990b), punch velocity (Roberts and Rowe, 1985) and the deformation of the die and punch of the tableting machine (Belda and Mielck, 1998) are among the many factors that affect the value of this technique.

Maganti and Çelik (1993, 1994) applied the Heckel equation to data obtained for the compaction of MCC powder and pellets as well as uncoated and coated pellet formulations. The slopes of the linear portion of the Heckel plots differed for the powder and pellets form, suggesting that changing the shape, size and surface properties of the MCC particles may have affected the compaction properties. When the Heckel plots were compared for coated and uncoated pellet formulations, these workers observed an increase in the slopes of the linear portion with increasing amount of coating. In an attempt to differentiate the intergranular porosity from the total porosity of their MCC pellet compacts Johansson and Alderborn (1996) employed the Heckel plot and were able to observe a marked difference in the profile when the coated and uncoated pellets were plotted together.

In their experiment to study the compression and consolidation behaviour of MCC, MCC/lactose, MCC/dicalcium phosphate dihydrate pellets and powder mixtures Schwartz

et al. (1994) obtained a curve with a continuous decrease in slope when their data was plotted by Heckel equation. It was, therefore, difficult for them to calculate the compressibility and the yield pressure. They modified the equation to include an exponential term that provides the change in density due to the 'viscoelastic resistance', equation (27).

$$\ln\left(\frac{1}{1-D}\right) = KP + A - B\exp(\alpha P) \qquad \text{.....(27)}$$

where " B" is a constant. They claimed that the exponential term to be the change in density due to the viscoelastic resistance, while the linear portion being the ultimate plastic flow after the effect of viscoelastic resistance vanishes. Therefore, the more compressible the bead, the greater the exponential term, hence the viscoelastic resistance vanishes faster with pressure. They concluded that MCC pellets were the least compressible and with highest visco-elastic property, while MCC/dicalcium phospahte dihydrate pellets were the most compressible and with the least viscoelasticity. The ability of a material to be reduced in volume to a greater extent when compressed, however, does not ensure the formation of strong compacts (consolidation).

1.7.2.2 CONSOLIDATION

Consolidation is an increase in the mechanical strength of the materials resulting from particle-particle interaction during compression. All of the deformation and/or fragmentation effects may be accompanied by the breaking and formation of new attachment between the particles, which give rise to consolidation as the deformed and/or new surfaces are compressed together (Marshall, 1986).

Such coherence between the particles in the die is thought to be due to two processes. First, due to cold welding, a process when the surfaces of two particles approach each other closely enough, so their free surface energies result in a strong attractive force. Second due to fusion which is dependent on heat transmission capacity and melting point of the material. If a force is applied on the bed, the pressure is transmitted through the particle contacts. Under appreciable forces, this transmission may result in generation of considerable frictional heat, which could melt the contact area giving rise to fusion after solidification. The process of both "cold" and "fusion" welding is influenced by several factors. Marshall (1986)described these as:

1-The chemical nature of the material

2-The extent of the available surface

3-The presence of surface contaminants

4-The inter surface distances.

Different measuring techniques had been used to assess consolidation. In most pellet compacts, the measurement of the tensile strength of the compacts in terms of diametral compression (Fell and Newton, 1970a) is used (eg. Salako et al. 1998; Lundquvist et al. 1997).

Roberts and Rowe (1987) used Heckel plot to determine the yield pressure, from which in combination with other factors, they claimed that they were able to predict the consolidation mechanism of some pharmaceuticals and other materials (Table-1). Moreover, Celik (1994) argued that the application of Heckel plot to the compaction of pharmaceutical particles permits an interpretation of the consolidation mechanism. Three different types of volume reduction mechanism of pharmaceuticals can be drawn form the Heckel equation by compressing particle of different particle sizes (York and Pilpel, 1973). This could also be expressed as three means of consolidation mechanisms as proposed by Celik (1994):

> *(i) a plot exhibited by different particle size fractions of a material that consolidates by plastic flow. Variations in initial powder bed density result in different final bed densities under any particular applied pressure. (ii) a plot exhibited by materials that consolidate by particle fragmentation, a single relationship occurs above a certain pressure irrespective of the initial bed density. This feature is also independent of particle size and is thought to be due to the progressive destruction of the particles by fragmentation and their subsequent compaction by plastic deformation. (iii) a plot attributed to the absence of a particle rearrangement stage coupled with plastic deformation and the possible melting of asperities.*

Another method used in the field of particle compaction was proposed by Leuenberger (1982) who related the two important indices of particle compression: "compactability" (adequate strength) which is termed "consolidation" in this work, and compressibility (ability of the material to undergo volume reduction under pressure). His equation describes the

deformation hardness P_{dh} of the compact as a function of the applied pressure σ_c and the relative density ρ_c

$$P_{dh} = P_{max}[1 - \exp(-Y \sigma_c \rho_r)] \quad \text{.....(28)}$$

The parameter P_{max} is equal to the theoretical maximal possible deformation hardness as $\sigma_c \rho_c$ approaches infinity, and P_{max} describes the consolidation while the parameter Y, termed compression susceptibility, describes indirectly compressibility. Leuenberger observed a good correlation when he applied the equation-28 to the consolidation of powders. He noted that a low P_{max} value shows a relatively poor consolidation, and a high value of Y indicates that the theoretical limit of hardness and a sharp decrease in compact porosity may be attained with relatively low compaction pressure. Schwartz et al. (1994) applied this equation in determining the consolidation of their pellet compacts. The only modification they did was to express the equation in terms of tensile strength.

$$\sigma = \sigma_{max}[1 - \exp - (Y DP)] \quad \text{.....(29)}$$

Where, σ is the tensile strength (kg/cm^2), σ_{max} is the maximum tensile strength obtained when relative density approaches infinity and P is the applied pressure (MPa), Υ (MPa^{-1}) is again defined as compression susceptibility.

Another common method for assessment of the compaction behaviour of pharmaceuticals is the use of compressional force verses punch displacement profile (F-D curves), from which the work involved during tablet compaction can be calculated (De Blaey, 1971). Krycer et al. (1982) suggested that since particles with different packing characteristics and different elastic-plastic deformation properties absorb varying amount of energy, it might be more useful to measure the work of compaction rather than other characteristics. Fell and Newton (1971) indicated that the work done on compaction of a powder mass was utilised for both volume reduction and particle bonding but that only latter contributed to the strength of the tablets. Similarly Marshall (1986) pointed out that an appreciable amount of energy supplied is converted to heat, used to overcome the friction between the particles and machine part, or is associated with the mechanical operation of various machine parts, which of course does not contribute towards the main objective of the process. However, Celik and Marshal (1989)

observed that the rank order of the total energy involved during compaction of the powders and rank order of the tensile strength of their compacts were similar.

In their compaction study of powder and pellets of MCC, Maganti and Çelik (1993) reported that the total work of compaction value and the strength of the compacts of MCC pellets were both significantly less than those of the powder form, suggesting that the degree of coherence of this material has been affected considerably by change in its shape, size and also possibly by the reduction in the number of potential connection sites that occur due to the pelletization process. In another work, Maganti and Çelik (1994) compared the total work of compaction (TWC) values by integrating the area under the force/displacement curve for uncoated and Surelease®-coated pellets. They reported a decrease in TWC values with an increase in the amounts of coating material at corresponding pressures. They also observed a similar relation in the strength of the ejected compacts.

Maganti and Çelik (1993) tried to compare their powder and pellet compaction data using another technique called Average Power of Consumption (APC), which was calculated by dividing the cumulative total work of compaction by the corresponding contact time. They reported that the compacts of the pellets of MCC exhibited higher APC values at corresponding pressure than that of the powder form of MCC. They concluded that the short contact time was due to the absence of particle rearrangement stage.

Volume reduction is necessary to form a coherent tablet from the pellets, since the pellet surfaces must come into close proximity with each other to develop a significant attraction force. This makes it impossible to distinguish between the compression and consolidation of the tableting process. This notion can be illustrated in the four step volume reduction sequences suggested by Johansson and Alderborn (1996). In their MCC pellets compaction process, they observed the sequential steps of volume reduction and related it to the consolidation mechanism of the aggregate compacts.

(i) Repositioning of the aggregates but no inter-aggregate bonding;

(ii) Local deformation and limited attrition of aggregate surfaces, leading to some inter-aggregate bonding of low force;

(iii) Bulk deformation and densification of aggregates leading to bonding of high forces and coherent compacts are formed;

(iv)Minute aggregate deformation with a marked effect on inter-aggregate bonding forces

1.7.3 DECOMPRESSION

In tableting, the compressional process is followed by decompression stage, as the applied force is removed. This leads to a new set of stresses within the tablet as a result of elastic recovery. Irrespective of the consolidation mechanism, the tablets must be mechanically strong enough to accommodate this stress, otherwise, structural failure will occur. Wang et al. (1995) considered the viscoelastic properties of pharmaceutical substances as important determinant factors in compaction process. They suggested that the elastic recovery, defined as the magnitude of expansion of compacts at ejection relative to their dimensions under maximum pressure in the die, is an indirect approach for measuring disruptive effects of instantaneous elastic deformation during decompression state. This was related to the final strength of the compact by Maganti and Çelik (1993). They reported MCC pellets had higher volumetric strain recovery than the MCC powder compacts, but their relative compact strength was the reverse. The time interval for dimensional expansion measurement should be selected to signify the time dependent recovery, which a compact slowly undergoes at zero stress in the post- ejection stage, a phenomena generally regarded as a viscoelastic behaviour (Wang et al. 1995). The time to reach equilibrium is, however, material and temperature dependent. Armstrong and Haines-Nutt (1972) determined the elastic recovery, ER_0 % , as:

$$ER_0\% = 100\left(\frac{H_e - H_c}{H_c}\right) \qquad \text{.....(30)}$$

Where H_e and H_c are the thickness of the compacts after ejection and at maximum load in the die, respectively. The above equation, however, does not take into account the radial expansion of the compact. For cylindrical compacts obtained by using flat faced punches this parameter was taken into consideration using the following equation by Maganti and Celik (1993).

$$ER\% = 100\left(\frac{D_e^2 H_e^2 - D_c^2 H_c^2}{D_c^2 H_c^2}\right) \qquad \text{.....(31)}$$

where D_e and D_c are the diameters of the compacts after ejection and at maximum load in the

die, respectively. Assuming that there is negligible die expansion under applied load, the diameter of the die may be used as D_c. Maganti and Celik (1993) compared the Volumetric Strain Recover (VSR) values of the compacts of powder and pellet forms of their formulation, and observed that the compacts of pellets had higher VSR values. They concluded that this was attributed to the greater expansion of the compact of pellets during the decompression and ejection phase of the compaction event. A large decrease in mechanical strength of the compacts of the pellets suggested that many of the connections formed during compaction did not survive the unloading and ejection phases. In another work Maganti and Celik (1994) reported that both the VSR values and the mechanical strength of the compacts of pellets decreased when pellets were coated with 10% of Surelease. However, further increase in the amount of coating (15% and 20%) resulted in lower mechanical strength of the compacts.

1.8 DISSOLUTION TEST OF COMPACTED COATED PELLETS

In membrane moderated controlled-release system, the active material diffuses form the core, through the rate-controlling membrane, into the surrounding environment. Typically, such factors as membrane porosity, tortuosity, geometry, and thickness play an important part in determining the rate at which the drug can pass through the coating. A discussion of these factors (and appropriate mathematical treatment) has been given by (Tojo et al. 1983). The mathematical treatments, however, ignore the impact of structural irregularities of the membrane such as flaws (stress-induced cracks in a coating of low mechanical strength) and presence of pores that result from incomplete coalescence (Donbrow and Friedman, 1975; Donbrow and Samuelov, 1980; Rowe, 1986). That is why, it is a common practice to use dissolution test as a means of assessing the membrane damage during tableting of coated pellets.

The direct contact of the coated pellets during compression is thought to be the main reason for the rapture and damage of the film, hence enhancement of drug release (Lopez-Rodriguez et al. 1993; Bodmeier, 1997). Thus, incorporation of a soft deformable placebo pellets (Lundquvist et al. 1998) and different inert tablet excipients (Ragnarsoson and Johansson, 1988; Bechard and Leroux 1992; Aulton et al. 1994; Wagner et al. 1999) as a cushion were some possible solutions. For instance, Torrado and Augsburger (1994) incorporated some excipients during compression of coated theophylline pellets and compared their effect on

protecting the film indirectly thorough dissolution studies. The order of the excipients in least damaging the coating was: polyethylene glycol 3350 < microcrystalline cellulose < crospovidone < lactose < dicalcium phosphate. Moreover, combination of 50% MCC, 25% polyethylene glycol 3350, and 25 % crospovidone was found to be the most suitable for minimizing the damage to the coating. In addition to the water-insoluble waxes, incorporation of some powdered polymers prior to compaction of the coated pellets showed a slower rate of drug release (Juslin et al. 1980). They showed that the addition of powdered Eudragit RSPM to the Eudragit RS 100 coated phenazone pellets prior to compression retarded the drug release. It was speculated that the powdered polymer acted as a repairing agent for the broken parts of the coating material.

To reduce the segregation and nonuniform drug distribution of the excipient-pellet mixture due to the variation in density and particle size, granulated or excipients with larger particle size were used by Wagner et al. (2000), and soft drug-free placebo pellets, which preferentially deform during compaction were used by (Lundqvist et al. 1998) as diluents at different proportion to the drug pellets.

Bansal et al. (1993) observed a reduction in drug release of the ethyl cellulose coated niacin/MCC pellet when compacted by a higher pressure compared to a lower pressure. This was assumed to be due to fusion of the coating materials which could reduce the disintegration of the compacts to pellets. Thus, a layer had to be formed between the pellets to prevent such adhesion or fusion of the coated pellets. Bechard and Leroux (1992) applied an HPMC-overcoat to the chlorpheniramine maleate pellets coated with aqueous ethyl cellulose pseudo latex plasticized with 24% dibutly sebacate to weight gains of 25, 30, 35% in order to reduce tackiness/sticking. Moreover they included different excipients during compaction to modulate the disintegration time. Addition of MCC powder provided tablets, which disintegrate within 10s, while pellet compacts prepared with spray dried lactose, sorbitol, pregelatinized starch, compressible sugar disintegrated within 7-10 min. PEG 8000 containing compacts were actually eroded over a 35 min period. The coated pellets had sustained release properties, however, the polymeric coating did not withstand the compaction. The ethyl cellulose coating was too weak and ruptured resulting in more rapid drug release. Even at lowest compression force of 5 kN, rupture of the coating occurred irrespective of the filler used.

1.9 NON-CONTACT LASER PROFILOMETRY

In pharmaceutical technology there is an ever increasing desire to improve and optimize the function and quality of pharmaceutical tablets. One factor related to tablet quality that has great importance is surface roughness. Surface roughness was observed to be closely related to the tablet porosity (Ozkan and Briscoe, 1996) dissolution rate (Healy et al. 1995) fracture by crack initiation and propagation (Podzceck, 1998b) compaction pressure (Toyoshima et al. 1988; Riippi et al. 1998; Podczeck et al. 1999c) powder properties (Podczeck et al. 1999c) mixing time and lubricant added during tableting (Toyoshima et al. 1988).

According to the British Standard (BS 1134, 1972), the surface roughness of materials is evaluated by a profilometry, which classically uses a transducer fitted with sapphire or diamond-tipped stylus mounted on a pick-up arm. The transducer is driven along the surface at a steady rate. The vertical movement of the stylus as it follows the surface irregularities produces an electrical signal proportional to the local height of the surface. This is then processed in various ways after amplification to give a three-dimensional surface roughness values. Nadkari et al. (1975) and Rowe (1977, 1978a, 1979) employed the technique to interpret the relationship between tablet surface roughness and film adhesion. Moreover, the effect of some formulation and processing variables (Rowe, 1978b) and the particle size of an inert additive (Rowe, 1981b) on the surface roughness of tablets were investigated using the stylus instrument. However, the inability to measure directly the three-dimensional surface profile, the limited resolution due to relatively larger radius of the stylus (2.5-5μm), and the possible destruction of the surface as the stylus runs along the surface (Healy et al. 1995) the longer duration and labour it needs (Riippi et al. 1998) as well as its irreproducible results (Silvennoine et al. 1999), limited the application of such instrument on pharmaceutical compacts. Alternatively, (Healy et al. 1995) used a non-contact laser profilometry to examine the surface texture of model solid-dosage forms prior to and following dissolution up to various times. Podczeck (1998b) employed the same technique to measure the change in surface roughness of the tablets made from polyethylene glycol powders of various molecular weights after friability test. In a further study Podczeck et al. (1999c) established the powerfulness of this technique in identifying the influence of powder properties and tableting conditions on the surface roughness of tablets in comparison to a single line profile measurement.

A non-contact laser profilometer uses an infrared light from a semiconductor laser focused on the surface by an objective lens (Figure-1.4). The light reflected by the object surface is directed by a beam splitter through a prism, and is imaged as a pair of spots onto an arrangement of photodiodes. When the objective lens is exactly at its focal distance from the surface, both diodes are illuminated equally. If the distance between the object surface and the objective lens is altered, the imaged focus point is shifted and the illumination of the photodiodes become unequal. This generates a focus error signal by means of a differential amplifier. A control circuit monitors the focus error signal and controls the position of a moveable lens suspended within the sensor, so that the focal spot of the beam remains coincident with the measurement surface. The changing illumination of the photodiode is translated in to amplitude parameters, which measure the surface roughness, such as R_a, R_q, R_t, R_{tm} and FD.

The R_a (roughness average) value (Fig-1.5) is the most widely used parameter of surface roughness. In the case of a line scan of the surface, it is the arithmetic mean of the departure of the profile from the centre line and is expressed by equation-32. In an area scan it is the arithmetic average of the absolute values of all points of the profile and takes the form of(33)

$$R_a = \frac{1}{n}\sum_{i=1}^{n} |Z_i| \qquad \text{.....(32)}$$

where, n is the number of measurement points and Z_i is the i^{th} point

$$R_a = \frac{1}{nm}\sum_{i,j=1}^{n,m} |Z_{ij}| \qquad \text{.....(33)}$$

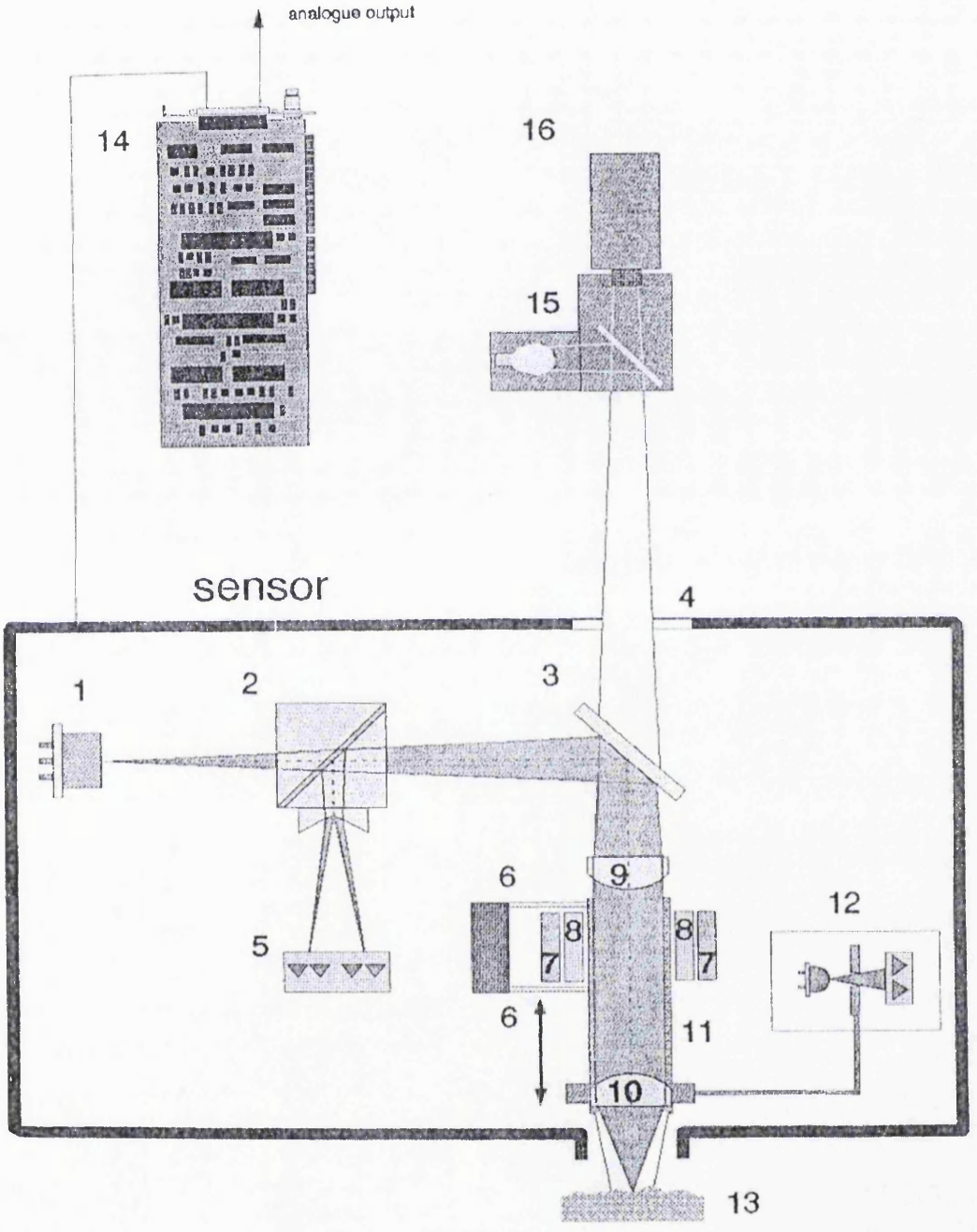
where n is the number of measurement points, Z_{ij} is the i^{th} point in th j^{th} row where the number of rows is m.

The R_q (μm) value (Fig-1.5) is the "root mean square deviation" of all points of the profile from the centre line and characterises the variability of the profile from the centre line.

$$R_q = \sqrt{\frac{1}{n}\sum_{i=1}^{n} y_i^2} \qquad \text{.....(34)}$$

The maximum peak to valley height, R_t, represents the difference between the maximum and minimum points of the profile (Fig-1.5). In the case of a line scan of the surface, the R_{tm} value is the arithmetic average of the 5 sampling sections of R_t values obtained during the

assessment and is expressed by equation-35.



1. Laser diode, 2. prism with beam splitter, 3. beam splitter, 4. window, 5. photodiodes,
6. leaf spring, 7. coil, 8. magnet, 9. collimator lens, 10. objective, 11. tube,
12. light barrier measurement system, 13. measurement object, 14. PC board,
15. microscope with illumination, 16. CCD camera.

Fig-1.4:- Schematic representation of none contact laser profilometer (adopted form the UBM, manual, 1995).

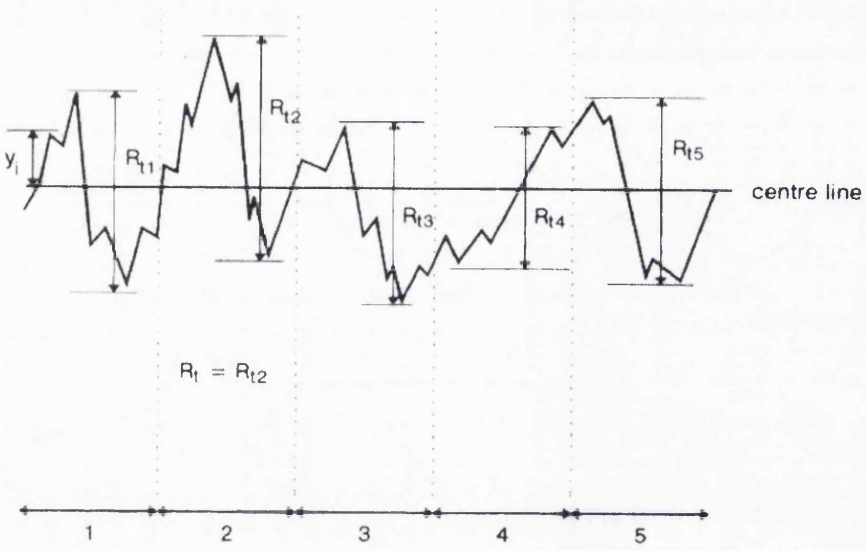


Fig-1.5:- Simple roughness parameters (adopted form Podczeck, 1998a), where y_i, or R_p is distance between an asperity tip and the centre line of the roughness profile; R_{t1} - R_{t5}, are maximum peak-to-valley height for sampling section 1 to 5; and R_t, is maximum peak-to-valley height.

$$R_{tm} = \frac{1}{5}\sum_{i=1}^{1} |R_{ti}| \qquad \text{.....(35)}$$

In case of an area scan, the R_{tm} value is the arithmetic average of the maximum peak-to-valley height R_{ti} in each of 25 rectangles which result from splitting the surface into a 5X5 grid. The fractal dimension, FD, is a scale-dependent method of characterizing surface topography (Wieland et al. 2000). A large number of analytical strategies have been developed to allow the measurement of fractal dimensions (eg. Allen et al. 1995). In a three-dimensional roughness profile the fractal dimension takes up values between 2 (perfectly smooth surface) and increases with the surface roughness up to 3. In practice, however, the fractal dimension was found to be less sensitive to changes in the surface roughness identified by the other parameters (Riippi et al. 1998; Podczeck et al. 1998b, 1999b). In pellet compacts, the variation in the smoothness of the pellets surface could be underestimated by the macroscopic curvature of the pellets due to incomplete deformation to form flat-faced tablets. The impact of such convex structure on surface roughness parameter measured by non-contact laser profilometer was noted by Silvennoinen et al. (1999). It was in such

condition Salako et al. (1998) introduced the surface roughness parameters as a means to assess the deformability of the soft and hard pellets after compaction. Moreover, (Row, 1979) suggested that the nature of the overall surface profile could be indicated by the ratio of some of the parameters. For instance, as the ratio between the distance between the highest peak and centre line, R_p, to the distance between the highest peak and the deepest valley, R_t, decreases the peaks becomes more rounded and broad based. Thus, determination of the plastic (permanent) deformability of the pellets from the surface roughness parameters becomes possible as used by Salako et al. (1998).

1.10 OBJECTIVES

I. To produce pellets of different mechanical properties based on:

A. Formulation variables:

-Using different excipients

-Using different binding liquids

-Mixing the different excipients and binding liquids

B. Other factors:

-Using different drying techniques,

-Producing pellets of different sizes

II. To coat (different levels) model drug pellets produced by a binary mixture of:

-each of the excipient with MCC

-each of the binding liquids with water

III. To determine the structural and mechanical properties of the pellets in terms of: density, pore size and size distribution, shape, size and size distribution, surface properties, tensile strength, shear strength, elastic modulus, deformability, linear strain, Weibull constant and modulus.

IV. To compact the pellets by the same compression force or to the same final density and characterize the compaction process in terms of:

-Pressure needed to compact them to the same density

-Compressibility of the pellets-bed

-Kawakita "b" value and Heckel "k" values

-Force/displacements profiles

V. To characterize the properties of the compacts in terms of tensile strength, volumetric elastic recovery, porosity, surface nature and to examine the rate of drug release of the compacts from drug pellets coated by different levels and compacted by different pressures.

VI. To consider some methodological alternatives by studying the application of:

-Dynamic Mechanical Analyser (DMA) in determining the elastic (Young's modulus and storage modulus) and plastic (loss modulus or phase angle) deformability of the pellets and the coating material.

-Non-contact laser profilometer in determining the plastic deformability of the pellets and the coat in their compacts by examining the surface roughness parameters.

VII. -To investigate the effect of each formulation and processing factors as well as the coating levels on the mechanical properties of the pellets, and to assess the effect of the variation of these mechanical properties on the compaction mechanism and the properties of the compacts using different statistical techniques.

-To study and compare the compaction mechanism and the properties of the compacts of the pellets with the compaction mechanism and the properties of compacts of powder mixture of the same composition.

CHAPTER - TWO

MATERIALS AND METHODS

2.1 MATERIALS

2.1.1 EXCIPIENTS AND PELLETIZATION ENHANCING MATERIAL

2.1.1.1 MICROCRYSTALLINE CELLULOSE (MCC)

Microcrystalline Cellulose, a pelletization enhancer, is a purified and partially depolymerised cellulose that occurs as white, odourless, tasteless, rode shaped rigid crystalline powder composed of porous particles (Wheatley, 2000). It is prepared from alpha-cellulose. It is commercially available in different particle sizes and moisture grades, which have different properties and applications (BP-1999). MCC is practically insoluble but dispersible in water; practically insoluble in dilute acids; insoluble in most organic solvents. It is slightly soluble in dilute alkalis (Merck Index 1996).The microcrystalline cellulose (MCC) used was Avicel PH-101, batch no. CA01148, (FMC International, Little Island, and Cork, Ireland) and had a mean volume particle diameter 54.80±0.54μm as measured by Malvern master sizer (Malvern, UK). It was used as received and incorporated in all the formulations studied as pelletization enhancer.

2.1.1.2 LACTOSE

Lactose, milk sugar, is a natural disaccharide consisting of galactose and glucose obtained from milk (BP-1999). This sugar occurs as an odourless white monoclinic sphenoidal crystalline powder with a slightly sweet taste. Lactose is soluble, 200g/l, in water (Merck Index, 1996; Kibbe, 2000). The lactose used was SorbaLac® 400 having a mean volume particle diameter of 16.80±0.32μm, batch no. 022-000405, (MEGGELE Gmbh: Wasserburg, Germany).

2.1.1.3 GLYCERYL MONOSTEARATE

Glyceryl monostearate (GMS) is a white or almost white, hard, waxy mass or unctuous powder or flakes. It is prepared by the esterification of glycerin with a mixture of fatty acids, mainly stearic acid, and by interesterification of hydrogenated edible oils such as palm oil with glycerin (Wade and Weller, 1994). As the product obtained from the esterification processes is a mixture of esters, the composition and hence the physical properties of GMS vary from manufacturer to manufacturer. Most grades are tailored for specific applications or made for user specifications and thus have varied physical properties (BP-1999; Taylor, 2000). It is practically insoluble in water but may be dispersed in hot water with the aid of

small quantity of a surface active agent (Merck Index-1996). The glyceryl monostearate (GMS) used was IMWITOR® 900 Pulver, batch no. 608-233, (CONDIA Chemie Gmbh, Witten, Germany). The GMS was sieved and particle size smaller than 125 μm was used in this experiment.

2.1.2 MODEL DRUG (PARACETAMOL)

Paracetamol is a white, crystalline powder. It is soluble in 70 parts of water, 13 parts of ethanol, and 40 parts of glycerol. The paracetamol used in this project was acetaminophen or paracetamol fine crystal (90 -125μm), batch number AFPJ043, (Knoll AG, Ludwigshafe, Germany).

2.1.3 COATING MATERIAL

Surelease® is an aqueous dispersion of ethyl cellulose containing dibutyl sebacate (plasticizer), oleic acid (stabilizer/co-plasticizer), and ammonium hydroxide solution (aqueous base). It appears as an off-white opaque liquid dispersion and possesses the characteristic odour of ammonia. The Surelease® (Clorcon, Dartford, UK) used was from a Batch number of: IN 502749.

2.1.4 BINDING LIQUIDS

Three binding liquids were used in this project. Freshly purified water by reverse osmosis (USF-Elga, Elga Ltd., High Wycombe, England), ethanol or absolute alcohol, (BDH GPR, Merck Ltd., Poole, UK), and glycerol. Glycerol is a clear , colourless, odourless, viscous, hygroscopic liquid (Price, 2000; BP. 2001). The glycerol used was laboratory grade with batch number of K281 19660 035(BDH, Merck Ltd., Poole, UK).

2.2 METHOD

2.2.1 PRODUCTION OF PELLETS

2.2.1.1 MIXING

According to the standard operation procedure prepared for each experiment, first the weighed powders on a sensitive balance (SAUTER RC 1631, August Sauter GmbH, Ebingen, Switherland) were blended in a planetary mixer (Model A200, Hobart LTD, London, UK) for 10 minutes. The speed of the impeller was at the lowest rate to reduce its effect on the surface properties of the powder. The liquid binders were also mixed separately (if more than

one liquids were included in a formulation) and were added into the mixed powder using a syringe. The rate of addition of liquid was slow approximately 50 ml/min. The mixing process was continued for further 15 minutes. The sides of the bowl and the stirrer were scraped every 5 minutes to detach the material adhering and to ensure a homogenous mixture. The wet mass was placed in a sealed container until it was extruded in few hours time.

2.2.1.2 EXTRUSION

The wet mass was extruded using a ram extruder mounted in a mechanical press (Lloyd Instruments, MX50, Warsash, Southampton, UK), which was fitted with a 50 kN load cell. About 100g of the wet mass was first packed and manually consolidated in the stainless streel barrel of a 2.54 cm internal diameter and approximately 20 cm long fitted with a centrally mounted die having 1.0 mm diameter and 5.0 mm length (L/R=10) by inserting a stainless steel piston. The cross-head positioned above the piston-barrel-die assembly was driven down at a constant speed, which was 200 mm/min in all experiments unless stated, to extrude the wet mass. The extrudate was collected in a plastic bag before it was spheronized. In a specific experiment where the effect of the speed of extrusion was studied, a die having 1.5 mm diameter and 15.0 mm length (L/R = 20) was used. The force acting on the material during extrusion was recorded as a function of time, and a force-time profile was produced on an attached computer. The average of about 250 points in the steady state flow stage (Harrison, 1982) of the force/displacement curve was calculated and recorded as an average extrusion force of the run. The mean of at least 10 runs was used to describe the steady state extrusion force of a formulation in the given experimental system.

2.2.1.3 SPHERONIZATION

About 40g of extrudate, at a time, was spheronized on a 12 cm diameter spheroniser (Model-120, G.B. Caleva Ltd. Sturminster Newton, Dorset, UK) fitted with a cross hatch grooved plate, for about 15 minutes at a speed of 1800 rpm. The load was adjusted after a trial and error experiments to be approximately 40g in each run, and the time was determined by visual observation of the roundness of the pellets formed, however, it was approximately 15 minutes for all formulations unless specifically stated. The spheroniser was partially covered to limit the condensation of the binding liquid. The variation related to the processing parameters of the spheronization have been specified in each experiments. For the last set of experiments (PART-III) where drug was incorporated in the pellets, a spheronizer with

22.5cm diameter (G. B. Caleva, Sturminster Newton, Dorset, UK), fitted with a parallel grooved plate was used. About 250g of extrudate was spheronized at a speed of 1000 rpm. The time was 15 minutes again in all the formulations, unless differently stated.

2.2.1.4 DRYING

Unless stated, all pellets were dried in a laboratory fluid bed drier (Laboratory fluid bed dryer Model No. FBD/L70, PRL Engineering, Mostyn, Flintshire, UK). About 200 g of the pellets were placed in the vessel with a perforated base, which enables air to pass through. A high velocity of hot air (60^0C) separated the pellets and enabled them to move freely. The gas was distributed evenly through small orifices supporting the pellets at a rate sufficient high to cause incipient fluidization but not so high as to give the appearance of a vigorously boiling bed. This technique was efficient to dry the pellets in 30 minutes.

In a specific experiment where the effect of different drying techniques were studied, MCC pellets, produced with water/ethanol mixture, were additionally dried in a hot air oven (Pickerston Instruments Ltd., Romfolk, England), freeze drier (Micro Modulyo, Edwards, Sussex, England), and were placed in a desiccator with dried silica-gel for different duration of time. Pellets were spread on a shallow tray and were placed in the compartments of the oven, set at 60^0C. The pellets dried by convection due to constant flow of the heated turbulent air over their surface. This continued for 24 hours. In freeze drying system the wet pellets were first frozen by the addition of liquid nitrogen, and were then subjected to low pressure (below the triple point, 4.579 mm Hg and 0.0099 ^{0}C) by high vacuum. The heat supplied by conduction or radiation, or by both changed the ice directly to vapour leaving only the solid structures. This process took 14 hours to produce dried pellets. Some pellets were placed on a perforated plate in a sealed desiccator with a dried silica-gel. The silica-gel absorbed the water vapour from the atmosphere of the sealed desiccator. As the vapour pressure in the desiccator reduced, water vaporized from the pellets until they were dried. This technique took 5 days to dry the pellets. Finally, the moisture content of the pellets was measured using Thermogravimetric analyzer (TGA) (HI-RES TGA 2950, TA-instruments, Leatherhead, Surrey, UK). The dried pellets were placed in a sealed container until further analysis.

2.2.1.5 FILM COATING

The pellets containing the model drug were coated in a fluid bed coater (Aeromatic AG,

Germany) which had a 8.5 cm diameter perforated bottom plate and with a bottom spray pneumatic nozzle. Preliminary studies established that the optimum conditions, i.e. even coating with no pellet agglomeration was possible with 40 g of pellets per batch, inlet air temperature of 60^0C, outlet air temperature of 40^0C, atomized air pressure of 0.2 bar, and coating feed rate of 0.6 ml/min. The coating suspension was heated to 60^0C and was applied for 45 minutes for each 5% weight gain. Each batch of the pellets was coated at three levels (i.e. 5%, 10%, and 20% w/w). To assess friability, some uncoated pellets were fluidized in the coater without the spray of the coating material for 60 minutes.

2.2.2 STRUCTURAL CHARACTERIZATION OF THE PELLETS

2.2.2.1 SIZE ANALYSIS

Sieve analysis (Ph. Eur. Method 2.9.12) was carried out to determine the weight size distribution of each batch of pellets and to separate pellet of the size fraction between 1.0mm to1.18mm for further analysis. A set of sieves, BS sieves (Endecotts Ltd., London) were chosen ranging from 710 μm to 2.8 mm in a $\sqrt{2}$ progression according to the British Standard. In addition an aperture size of 1.18 mm was inserted in between the 1.0mm and 1.4 mm sieves to obtain tighter size range. About 100 g of pellets were sieved for 15 minutes using a vibratory mechanical sieve shaker (Endecotts, Ltd. London). The weight of pellets retained on each sieve was recorded and presented as a cumulative weight percentage oversize curve, form which the median (50%), and the inter-quartile (75%-25%) pellet diameter by weight was determined. The sieve diameter produces a measure of the size of the smallest square aperture through which the pellets would pass. Therefore, the result was biased towards the smallest diameter of the pellets and hence was related to the width rather than the length. Pellets from some formulations were observed to acquire static electrical charges during sieving, possibly from the friction between the pellets and the pellets with the sieves.

2.2.2.2 SHAPE ANALYSIS

The two dimensional shape factor, $e_{R,}$ Podczeck and Newton (1994) of the pellets was determined. One hundred pellets of each batch were placed on a black slides and analyzed with Seescan image analyzer (Solitaire 512, Seescan, Cambrige, UK) connected to a black and white camera (CCD-4 miniature video camera module, Rengo, Toyohashi, Japan) and zoom lens (18-108/2.5 Olympus, Hamburg, Germany). A top cold light source (Type FLQ 85E; Olympus Co. Europe) was used to reduce the influence of shadow on the image

processing, as has been described by Podczeck and Newton (1995). The two dimensional shape factor, $e_{R,}$ was calculated in accordance with the method described by Podczeck and Newton (1994). The illumination technique, position of the light source, minimum pixel resolution, and number of pellets measured (Podczeck et al. 1999a) were optimized for the size range of pellets used in this experiment. For comparison, the results of aspect ratio, circularity, and projection sphericity were also measured.

2.2.2.3 DENSITY AND POROSITY

The apparent pellet density (Ph. Eur. 2.9.23, BP. Appendix XVII K) was determined by using helium pycnometer (Multi-Pycnometer, Quantachrome Corporation, UK). The technique employs Archimedes principle of fluid displacement to determine the volume. The displaced fluid is a helium gas which can penetrate the finest pores, one Angstrom (10^{-10}m), to ensure maximum accuracy. The apparent density is determined by measuring the pressure difference when a know quantity of helium under pressure is allowed to flow from a precisely known reference volume into a sample cell containing the pellets. This is performed after the system is purged with helium to remove the adsorbed gases from the pellets. By applying the gas-law and standard calibration using steel balls, the reference volume (V_R) and the total volume of the system (V_C) is determined. The apparent pellet density was then determined as a ratio of the mass of the pellets to the apparent volume of the pellets determined from equation (36):

$$V_p = V_c - V_R[(P_1/P_2) - 1] \qquad \text{..... (36)}$$

where V_p is the apparent volume of the pellets, V_c is the total volume of the system, P_1 and P_2 are pressure of the definite amount of the gas in a reference volume (V_R) and in sample cell respectively. Three experiments were undertaken for each batch of pellets, and their average value was recorded as the apparent density of the pellets.

Had this technique been used to measure the effective density of the pellets, the volume contributed by the open pores would have been exncluded. This would underestimated the effective volume of the pellets and thus would overestimated the effective density of the pellets. Selkirk and Ganderton, (1970) suggested the usage of mercury porosimeter to

determine the effective granule density. In such a technique, the volume of open pores larger than some size limit are excluded. This pore size limit or minimal accessible diameter depends on the maximal mercury intrusion pressure applied during the measurement. Various densities can be obtained from one sample since, for each applied mercury intrusion pressure, a density can be determined that corresponds to the pore size limit at that pressure. In this work, 200 pellets were counted and weighed from each batch. Their mass was divided by their volume, which was calculated from the average diameter of the pellets assuming that their shape was a perfect sphere. Furthermore, the volume of the 5%w/w coated pellets was determined by employing the helium pycnometer, in an attempt to estimate the effective pellets density.

Bulk and tap density values were determined based on the European Pharmacopeia (Ph. Eur. 2.9.15 and BP Appendix XVII D, 2000). One hundred grams of pellets were poured into a 100 ml glass measuring cylinder. The ratio of the weight of the pellets to the volume before the tapping was taken as the minimum bulk density. Tap density was determined by dropping the cylinder 250 times per minute over a distance of 3mm. This was carried out by mounting the cylinder on a machine operated by a rotating ram (Tap Density Volumeter, Type-JTV-1, Copleys, Scientific Ltd., Nottingham, UK). All reading were taken after 1000 taps. The average of the three experiments was taken as the minimum and maximum (bulk and tapped) densities of the pellets. The Hausner ratio (Hausner, 1967), which is the ratio of the tapped to bulk density, was calculated.

2.2.2.4 SURFACE AREA AND PORE SIZE DISTRIBUTION

A. Moisture Removal:

First the pellets were dried to constant weight by infrared radiation in a moisture balance (Sartorius, Model YTC 01LTthermo Control Unit, Sortarius GmbH, Gottingen, Germany). Afterwards, they were desiccated with dried silica gel to protect the adsorption of moisture until they were analysed.

B. Outgassing:

Pellets were prepared for surface area and pore size analysis on the SA 3100 analyser (SA 3100 surface area analyser, Beckman Coulter, Miami, Florida, USA) by outgassing.

Outgassing removes adsorbed gases and moisture from the sample surface by evacuating them from the sample tubes with vacuum pump. The sample tubes were heated by the outgassing furnace to 90^0C and the outgassing process continued for 90 minutes.

C. Analysis:

The adsorbate gas (nitrogen) was added in known quantities into the evacuated tube containing the pellets. Gradual increase in the quantity of the nitrogen gas increased the pressure in the sample tube. During this process, the sample tube was kept at a constant temperature. When the pressure in the tube had equilibrated following each introduction of nitrogen gas, the pressure was recorded. The pressure readings were used, in turn, to calculate the volume of gas adsorbed. The volume of gas adsorbed was measured as a function of relative pressure. Relative pressure was the ratio of the pressure in the sample tube to the saturation vapour pressure of the adsorbate gas (i.e. the pressure at which the adsorbate gas liquefies). The saturation pressure was measured for every sample tube pressure data point. During the measurement, the sample was maintained at a temperature where liquefaction of the adsorbate gas can take place on the sample. To maintain this temperature, the sample tube was immersed in a dewar of liquid nitrogen during analysis. The surface area, pore size distribution, and pore volume parameters were calculated from the isotherm data.

A specific relative pressure range (0.05- 0.2) was chosen and the isotherm data was used to calculate the BET function (equation-18), which was plotted against the relative pressure (P_0/P), to give a straight line having a slope $(C-1)/V_MC$ and intercept $1/V_MC$. The BET surface area (m^2/g) was then determined form the following expression:

$$S_{BET} = \frac{V_M \times N_A \times A_M}{M_V} \qquad \text{.....(37)}$$

where, S_{BET} is the BET surface area, N_A is Avogadros number (6.02×10^{23}), A_M is the cross section area occupied by each nitrogen molecule ($0.162nm^2$), and M_V is the gram molecular volume (22414 mL).The pore size and size distribution were determined from equations (19) and (20) respectively. For Nitrogen at 77.3K (liquid nitrogen temperature), the contact angle, θ, is 0^0, molar volume, V, is 23.6 ml/mole, and surface tension, γ, is 8.85 dynes/cm.

2.2.3 MECHANICAL CHARACTERIZATION OF PELLETS

2.2.3.1 MECHANICAL STRENGTH

The mechanical strength of 30 pellets from each batch was determined as the crushing load needed to break the pellets using CT-5 (Engineering system, Nottingham, UK). The speed of the upper mobile platen fitted with 5kN load cell was set at 1mm/min. For the 'brittle' pellets, the platen returned back automatically when a significant drop in the load was observed. For the 'non-brittle' pellets, however, the reduction in the load was noted on the force/time graph (Servogor-120, J. M. Instruments., Kent, UK) before they broke. Compression was then stopped and the first peak was recorded as a breaking load. The tensile strength was derived from the crushing force and pellet diameter using equation (6) by Shipway and Hutchings (1993).

The Weibull-modulus, m, which is a measure of the variability of the failure properties of a pellet batch and the Weibull-constant, $X_{0,}$ a characteristic strength value of the pellets were analyzed by using the numerical methodology described by Erck (1994) and used by Salako et al.(1998). This technique takes the form of equation (8). Linear regression having the form of equation (38) was used to determined the model parameters;

$$\ln(-\ln[1-P(x)]) = m\ln(x - x_u) - m\ln(x_0) \quad \text{.....(38)}$$

The goodness of the fit of the data using this equation was measured using residual analysis and are summarized with the values of the root mean square deviation.

The shear strength of the pellets was also determined according to Adams et al. (1994) using equation (7). About 5 to 10 points which would make the R^2 value of the linear regression about 0.99 were chosen. The average of three values have been taken as the shear strength of the pellets.

2.2.3.2 LINEAR STRAIN, DEFORMABILITY AND 'ELASTIC MODULUS'

During the diametral compression of the pellets, an attached plotter(Servogor-120, J. M. Instruments., Kent, UK) plotted the load/time profile (kg/min). By determining the proportion of the horizontal distance of the plotter to that of the platen displacement, and converting the load (kg.) to force (N), a force/displacement profile was produced. Three different

measurements were made from this curve, namely: (i) The inverse of the slope of the force/displacement curve, from the initial point where the platen started to exert pressure on the pellet up to the maximum load at which the pellets failed in tension, was determined. The average of 30 samples from each batch was taken as the deformability of the pellets. (ii)From the unidirectional decrease in the dimension of the pellet along the direction of the compressing force, linear strain or "shrinkage" was also determined as a ratio of decrease in height of the pellets before they broke to their original height. (iii) The 'elastic modulus' was determined as a ratio of the pressure to the linear strain as described by Dyer et al. (1994).

2.2.3.3 DYNAMIC MECHANICAL ANALYSIS

Dynamic mechanical analysis was carried out using DMA7 (Perking Elmer Corp., High Wycombe, UK) with a parallel plate geometry in conjunction with a personal computer (DELL, Optiplex Gx1). The DMA7 was attached to the computer via TAC7/DX thermal analysis instrument controller, which was controlled by Pyris software for windows. TAC7/DX thermal analysis controlled the analyser and digitized the analog output from the detector before sending it to the computer.

A single pellet was placed in the centre of the sample platform. A parallel plate measuring system with a plate diameter of 3mm was employed, which comprises a central core and probe. The central core rod was suspended in a magnetic field and ran the length of the analyser. It was driven by a linear force motor, which in turn was commanded by a computer. The probe was attached to the lower end of the core rod lowered down to hold the sample in place for testing. The environmental system included the purge gas helium-cooling device, and the furnace, which was raised and locked into place. The prescribed force generated by the force motor was applied to the sample through the core rod. Helium gas was used as purge in the furnace and an electrical intra-cooler (fridge) provided an isothermal environment outside the furnace. The purge gas was supplied through the top of the measuring system and provided uniform atmosphere for the sample. Stresses induced in the sample were transmitted through the lower test fixture to a detector where deflections were converted to electrical signals and relayed to a TAC7/DX thermal analysis instrument controller. The thermal analysis instrument controller then resolved the signals into elastic and viscous components of the complex modulus and the phase angle as their function.

The samples were equilibrated at 20±0.1^{0}C and purged with helium (20ml/min) during testing. The results were the mean and standard deviation of 20 pellets. Static scans to obtain a value for the elastic modulus of the pellets were performed between 0 and 2600 mN at a rate of 200 mN/min. Dynamic scans to evaluate the viscoelastic properties of the pellets were undertaken employing a static force of 2000 mN, static tension control of 120% and a frequency of 1 Hz. From the dynamic scans, a wide variety of measurements can be obtained. Here, the storage modulus and phase angle as a function of dynamic force were recorded. Moreover, the slope of the linear portion of the storage modulus-dynamic force curves were determined.

2.2.3.4 FRIABILITY

The friability of the pellets was tested by tumbling 5 g of pellets from each batch in a Roche friabilator (School of Pharmacy, University of London, London, UK) fitted with and without 20 (4 mm diameter) glass beads. The pellets were tested with and without talc spray. After rotating for 1000 times they were collected and placed on a tarred sieve (0.71mm size) and were hand shaken under negative pressure of Alpine air jet sieve (Alpine Augusburg, Germany) for two minutes. The percentage of friability, F(%), was determined by equation (39) based on initial weight (W_i) and weight retained (W_r) on the sieve.

$$F(\%) = 100\left(\frac{W_i - W_r}{W_i}\right) \qquad \text{.....(39)}$$

At first, the pellets stuck on the wall of the frabilator , then they started to fall down after talc was sprayed on them. However, the loss in weight was less than 1% in all batches.

2.2.4 COMPACTION OF PELLETS

2.2.4.1 COMPACTION MECHANISM

The pellets were compacted by Universal Testing Instrument (Instron Ltd. Model TT, High Wycombe, UK) equipped with flat-faced punches having a die of 12.0 mm diameter. After lubrication of the punch and die by dusting magnesium stearate, 550, 600, 650, 700 mg of the pellets from each formulation were weighed on analytical balance (Sortorius 201 MP2, Gottingen, Germany) and then manually filled into the die. The pellets were compacted at a constant speed of 0.5 cm/min in two different ways:

A. Pellets of the same masses were compressed to a predetermined tablet thickness to produce compacts of the same density or

B. To constant upper punch pressure (130 MPa and 146 MPa)

In all cases, the compressing pressure was released immediately after it reached its maximum pressure and the tablets were ejected manually. The rate of decompression was of the same constant speed as that of compaction i.e. 0.5 cm/min. A force/time curve was plotted (Recorderlab, Gould, Surrey, UK), from which the compaction mechanism of the pellets was studied in terms of:

- A compression pressure needed to produce compacts of the same density:
- Compaction pressure versus in die punch displacement curve:
- Compressibility of the pellets as a ratio of the reduction in the height of the pellet bed to the original height of the bed at the onset of the pressure:
- Heckel plot and determination of the k-value "deformability constant" or yield stress by using equation (24):
- Logarithm of pressure to relative density plot in an attempt to identify the breakage of the pellets as described by Messing et al. (1982)
- Determination of Kawakita's constant "b" value the coefficient of compression (equation-23):

C. Pellet or powder formulations of the same bulk volume (determined by die size, 10 mm diameter and 12 mm deep) were also compressed by an eccentric tableting machine to the same in die tablet thickness (4 mm)(Manesty F3, Manesty Machines Ltd., Liverpool, England) at a rate of about 3500 tablets per hour.

2.2.4.2 CHARACTERIZATION OF PELLET COMPACTS

2.2.4.2.1 STRUCTURAL CHARACTERIZATION OF COMPACTS

Immediate after decompression, the tablets were ejected manually and their dimensions (±0.001cm) were measured by a micrometer (Mecer, St. Albans, UK). Five samples were directly analyzed for their strength, while some were stored in the ambient temperature and humidity for a definite period of time, as described in each experiment, after which their dimensions were again measured before they were further analyzed. The post-compaction tests performed on the ejected tables included the determination of weight, thickness,

diameter, porosities, volumetric elastic recovery, tensile strength, dissolution test, visual studies of their scanning electron micrograph (SEM), surface roughness and deformability of the compacted pellets. Each test was performed on replicates as mentioned in each result section. The same analytical balance was used to determine the post-compaction weight of the tablets. The thickness and diameter of each tablet was measured three times and at different positions by a micrometer and the average was determined.

The out-of-die total tablet porosity, and inter-granular porosity (the ratio of the difference of the tablet and apparent pellet density to the density of the tablet) was determined from the dimensions of the tablet (thickness and diameter), with comparison to the apparent density of the pellets measured by helium pycnometer (See 3.2.2.3). This is with the assumption that the closed pores of the pellets were not affected during compaction.

The original thickness and diameter of the compacts as measured immediately after ejection and the dimensions measured after a certain period of storage time were used to compute the volumetric elastic recovery (VER) of the compacts according to equation (31). Electron micrographs of the pellets and their compacts surface and cross section areas were taken with the aid of a scanning electron microscope (Philips XL20, Eindhoven, Holland). They were examined for the change of the shape as well as for the presence of pellet fracture on the surface of the compacts.

2.2.4.2.2 TENSILE STRENGTH OF COMPACTS

The tensile strength of the compacts was calculated from equation (40) given by Fell and Newton (1970a) after the tablets were compressed diametrically until fracture occurred in tension. This was performed by tablet strength measuring instrument CT-40(Engineering System, Nottingham, UK) at a compressing rate of 1mm/min

$$\sigma = \frac{2P}{\pi dh} \qquad \text{.....(40)}$$

where, P is the tablet crushing force (N), d is the tablet diameter (m), and h is the tablet thickness (m).

2.2.4.2.3 NON-CONTACT LASER PROFILOMETER

The profilometer (UBM Messtechnik GmbH, Ettlingen, Germany) used in this work had a light spot diameter of 1 μm and a measurement range of ±500 μm. Area scans of the top and bottom surfaces of tablets produced form the different formulations and compacted by different pressures were performed. The traverse lengths were 6.5 mm in the X direction and 6.5 mm in the Y direction, with a resolution of 100 points/mm in the X and Y directions and scanning frequency of 100 points/min. Scans were linearly levelled to remove any underlying slope on both axises and R_a, R_q, R_{tm} and FD were determined from 5 samples in each batch of tablets based on the equations (32-35). The mean and standard deviation of the 5 samples were calculated and recorded.

2.2.4.2.4 DISSOLUTION TEST

The dissolution tests were carried out in a dissolution tester (Caleva , Model 8ST-M, Dorset, UK) according to the USP XXI (Paddle method). The medium was distilled water at 37^0C and the paddle speed was 100 rpm. Four hundred milligram of uncoated and coated drug pellets as well as 400 mg coated and uncoated pellets compacted by different pressures were also tested with 5 replicates.

PART - II

CHAPTER - THREE

THE EFFECTS OF EXCIPIENTS ON THE MECHANICAL PROPERTIES OF PELLETS AND THE PROPERTIES OF THEIR TABLETS

In an attempt to understand the effects of composition of excipients in producing pellets of acceptable structural characteristics and the effect of their proportion on the mechanical properties of the pellets as well as the properties of their compacts, pellets were produced by a standard extrusion and spheronization procedure (2.2.1) from a binary mixture of GMS or lactose with MCC and sufficient amount of water (Table-3.1).

No.	MCC	GMS or Lactose	Water
1	10	0	10
2	8	2	8
3	6	4	6
4	4	6	4.6
5*	2	8	3.6

Table:-3.1: Pellet formulations from a binary mixture of GMS or lactose with MCC. (Formulation-5 indicates only for GMS and MCC mixture).*

Pellets of 1.0-1.18 mm size fraction were separated (see 2.2.2.1) and characterized structurally (section 2.2.2) and mechanically (section 2.2.3). Some pellets from each formulation were compacted (2.2.4.1A, B and C) and the compaction mechanism and the properties of the compacts were analysed as described on sections (2.2.4.1) and (2.2.4.2) respectively. Moreover, a binary powder mixture containing 60%w/w of either GMS or lactose was blended with 40%w/w MCC powder and were used to produce tablets by the procedure described in (section 3.2.4.1B and C) and their compaction mechanism (2.2.4.1) and properties of the compacts (2.2.4.2.1-2) were analysed and compared with pellet compacts of the same composition. Finally, the three excipients were mixed to give a factorial designed experiment (section 3.3) to produce pellets of different composition. The properties of the pellets, their compaction mechanism and the properties of their compacts were analysed similarly.

3.1 THE EFFECTS OF GLYCERYL MONOSTEARATE

3.1.1 PRODUCTION AND CHARACTERIZATION OF PELLETS

It was not possible to produce pellets by extrusion and spheronisation using only GMS. Thus, the effect of GMS in the properties of pellets and their compaction mechanism was examined based on the addition of different amounts of GMS to MCC : Water (1:1) wet mass (Table-3.1). At the 60%w/w GMS content, however, some more water was added equal to 10% the weight of the GMS in the formulation (Table-3.1). This enabled the wet mass to be extruded through the 1 mm die diameter and produce smooth extrudates which were subsequently spheronized into pellets within 15minutes. The drying temperature of these pellets was 40^0C, lowered by 20^0C from the formulations which did not contain glyceryl monostearate. That was due to the low melting point of GMS (57^0C). The drying time was increased by 15 minutes in order to reduce the water content of the pellets by extended exposure to the moderately heated turbulent air in the fluid bed drier. The surface of the produced pellets was smooth and glassy. There was no static charging of the pellets during sieving.

The force needed to extrude the wet mass through the die of 1 mm diameter and 5 mm length was observed to increase with the increase of the percentage of GMS in the formulation (Fig-3.1.1). However, the difference was insignificant. This indicates the plasticity of the wet mass that contained GMS, which enabled the relatively drier mass to squeeze through the die to form smooth extrudates. The force was observed to increase during the course of extrusion, mainly for those having a higher GMS content. This slight change was presumably due to the change in the distribution of the water in the wet mass. As GMS is insoluble and not easily wetted by water (contact angle 119^0, Boutille, 1995), the solvent may have drained downwards to leave a relatively drier mass in the barrel which needed a greater force to extrude.

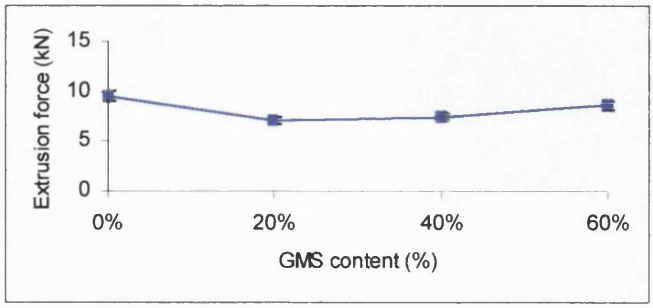


Fig-3.1.1:-The effect of the amount of GMS on the extrusion force of MCC/GMS wet mass.

Had a dry powder of MCC been added instead of GMS in the starting MCC: water mixture,

the extrusion forces would have increased significantly as will be shown latter (Section 3.3). The lubricant effect of GMS, however, ensured that the wet mass reduced the extrusion force differences with its increase in the dry mass content.

The median size of the pellets produced was approximately the same in all the formulations, although a slight trend of increase with the increase of the GMS content was observed (Table-3.1.1). This statistically insignificant difference could mainly be due to the ability of the glyceryl monostearate to bind the constituents of the wet mass, hence reduce fragmentation, even at its relatively lower percentage in the formulations.

Structural and Mechanical Properties of Pellets	Amount of GMS in the dry mass (%)			
	0%	20%	40%	60%
Median particle diameter (mm)	0.95	0.96	0.97	0.97
Interquartile range (mm)	0.34	0.29	0.33	0.34
Bulk Density (g/cc)	0.88(0.08)	0.80(0.08)	0.71(0.07)	0.64(0.06)
Tapped Density (g/cc)	0.94 (0.09)	0.83(0.08)	0.73(0.07)	0.68(0.07)
Hausner ratio	1.06(0.05)	1.04(0.04)	1.03(0.07)	1.06(0.04)
Apparent pellet density (g/cc)	1.42(0.1)	1.33(0.1)	1.26(0.1)	1.17(0.1)
porosity (sealed) (%)	8.08(0.9)	6.60(0.7)	3.00(0.2)	0.40(0.0)
Shape factore, e_R	0.59(0.04)	0.57(0.04)	0.57(0.05)	0.54(0.04)
Aspect ratio	1.09(0.1)	1.11(0.01)	1.15(0.1)	1.14(0.1)
Circularity	0.909(0.1)	0.923(0.1)	0.914(0.1)	0.918(0.1)
Projected sphericity	0.89(0.04)	0.87(0.03)	0.86(0.04)	0.85(0.02)

Table:- 3.1.1: The structural properties of GMS/MCC pellets. The density and shape analysis were performed on pellets from size fraction of 1.0mm to 1.18mm.The values in parenthesis indicates the standard deviation.

The size range of the pellets was very small and all the formulations were of almost equal spread in size. Pellets of very small size were not produced presumably due to the lower fragmentation propensity of the extudates in the spheronizer and during the turbulent fluidization during drying. This again shows resistance of GMS to abrasion. There was no aggregation in the spheronizor either, showing the water insolubility of this excipient reduced

the wetting of the surface and consequently stickiness. Basit et al. (1999) had a similar observation on size distribution when GMS was incorporated in their pellets.

There was a constant decrease in the bulk and tapped density of the pellets with the increase of GMS content in the formulations (Table-3.1.1). All the pellets seemed to have a smooth surface which avoids the possible variation in the rearrangement of the pellets due to friction, and all had a similar size and size distribution. Thus, the main reason for the variation in the bulk densities of the formulations could only be the wide difference in the apparent particle density of the constituents of the formula (Table-3.1.1). At 60%w/w GMS, the apparent particle density of the dry mass of the formulation, as calculated theoretically, was only 82.4% of that of formulation containing 20% w/w GMS. Therefore, it was inevitable to have such density variation in the formulations. The very small difference in the bulk and tapped density (i.e. initial and final bulk densities) of each formulation show the high packing characteristics of the spheres as the values in Hausner ratio indicated (Table-3.1.1).

There was a constant decrease in the porosity (closed pores) of the pellets with the increase of the GMS in the formulation (Table-3.1.1). This was calculated from the determination of the apparent density by a helium pycometer. As a result this could be termed "sealed or internal porosity", for the helium gas was able to access the open pores and exclude them from the volume of the pellets from which the apparent density and porosity were calculated. In a formulation where no GMS was incorporated, the internal porosity of the pellets was 8%. This diminished gradually to about 0.4% at 60%w/w GMS. Considering the experimental error, this could be due to the ability of the GMS to fill in the air pockets in the MCC fiber network.

The pellets produced had a reasonable spherical shape when visually observed. The values for the shape factor (Podczeck and Newton, 1994) revealed a slight trend to decreasing in sphericity with increase in GMS content. The dryness of the extrudates with the increase in GMS content could be the reason for their inability to be rounded more during spheronization. Although incorporation of GMS improved the suitability of the wet mass for the process of extrusion and spheronization, the moisture content of the formulations seems to have the most significant roll in improving the structural properties of the pellets.

3.1.2 MECHANICAL PROPERTIES OF THE PELLETS

The change in the mechanical properties of the MCC pellets was significant and consistent with the increase of the proportion of GMS incorporated. There was a steady decrease in tensile strength of the pellets with the increase of the GMS content (Fig-3.1.2). These differences were found to be statistically significant (P<0.001) (Table-3.1.2).

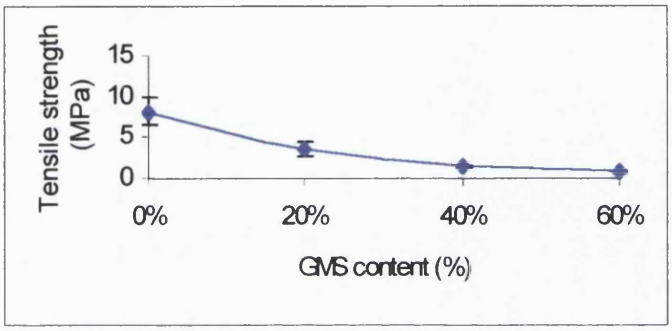


Fig-3.1.2:- The effect of the amount of GMS on the tensile strength of MCC/GMS pellets from 1.0 -1.18 mm size fraction

The rate of decrease in tensile strength decreased with an increase of GMS content up to insignificant difference (P<0.001) between 40% w/w and 60%w/w GMS content of the dry mass.

GMS content	Mean Tensile Strength (MPa)	Standard Deviation	MS	F	P
0%	8.17	1.61	-	-	
20%	3.55	0.85	320.04	192.85	<0.001
40%	1.37	0.27	693.86	520.7	<0.001
60%	0.76	0.2	823.39	625.09	<0.001

Table-3.1.2:- Results and ANOVA of the effect of addition of GMS on tensile strength of MCC pellets of 1.0-1.18mm size fraction

The tensile strength of the MCC/GMS pellets was also affected by the moisture content of the formulation. When extra water equal to 10% w/w of the dry mass was added in a formulation having equal mass of GMS and MCC (1:1), the tensile strength of the pellets increased by 20.6%.

As an inert material, GMS does not seem to have affected the chemical nature of MCC. Due

to its soft nature, however, it may have hindered the formation of rigid MCC structure as was observed in MCC pellets. In all the results in this project, MCC pellets were found to be the strongest, especially at a higher original water content. The incorporation of GMS as a dry powder reduced the overall water percentage of the formulations, as well as the amount of MCC in the dry mass of the formulation (Table 3.1). Thus, the reduction in the strength of the pellets could be due to the overall decrease in the moisture content in the formulations as well as the incorporation of a soft material. Pinto et al. (1993) and Lundqvist et al. (1997) had a similar observation. They called their pellets having GMS "soft pellets" to illustrate their weak strength and ease of deformability.

Some Mechanical Properties of Pellets	Amount of GMS in the dry mass (%)			
	0%	20%	40%	60%
Weibull-constant	9.268	4.186	1.574	0.879
Weibull-modulus	4.812	3.339	4.044	3.225
Shear Strength (MPa)	2.96±0.12	1.45±0.09	0.10±0.01	0.01

Table:- 3.1.3: Some mechanical properties of GMS/MCC pellets of 1.0-1.18 mm size fraction.

The shear strength of the pellets was also observed to decrease with the increase of GMS content in the formulations (Table-3.1.3). The rate of decrease was increased up to 10 fold from the 40% to 60%w/w GMS in the dry mass. Compared to the tensile strength, the shear strength of the formulations was lower, indication the failure of the pellets by shearing during compaction as well as their lower brittleness. With the increase of GMS content, the ratio of shear to tensile strength was further decreased. The values of the Weibull-modulus (Table-3.1.3) were, however, inconclusive. The relatively lower value at 60%w/w GMS could be an indication of the brittleness of the crust formed during drying of the pellets. Increase in deformability of the pellets with the increase in the GMS proportion was also one of the observations of this work (Fig-3.1.3).

There was more than a three fold increase in deformability of the pellets with the incorporation of 60%w/w GMS, while it increased by 140% and 220% with the addition of 20%w/w and 40%w/w GMS respectively. The rate of increase in deformability decreased with the increase of the GMS proportion. This shows an inherent deformability of this material. A

similar observation was noted by Pinto, (1992) and Lundqvist et al. (1997) in their "soft pellets" in which about 20 %w/w of the dry mass was GMS. The slope of the force/displacement curve, however, was not strictly linear. Especially at the relatively higher force, the GMS-rich pellets yielded to deviate form the linearity. Thus, in this calculation the linear portion of the curve was taken as it was used by Wickberg and Alderborn (1992). Moreover, the sensitivity of the plotter required adjustment to be able to identify the force at which the pellets failed.

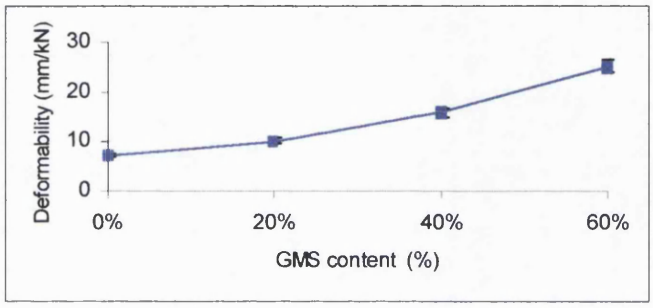


Fig-3.1.3:- The effect of the amount of GMS on the deformability of MCC/GMS pellets from 1.0 -1.18 mm size fraction

The linear strain of the pellets decreased with the increase of GMS in the formulation (Fig-3.1.4). The rate of decrease in linear strain decreased with the increase of GMS. The difference between 40% and 60%w/w GMS was insignificant. As a deformable material, the addition of GMS was expected to increase the linear strain of the pellets. However, the significant reduction in the strength of the pellets with the incorporation of GMS, induced an early failure of the pellets before they were strained to a greater extent. The pellets snapped by a small compression force, although they were subjected to extended strain after that early pressure peak.

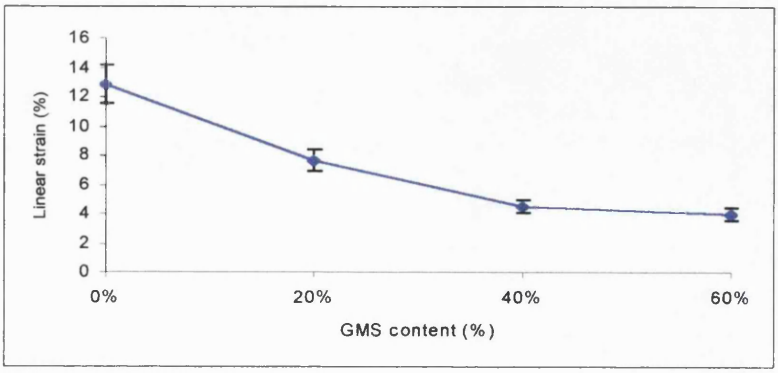


Fig-3.1.4:- The effect of the amount of GMS on the linear strain of MCC/GMS pellets from 1.0 -1.18 mm size fraction

The 'elastic modulus' was also observed to decrease with the increase of the amount of GMS in the formulations (Fig-3.1.5). The rate of decrease in 'elastic modulus' was almost linearly proportional to the amount of GMS in the formulation. Incorporation of 60%w/w GMS reduced the 'elastic modulus' by 30%. This is again due to the nature of the GMS and the structure it formed with MCC in the formation of the pellets.

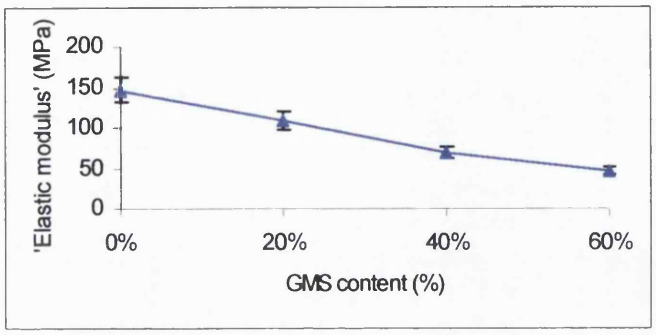


Fig-3.1.5:- The effect of the amount of GMS on the 'elastic modulus' of MCC/GMS pellets from 1.0 -1.18 mm size fraction

3.1.3 THE COMPACTION MECHANISM OF GMS CONTAINING PELLETS

The pressure needed to compress 700 mg pellets of the various formulations to approximately the same in die tablet thickness (2.2.4.1 A) was found to differ. It increased with the increase of the percentage of GMS in the formulations (Fig-3.1.6). The rate of increase in compressing pressure was linearly proportional to the increase of GMS content of the pellets.

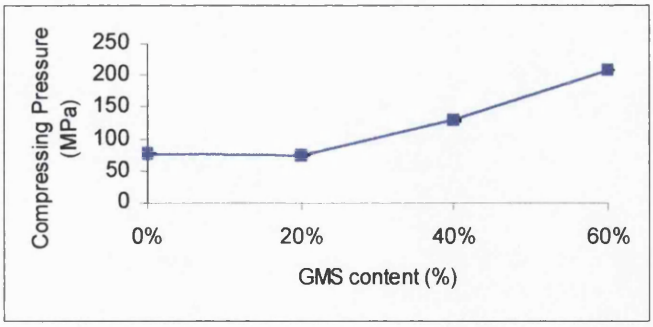


Fig-3.1.6:- The effect of the amount of GMS on the compression pressure of 700 mg of MCC/GMS pellets of 1.0 -1.18 mm size fraction to tablets of the same dimensions.

In a similar way, the work of compaction increased with the increase in the GMS content of the formulations (Fig-3.1.7). The pressure/displacement curve of the different formulations was also different. This was a reflection of the variations in their surface and bulk deformability of the pellets. The more deformable formulations were compressed to a greater

extent before the compression pressure was built up. This showed their ability to spread over each other until the porosity is reduced significantly, thereafter the pressure increased rapidly indicating the elastic deformation on the solid structures of the constituents.

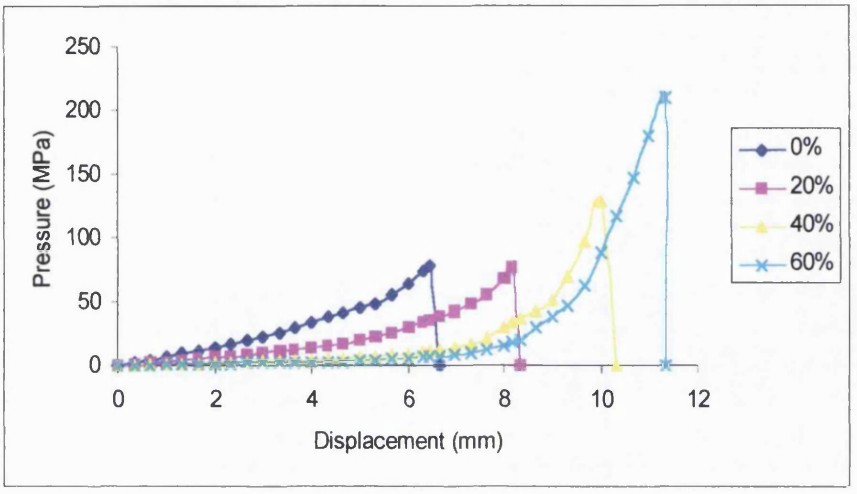


Fig-3.1.7:- The effect of the amount of GMS on the pressure/displacement profile obtained during compaction of 700 mg of MCC/GMS pellets of 1.0-1.18mm size fraction

The main reason for the requirement of a higher compaction pressure and work of compaction for compressing the same amount of pellets to the same tablet dimension is the difference in the relative density of the formulations. With the increase of GMS content, the density of the formulations decreased steadily. Thus, when all the formulations were compacted to the same tablet dimensions, the relative porosity of the tablets became different, the formulations having a higher GMS content were compressed to the lower porosity. As a result these pellets had to deform (plastically and elastically) to a greater extent, which required a higher pressure or expenditure of more energy.

Another reason could be the difference in the compressibility of the formulations. Formulations which have a higher content of GMS had a higher compressibility, as determined from the decrease in volume of the pellet beds. There was a 20% increase in compressibility of pellets when the 60%w/w of the formulation was GMS compared with that without GMS. Moreover, the Kawakita coefficient of compressiblity (Table-3.1.4) had the same trend. During such reduction in the volume (porosity) of the pellet-bed, the first step is rearrangement of the pellets, followed by deformation. There was no substantial loss of energy in rearranging GMS-rich pellets. This was illustrated in the curve, which was almost parallel

to the x-axis representing the displacement without a significant change in the compressing pressure. Hence, only deformability is responsible for the discrepancy in the compressibility and variation in the compaction mechanism.

For the first three formulations, the Heckel plots seems to have approximately similar slopes at pressures between 25 to 75 MPa. (Fig-3.1.8). The determination of the yield pressure (an inverse of the slope obtained form the regression of the region above 75 MPa.) illustrated that the 20% and 40%w/w GMS containing pellets had a lower value than MCC-pellets while that of 60%w/w GMS had a higher value (Table-3.1.4) for no apparent reason.

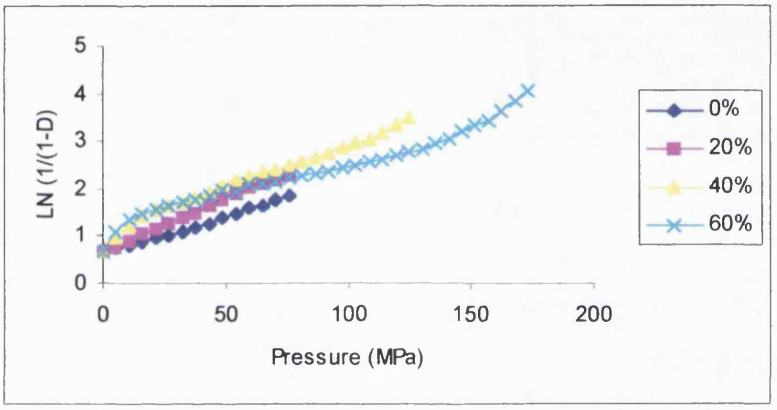


Fig-3.1.8:- The effect of the amount of GMS on the Heckel plot derived from the compaction of 700 mg of MCC/GMS pellets of 1.0 - 1.18 mm size fraction.

As a deformable material, GMS was expected to reduce the yield pressure, which it did for the first two formulations. However, an increase in yield pressure with increase in GMS content from 20% to 60%w/w GMS content was observed in this work. The main reason could be the selection of the range of pressure and number of points used in the determination of the slope. Although the highest possible correlation ($R^2 \approx 0.98$) was considered by reduction of the number of points (minimum 10 points) the yield pressure of the 60%w/w GMS was the highest. This formula had a curve of three sections. The first and third had a higher slope, which could result in the lowest yield pressure. However, these sections were not considered for they were assumed to occur during the pellet rearrangement and elastic deformation sections respectively.

GMS content	Yield Pressure		Kawakita compressibility constant	
	R^2	1/K (MPa)	R^2	b (MPa^{-1})
0%	0.99	53.76(2.5)	0.9867	0.0166(0.002)
20%	0.99	46.51(2.7)	0.999	0.0403(0.006)
40%	0.98	52.35(4.0)	0.9992	0.0997(0.010)
60%	0.97	81.3(6.0)	0.9981	0.0767(0.004)

Table-3.1.4:- The Effects of the amount of GMS on yield pressure form Heckel plot and the Kawakita compressibility constant. The values in parenthesis indicate the standard deviation.

A curve was again drawn to relate the relative density of the pellet bed in the die with the applied pressure in an attempt to identify the point where the pellets failed (Messing et al. 1982). The correlation values increased as the linear curves were not broken with the increase of the GMS content in the formulations (Fig-3.1.9).

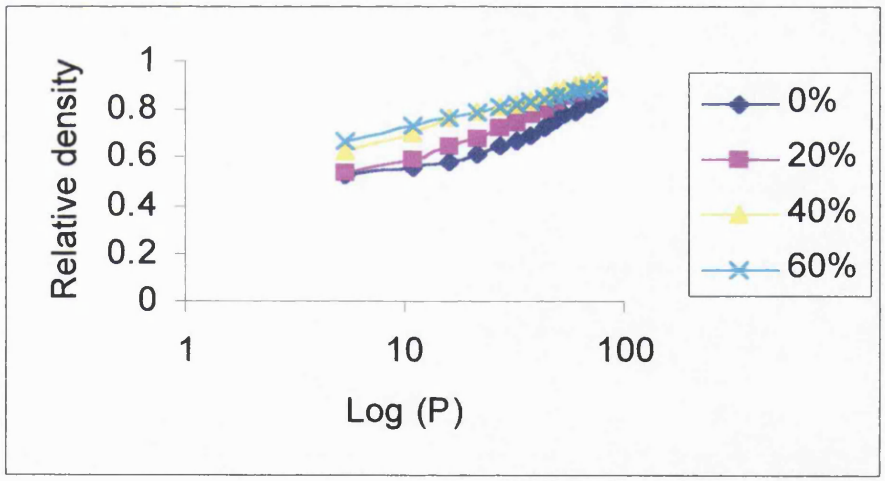


Fig-3.1.9:- The effect of the amount of GMS in MCC/GMS pellets on the compaction mechanism of 700 mg pellets of 1.0-1.18mm size fraction as measured in terms of relative density versus logarithm of pressure

This indicated the reduced propensity of failure of the pellets during compression. The previously determined deformabity of the these pellets was in agreement with this finding. The deformable ones had no any indication of pellet failure during compaction, which was illustrated by the linear curve. For the less deformable pellets (0% and 20%w/w GMS), however, the linear curves were broken at a certain point showing formation of cracks or total failure of the pellets according to Messing et al. (1982). Furthermore, the pressure at which

the MCC pellets failed was shown to be greater than that of 20%w/w GMS.

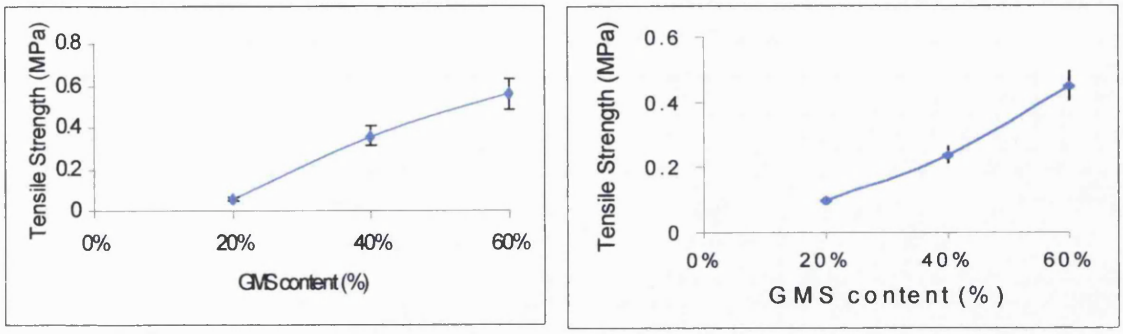
3.1.4 THE PROPERTIES OF THE COMPACTS

Pellets of the same mass were compressed to tablets of similar dimensions (2.2.4.1A) to provide tablets with the same density. Pellet-beds of the same bulk volume, as set by the die volume, were also compressed to tablets (2.2.4.1.C). The dimensions of both these sets of compacts were measured immediately after ejection from the die. There was almost no difference in the diameter of the tablets from that of the respective die diameter. The out of die tablet thickness, however, had a wide variation.

The higher the percentage of the GMS, the thicker were the tablet produced (an increase of 6.4% was observed with the increase of GMS form 20% to 60%w/w). In compressing these tables, it was noted earlier that, the higher the GMS content, the higher was the compressing pressure. It should be noted that the Instron, where the pellets were compacted, had minimal degree of deformability of its punches and frame at the range of pressures these tablets were produced. This was established by measuring the displacement while compressing the two punches against each other in the pressure ranges used. Moreover, the necessary correction was made by subtracting the displacement due to deformation of the punches. Thus, the main reason for the change in the dimension could be the instant elastic recovery of the compacts during decompression. The results of Heckel plot agrees with this assumption. It indicated that the pellets with a higher GMS content were compressed and deformed elastically at the end of the compression cycle, as was illustrated by the non-linear portion of the upper curve.

The strength of the tablets was determined 72 hours after production using a diametral compression test (2.2.4.2). In both cases, the strength of tablets produced from pellets having a higher amount of GMS were greater (Fig-3.1.10a&b), the difference being statistically significant ($P<0.01$). The rate of increase in strength with the increase of the amount of GMS was linearly proportional in both type of tablets (i.e. those produced from the same mass and those produced from the same volume). This indicates the ability of GMS to increase the inter-pellet connections to form rigid structures. The higher degree of deformability of these pellets enabled the reduction of the inter-pellet porosity that brought the surfaces of the pellets to closer proximity, which enhanced the interaction at surface level, consequently the formation of rigid structures. These produced rigid tablets which needed a greater force to

initiate and propagate cracks to ensure failure during the diametrical compression test. This could be due to their smooth and less porous compacts (Plate-3.1a, p78).



(a) (b)

Fig-3.1.10:- The effect of the amount of GMS in the MCC/GMS pellets, on the tensile strength of their tables produced(a) from the same mass and to the same volume by Instron (b) from the same bulk volume by eccentric tableting machine .

The volumetric elastic recovery, as measured form the difference in dimensions of the tablet immediately after ejection and after 72 hours storage at ambient temperature and humidity, was found to be related with the amount of GMS in the formulations (Fig-3.1.11). Pellets with a higher amount of GMS showed a greater volumetric elastic recovery.

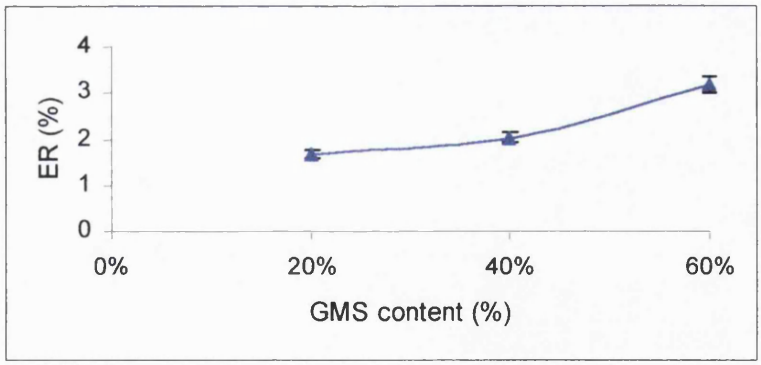


Fig-3.1.11:- The effect of the amount of GMS in MCC/GMS pellets on the volumetric elastic recovery of their 700 mg compacts as measured after 72 hours.

The bed of pellets which was compressed by a greater pressure (Fig-3.1.6), and compressed to a greater extent (compressibility) showed a greater volumetric elastic recovery. This could be due to the reversible elastic deformation created by a higher compressing pressure. The higher the GMS content, the lower was the density of the pellets. When one compresses the same mass of all these formulations to the same tablet dimension, it would mean that they are compressed to different solid fractions. The less dense pellets would be compressed to a lower porosity, which nearly reached solid fraction of 1. In some cases the compact appeared as to

have been compressed such that the elastic deformation of the solid structure recovered rapidly during decompression. Further recovery with the extended time was limited (Fig-3.1.11).

3.1.5. COMPARISON WITH POWDER COMPACTS

Seven hundred milligram of the 60%w/w GMS content pellets and powder mix of the same composition were compacted to tablets of the same thickness (2.2.4.1A). Tablets were also made form the same bulk volume of the pellets or powder mixture (2.2.4.1C). The compaction mechanism and properties of the tablets (2.2.4.2.1-2) were analyzed.

The pressure needed to compress pellets of the same mass to the same tablet thickness was greater than that of powder mixture by about 5MPa. This indicates that a greater force was needed to deform the structure of the pellets to obtain tablets of the same dimensions. As previously noted, the porosity of the pellet compact was very low, indicating a nearly complete elimination of the void which was at least 26% when the "spheres" were arranged in the most packed rhombohedral manner. The smooth surface of the tablets, with no sign of the pellet boundaries, could be taken as a proof to this assumption (Plate-3.1a, see p-178). The out of die porosity of the tablets formed from pellets and the powder mixture did not have a significant difference. Their difference was only by less than 0.5%. This shows the formation of a similar overall structure after compaction.

The mechanism of compaction plotted as a pressure/displacement curve (Fig-3.1.12) illustrated that the crucial pressure needed to compact the pellets or powder mixture was exerted on the last 1 mm thickness reduction of the compacts. The platen was displaced for about 4 mm without any difference in the pressure in both formulations. Neither needed a pressure more than 10MPa. This indicated the ease of deformability of the GMS-rich powder mixture and pellets. Due to its higher packing ability (i.e, relatively lower compressibility) the pellet-bed was the first to reach to the final tablet thickness, while it took a longer time to rearrange the powder particles, hence to build the pressure needed to compress them to a tablet of the same thickness.

The work of compaction (area under the curve), did not seem to have a large variation in the compaction of the powder or pellet-bed. That was because the difference in the curve was

only at the part where insignificant pressures were registered. This indicates, the low strength of the GMS-rich pellets and their significant degree of deformability, which enabled them to be comparable with a similar powder mixture in terms of compaction mechanism.

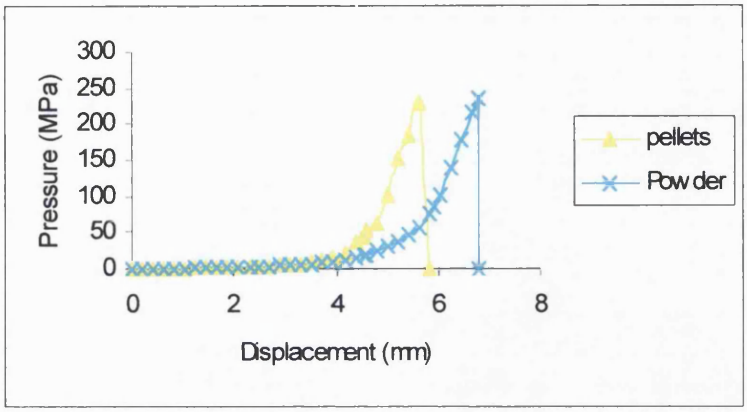
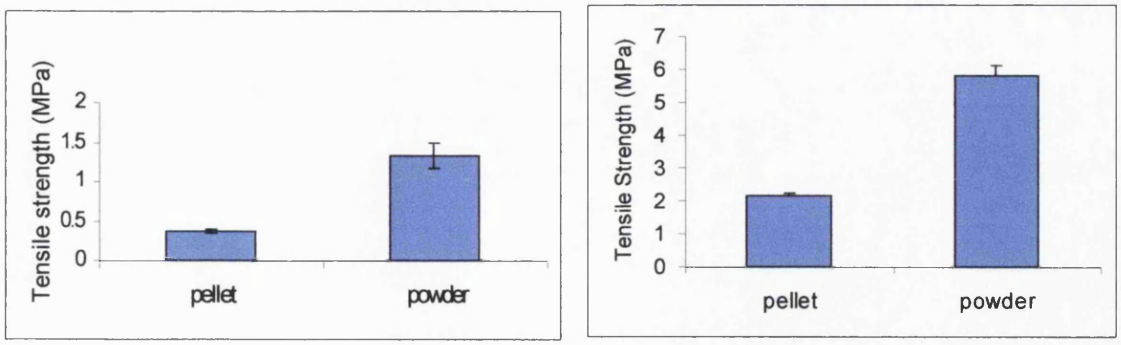


Fig-3.1.12:- Comparison of the compaction mechanism of tablets produced from 700 mg pellets of 1.0-1.18mm size fraction and 700 mg of powder having the same composition (60%w/w GMS in MCC/GMS mixture).

These compacts had different strengths as measured by diametral compression. The values of the strength of the tablets prepared from the powder mixtures were about three times higher than those of pellet compacts in both of the tableting machines (Fig-3.1.13a&b). This means, the tablets from the same mass to the same tablet dimensions, and the tablets from the same original bulk volume had a similar relation in terms of the strength of the powder and the pellet compacts.



(a) *(b)*

Fig-3.1.13:- Comparison on the tensile strength of (a) eccentric tableting machine (b) Instron tablets produced from 700 mg pellets of 1.0-1.18mm size fraction and 700 mg of powder having the same composition (60%w/w GMS in MCC/GMS mixture).

The main reason for such discrepancy in the strength of the tablets seems the difference in the nature of the constituents. The powder, had to be mixed, wetted, extruded, spheronized and

dried to be changed to pellets. These all processes may have affected their rigid tablets forming ability. Also, the variation in particle size and size distribution, consequently the difference in surface area could be another reason. In the eccentric tableting machine the mass of the tablets was determined by the die volume. As a result the low bulk density of the powder mixture, produced lighter (by 15%) and slightly more porous (by 6%) tablets. However, these did not affect the relative strength of the tablets considerably (Fig-3.1.13).

The dimensions of the tablets produced form the same mass in an Instron were measured immediately after their ejection and again after 72 hours of their storage at ambient temperature and humidity. From the difference of these dimensions, the volumetric elastic recovery was calculated and was found to be approximately the same. The insignificant difference in the elastic recovery again proved the total change in the structure of the pellets. After compaction, the pellets and the powder-mix were plastically deformed in the same way. The loss of plasticity of the GMS during pelletization process could then be assumed to be trivial.

From this work, it is possible to conclude that, GMS-rich powder mixture and pellets exhibit a similar mechanism of compaction, volumetric elastic recovery and final tablet porosity. This was attributed to the inherent and unchanged deformability of GMS. The difference in the strength was, however, presumably due to the effect of the pelletization process on the surface nature of the pellets mainly on the MCC part of the mixture. This was proved by the failure of th pellet compacts through the boundaries of the pellets during diametrical compression (Plate 3.1b).

3.2 THE EFFECTS OF LACTOSE

3.2.1 PRODUCTION AND CHARACTERIZATION OF PELLETS

The intent of this section is to observe the step wise change in the structural and mechanical property of pellets (2.2-3), their compaction mechanism (2.2.4.1), and the properties of their compacts (2.2.4.2) with the gradual increase in the proportion of lactose in the MCC/lactose pellets (Table-3.1). The proportions of the excipients and water content of the formulations was experimentally found to be within the limit in which pellets could be formed by a standard extrusion and spheronization process (section 2.2.1).

The attempt to produce pellets from 100%w/w lactose as a dry mass was not successful. A lumpy material was first extruded with a small extrusion force. The force gradually surged to extrude the drier mass left in the barrel. Due to the none uniform distribution of water, there was no steady state flow stage as observed by Harrison et al. (1985a), and it was not possible to produce spheres as attested by Schwartz et al. (1994) due to the agglomeration of the very wet extrudates. Even in 60%w/w lactose content, the formulation had to be optimized. In this formula, water equal to 10% of the mass of lactose was added during wet massing, and a five more minutes was added to the spheronization time (total of 20 minutes).

The extrusion force of the wet mass increased with the increase of the amount of lactose in the dry mass (Fig-3.2.1). The higher the lactose content the higher was the rate of increase of the extrusion force. More than one reasons could be stated. MCC is more plastic than lactose, so it can deform and squeeze through the die without excessive extrusion force. The main reason, however, could be the variation in the moisture content of the formulation as a whole. The higher the lactose content, the lower was the overall water content of the formula (i.e. 50%, 40%, 30%, 27% w/w water to the dry mass for formulations containing 0%, 20%, 40% and 60%w/w lactose in the dry mass respectively), which reduced the die lubrication (Pinto, 1982) and increased the upstream pressure loss (Harrison et al. 1987)

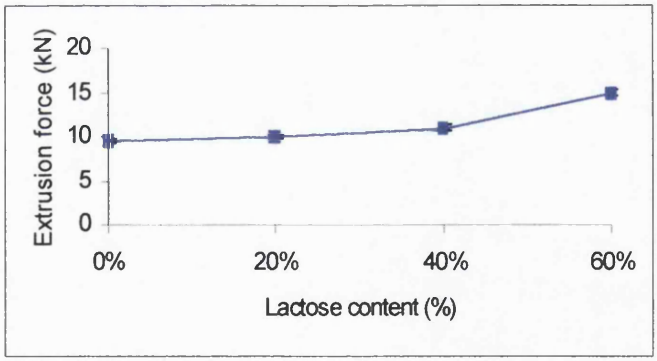


Fig-3.2.1:-The effect of the amount of lactose in MCC/lactose wet mass on the extrusion force through die of 1.0 mm diameter and 5mm long.

(Table-3.2.1) summarizes some structural properties of the pellets. There was a slight increase in the median diameter of the pellets with the increase of the lactose content, although marginal. However, the interquartile range decreased with the increase of the lactose content steadily, opposite to the report by Schwartz et al (1994). This could be due to the increase of the surface stickiness of the pellets with the increase of the water soluble excipient, lactose. This could have reduced the fine particles and has incorporated them to the bigger ones to

increase their size.

Although to a small extent, the bulk and tapped densities of the pellets was observed to decrease with the increase in the amount of lactose content. The Hausner ratio implies the small difference between the bulk and tapped densities in each formula, due to the good packing characteristics of the spheroids. The inefficiency of the technique which induces friction (Podczeck, 1998 and Abdullah and Geldart, 1999) could be one of the reasons to reduce the difference between the bulk and tapped densities. The difference in their surface nature, as indicated by the difference in open pores (as discussed later), could have affected the slippage of the pellets over each other to re-pack. The formula with a highest interquartile range was highly packed reflecting the effect of the size distribution as well.

Structural and Mechanical Properties of Pellets	Amount of lactose in the dry mass (%)			
	0%	20%	40%	60%
Median particle diameter (mm)	0.95	0.98	1.04	1.06
Interquartile range (mm)	0.34	0.28	0.26	0.15
Bulk Density (g/cc)	0.88 (0.07)	0.91(0.09)	0.8(0.09)	0.77(0.06)
Tapped Density (g/cc)	0.94(0.08)	0.95(0.1)	0.88(0.09)	0.83(0.09)
Hausner ratio	1.06(0.2)	1.05(0.1)	1.10(0.15)	1.08(0.1)
Apparent pellet density (g/cc)	1.42(0.09)	1.41(0.08)	1.51(0.07)	1.55(0.06)
Apparent porosity (sealed) (%)	8.08(0.9)	8.62(0.9)	2.33(0.3)	1.81(0.2)
Effective Pellet density (g/cc)	1.74 (0.2)	1.59(0.3)	1.55(0.3)	1.42(0.2)
Shape factore, e_R	0.59(0.02)	0.65(0.02)	0.63(0.03)	0.52(0.06)
Aspect ratio	1.09(0.2)	1.05(0.1)	1.06(0.2)	1.13(0.2)
Circularity	0.91(0.08)	0.87(0.08)	0.87(0.09)	0.88(0.09)
Projected sphericity	0.89(0.08)	0.90(0.10)	0.90(0.10)	0.87(0.09)

Table-3.2.1: The structural properties of MCC/lactose pellets of 1.0-1.18 size fraction. The values in the parenthesis indicate the standard deviation.

The value of the porosity determined by the helium pycnometer (sealed pores) decreased with the increase of the lactose content. The effective pellet density decreased with the amount of lactose. Both indicate that the higher the amount of lactose the higher the percentage of the open pores. In its higher content, MCC could presumably seal the surface of the pellets by

shrinkage during drying (Kleinebudde et al.1994a) and may have made the pellets to have a higher internal porosity. Similarly, Wang et al (1995) reported that the porosity of 80% w/w MCC in the MCC/lactose pellets to be about 4 times greater than that of 80%w/w lactose content pellets.

It was possible to claim that the pellets were spherical in shape, although at the highest lactose content the value of the shape factor was lower by 0.084 than that limit of 0.6 proposed by Podzceck and Newton (1994). The formula with the highest two dimensional shape factor was found to be that with the incorporation of 20%w/w lactose. This could be considered the optimum formula to improve the shape and surface nature of such combination unless other factors are changed. In their factorial designed experiment Pinto et al. (1993) compared indirectly some properties of pellets of different MCC to lactose ratio keeping all other variables constant. They compared 3:4 MCC to lactose ratio with that of 5:4 and observed a better sphericity on pellets having a higher lactose content.

3.2.2 MECHANICAL PROPERTIES OF THE PELLETS

An increase in lactose content in the MCC/lactose pellets resulted in decrease in the crushing load, hence, the tensile strength of the pellets (Fig-3.2.2).

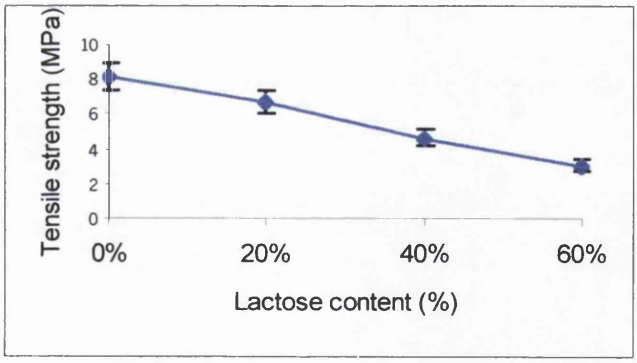


Fig-3.2.2:- The effect of the amount of lactose in MCC/lactose pellets, on tensile strength of pellets of 1.0-1.18mm size fraction.

At the highest lactose content, all the pellets broke instantly (snapped) when compressed, while at 40%w/w lactose 23 of the 30 pellets snapped, whereas none of the MCC pellets snapped, instead compression continued after the first force peak in the force/displacement curve. This shows the brittleness of lactose as noted by Newton et al. (1993). Similarly, BinBaie et al. (1996) reported that the tensile fracture stress of Avicel PH 101 was more than

twice that of lactose using compacted beam specimens and extrapolating the values to that of zero porosity. This could be due to the ease of crack propagation of the specimen with the increase of lactose content. The higher prevalence of open pores noted earlier could also be considers as flaws which initiated such cracks. However, as will further be investigated in the following section and chapters, the effect of the total water content in the formulations seems to be the most important factor as noted by Pinto et al. (1993).

One-way analysis of variance (Table-3.2.2) illustrated the significance of the decrease in tensile strength, compared to that of MCC pellets. All the other formulae also had a significant strength difference between themselves, as examined similarly. The rate of decrease in strength was linearly proportional to the content of lactose. An R^2 value in the linear regression was found to be 0.9947. This implies the presence of a factor proportional to the lactose and water content in the formulations.

Lactose content.	Mean tensile strength (MPa)	STDEV	MS	F	P
0%	8.17	1.61	-	-	-
20%	6.73	0.94	31.31	18.03	<0.001
40%	4.61	0.56	190.22	130.6	<0.001
60%	3.06	0.55	391.61	270.4	<0.001

Table-3.2.2:- Results and ANOVA of the effect of lactose proportion on the tensile strength of MCC/ lactose pellets of 1.0 - 1.18 mm size fraction. d.f.=1.

In a different experiment, pellets of the same size fraction having 75/25 lactose to MCC proportion were produced by a standard extrusion and spheronization process using different proportion of water to the dry mass, namely, 25%, 40%, and 47%w/w. The tensile strength of the resultant pellets was observed to increase with the increase of the proportion of water in the formulations. Increasing the water content to the highest proportion in this work, increased the strength of the pellets by about 30%. A similar result was observed with pellets having 50%w/w lactose in the dry mass. Here, the range of water added in relation to the dry mass was, 50%, 55%, and 60%. The tensile strength of the pellets increased with the increase of the proportion of water. This was statistically significant ($P<0.05$). The main reason for the increase of the strength of the pellets was the increase in the proportion of dissolved and re-

crystallized lactose particles during the process of wet massing and drying respectively. In all cases the water content was less than that needed to dissolve the whole lactose powder present in the formulations (1 part of lactose dissolves in 4.63 parts of water). However, with the increase of the water content, the proportion of dissolved, and re-crystallised pellets increased. Hence, stronger solid bridges, which made the pellets stronger may have been formed.

In the formulations containing 20%w/w or less amount of lactose, the addition of extra 10%w/w water during wet massing resulted in agglomeration of the pellets during the spheronization process. This indicates that if the extra water added (compared to the aforementioned proportion) in the formulation is more than that which could dissolve the lactose, it migrates towards the surface of the pellets during spheronization process as a result of the centrifugal force. Thus the pellets stick to each other and agglomerate. Therefore, the sensitivity of "lactose-pellets" to water content is not merely related to the absolute water content, but to its proportion to the "unretained" water in the MCC structure, which was reported to act as a sponge (Fielden et al. 1993). Moreover, the way lactose was mixed with MCC and water showed difference in tensile strength of the pellets produced. One part of lactose (12.5%) was first dry mixed with seven parts of MCC for 5 minutes then seven parts of water was added slowly in the first experiment, while in the second experiment one part of lactose was dissolved in the seven parts of water then mixed with the seven parts of MCC. The same experiment was carried out for the 20%w/w lactose content of the dry mass, which is a little more than that of the solubility of lactose in the water. The tensile strength of the pellets produced by first dry mixing the powders was found to be significantly lower in both 12.5% and 20%w/w lactose contents ($P < 0.05$). One of the possible reasons could be the difference in the distribution of the two excipients in the dried pellets.

It is difficult to understand as to how lactose is affecting the strength of the pellets, as its distribution within the pellet after drying is not clearly known. So it could only be assumed that lactose was reducing the amount of water which, according to Millili et al. (1990), enhanced the hydrogen bonds between the MCC particles, hence, the propagation of the crack during stress might have become easier. The migration of water to the surface of the pellets during drying may possibly include lactose, for it is a soluble material. This could produce a porous surface rich in crystalline lactose that induce crack initiation and propagation

respectively. The increase in the strength with the addition of extra water could be due to more lactose dissolution and re-crystallization and formation of strong solid-bridges during the evaporation of the water in drying.

Some Mechanical Properties of Pellets	Amount of lactose in the dry mass (%)			
	0%	20%	40%	60%
Weibull-constant	9.268	7.393	5.038	3.328
Weibull-modulus	4.812	5.484	6.938	4.345
Shear Strength (MPa)	2.96 ±0.4	2.27±0.3	1.82±0.2	1.39±0.2

Table:-3.2.3: Some mechanical properties of MCC/lactose pellets of 1.0-1.18 mm size fraction.

The shear strength of the pellets was also observed to decrease with the increase of lactose content in the formulations (Table-3.2.3). The shear strength had the same proportion to the respective tensile strength, which was about 2.5 fold. This agrees with Adams et al. (1994) suggestion of characterizing the strength of agglomerates from their uniaxial compression studies. Compared to the tensile strength, the shear strength of the formulations was lower, indicating the possibility of failure of the pellets by shearing during compaction. With the exception of 60%w/w lactose content, the Weibull-modulus was observed to increase with the increase of the amount of lactose in the formulations (Table-3.2.3), implying the decrease in the relative brittleness of the pellets. At the highest lactose content, however, an extra water was added in the wet mass, that could have affected the presence and distribution of the flaws on the pellets.

With the increase of the amount of lactose, less force was needed to compress the pellets by a unit displacement. The inverse of the slope of the force/displacement curve produced during the diametral compression has been presented as "deformability" on (Fig-3.2.3). In other words pellets with lower amount of lactose (higher amount of MCC) were pressed for a shorter distance (deformed) by the same unit of force. The addition of some more water in the wet mass of 60%w/w lactose seemed to have affected the pellets, for it produced less deformabile pellets than 40%w/w lactose (Fig-3.2.3).

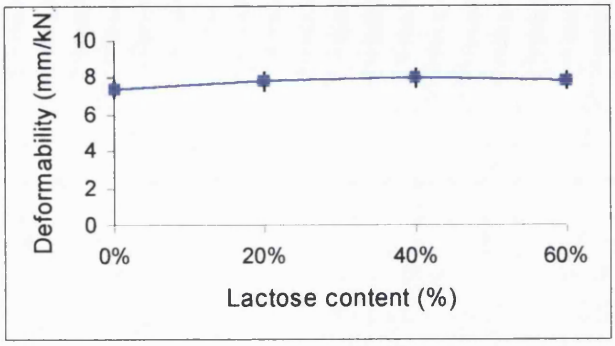


Fig-3.2.3:- The effect of the amount of lactose in MCC/lactose pellets on the deformability of pellets of 1.0-1.18mm size fraction.

The linear strain of the pellets decreased with the increase in the amount of lactose in the formulation (Fig-3.2.4). This shows the brittleness of the pellets with increase in the amount of lactose. The pellets snapped quickly under test, presumably due to the higher proportion of flaws (pores) and faster propagation of the crack with the increase of lactose content. The reduction in the strength could also be the reason for their quick failure before they were strained to a greater extent. Newton et al. (1993) concluded that lactose was more brittle in character than MCC from an assessment of the tensile and compressive strength of cylindrical compacts of lactose and MCC by diametral compression and axial loading and determination of the ratio of the compressive to the tensile strength.

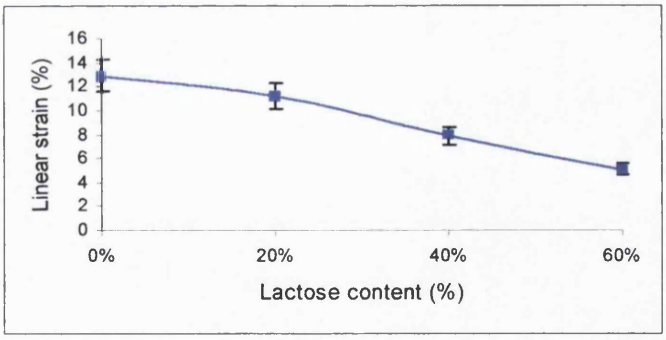


Fig-3.2.4:- The effect of the amount of lactose in MCC/lactose pellets on the linear strain of the pellets of 1.0-1.18mm size fraction.

The 'elastic modulus' of the pellets decreased slightly with the increase of the lactose content (Fig-3.2.5). This again shows a slight reduction in the rigidity of MCC pellets with the incorporation of lactose. However, the very low difference in absolute value of the 'elastic modulus' that ranged between 160 and 167 MPa. questions the validity of the technique. At 60%w/w lactose content, there was an increase in the 'elastic modulus' value which could be again due to the effect of the extra water added to extrude the formulation.

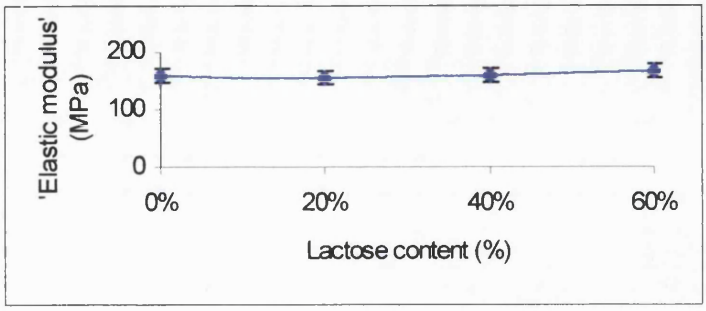


Fig-3.2.5:- The effect of the amount of lactose in MCC/lactose pellets on the 'elastic modulus' of the pellets of 1.0-1.18mm size fraction.

At this stage it is possible to conclude that a stepwise addition of lactose to MCC : water pellets decreased tensile strength and linear strain of the pellets, while it increased the extrusion force, porosity, and sphericity of the pellets up to an optimum percentage. Its effect on deformability and 'elastic modulus' was limited. In addition, the strength of the pellets was affected by the quantity of water in the formulations as a whole, as well as the way lactose was added in the mixture.

3.2.3 COMPACTION MECHANISM OF THE PELLETS

Seven hundred milligrams of pellets of each formulation containing different proportions of lactose were compacted to the same tablet thickness as described in section (2.2.4.1A). Lactose and MCC particles have a slight difference in their apparent particle density. Thus in this process, the pellets could be regarded as they were compressed to tablets of the same final solid fraction or porosity. However, they had different tapped and effective densities, which varied the pre-compression pellet-bed thickness. The higher the lactose content, the lower was the tapped and effective densities, hence, the higher the pellet-bed thickness before compression. This resulted to different extent of compressibility (reduction in volume during compression) of the pellet-beds (Fig-3.2.6).

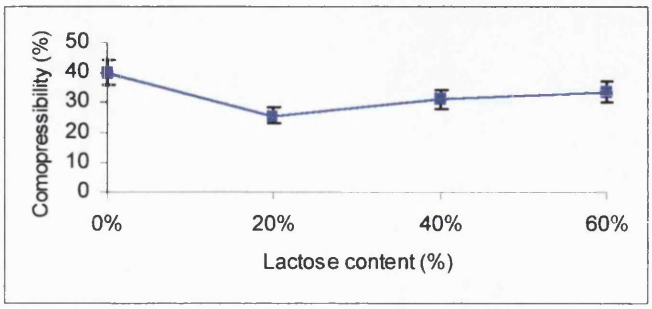


Fig-3.2.6:- The effect of the amount of lactose in the MCC/lactose pellets on the compressibility of the pellets of 1.0-1.18mm size fraction.

The higher the lactose content the greater was the compressibility, as it was expressed in percentage decrease in compact thickness from the thickness derived from a tapped density, or that at the onset of the compressing force. The lactose-rich pellets had to undergo a radical structural change to be compressed to the same tablet thickness. The smoothness of the surface, the fracture of the pellets observed in the SEM (Plate-3.2.a&b, see p-178) confirms this results. Moreover, the need of different forces for compression of pellets of the same mass to the same pre-set tablet thickness supports this argument. With the increase of lactose content in the formulation there was an increase in compression pressure required (Fig-3.2.7).

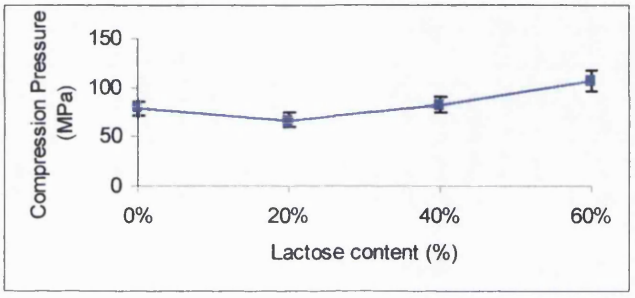


Fig-3.2.7:- The effect of the amount of lactose on the compression pressure of 700 mg of MCC/lactose pellets of 1.0 -1.18 mm size fraction to tablets of the same dimensions.

The increase in pressure to compress the same mass of pellets having different lactose content was linearly proportional to the percentage of lactose as a dry mass having R^2 of 0.98. Lactose-rich pellets needed a greater pressure, however, the pressure needed to compact MCC pellets was higher than that for 20%w/w lactose pellets. This shows that comparison of the presence and absence of lactose in the formulations is different from the change in the relative amount of lactose on those formulations containing lactose. The strength of the MCC pellets could be responsible for such discrepancy. Nevertheless, since MCC pellets were not able to form compacts, further analysis will only deal with comparison of the three formulations having a different lactose content.

Wang et al. (1995) produced pellets with formulations containing 20% anhydrous lactose and 80%w/w microcrystalline cellulose as well as 20%w/w microcrystalline cellulose and 80%w/w anhydrous lactose. They compacted their pellets by compressing them to a solid fraction of 0.8 and 0.87. They reported that at the lower range of solid fraction, 0.80, lactose-rich pellets were much more compactable and compressible. They needed only 89MPa compared to160 MPa for MCC-rich pellets to reach a solid fraction of 0.80. This confirms the higher

compressibility of the lactose-rich pellets. However, as the plot of pressure/platen displacement profile of the pellet beds illustrated, the pressure of lactose-rich pellets at a lower solid fraction of the compact could be less than that of MCC pellet. This reflects the strength of the MCC pellets before the yield point.

The increase in lactose content increased the work of compaction, as could be expressed by integrating the area under the curve (Fig-3.2.8). This was again of the same trend to that of compressibility and compaction pressure. The mechanism of compaction of the formulations containing lactose seems to be roughly similar at higher lactose contents, as their curves in the pressure/ displacement curve are nearly superimposed. The difference in the extent of their compressibility, however, affected different pressures, hence resulting in different works of compaction.

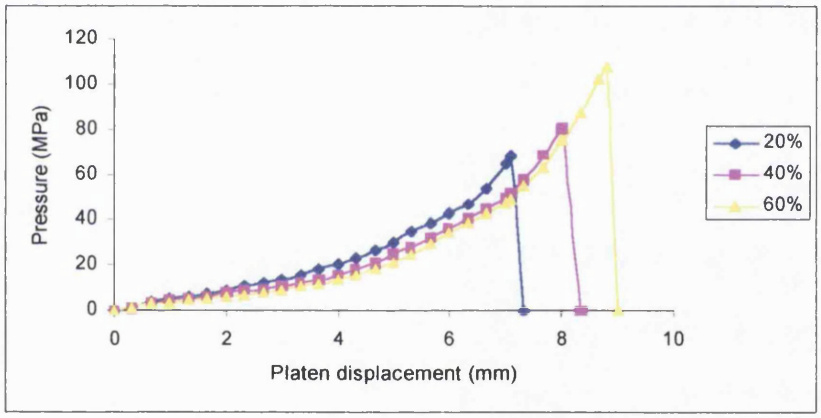


Fig-3.2.8:- The effect of the amount of lactose in MCC/lactose pellets on the compaction mechanism of 700 mg pellets of 1.0 -1.18 mm size fraction.

Form these results, one can understand the sequential interdependent effects of lactose on porosity, compressibility, compression pressure and work of compaction. With the increase of lactose content, the porosity of the pellet bed was increased. This can be noted from the reduced bulk and tapped density of the pellets with the increase of lactose in the MCC/lactose mixture. This illustrates that a relatively greater compressibility is needed to compact them to the same tablet thickness or the same solid fraction. This was achieved by a higher compressing pressure which might have deformed or crushed the pellets to the same tablet thickness. The increase in compressibility means extension of the compaction process to a greater displacement, and the higher compression pressure also increase the area under the pressure/displacement curve. As a result a higher work of compaction is needed to compress pellets of a higher lactose content. Therefore, it is possible to conclude that the work of

compaction is a function of compressibility of the bed and the compression pressure needed.

From the inverse value of the linear upper portion of the slope of the Heckel plot (in the range of 50 to 100 MPa), the yield pressure of the pellets was determined as described in section (2.2.4.2). A decrease in the slope of the Heckel plot was observed with the increase of lactose content in the formulations (Fig-3.2.9).

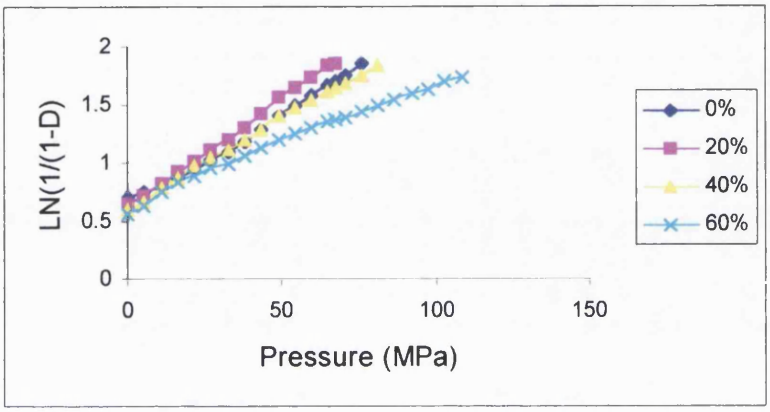


Fig-3.2.9:- The effect of the amount of lactose in MCC/lactose pellets on the Heckel plot derived from the compaction of 700 mg pellets of 1.0 -1.18 mm size fraction.

The yield pressure above which plastic deformation occur increased with the increase of lactose content (Table-3.2.4). This was in agreement with the conclusion of Hersey et al. (1973) that lactose consolidates primarily by fragmentation followed by plastic deformation.

Lactose content	Yield Pressure		Kawakita compressibility constant	
	R^2	1/K (MPa)	R^2	b (MPa^{-1})
0%	0.99	53.76(4)	0.9867	0.0166(0.002)
20%	0.99	48.54(5)	0.9866	0.026(0.004)
40%	0.99	60.98(5)	0.9987	0.0315(0.007)
60%	0.99	87.72(9)	0.9992	0.0329(0.006)

Table-3.2.4:- The effect of the amount of lactose on yield pressure form Heckel plot and the coefficient of compressibility from Kawakita equation. The values in the parenthesis indicates the standard deviation.

In their study to compare MCC pellets with lactose-rich MCC/lactose pellets, Schwartz et al. (1994) used the Heckel plot. They measured the out-of-die relative densities of the tablets. The results for their modified equation were computed by using nonlinear regression, from

which they claimed that they were able to identify the viscoelastic resistance, the onset of plastic flow, and the fracturability of the pellets. Their MCC/lactose pellets were primarily lactose. This bead system showed a reduction in viscoelastic resistance. The pellets underwent shearing more easily and thus exhibit a greater degree of fracture, as later was proved by photomicrograph. In this work, the MCC-rich pellets yielded earlier to preferentially deform, while the lactose-rich pellets were observed to fracture (Plate-3.2.b, see p-178) as their yield pressure was relatively higher (Table-3.2.4).

The plot of the relative density versus the logarithm of the compaction pressure as proposed by Messing et al. (1982) indicated the failure of the pellets by fracture during compaction. The pressure at which the linear curve flexed was different for pellets from different lactose content (Fig-3.2.10).

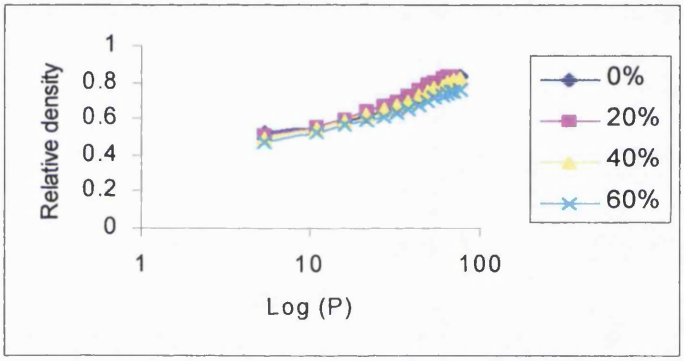


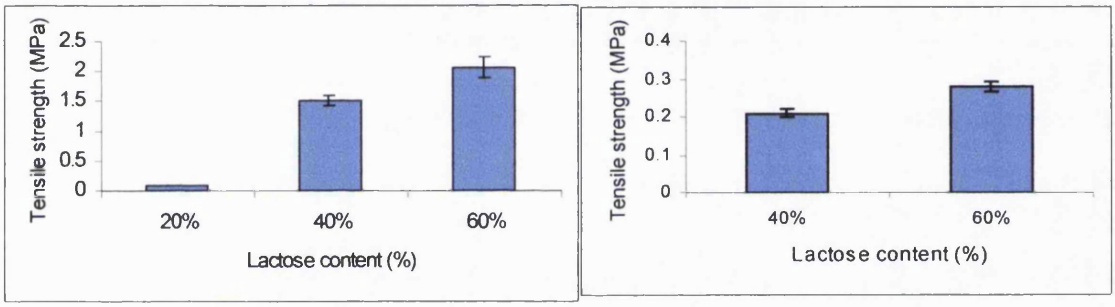
Fig-3.2.10:- The effect of the amount of lactose in MCC/lactose pellets on the compaction mechanism of 700 mg pellets of 1.0 -1.18 mm size fraction as measured in terms of relative density versus logarithm of pressure.

The results showed that the compression pressure at which the pellets failed, increased with the increase of the lactose content. This is in the reverse order of the strength of the individual pellets. This could be due to the transmission of the stress laterally to the neighboring pellets before failure by fracture during uniaxial compression. However, these results showed that all the pellets failed at some point, unlike the "GMS-pellets" which produced uninterrupted linear curve.

3.2.4 THE PROPERTIES OF THE COMPACTS

It was not possible to produce tablets from pellets which contained 0% and 20%w/w lactose at the specific setting of the Instron mentioned in section (2.2.4.1 A). The main reason could be the surface nature of these pellets which failed to cohere and produce rigid tablets,

although they were compressed with a comparable pressure to the other formulations. Pellets having 40% and 60%w/w lactose content were able to produce tablets of different dimensions. Tablets with higher lactose content had a greater tablet thickness, although only by 2%. The strength of these tablets, as measured by diametral compression, was affected by the content of lactose in the pellets. Pellets with a higher lactose content produced compacts of higher tensile strength (Fig-3.2.11-a). A mass of pellets from the different formulations having the same bulk volume were compressed to tablets using an eccentric tableting machine, Manesty F3, (2.2.4.1C). An immediate measurement of the dimensions and strength of the tablets was performed. Pellets containing less than 20%w/w lactose, did not produce tablets while those containing 40% and 60%w/w lactose produced strong tablets (Fig-3.2.11-b).



(a) *(b)*

Fig-3.2.11:- The effect of the amount of lactose in the MCC/lactose pellets, on the tensile strength of their tablets produced (a) from the save bulk volume by eccentrict tableting machine (b) from the same mass and to the same volume by Instron.

All MCC pellets prepared with water and having an average 1 mm diameter never produced compacts, while the granules produced form the same wet mass produced compacts of reasonable strength. There have been similar reports from many other researchers. Schwartz et al. (1994) reported that the non-compressible MCC pellets formed soft tablets, MCC/lactose beads (mainly lactose), however, formed hard tablets. That was because, their lactose-rich pellets fragmented and did cohere concurrently in the process of tablet formation. Wang et al. (1995) observed a weak compact tensile strength between the MCC-rich pellets while lactose-rich pellet compacts were stronger. The pellets in the weak compacts did not form a network of connections, they reported after visually inspection revealed that the beads were not fragmented, but simply distorted. Even after their increase in the compression pressure to alter pellet structure, it contributed very little to inter-pellet coherence, presumably

due to the poor compactibility of the MCC-rich pellets. They ascribed the poor compactability of the MCC-rich pellets to the loss of plasticity of MCC during the extrusion/spheronization process. As a result the strong pellet surface might confine the fibrous nature of MCC and limit the mechanical interlocking effect of the MCC-rich pellets.

To summarize, this work revealed that the higher the compressing pressure and the greater the compressibility of the pellet bed the stronger the compacts become. Moreover, the surface nature of the pellets and their strength had a profound effect on the ability of the formation of the inter-pellet interaction and creation of new surfaces that can form rigid tablets.

Seventy two hours after production, the dimensions of the tablets were measured again and compared with those measured immediately after ejection. The volumetric elastic recovery of the tablets was then calculated from the difference of these dimensions. The objective of the elastic recovery test was to describe qualitatively the viscoelastic properties of the compacted pellets. A longer time period was selected compared to that used by Wang et al. (1995) for a complete relaxation to occur. Pellets with 60%w/w lactose had a relatively higher elastic recovery than those of 40%w/w lactose, although to very small extent (1.5%).

Wang et al. (1995) observed that lactose-rich pellet compressed to 0.80 solid fraction had more elastic recovery than those compressed to 0.87, while the opposite was true for MCC-rich pellets. Generally, the volumetric elastic recovery of compacts of MCC-rich pellets was more than twice that of lactose-rich pellets. The authors suggested that the lactose-rich pellets showed a tendency towards a lower energy recovery, which indicated a decrease in viscoelastic property. This shows that the MCC has passed the range of pressure at which the plastic deformation could occur at a far lower pressure and had started to deform elastically. However, lactose had to be compressed to higher extent to ensure a permanent deformation or failure in fracture. Moreover, in lactose-rich pellets, the energy derived from a higher compression stress, could have predominantly been consumed by the formation of a network to produce rigid structures via irreversible structural change or failure of the pellets in the compact. On the other hand, the results in this work highlighted that at a lower compaction pressure, neither the lactose-rich pellets were sufficiently compressed to totally fail by fracture nor were they compressed above their yield strength to deform plastically. As a result they

were able to relax elastically with time. Pellets with higher MCC content (60%w/w), however, were deformed plastically and had a lower elastic recovery.

3.2.5 COMPARISON WITH POWDER COMPACTS

To aid for the understanding of the compaction mechanism and the properties of the compacts of 60%w/w lactose content pellets, a mixture of the same composition of MCC and fine lactose powder were made and compacted in a similar setting of the tableting machines (Instron and Manesy F3). The pressure needed to compress the same mass of powder and pellets, the pressure/platen-displacement curve, the properties of the tablets produced were compared.

The compaction pressure needed to compress 700 mg of the pellets was greater than that of 700 mg powder mixture by about 10MPa. This indicates that more force was needed to crush the structure of the pellet to obtain tablets of the same dimensions to those formed from the powder mix. This was supported by the change in the structure of the pellets after compaction which could be seen from the SEM on (Plate-3.2 a&b, see p-178) and retrieved pellets. The final porosity of the tablets formed from both systems was approximately equal showing that they were compressed to the same extent.

The compressibility of the powder and pellets was, however, different. It took a longer time to rearrange the particles in the powder mixture, to build the pressure needed to fracture or deform the particles and compact them to tablets when the same punch speed was used. For pellets however, the pressure increased rapidly. This indicates that the spherically rounded pellets were more packed at the beginning and their relatively smooth surfaces may have lowered the friction between the pellets during their rearrangement. The pressure/punch-displacement curve (Fig-3.2.12) illustrates that at the first-half portion of the displacement, no reasonable pressure was exerted on the powder mixture. However, the record of the pressure started much earlier with the powder bed than that of pellet bed. The difference in the work of compaction did not seem to have a significant variation. That is because the higher compression pressure of the pellets was counterbalanced by the higher compressibility of the powder, which forced the extension of the displacement. The more energy lost for crushing of the pellets may have been compensated by the higher energy needed to overcome the frictional force between the powder particles.

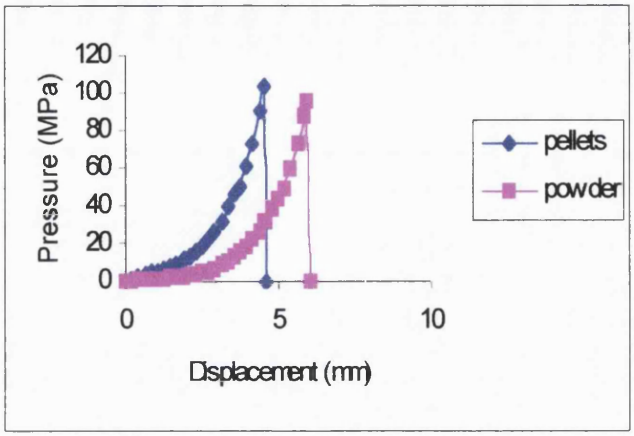
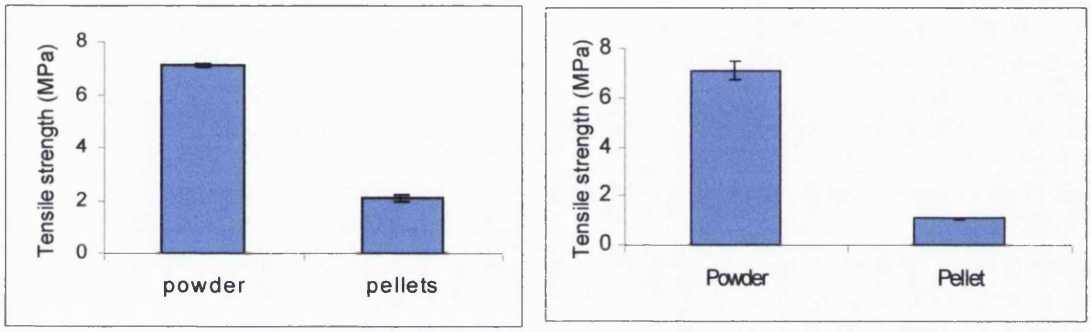


Fig-3.2.12:- Comparison on pressure/platen displacement profile for tablets produced from 700 mg pellets and powder of 1.0 -1.18 mm size fraction containing 60%w/w lactose in MCC/lactose mixture.

Maganti and Celik (1993) determined the work involved for compaction TWC (Total Work of Compaction) of lactose/MCC pellets and powder mixture of the same composition. They reported that the TWC of the pellets was significantly less than that of the powder, suggesting that this has been considerably affected by the change in shape and size. They also reported that the compacts of the pellets exhibited higher APC (Average Power Consumption) value at corresponding pressure than those of powder form. This can be attributed to the shorter contact time (the time during which the upper punch remained in contact with the material) due to the absence of material rearrangement stage which was observed for the case of powder. Both these observations signify the greater compression pressure needed to crush the pellets and the extended displacement of the powder bed due to their higher compressibility as suggested earlier, although both systems had the same speed of compaction (section 2.2.4.1 A).

The compacts formed from pellets or powder mix had different tensile strength values. The tensile strength of the tablets from the powder mixture were seven times higher than those produced from the pellets by the Instron. In tablets produced from the same bulk volume of powder bed and pellet bed in the eccentric tableting machine, however, the difference in the strength was only about four fold (Fig-3.2.13 a&b). The main reason for the difference in the strength of the tables seems the difference on the particle size of the components and the change in nature of the material during pellet formation. The powder has a lower particle size and thus a higher surface area. This could help it to have a greater interaction area and greater

strength. In pellets, however, the inter-granular interaction is very limited due to the relatively smaller surface area. Also, probably by the reduction in the number of its interaction sites due to the pelletisation process. For instance, the surface of the pellets is smoother which reduced the mechanical interlocking. Hence, much of the interaction is expected from the newly created surfaces due to the fracture of the pellets.



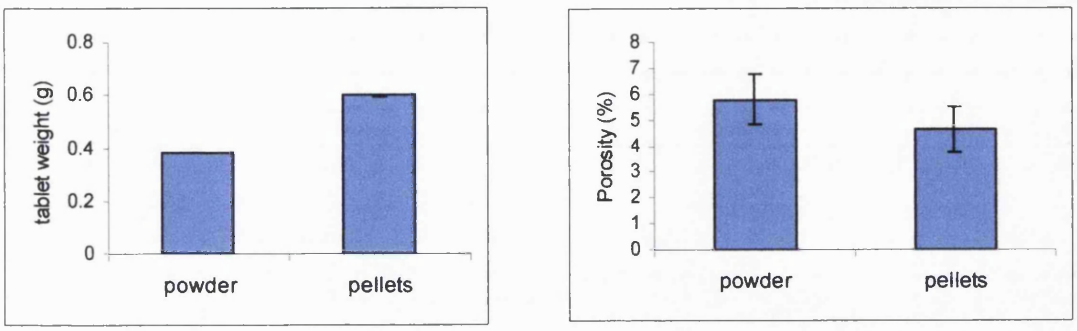
(a) *(b)*

Fig-3.2.13:- Comparison on the tensile strength of (a) eccentric tableting machine (b) Instron tablets produced from 700 mg pellets of 1.0 -1.18 mm size fraction and 700 mg of powder containing 60%w/w lactose in MCC/lactose mixture.

Wang et al. (1995) made a similar observation. During powder compaction, particles were rearranged and distorted, then plastically deformed and/or fragmented to create new contact areas for bond formation. The molecular, atomic or inter-particular interaction such as cohesion or adhesion was regarded as the most important mechanism for bonding. In the pellet compacts, however, the mechanical interlocking was regarded as a major contributor to the formation of the inter-granular bonds. Due to the change in pellet surface nature, however, this was not an important factor. A similar argument was also presented by Schwartz et al. (1994) in the comparison of their MCC powder and pellet compacts. Moreover, the strength of their beads which resisted failure and their lower compressibility hindered the formation of strong compacts. They claimed as to have noted few connections between the pellets from the electromicrograph.

The variation in the strength ratio of the tablets produced to the same dimensions in each of the two tableting instruments was mainly due to the porosity difference. In the Instron the same mass from both preparations was compacted to the same tablet thickness, as a result they had the same tablet porosity. In the eccentric tableting machine, however, the mass of the tablets was determined by the die volume. As a result the low bulk density of the powder,

produced tablets of lower mass (Fig-3.2.14a) and higher porosity (Fig-3.2.14b). Thus, the reduction in the relative strength of these porous tablets was inevitable.



(a) *(b)*

Fig-3.2.14:- The weight (a) and porosity (b) of tablets produced form the pellets or powder of the same bulk volume containing 60%w/w lactose in MCC/lactose mixture using eccentric tableting machine.

The volumetric elastic recovery of the compacts was determined after 72 hours using equation (31). Compacts from pellets had a greater expansion (Fig-3.2.15).

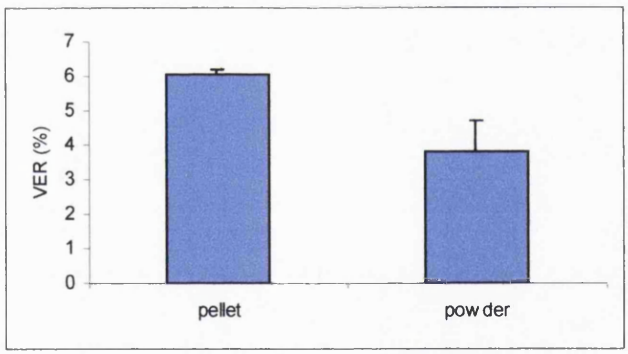


Fig-3.2.15:- Comparison on the volumetric elastic recovery of tablets produced from 700 mg pellets of 1.0 -1.18 mm size fraction and 700 mg of powder of 60%w/w lactose in MCC/lactose mixture.

This again shows that the structures in the pellets were not fully crushed. Some of the elastically stored energy was released to expand the compact. This could be one of the reasons which reduced the tablet strength for it could disrupt the rigid structure formed.

Therefore, at this stage it is possible to conclude that, lower compressibility, the change in the surface nature during the pelletization process, lower and smooth surface area, as well as the higher volumetric elastic recovery were the main reasons for the reduction of the strength of pellet-compacts, compared to that of powder compacts of the same formulation. Moreover,

the wider particle size distribution of powder particles may have reduced the inter-particle voids, hence, increased contact area that may have enhanced the formation of rigid structure. The mechanical interlocking between the powder particles may have also been reinforced by the irregularity of the powder particle shape, compared to that of pellets.

3.3 A FACTORIAL DESIGNED EXPERIMENT WITH MIXED EXCIPIENTS

3.3.1 INTRODUCTION

In this section, the effect of three formulation factors, namely, MCC, lactose, and GMS on the mechanical properties of pellets and the properties of tablets produced from the pellets were investigated. The factors were indicated by their initials (Table 3.3.1, column 1). Their levels were based on the "concentration" or the percentage by weight of each excipient in the dry mass. Since a detailed study of the effect of each factor was made on a binary mixture of the factors in the previous two sections (Section 3.1 and 3.2), only two levels were taken here for the sake of economy and simplicity. Thus eight trails were made at random to ensure unbiased full factorial design. This is called a 2^3 factorial designed experiment, three factors each at two levels. The experiment was repeated with 7/1 water to ethanol composition as liquid binders to enhance the compactability by producing more porous pellets (Millili and Schwartz, 1990).

It was not possible to use "the rule of thumb" in designing the quantity of the factors, as the feasibility of the production of the pellets from the formulations was determinantal. As a result the variation in concentration of each excipient was limited to 10%w/w of the total dry weight (Table-3.3.2). At least 60% of the dry mass was MCC due to its unique favourable properties for pelletization (Reynold, 1970).

As shown, on the first column of (Table-3.3.1), the low and high levels of factors in a particular run are denoted by the lower and upper cases of their initials, respectively. The signs on column 2, 3, and 4 are given based on the levels of the excipients. A positive sign is depicted when they are at their higher levels where they would positively affect their response. In the latter columns, the interaction of the factors is shown as a product of their individual sign in that particular experiment.

Factor combination	Levels of a factor			Interaction [a]			
	MCC	Lactose	GMS	MCC+Lac	MCC+GMS	Lac+GMS	MCC+Lac+GMS
mlg	-	-	-	+	+	+	-
Mlg	+	-	-	-	-	+	+
mLg	-	+	-	-	+	-	+
MLg	+	+	-	+	-	-	-
mlG	-	-	+	+	-	-	+
MlG	+	-	+	-	+	-	-
mLG	-	+	+	-	-	+	-
MLG	+	+	+	+	+	+	+

Table-3.3.1:-Signs to calculate effects in a 2^3 factorial experiment

Where, m/M, l/L, g/G represents MCC, lactose, GMS content at their low (lower case) and high (higher case) levels.

(-) factor at lower level; (+), factor at high level.

[a] Multiply signs of factors to obtain signs for interaction terms in combination

The starting formula for this work was the formula that had the minimum quantity of each factor (mlg) (Table-3.3.2 a&b). This constitutes 80%w/w MCC, 10% lactose and 10%w/w GMS of the dry mass. In the first set of experiments, the liquid binder used was water. It was equal to 80%w/w of the starting dry mass. In all the experiments there was no change in water content, but the level of excipients. In a second set of experiments, the same amount of liquid binder was used. However, 12.5%w/w of the water was replaced by ethanol to produce more porous pellets. Powder equal to 10%w/w of the starting dry mass of the formulation was added from each excipients in their highest content (Table-3.3.2). Only on this proportion was robust production of normal pellets possible. A higher amount of excipients and lower quantity of solvent would result in a dry mass which was too stiff to extrude, while a higher quantity of the moisture and lower excipients quantity would be too wet to spheronize without agglomeration. Moreover, addition of excipients less than this specified amount would not have a noticeable response.

(Table-3.3.2 a&b) presents the ratio of each constituent in the formulations. In every set of experiment concerning the properties of the pellets, the sample size was 30 pellets, while it was 5 tablets for those dealing with the properties of the tablets.

S/N	Formula	Excipients			Liquid binders	
		MCC	Lactose	GMS	Water	Ethanol
1	mlge	8	1	1	8	0
2	Mlge	9	1	1	8	0
3	mLge	8	2	1	8	0
4	MLge	9	2	1	8	0
5	mlGe	8	1	2	8	0
6	MlGe	9	1	2	8	0
7	mLGe	8	2	2	8	0
8	MLGe	9	2	2	8	0

Table-3.3.2(a) The ratio of each constituent in the wet mix of the factorial designed experiment to produce pellets of 1.0-1.18mm size fraction. The three factors were , MCC content (m/M), Lactose content (l/L), Glyceryl monostearate (g/G), and the absence of ethanol is indicated by (e).

S/N	Formula	Excipients			Liquid binders	
		MCC	Lactose	GMS	Water	Ethanol
1	mlgE	8	1	1	7	1
2	MlgE	9	1	1	7	1
3	mLgE	8	2	1	7	1
4	MLgE	9	2	1	7	1
5	mlGE	8	1	2	7	1
6	MlGE	9	1	2	7	1
7	mLGE	8	2	2	7	1
8	MLGE	9	2	2	7	1

Table-3.3.2 (b):- The ratio of each constituent in the wet mix of the factorial designed experiment to produce pellets of 1-1.18mm size fraction. The three factors were, MCC content (m/M), Lactose content 9(l/L), Glyceryl monostearate (g/G), and the presence of ethanol in the binding liquid is indicated by (E).

In this project, the effects of three formulation factors on the mechanical properties of the pellets were studied in terms of their tensile strength, deformability, linear strain, and 'elastic

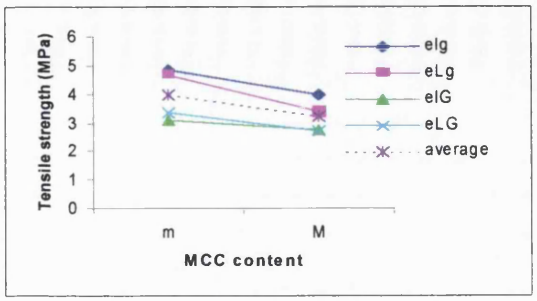
modulus'. In addition, their effects on the force needed to compress an equal mass of the pellets to a pre-determined tablet dimensions, the tensile strength, and the volumetric elastic recovery of the tablets were investigated. The average effects of each factor was analysed using the Yate's algorithm and their significance was tested by ANOVA as described by Bolton (1990). Moreover, the properties of the pellets produced by the seven formulations were compared with that of the starting formula and were analysed for their significance by the one-way analysis of variance (Table-3.3.3,4, and 5). The interaction of the factors has been illustrated with the unparallel plots in the presented graphs. However, there are limited explanation for these effects as the analysis needed a clear knowledge of the distribution of each excipient within the pellets as well as the way they interacted with each other and other excipients. Such information is not yet available.

If factors known to influence the experimental results, but of no interest to the experiment are allowed to vary unintentionally, the effect caused by the random variation of these factors will become part of the residual error (i.e. an error remaining after the ANOVA removes the variability due to the factors and their interaction) (Bolton, 1990). In this work, it was attempted to keep the water content of the formulation equal to that of the starting formula, for its effect will be studied separately (chapter-4). However, with the addition of more excipients in the subsequent formulae, the total water content of the formulation was reduced. This increased the residual error, as a result decreased the sensitivity of the average effect of the factors. Therefore, the error mean square for the statistical test and estimation in the overall effect of the three formulation factors was determined by pooling the mean squares of two or more higher-order-interactions. The choice was made based on those having the least mean square values, as used by Bolton (1990).

3.3.2 THE PROPERTIES OF PELLETS

3.3.2.1 TENSILE STRENGTH

The tensile strength of the pellets from the seven different formulations was lower than the pellets produced from the starting formula that contains the lower levels of each formulation factor (Table-3.3.3 a & b). The decrease in the proportion of water during granulation, as a result of the addition of extra dry powder of the excipients in each subsequent formula could presumably be one of the reasons. Compared to the starting formula (mlge), there was an inversely proportional relation between the strength of the pellets and the amount of water



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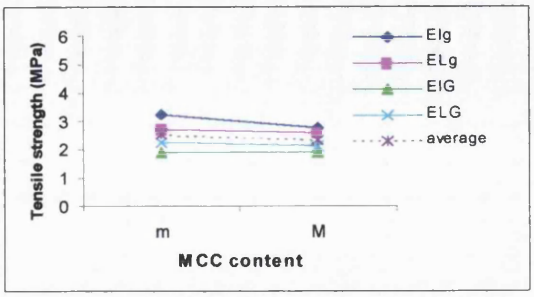

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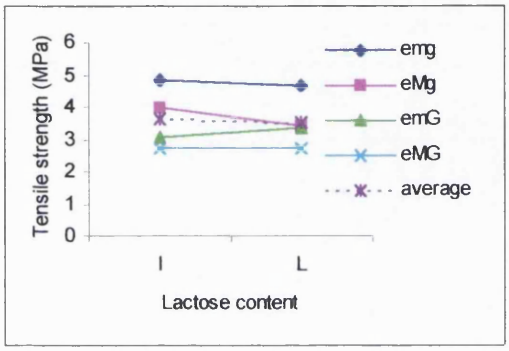

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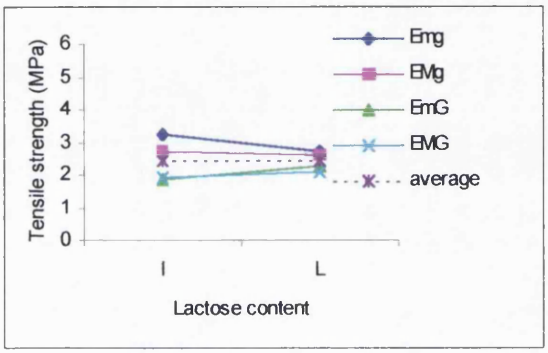

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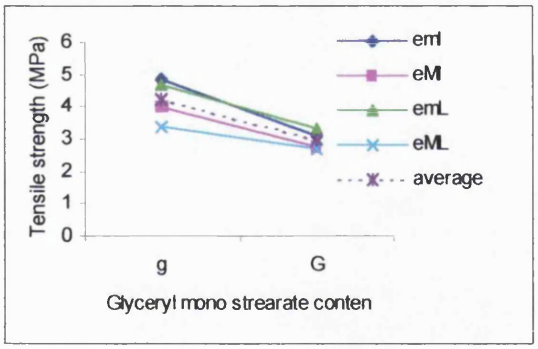

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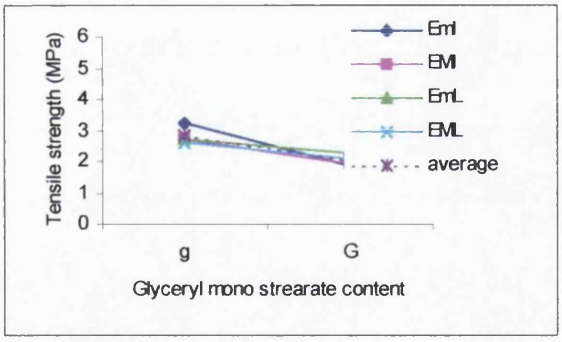


F.

Fig-3.3.1:- The effect of MCC (A and D), lactose (B and E), and GMS (C and F) at their lower (lower case) and higher (upper case) levels on the tensile strength of pellets produced by the factorial designed experiment. The letter "e" stands for those formed without ethanol, while "E" stands for those formed with the mixture of water and ethanol. The mean pellet diameter was 1.09mm, n=30.

A.

Factor	Tensile strength (MPa)	Standard Deviation	df	Mean Square	F	P
mlge	4.85	0.9638	-	-	-	-
Mlge	4	0.7552	1	10.834	14.45	< 0.001
mLge	4.69	0.708	1	0.402	-	-
mlGe	3.11	0.6059	1	45.25	69.82	< 0.001
MLge	3.42	0.7561	1	30.655	40.85	< 0.001
MlGe	2.77	0.5656	1	64.958	104.02	< 0.001
mLGe	3.37	0.7206	1	33.074	45.68	< 0.001
MLGe	2.71	0.4606	1	68.442	119.96	< 0.001

B.

Factor	Tensile strength (MPa)	Standard Deviation	df	Mean Square	F	P
mlgE	3.28	0.5066	-	-	-	-
MlgE	2.77	0.4251	1	3.93	17.97	< 0.001
mLgE	2.73	0.3951	1	4.507	21.84	< 0.001
mlGE	1.91	0.233	1	28.367	182.44	< 0.001
MLgE	2.61	0.392	1	6.885	33.56	< 0.001
MlGE	1.93	0.3404	1	27.438	147.31	< 0.001
mLGE	2.28	0.3806	1	15.179	75.61	< 0.001
MLGE	2.14	0.3359	1	19.578	105.97	< 0.001

Table-3.3.3:-Results and ANOVA for the 2^3 factorial designed experiment. The effect of MCC content (m/M), Lactose content (l/L), and Glyceryl monostearate content (g/G) on the tensile strength of pellets of 1-1.18mm size fraction. Where (A) represents those formed with water, while (B) formed with a water/ethanol mixture.

in the formulations. However, the extent of each factor's effect on decreasing the tensile strength of the pellets was different. At a proportional water content, the addition of GMS reduced the tensile strength to the greatest extent (Fig-3.3.1 c and f). The addition of lactose reduced the strength of the pellets to the least extent (Fig-3.3.1 b and e). All the formulations reduced the tensile strength of the pellets significantly at (P<001) except lactose at (mLge).

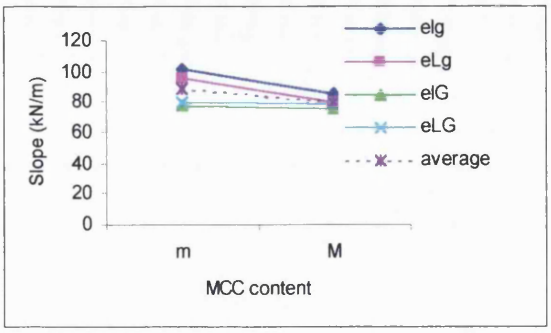
The relative higher strength of the lactose-rich pellets (mLge) was presumably due to the re-crystallization of the dissolved lactose during drying. This may have formed a stronger solid bridges which might have resisted a failure of the pellets at relatively lower stress.

The average effect of each formulation factor at the four different constant levels of the other factors was also observed to decrease the strength of the pellets with a different magnitude (Table-3.3.7 a & b). The rank of the factors in decreasing the tensile strength of pellets in descending order was GMS (25.7%), MCC (16%), and lactose (2.8%). The effect of GMS and MCC was significant at($P<0.05$). This coincided with the results of the previous experiments (binary mixture of excipients). The same trend was also observed when the composition of the solvent was changed. However, it was to a lower extent. This could be due to the reduction in the strength of the pellets from the starting formula (mlgE) as a result of the addition of ethanol.

Interaction seem to occur between formulations containing lactose and GMS at their higher levels, especially when the water and ethanol mixture was used as a liquid binder. This was illustrated by the intersection of the lines (Fig-3.3.1 c&f). The variation in their solubility in the binding liquid could be a possible reason.

3.3.2.2 DEFORMABILITY

The slope of the force/displacement curves of these pellets of 1.0 - 1.18 mm size fraction was observed to decrease in all the subsequent formulations compared to that of the starting formula (mlge) (Fig-3.3.2 a & b). This indicated the increase in the deformability of the pellets. In all the formulations the increase in deformability of the pellets was statistically significant at ($P<0.05$), except when lactose was the only added excipient (mLge) (Table-3.3.4 a). This shows the brittle nature of lactose as stated earlier. However, the relative higher strength of lactose-rich pellets could also be the reason for the steeper slope of the force/displacement curves, although the pellets were compressed (displaced) to a higher extent relative to the other formulations (Section 3.3.2.3). In the second set of experiments where water and ethanol were used as liquid binders, the order of the effect of the seven formulations in the deformability of the pellets produced was similar, yet the extent of their effect was different. The effect of GMS increased further, the effect of MCC was reduced by ten fold, while lactose showed an opposite effect (reduction in deformability compared to the



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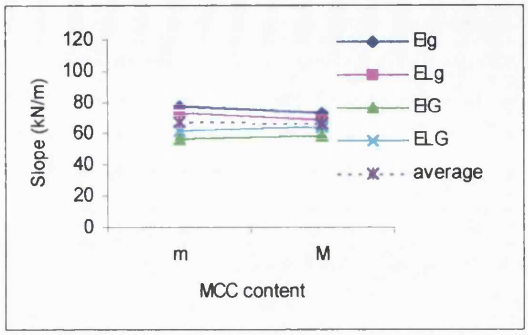

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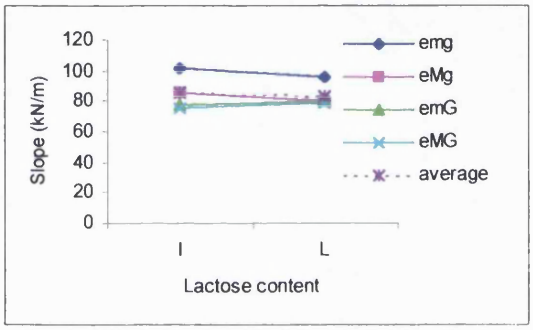

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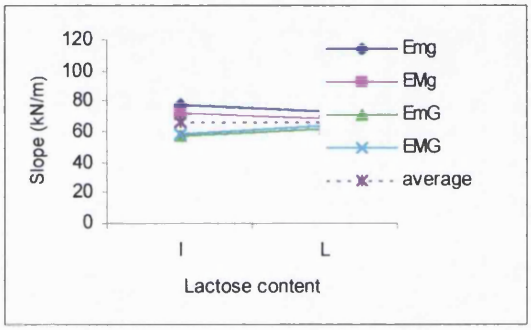

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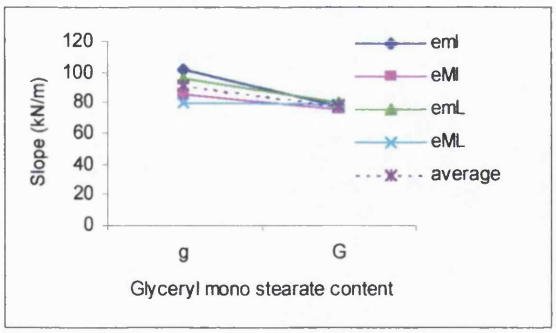

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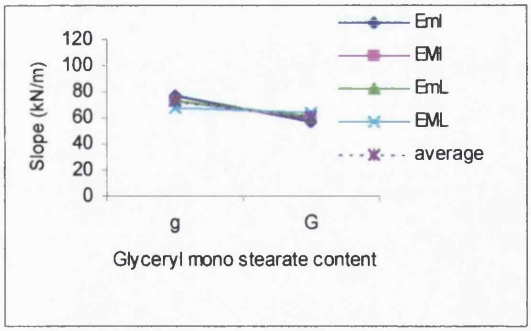


F.

Fig-3.3.2:-The effect of MCC (A and D), lactose (B and E), and GMS (C and F) at their lower (lower case) and higher (upper case) levels on the slope of the force/displacement curve of the pellets produced by the factorial designed experiment. The letter "e" stands for those formed without ethanol, while "E" stands for those formed with a mixture of water and ethanol. The mean pellet diameter was 1.09mm, n=30

A.

Factor	Slope kN/m	Standard Deviation	df	Mean Square	F	P
mlge	102.36	11.87	-	-	-	-
Mlge	86.53	11.02	1	3761	28.68	< 0.001
mLge	96.43	13.49	1	528	3.27	0.076
mlGe	78.11	12.19	1	8825	60.96	< 0.001
MLge	80.68	10.2	1	7051	57.57	< 0.001
MlGe	75.47	11.39	1	10851	80.18	< 0.001
mLGe	80.23	13.16	1	7352	46.82	< 0.001
MLGe	79.34	9.28	1	7950	70.01	< 0.001

B.

Factor	Slope kN/m	Standard Deviation	df	Mean Square	F	P
mlgE	77.81	11.594	-	-	-	-
MlgE	72.95	9.754	1	354	3.08	0.084
mLgE	73.52	7.918	1	275.3	2.79	0.1
mlGE	57.2	7.344	1	6366.3	27.6	< 0.001
MLgE	68.54	6.222	1	1289.1	14.89	< 0.001
MlGE	59.4	7.331	1	5083.2	54.03	< 0.001
mLGE	61.8	9.562	1	3843	34.03	< 0.001
MLGE	64.64	8.395	1	2601	25.39	< 0.001

Table-3.3.4 :-Results and ANOVA for the 2^3 factorial design. The effect of MCC content (m/M), Lactose content (l/L), and Glyceryl monostearate content (g/G) on the Slope (Force / Distance) of the pellets of of 1-1.18mm size fraction. Where (A) represents those formed with only water while (B) represents those formed with water/ethanol

starting formula) (Fig-3.3.2 a-f). This could be related to the drastic reduction in strength of the pellets with the replacement of part of the water by ethanol. The pellets snapped quickly due to less dissolution and re-crystallization, and formation of solid bridges of lactose. GMS was the excipient least influenced by the mixture of binding liquids. The average effect of each formulation factor at the four different constant levels of the other factors was also observed to increase the deformability of the pellets with different extent (Table-3.3.7 a &b). The rank of the factors in increasing the deformability of pellets in descending order was

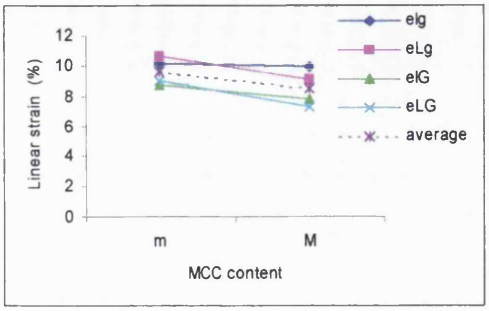
GMS (18%), MCC (11.3%), and Lactose (1.2%). The effect of GMS and MCC was significant at ($P<0.01$). This work confirmed the previous conclusion which stated that the replacement of more MCC powder by GMS increased the deformability of the pellets (Section 3.2).

The figures (Fig-3.3.2 a, b &c) show that there had been an interactions between some factors. The effect of lactose and MCC addition at the same time (MLge) were additive compared to their separate addition, (Mlge) and (mLge) respectively. The addition of lactose and GMS together (mLGe) had a lower effect compared to the addition of GMS alone (mlGe). This shows the absence of an interaction between the lactose and MCC effects, while antagonistic interaction between lactose and GMS. All other dual effects were less than additive but more than the effect of each factor separately.

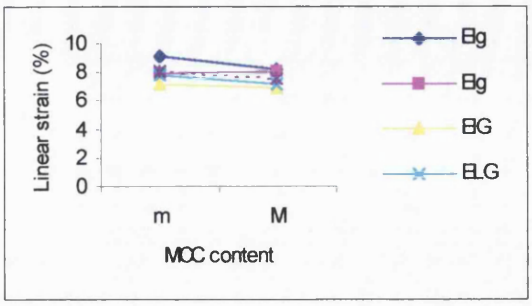
As discussed previously , the slope used to determine the deformability was calculated form the point where the highest crushing force was registered. However, there was variation in the route of the plot after this point was reached. In lactose-rich pellets, the force dropped to zero force instantly as a result of a total breakage of the pellets. This indicated the brittleness of the pellets. In the case of GMS-rich pellets, however, the displacement was extended after reaching the first force peak. The exclusion of this further strain may underestimate the deformability of GMS-rich pellets.

3.3.2.3 LINEAR STRAIN

The linear strain of the pellets of the six formulations was lower than that of the starting formula, which contained all factors at their lower levels (mlge) (Table-3.3.5 a). When lactose was the only added excipients (mLge), however, the linear strain increased by about 4%. The results had relatively high variability. The strain of these pellets may include that of elastic and plastic deformation. The deformable materials, GMS and MCC, did not increase the linear strain. The decrease in water content, with the addition of MCC and GMS, might have reduced the strength of the pellets, likewise their ability to be strained to a greater extent. In all formulations containing GMS at its higher level, the reduction in linear strain was statistically significant ($p<0.05$). In their overall average effect, however, all the factors reduced the linear strain of the pellets. The rank of their reduction in descending order was, GMS (16.5%), MCC (10.5%), and lactose (1.2%) (Table-3.3.7 a&b). It was in the same



A.



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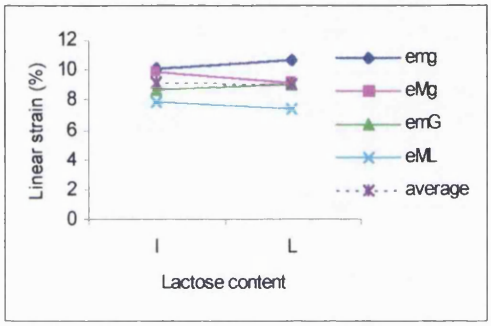

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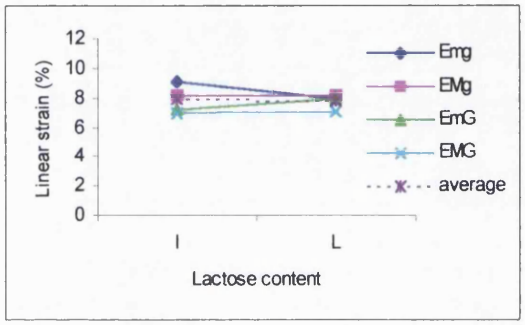

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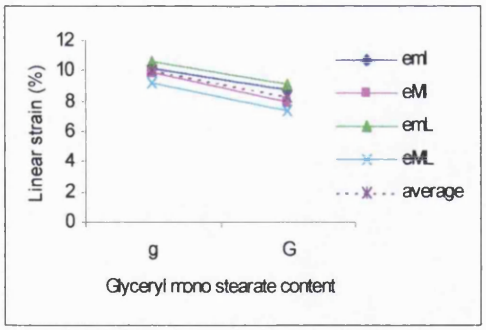

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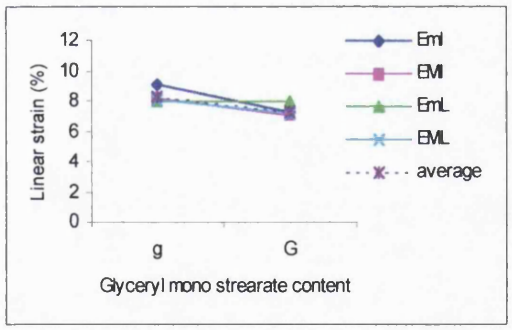


F.

Fig-3.3.3:-The effect of MCC (A and D), lactose (B and E), and GMS (C and F) at their lower (lower case) and higher (upper case) levels on the linear strain of the pellets produced by the factorial designed experiment. The letter "e" stands for those formed without ethanol, while "E" stands for those formed with the mixture of water and ethanol. The mean pellet diameter was 1.09mm, n=30

A.

Factor	Linear Strain (%)	Dtandard Deviation	df	Mean Square	F	P
mlge	10.17	1.919	-	-	-	-
Mlge	9.94	1.6	1	0.79	-	-
mLge	10.64	2.269	1	3.33	-	-
mlGe	8.79	1.949	1	28.41	7.59	0.008
MLge	9.19	2.221	1	14.44	3.35	0.072
MlGe	7.91	1.431	1	76.3	26.62	< 0.001
mLGe	9.11	1.936	1	16.78	4.51	0.038
MLGe	7.4	1.428	1	114.68	40.06	< 0.001

B.

Factor	Linear strain (%)	standard Deviation	df	Mean Square	F	P
mlgE	9.16	1.589	-	-	-	-
MlgE	8.24	1.573	1	12.63	5.05	0.028
mLgE	7.98	1.245	1	21.06	10.34	0.002
mlGE	7.3	1.146	1	51.91	27.05	< 0.001
MLgE	8.17	1.341	1	14.82	6.86	0.011
MlGE	7.03	1.418	1	67.92	29.95	< 0.001
mLGE	7.95	1.133	1	21.98	11.54	0.001
MLGE	7.17	1.422	1	59.27	26.07	< 0.001

TABLE-3.3.5:-Results and ANOVA for the 2^3 factorial design. The effect of MCC content (m/M), Lactose content (l/L), Glyceryl monostearate content (g/G) on the linear strain of pellets of 1-1.18mm size fraction. Where (A.) represents those formed with water while(B) represents those formed with water/ethanol mixture.

order of their increasing effect in deformability in a descending order. This appears contradictory, if one assumes they had the same strength. However, their effect in reduction of the strength of the pellets was in the same order, indicating their early failure before

considerably strained. With the incorporation of ethanol in the binding liquid, the order of their decreasing effect in the linear strain of the pellets was the same but was to a less extent. The overall effects of MCC and GMS were significant ($P<0.01$). In the presence of ethanol, the gross effect of GMS was the only significant observation ($P< 0.05$).

Addition of lactose with the other two excipients had different interactions (Fig-3.3.3 b&e). It extended the effect of MCC, while reducing the effect of GMS. There was no apparent reason for this observation. GMS also influenced the effects of the other excipients substantially when they were formulated with water/ethanol mixture (Fig-3.3.3f).

In the presence of ethanol, addition of lactose (mLgE) reduced the linear strain of the pellets more than that of addition of MCC in (MlgE).This could presumable be due to the change in its solubility. However, the overall effect of lactose in reducing the linear strain was lower in both sets of experiment than that of MCC. MCC and GMS showed an additive effect in their linear strain reduction effect, which could be again due to the production of weaker pellets, for they are susceptible to failure before been strained to a greater extent.

3.3.2.4 'ELASTIC MODULUS'

The assessment of the effects of the three formulation factors on the 'elastic modulus' of the pellets was made on the average effect of the factors using Yates algorithm. It is an alternative approach to indicate relative effect of the factors at both their levels. The 'elastic modulus' of the starting formula (mlge) was decreased by all the factors, but to a different extent when only water was the liquid binder (Table-3.3.6 a). The rank in the overall 'elastic modulus' decreasing effect in descending order was, GMS (13.2%), MCC (7.8%), and lactose (1.9%). This is of the same order as that of increasing the deformability of the pellets. The least effect in increasing deformability (Section 3.3.2.3) and least stiffness reduction effect may imply that the relative brittleness of "lactose-rich" pellets, as brittle materials are commonly stiff and less deformable. The overall effects of GMS and MCC in reduction of the 'elastic modulus' of the pellets was, however, statistically significant ($P<0.01$). Compared with their effect on deformability (3.3.2.3), it is possible to conclude that they deform more plastically, for their effect on 'elastic modulus' was less.

A.

Factor	average change Elastic Modulus (MPa)	d.f.	Mean Square	F	P
MCC	-37.40	1	2797	523.8	0.002
Lactose	-8.71	1	152	28.4	0.033
GMS	-63.06	1	7954	1489.0	<0.001

B.

Factor	mean change in elastic modulus (MPa)	d.f.	Mean Square	F	P
MCC	-5.230	1	547.0	107.7	0.009
Lactose	-4.087	1	33.4	65.8	0.014
GMS	-58.960	1	6951.0	13697.0	<0.001

Table-3.3.6:- Yates Analysis of the factorial designed experiment for the determination of the mean effect of each factor on the properties of the of 1-1.18mm size fraction. Where (A) are pellets formulated by water and (B) formulated by water/ethanol. The error mean square was determined from MLg and MLG in both cases with 2 d.f.

In the presence of ethanol, the effect of all the factors reduced considerably (8 to 19 fold), while retaining the same order (Table-3.3.6 b). Here lactose was observed to increase the 'elastic modulus' of the pellets although to very small extent. The decreasing effect of the other two factors was again statistically significant ($P<0.01$), while that of lactose was less significant ($P<0.05$). These results are in agreement with the effect of the factors assessed in the binary mixture of the factors (Section 3.1 and 3.2).

3.3.2.5 CONCLUDING REMARKS

The factorial designed experiment has revealed the effect of the three formulation factors on the properties of the pellets at wider range of experimental conditions. (Table-3.3.7 a & b) summarizes the average effect of each factor at the two composition of the liquid binders. GMS reduced the tensile strength, linear strain and 'elastic modulus' of the pellets to the greatest extent. This was supported by its statistically significant effect. Lactose reduced the tensile strength, linear strain, and 'elastic modulus' to the least extent. Its effect was sensitive to the presence of ethanol. The three factors had increased the deformability of the pellets when they were formed with water, although lactose's effect was statistically insignificant

showing its brittle nature. As deformable materials, GMS and MCC had a significant effect in increasing the deformability.

A.	Tensile strength (MPa)		Deformability (mm/kN)		Linear Strain (% ofl pellet diameter)		Elastic Modulus (MPa)	
Factors	water	water + ethanol	water	water + ethanol	water	water + ethanol	water	water + ethanol
MCC	-0.778	-0.189	1.100	0.122	-1.067	-0.443	-37	-5
Lac	-0.137	-0.034	0.113	-0.258	-0.118	-0.118	-9	4
GMS	-1.249	-0.785	1.757	2.804	-1.679	-1.023	-63	-59

B.	Tensile strength (%)		Deformability (%)		Linear Strain (%)		Elastic Modulus (%)	
Factors	water	water + ethanol	water	water + ethanol	water	water + ethanol	water	water + ethanol
MCC	-16.0	-5.8	11.3	0.9	-10.5	-4.8	-7.8	-0.1
Lac	-2.8	-1.0	1.2	-2.0	-1.2	-1.3	-1.9	0.1
GMS	-25.7	-23.9	18	21.8	-16.5	-11.2	-13.2	-1.6

Table-3.3.7:- The average effect of the three formulation factors as analysed by Yates algorithm. Their average effect on changing the four properties of the pellets of 1.0-1.18mm size fraction, is presented in (a) as deviation from the property of the starting formula, (b) as a percetntage of deviation for the property of the starting formula (mlge). The minus sign indicates the reduction in the value of the property.

The average effect of all the factors studied was in agreement with their effect on binary mixtures. The amount of powder added to change their levels from low to high was very limited in this work. As a result the dominance of MCC may have reduced the possible wide difference in the effects of the factors studied. However, this work was successful in illustrating the factors' effect and analysing their significance.

3.3.3 THE PROPERTIES OF THE TABLETS

Pellets produced from the factorial designed experiment were compacted to tablets according to the procedure explain in (2.2.4.1A). First, 650 mg pellets of the 16 different formulations were compacted to the same tablet thickness, while secondly 700 mg of pellets from all the formulations were compacted by approximately the same compressing pressures of 130 MPa and 146 MPa as described in (2.2.4.1B). Five tablets were compacted in each case. In these three set of experiments, the mean effect of each factor was studied on the compression force

needed to compact the pellets to the same pre-determined tablet thickness (in the first set), the tensile strength and volumetric elastic recovery of the pellet compacts. Yate's algorithm was used to evaluate their significance. The net effect can be found from the difference in response of each formulation and that of the starting formula (mlge) from (Table-3.3.8).

A.

Formulae	Compressing pressure(MPa)	Tensile strength (MPa)	VER (%)
mlge	135.4 (8)	0.088 (0.016)	11.85 (2)
Mlge	131.3 (5)	0.043 (0.008)	11.31 (3)
mLge	136.0 (7)	0.087 (0.018)	11.29 (2)
mlGe	144.8 (9)	0.166 (0.040)	11.87 (1)
MLge	130.6(11)	0.052 (0.010)	11.41 (1)
MlGe	137.6 (7)	0.119 (0.050)	11.89 (2)
mLGe	145.3 (1)	0.246 (0.050)	11.77 (2)
MLGe	137.4 (10)	0.126 (0.050)	11.62 (3)

B.

Formulae	Compressing pressure(MPa)	Tensile strength (MPa)	VER (%)
mlgE	129.6 (11)	0.144 (0.02)	11.07 (2)
MlgE	128.2 (10)	0.068 (0.01)	10.98 (3)
mLgE	131.3 (11)	0.110(0.02)	10.61(2)
mlGE	145.0 (10)	0.320 (0.04)	10.82 (3)
MLgE	128.0 (10)	0.057 (0.06)	10.41(2)
MlGE	140.0 (11)	0.155 (0.02)	10.99 (1)
mLGE	144.1(12)	0.272 (0.03)	10.82(2)
MLGE	137.4(11)	0.140 (0.01)	10.91(1)

Table-3.3.8:- The mean result of the three properties of the pellet compacts produced from the 2^3 factorial designed experiment. Where (a) represents those pellet formed with water, and (B) represents those formed with a water/ethanol mixture.

3.3.3.1 COMPACTION PRESSURE

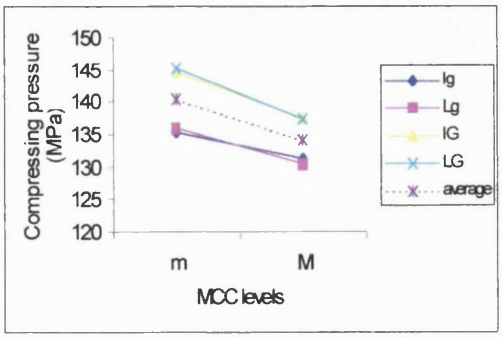
Fell and Newton (1970a&b) established a linear relation between compaction load and tablet strength up to a certain range, and charactered their tablets produced from different lactose forms in terms of their tensile strength. Moreover, they assessed the compression

characteristics of the same materials by determining the cumulative work done during compaction (Fell and Newton, 1971). In this work, the pressure needed to compact a definite mass of pellets, containing different excipients, to a constant pre-determined volume or density was determined in an attempt to assess its effect on the mechanical properties of the pellets (for that mater their constituents) in terms of their deformability or fragmentation after examining the change in their volume, shape and presence of cracks and fragments. In a similar way, Adams et al. (1994) were able to determine the shear strength of their granules from the relationship of the compressing pressure and the relative density of the compacts. In addition, the compressing pressure needed to reduce the volume of the pellet-bed from their minimum bulk volume to an equal pre-determined volume (equal density) can be used as an expression of the ease of their compressibility.

The pressure needed to compact 650 mg of pellets (1.0-1.18mm size fraction) to the same in die tablet thickness (4.0 mm) according to the procedure described in section (2.2.4.1A) was different for pellets from the different formulations (Table-3.3. a &b, column II). The pressure ranged from an average of 130.6 MPa (MLge) to 145.3 MPa (mLGe) and 128 MPa (MLgE) to 145 MPa in (mlGE) depending on the absence or presence of ethanol in the composition of the liquid binders respectively. The ranges and values of the same excipient contents were reasonably matched with the exception of a reduced pressure for lactose-rich formulations in the presence of ethanol.

The responses of all the formulations were different and had a minimum interaction between each other (Fig-3.3.4 a-f). This can be seen on the graphs, where parallel curves were obtained for each factor at different levels of the other factors. Likewise, the rank order of the effect of each factor was the same when the two types of binding liquids were used. In the presence of ethanol in the binding liquid, the effect of GMS in increasing the compressing pressure was enhanced, while those of MCC and lactose reduced, although to an insignificant level (Table-3.3.9 b).

The tensile strength of lactose-rich pellets was reduced in the presence of ethanol (section 3.3.2.1). The reduction in tensile strength of these pellets could be the reason for the reduction in the pressure needed to compress them to tablets of pre-determined volume.



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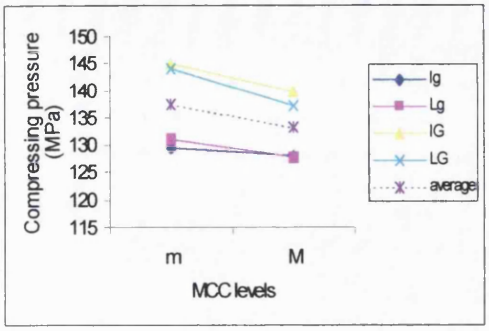

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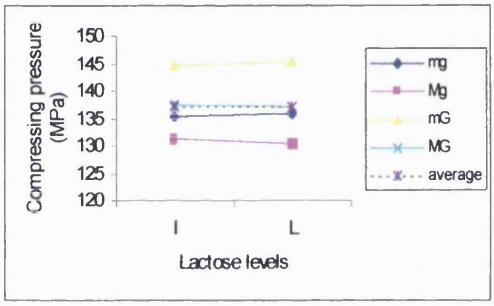

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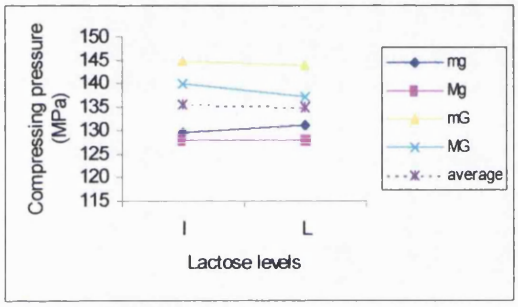

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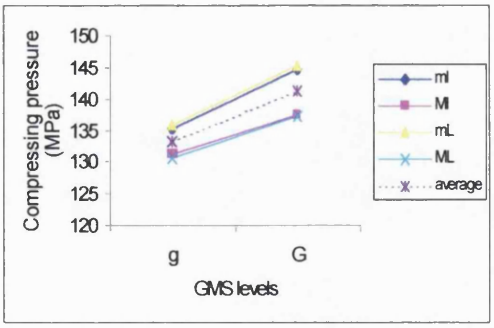

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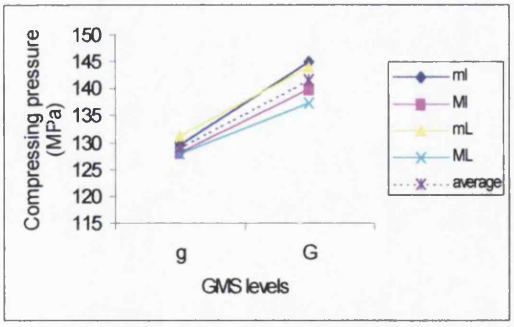


F.

Fig-3.3.4:-The effect of MCC (A and D), lactose (B and E), and GMS (C and F) at their lower (lower case) and higher (upper case) levels on the compressing force needed to compress 650 mg pellets of mean diameter 1.09 mm to a pre-determined tablet thickness. The letter "e" stands for those formed without ethanol, while "E" stands for those formed with the mixture of water and ethanol. n=30

A.

Factor	mean change in compressing pressure (%)	d.f.	Mean Square	F	P
MCC	-4.60	1	60813	65.3	0.001
Lactose	0.05	1	7	-	-
GMS	5.90	1	101813	109.5	0

B.

Factor	mean change in compressing pressure (%)	d.f.	Mean Square	F	P
MCC	-4.10	1	49220	22.6	0.009
Lactose	-1.40	1	5913	2.7	-
GMS	8.06	1	189882	87.3	0.007

Table-3.3.9:- Yates Analysis of the factorial designed experiment for the determination of the mean effect of each factor on the properties of the pellets of 1.0-1.18mm size fraction. Where (A) are pellets formed with water and (B) formed with water/ethanol. The error mean square was determined from Mlg, MlG, mLG and MLG in both cases with 4 d.f.

The overall effect of addition of lactose had an insignificant effect on both set of experiments (Table-3.3.9). An increase in GMS could be regarded to have the most significant effect in increasing the compaction pressure (significant in both solvent compositions at $P<0.01$). This was mainly due to the low relative density of this excipients which resulted to a higher in die solid fraction (lower porosity) at the specified punch displacement. Similar to the binary mixture results, after the GMS-rich pellets were deformed plastically with very little force, they reached relative density of about 1, after which the resistance of the solid crystal lattice to elastic deformation may have caused a rapid increase in the compaction pressure. The deviation from linearity of the Heckel plot also supports this assumption.

The reduction of the compressing pressure by addition of MCC was significant in both solvent systems. This could be related to the reduction in the strength of the pellets with the addition of MCC and its better deformability after reaching the yield pressure. Addition of further MCC would not affect the density of the pellets as 2/3 of their content was MCC. In addition, its apparent density is similar to that of lactose to produce tablets of equivalent solid fraction or density.

The different compaction pressures were not intended to produce tablets of the same porosity but tablets of the same in die density. That is because the materials had different apparent densities even in the event that the structure of the pellets was totally crushed. If it is assumed that the closed pores were not affected during compaction as reported by Johansson et al. (1995), a difference in the porosity would remain between the pellets, i.e. inter-granularly. The apparent densities of the pellets as measured by helium pycnometer (Table-3.3.10, column V) did not reflect that of the composition of its constituents, mainly due to the presence of closed pores. However, there was variation between the formulations, which indicated that the same mass of pellets of different formulation occupy different original volume (different bulk density). Hence, the compressibility of the pellets occurred to a different extent. Less dense pellets, such as GMS-rich pellets, were compressed from a higher initial volume to a constant pre-determined volume. Therefore, it was not the strength of these pellets which caused higher compaction pressure, but their compression to relatively greater extent or to lower porosity. Such closer particles rearrangement was probably countered by high friction forces in the contact points of the pellets. Increase in friction might thereby increased the pressure of compaction independent of any change in the deformation mechanism. This was again proved by determination of the total porosity of the compacts at the highest compression force in the die (Fig-3.3.5) after correction of die deformation. In this case, GMS pellets had a slight negative porosity, while the porosity of the others was positive but still different from each other. This could be the reason why GMS pellets required a higher compressing force. This high force is assumed to have caused compression of the solid crystal lattice. Therefore, compaction to the same density may

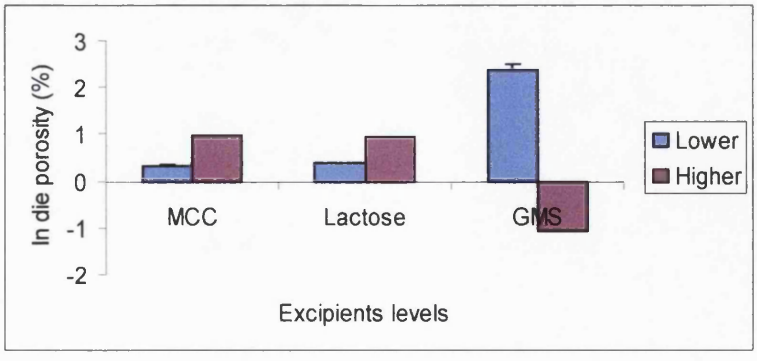


Fig-3.3.5:- The mean effect of the excipients at their lower and higher levels in the factorial designed experiment, in the in-die porosity of the tablets produced from the 650 mg pellets of 1.09 mm mean diameter.

Formula	Tablet				pellet apparent density (g/cm^3)	Tablet inter-pellet porosity (%)
	thickness (mm)	Diameter (mm)	Mass (mg)	Density (g/cm^3)		
mlge	4.38(0.1)	12.14(0.3)	650	1.285(0.10)	1.393(0.05)	7.75(1.0)
Mlge	4.36(0.1)	12.13(0.9)	650	1.291(0.05)	1.343(0.03)	3.81(0.2)
mLge	4.36(0.05)	12.13(0.7)	650	1.292(0.06)	1.377(0.05)	6.16(0.7)
mlGe	4.39(0.03)	12.12(1.0)	650	1.285(0.04)	1.348(0.07)	4.66(0.4)
MLge	4.37(0.2)	12.13(0.5)	650	1.290(0.02)	1.343(0.08)	3.95(0.3)
MlGe	4.39(0.1)	12.12(0.7)	650	1.285(0.01)	1.332(0.10)	3.56(0.4)
mLGe	4.39(0.1)	12.11(1.0)	650	1.286(0.03)	1.350(0.10)	4.76(0.5)
MLGe	4.38(0.2)	12.12(0.9)	650	1.288(0.08)	1.324(0.07)	2.75(0.1)
mlgE	4.36(0.1)	12.11(1.0)	650	1.294(0.07)	1.410(0.06)	8.18(0.9)
MlgE	4.36(0.3)	12.11(0.7)	650	1.295(0.05)	1.309(0.08)	1.05(0.1)
mLgE	4.35(0.3)	12.11(0.6)	650	1.300(0.06)	1.380(0.09)	5.83(0.2)
mlGE	4.36(0.5)	12.10(0.8)	650	1.297(0.09)	1.340(0.10)	3.18(0.2)
MLgE	4.34(0.3)	12.11(0.7)	650	1.302(0.10)	1.312(0.07)	0.74(0.0)
MlGE	4.37(0.4)	12.10(0.9)	650	1.295(0.10)	1.307(0.06)	0.88(0.0)
mLGE	4.36(0.2)	12.10(1.0)	650	1.297(0.10)	1.337(0.09)	2.99(0.1)
MLGE	4.36(0.3)	12.10(0.8)	650	1.296(0.09)	1.298(0.08)	0.18(0.0)

Table-3.3.10: Post-die tablet dimensions, apparent true density of the pellets, and inter-granular porosity of tablets of the 16 different formulations from the 2^3 factorial designed experiment. The letter "e" stands for the binding liquid without ethanol, while "E" describes the presence of ethanol mixed with water. The values in the parenthesis indicats the standard deviation.

not be the best way of comparing the pressures. Compaction to the same tablet density for materials of very low apparent density could result in a lower porosity, which induces higher friction, thus higher compressing force when compacted to the same volume. These results were in agreement with those observed on the pellets of binary mixture (Section 3.1 and 3.2). The lower the total porosity of the compacts the higher was the compaction pressure required (see p-173 for further works on the same pressure).

3.3.3.2 VOLUMETRIC ELASTIC RECOVERY

According to the reading of the dimensions of the compacts form the micrometer after 72 hours of their ejection and storage at ambient temperature and humidity, all the tablets increased in volume from their immediate out of die volume by more than 10%. (Table-3.3.8). The in die dimensions were not taken as the original tablet dimensions to reduce the error due to the deformation of the die or the punch of the instrument. Nevertheless, there was a remarkable instant elastic relaxation after the punch was lifted. This can be seen in the considerable thickness difference of the out of die tablets based on different formulations. The average effect of each excipient in the extent of elastic recovery was different (Fig-3.3.6).

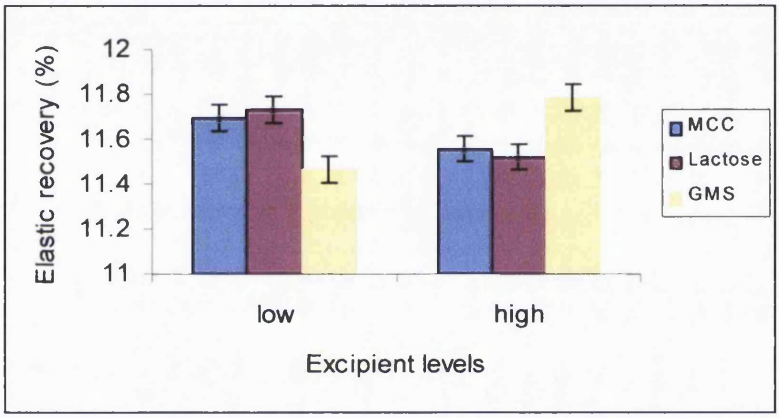


Fig-3.3.6:- The average effect of each excipient at its low and high levels of the factorial designed experiment on the volumetric elastic recovery of the tablets produced from the 650 mg pellets of 1.09mm mean diameter.

MCC had a very small reduction effect in the volumetric elastic recovery (VER) of the tablets. This was due to its irreversible plastic deformation as indicated by (eg. Rees and Rue, 1978 and Mashadi and Newton, 1987a,b). Lactose had a relatively higher VER reduction effect, which could presumably be due to the fragmentation of the pellets, as its consolidation is primarily by fragmentation (Hersey et al. 1973). This was clearly illustrated in pellets containing highest lactose as a dry mass (Plate-3.1b, see p-178). Wang et al. (1995) observed a similar decrease in elastic recovery of the MCC pellets with the addition of lactose and related it to the decrease in viscoelasticity of the specimen. Pellets containing a relatively higher amount of GMS were the only ones which increased the elastic recovery. This could presumably be due to the recoverable elastic deformation, as their in die porosity was observed to be about 1% below zero.

A.

Factor	mean change in elastic recovery (%)	d.f.	Mean Square	F	P
MCC	-0.30	1	37	2.8	-
Lactose	-1.75	1	86	6.3	-
GMS	2.70	1	208	15.2	0.02

B.

Factor	mean change in elastic recovery (%)	d.f.	Mean Square	F	P
MCC	-0.07	1	1.12	-	-
Lactose	-2.50	1	1540	67	0.014
GMS	1.06	1	276	12	-

Table-3.3.11:- *Yates Analysis of the factorial designed experiment for the determination of the mean effect of each factor on the properties of the pellets of 1.0-1.18mm size fraction. Where (A) are pellets formed with water and (B) formed with water/ethanol. The error mean square was determined from MLg, MlG, and MLG in both cases with 3 d.f.*

Only the mean effect of GMS had a statistically significant effect on the volumetric elastic recovery of the tablets, when water was the only binding liquid (Table-3.3.11a). In the presence of ethanol, however, the effect of lactose was extended further to a significant value ($P<0.05$), while the effect of MCC and GMS was reduced to insignificant levels. Generally, incorporation of ethanol as a liquid binder reduced the effect of each formulation in the VER (Table-3.3.7 b). This indicates the rearrangement of the primary particles in the space they occupy in the porous pellet was irreversible. This was proven by the permanent deformability of the de-aggregated pellets containing ethanol.

3.3.3.3 TENSILE STRENGTH

The tensile strength of all the tablets produced from 650 mg pellet compacted to the same dimensions and 700 mg pellets compacted by the same pressure was relatively low. Some of them could hardly be ejected form the die. Therefore extra care was taken during measuring the dimensions of the ejected tablets before crushing them diametrically. In the diametrically crushing experiments, not all the tablets failed in tension through their diameter. Especially the tablets containing a higher GMS had a triple cleft failure. All the failures were between the

pellets boundaries showing a weaker connection. The dominant presence of MCC could be the main reason for the less intergranular attachments. All the formulations produced tablets of different tensile strength when 650 mg of pellets were compacted(Table-3.3.8). The magnitude of the influence of each formulation was dependent on the proportions of the excipients' presence and the type of binding liquids (Fig-3.3.7a- f).

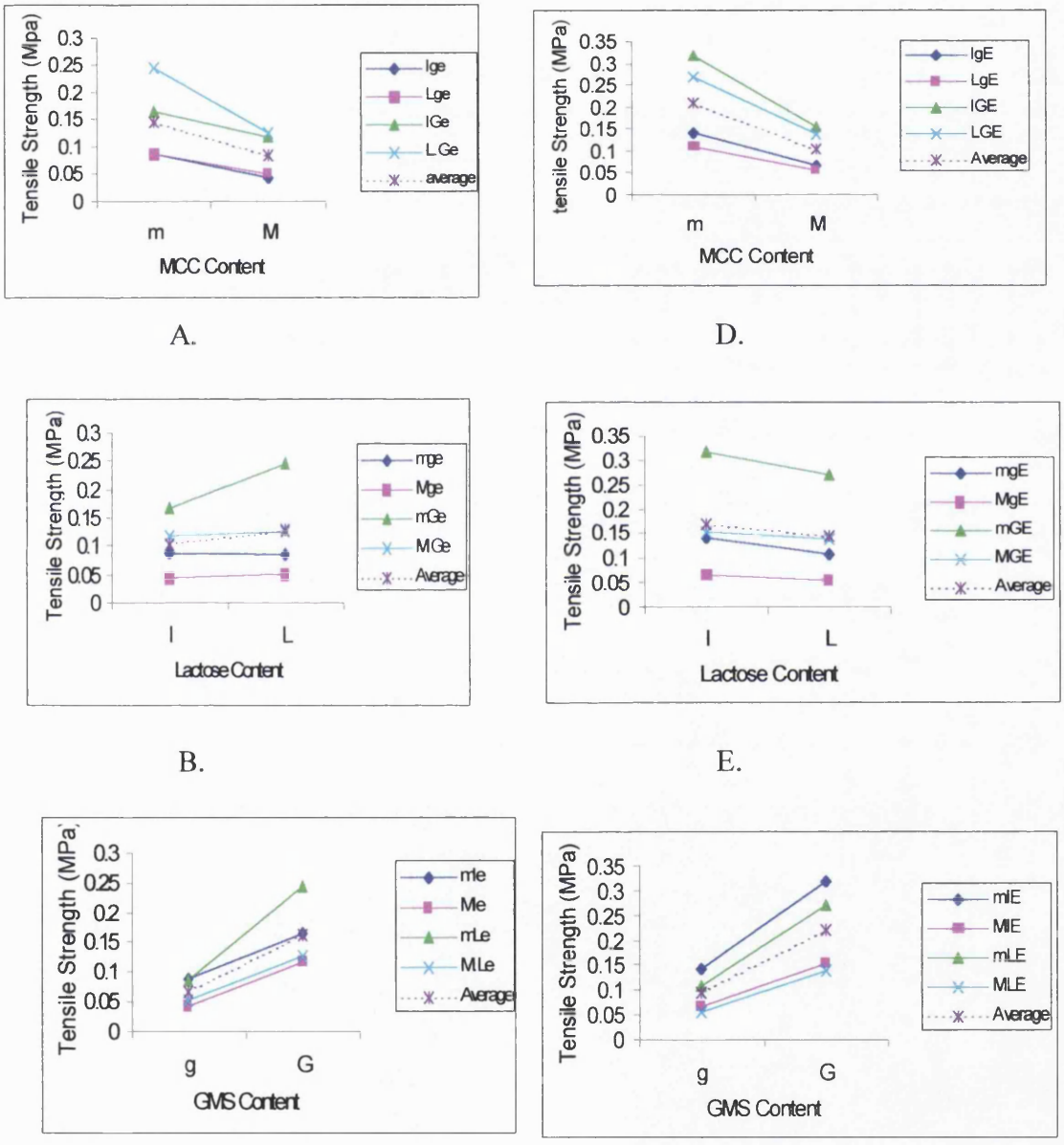


Fig-3.3.7:-The effect of MCC (A and D), lactose (B and E), and GMS (C and F) at their lower (lower case) and higher (upper case) levels on the tensile strength of the tablets produced from 650 mg pellets of the factorial designed experiment. Pellets mean diameter was 1.09 mm. The letter "e" stands for those formed without ethanol, while "E" stands for those formed with the mixture of water and ethanol., n=5.

The tensile strength of these compacts of different formulae related to the relative pressure needed to compress the same mass of the pellets to the same volume (Table-3.3.8). This means, those pellets compressed by the relative higher pressure produced stronger tablets.

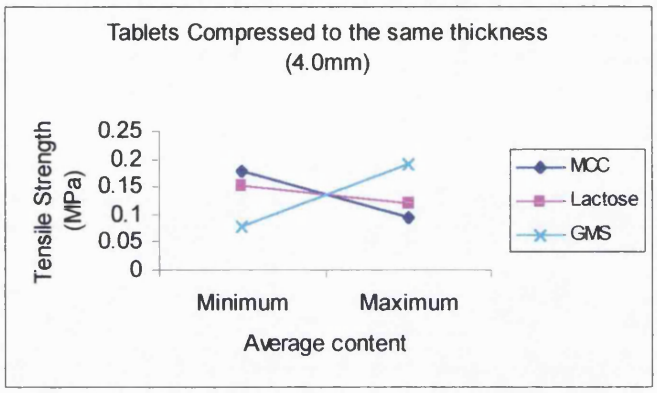


Fig-3.3.8:- The average effect of each factor (excipients) on the tensile strength of 650 mg tablets produced from pellets of the factorial designed experiment. The mean diameter of the pellets was 1.09 mm.

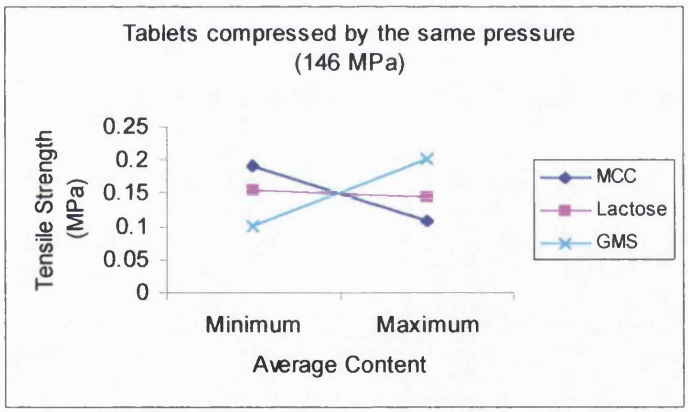


Fig-3.3.9:- The average effect of each factor (excipients) on the tensile strength of 700 mg tablets produced from pellets of the factorial designed experiment.The mean diameter of the pellets was 1.09 mm.

Increase in the MCC content reduced the tensile strength by the highest extent at all levels of the other factors, while increase in the GMS content increased values of the tensile strength to the highest extent (Fig-3.3.8 and 9). Although to a smaller extent, an increase in the lactose content increased the tensile strength when pellets were formed with water, but reduced slightly when formed with ethanol/water. The statistical analysis of the overall effect of each factor, revealed that MCC had a significant effect at ($P<0.05$) when only water was a binding liquid, but at ($P< 0.01$) when water was mixed with ethanol (Table-3.3.11).

A.

Factor	mean change in tensile strength (%)	d.f.	Mean Square	F	P
MCC	-70.1	1	7626	9.90	0.045
Lactose	26.1	1	1128	1.46	-
GMS	109.1	1	18721	24.29	0.008

B.

Factor	mean change in tensile strength (%)	d.f.	Mean Square	F	P
MCC	-74.00	1	22684	152.9	0.001
Lactose	-18.75	1	1458	9.8	0.051
GMS	88.20	1	32258	217.4	0.001

Table-3.3.12:- *Yates Analysis of the factorial designed experiment for the determination of the mean effect of each factor on the properties of the tablets. Where (A) are pellets formed with water and (B) formed with water/ethanol. The error mean square was determined from MLg, and MLG in both cases with 2 d.f.*

The effect of lactose was not significant on either case, while GMS had a significant effect in increasing the strength of the compacts ($P<0.01$) for both solvent compositions. The relatively small force needed to compress MCC-rich pellets to the same pre-determined volume could be assumed insufficient to force the surface of the pellets to closer proximity to allow interaction at a molecular level. This assumption was, however, disproved when MCC pellets were tableted by using higher pressure, and yet they were very weak. This observation agrees with the findings in the previous sections. Similarly, Maganti and Celik (1993) showed insensitivity of the strength of MCC pellet compacts to compaction pressure compared to MCC powder compacts. On their compaction, the pellets required lower pressure than the powder to obtain the same porosities. However, the tensile strength of the ejected powder compacts was significantly higher than that of pellets. Therefore, they concluded that the ability of the material to reduce in volume when compressed even to a higher extent did not ensure the formation of strong compacts. Thus, the main reason could be the change in surface nature of the pellets during their formation, which resulted in poor inter-granular coherence.

Even at its lowest content, since MCC constituents about 66.6%w/w of the dry mass, its effect dominated the addition of only 10%w/w of the dry mass of any other factor. However, addition of 10%w/w of lactose was at least able to reduce the tensile strength reduction effect of MCC in the presence of ethanol (Table-3.3.11 b). Moreover, its average effect in the absence of ethanol was observed to increase the tensile strength of the pellet compacts. Schwartz et al. (1994) made a similar observation. With the addition of more lactose they observed more fracture of the MCC pellets during compression which resulted to a stronger compact.

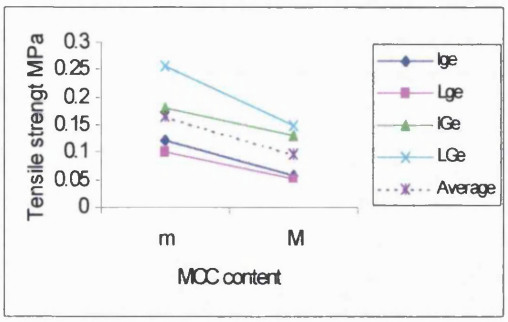
The average increase in GMS content in the factorial designed experiment increased the tensile strength of the compacts to the highest extent (109%). The smoothness of the surface of the compact, and the change in shape of the de-aggregated pellets indicated that the compaction process was by plastic deformation. Such compacts were compressed to the greatest extent. This may have helped the surfaces to come closer which enabled the formation of rigid structures. The increase in temperature due to the inter-particular friction, as these pellets were compressed by a higher force, could also be the reason for the formation of "fusion welding" as the melting point of GMS is relatively lower.

There was no any interaction between the factors when the pellets were formed with water and ethanol mixture. In the absence of ethanol, however, interaction was observed when lactose and GMS were at their higher levels. This could be due to the brittle nature of lactose was counteracted by the deformable nature of GMS.

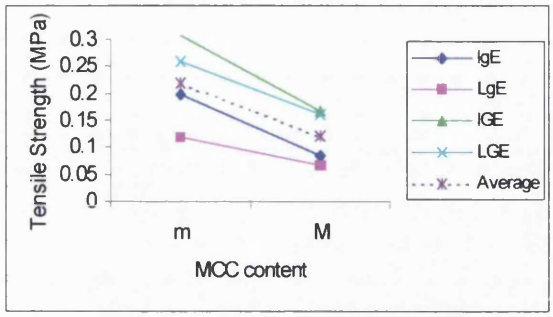
This work revealed that the strength of the tablets from the eight different excipient compositions increased when the ethanol was incorporated into the liquid binders. This effect was minimal when lactose was at its higher level. The increase in porosity of the pellets, hence deformability, enhanced the compressibility which inturn formed strong compacts as also reported by Millili and Schwartz (1990) and Johansson and Alderborn (1996). The smoother surfaces with indistinct pellet boundaries supports this assumption.

Seven hundred-milligram pellets from each of the formulations were also compacted to tablets by approximately the same pressures (146 MPa and 130MPa). In both cases, the relative effect of each formula, and the average effect of each factor on the tensile strength of the

tablets were of the same order. Thus, the analysis of the results of those tablets compressed by 146 MPa would be sufficient (Fig-3.3.10).



A.



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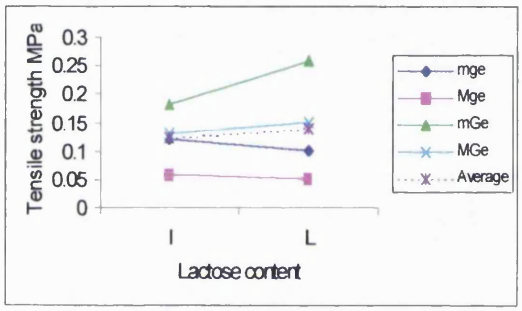
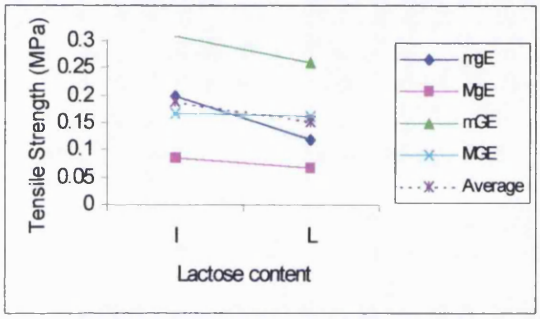
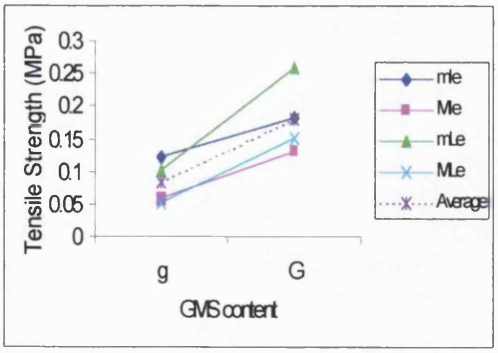


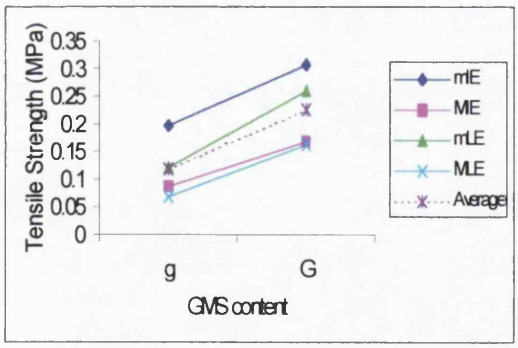
B.



E.



C.



F.

Fig-3.3.10:-The effect of MCC (A and D), lactose (B and E), and GMS) (C and F)at their lower (lower case) and higher (upper case) levels on the tensile strength of the tablets produced when 700 mg pellets of the factorial designed experiment were compressed by a constant 146 MPa. Pellets mean diameter was 1.09 mm. The letter "e" stands for those formed without ethanol, while "E" stands for those formed with the mixture of water and ethanol. n=5.

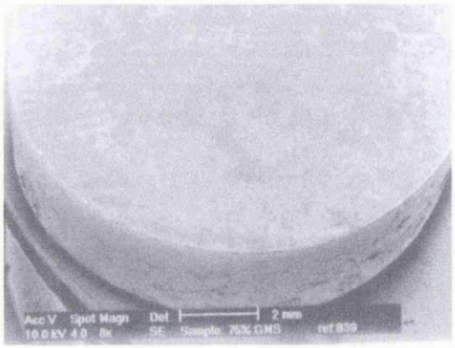
This work showed that the difference in the strength of the tablets compacted by 130 MPa and 146 MPa was very small specially for the GMS-rich pellets. This could be due to the ease of their deformability, which reduced their porosity as a result of lower pressure to form compacts of reasonable strength. Conversely, it could be due to the excessive volumetric elastic recovery as a result of a higher elastic deformation caused by a higher pressure.

The results indicate the dominance of MCC in these experiments compared to the work of Maganti and Celik (1995) who used MCC content as low as 20%w/w of the dry mass. Their lactose-rich MCC pellet compacts were relatively stronger when they were compressed by a higher force to 87% solid fraction than by a lower force to 80% solid fraction. In this work, the overall effect of each factor was the same when a definite mass of the pellets was compressed to the same volume or compressed by the same force (Fig-3.3.9 and10). The addition of 10%w/w GMS in each of the eight formulae containing a minimum amount of GMS resulted in an average increase of tensile strength of the compacts by 135%. The addition of 10%w/w of MCC in each of the eight formulae containing minimum amount of MCC resulted in an average decrease of the tensile strength of the compacts by 50%. Similarly increase of 10% w/w of lactose to the dry mass had only 15% reduction effect on tensile strength. Moreover, the rank order of the effect of these three factors was the same even when the composition of the binding liquid was altered.

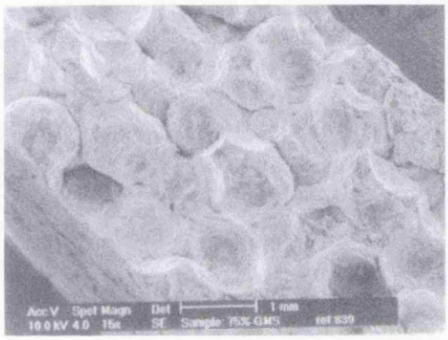
3.3.3.4 CONCLUDING REMARKS

The overall effects of each of the formulation factors have been extensively studied at two different set of factorial designed experiments. This revealed that the stronger MCC-rich pellets needed a relatively lower compressing pressure and produced weaker compacts which have lower tendency of volumetric elastic recovery. This was attributed to their plastic nature and the effect of the pelletization process on the surface of their pellets. The dominance of MCC in the dry mass of the formulations in this study, relatively hindered a significant response due to the addition of the other excipients. However, the low percentage added showed a considerable change in the properties of the pellets which were moderately reflected on the properties of their compacts. GMS-rich pellets increased the compression force, and produce compacts of greater strength and higher volumetric elastic recovery. This was assumed to be due to its greater deformability and lower apparent density. The lactose-rich pellets were observed to have moderately higher compressing pressure due to their relatively

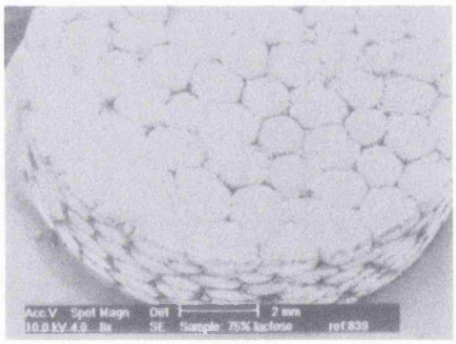
stronger pellets. The failure of these pellets during compaction was the main reason for the least volumetric elastic recovery of their compacts. Moreover, the exposure of new surfaces enabled the pellets to form inter-granular connection network to produce tablets of greater strength than the MCC-rich pellets.



3.1 a



3.1b



3.2a

3.2b

Plate-3 (1a) the surface, (1b) the cross-section of pellet compacts having a higher amount of glyceryl monostrearate; (2a) the surface, (2b) the cross-section of pellet compacts having a higher amount of lactose.

CHAPTER- FOUR

THE EFFECTS OF LIQUID BINDERS

The objective of this chapter is to observe the effects of the different liquid binders on the mechanical properties of MCC pellets, their compaction mechanism and the properties of their compacts. First, the effect of moisture content was considered, where MCC was mixed with different amount of water in the production of pellets. Secondly, MCC pellets were prepared with different water/ethanol mixture (100/0, 80/20, 60/40, and 40/60) as liquid binders. Both liquids evaporated during drying process leaving MCC particles to form the skeletal structure of the dry pellets. Thirdly, a similar water/glycerol proportions were used as liquid binders to produce MCC pellets. Glycerol was retained inside the pellets even after drying process. After a detailed study on the gradual change in the properties of the pellets with a stepwise change in liquid binders, a 2^3 factorial designed experiment was performed to study the effects of each liquid binder at two different levels of the others. Moreover, their ternary mixture at different proportions was used to produce 18 different batches of pellets. The structural (2.2.2) and mechanical (2.2.3) properties of the pellets were analysed followed by their compaction mechanism (2.2.4.1) and the properties of the compacts (2.2.4.2).

4.1 THE EFFECTS OF MOISTURE CONTENT

In this section, formulations containing only MCC were tested for their sensitivity to moisture content. Four different MCC : Water ratios (10/11, 10/10, 10/9, and 10/8) were analysed in terms of extrusion force, mechanical properties of pellets, and their compaction mechanism. The compacted pellets, for all moisture contents, produced very soft tablets which failed immediately after ejection form the die.

The extrusion force/time profiles of the MCC wet mass containing four different moisture contents indicated that there was an increase in ram extrusion force, at the steady state stage, with the decrease of moisture content (Fig-4.1.1). This was similar to the results of Harrison et al. (1985), Pinto, (1992) and Bains et al.(1991) even though the first two authors had added lactose while the latter had added barium sulphate to the MCC formulations. This could presumably be due to the decrease in die wall shear stress of MCC extrudate with the increase in moisture content of the formulation. During the process, water could have moved towards the die wall and formed a thin layer upon which the shearing took place, hence reduction in

the extrusion force resulted (Benbow and Bridgwater, 1993). Thus water seems to have served as a lubricant.

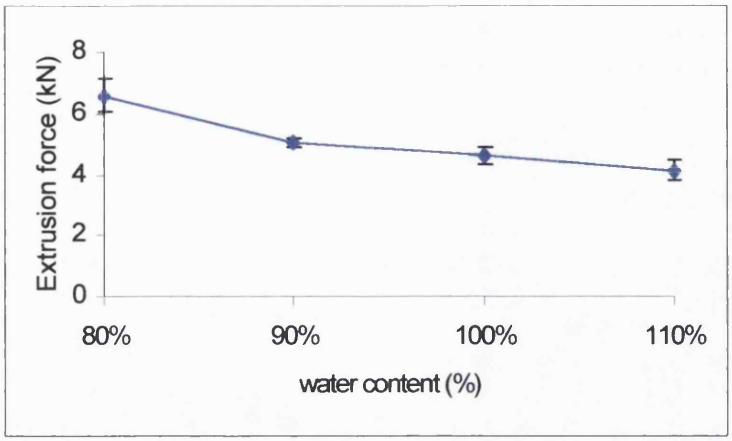


Fig-4.1.1:- The effect of the water expressed as % of the mass of MCC on extrusion force at ram speed of 200 mm/min.

The pellet size and size distribution was affected by the original water content of the wet mass. With the increase of water content the mean pellet diameter and size distribution of the pellets increased (Table-4.1.1). The extrudates produced from the formulation having 110% water content compared to the MCC mass, agglomerated during spheronization to form very large "balls", hence no further analysis was made on them. In the 1.0-1.4 mm size fraction, 13.3 %, 39.4%, and 45.8% of the pellets were retained form those formulations produced with 80%, 90%, and 100% water compared to the dry mass. The increase in modal proportion was also observed to be in reverse order to the water content of the formulations (Table-4.1.1). Fielden et al. (1993) made a similar observation. They reported a subsequently shift of the number and weight distribution curves to the right (larger size) at 37.5%w/w moisture content of their MCC and coarse lactose formulation, which indicates an increase in pellet size and distribution of sizes as spheronization progressed. For 33.3%w/w moisture content of the same formulation, however, they observed a shift towards the left. Otsuka et al. (1994) reported a similar findings. They obtained a larger mean particle size of granules from those produced by extrusion/spheronization process having 250ml/kg water than those having 150ml/kg water content. This shows that the extrudate with lower water content had insufficient plasticity, as a result they shattered on the spheroniser plate generating a large quantity of fines.

Structural and Mechanical Properties of Pellets	Amount of water to the mass of MCC (%)		
	80%	90%	100%
Mode (0.71-1.0mm size fraction) in(%)	85.9	59.3	47.3
Median pellet diameter (mm)	0.60	0.75	0.85
Interquartile range (mm)	0.25	0.40	0.45
Porosity (sealed) (%)	11.93±0.15	11.38±0.16	9.11±0.14

Table-4.1.1:- The size and size distribution of MCC pellets produced with different water content and the porosity of pellets in the 1.0-1.18mm size fraction.

The porosity of the pellets, as measured by helium pycnometer, was also dependent on the original moisture content of the wet mass. The 'sealed' porosity of pellets decreased with the increase of water content (Table-4.1.1). Otsuka et al. (1994) also observed a decrease in porosity with increase in water content. Their result from mercury porosimetry showed that the amount of water affected the internal porosity of the spherical granules. It decreased with increased in water proportion. The higher water content may have helped the MCC fibres to slip along each other and be rearranged in a more packed way to produce pellets of less porosity.

Extrudates from 80% water content to the dry mass could not produced spherical pellets. They were very dry and rigid and could not be rounded, thus, no more further analysis was performed. Pellets from 90% and 100% water content, however, were relatively spherical (0.53 shape factor) and the effect of the moisture content on the mechanical properties of the pellets of 1.0-1.18 mm size fraction was assess and compared. Pellets from the higher water content were stronger (Fig-4.1.2a), less deformable (Fig-4.1.2b), with higher linear strain (Fig-4.1.2c) and 'elastic modulus' (Fig-4.1.2d). Moreover, the shear strength of pellets produced with 100% water content to the dry mass(2.44 MPa) was 24% higher than those produced with 90% water (1.97 MPa). The overall shear strength was, however, about a third of the tensile strength. In their work to determine the effect of water added on the mechanical property of spherical pharmaceutical granules produced by extrusion/spheronization process, Otsuka et al. (1994) found a decrease in friability of the granules with the increase of added water. The magnitude of interaction between the different MCC fibres Millili et al. (1990)

could have been enhanced by increase in moisture content. In addition a decrease in internal porosity with increase of water content (Table-4.1.1) could have reduced the propagation of the crack, hence resisted failure.

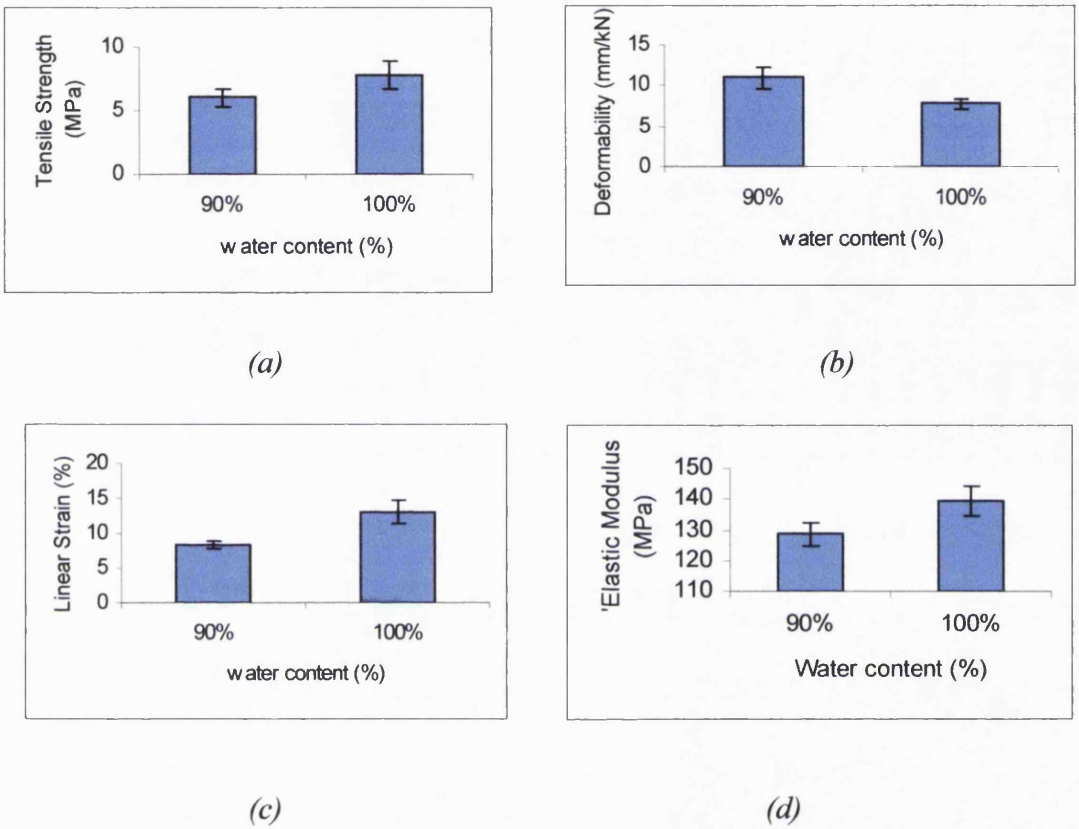


Fig-4.1.2:- Tensile strength (a), Deformability (b), Linear strain (c), and 'Elastic modulus' (d) of pellets of 1.0-1.18 mm size fraction produced by different water percentage to the mass of MCC.

The increase in deformablity with decrease in moisture content could be due to the increase in porosity of the pellets. The primary particles in the porous surrounding may have got enough space to rearrange themselves and deform the specimen to a greater extent before it broke. The 'elastic modulus', however, was in the reverse order, showing the rigidity of the nonporous pellets. This again could be due to the higher stress needed to elastically deform the nonporous pellets. Pellets with the higher moisture content had a greater linear strain, which seems to be related to the strength of the pellets. The stronger pellets were strained to a greater extent before failure compared to the weaker pellets which snapped instantly.

The difference in magnitude of the compressing pressure, measured when 600 mg pellets

produced form formulations of different water content were compacted to the same tablet thickness as described in (section 2.2.4 A), was minute, although it was slightly higher in pellets form formulations of higher water content. This could be due to the difference in strength of the pellets. However, both set of pellets had approximately the same force/ displacement curves (fig-4.1.3) and Heckel plots (Fig-4.1.4).

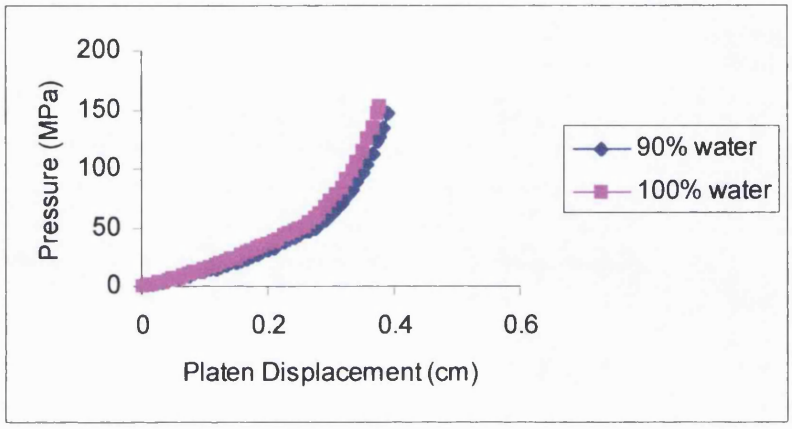


Fig-4.1.3:- The effect of different water percentage to the mass of MCC on the pressure/displacement profile during compaction of 600mg pellets of 1.0-1.18mm size fraction.

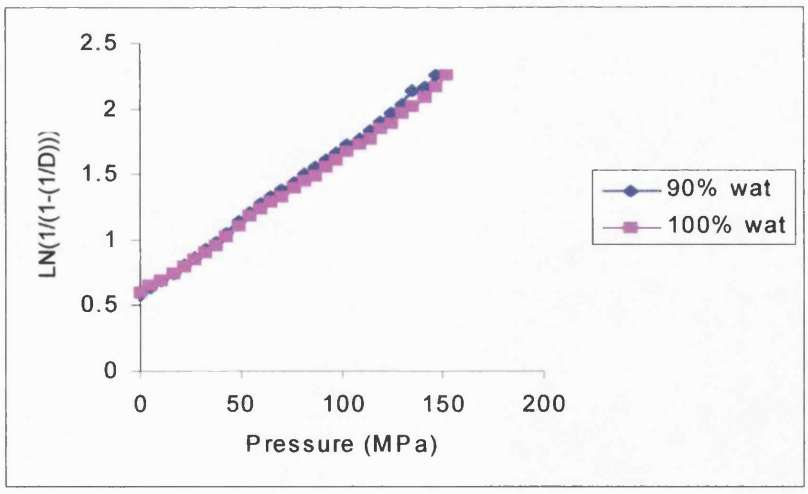


Fig-4.1.4:- The effect of different water percentage to the mass of MCC on the Heckel plot for 600mg pellets of 1.0-1.18mm size fraction.

A slightly higher compaction pressure of the pellets produced with higher water content and a slight higher displacement in the force/displacement curve of the pellets produced with the lower water content was observed. The displacement could be due to the relative higher

porosity of the pellets. That is because these pellets had to be compressed to a greater extent from their porous higher volume to the same final tablet thickness. The similarity in the Heckel plot, however, indicates the presence of the same material.

None of the pellets produced strong compacts which could be analysed in terms of their strength and dimensions. This could be due to their surface nature which did not enable them to cohere and form rigid compacts. However, from this work it could be concluded that the effect of moisture content upon the properties of MCC pellets produced by extrusion spheronisation process is considerable. With the increase of water content, the mean pellet size and size distribution, tensile strength, 'elastic modulus' and linear stain of the pellets increased, while the deformability, and "sealed" porosity decreased. The difference in compaction mechanism was, however, marginal as was noted by the similarity in force/displacement curve and Heckel plot. The reason for such similarity could be the water content limit within which spherical pellets could be formed, for it was not possible to produce pellets from a wide range of water content.

4.2 THE EFFECTS OF ETHANOL AS A LIQUID BINDER

In this section the dry mass to the liquid ratio was 1:1. Pellets were produced, using 0%, 20%, 40% and 60%w/w ethanol in ethanol/water mixture as the liquid binders, by a standard extrusion and spheronization procedure as explained in (section 2.2.1.2). The production of reasonable amount of pellets was possible only when the proportion of ethanol was 60/40 to water or less. Above this proportion, only very few pellets of the required size fraction could be produced. This was primarily due to the squeezing out of the solvents through the die during ram extrusion leaving a drier mass in the barrel which was difficult to extrude. Secondly the extrudates produced were very weak and consequently most of them were ground to powder during the process of spheronization within the first minute.

4.2.1 THE PROPERTIES OF THE PELLETS

There was a slight decrease in extrusion force with an increase in ethanol proportion in the binding liquid mixture (Fig-4.2.1). In a similar experiment when the length to diameter ratio of the die was increased from 5 :1 to 15 : 1.5, as well as when the wet mass was left open for more than 30 minutes before extrusion, the steady state stage of the extrusion force was higher in value. These show the increase in upstream force (Harrison et al. 1987) of the

process with increase in surface area of the inner die wall and with the increase of the ethanol proportion. At higher surface area of the inner die wall the steady increase in extrusion force was considerable mainly with the increase of the extrusion speed. The uncontrolled evaporation of the 'volatile' ethanol reduced the liquid content of the wet mass when it was left open, hence, reduction in plasticity and die lubrication could be the reasons for the increase in steady state extrusion force after the wet mass was left open.

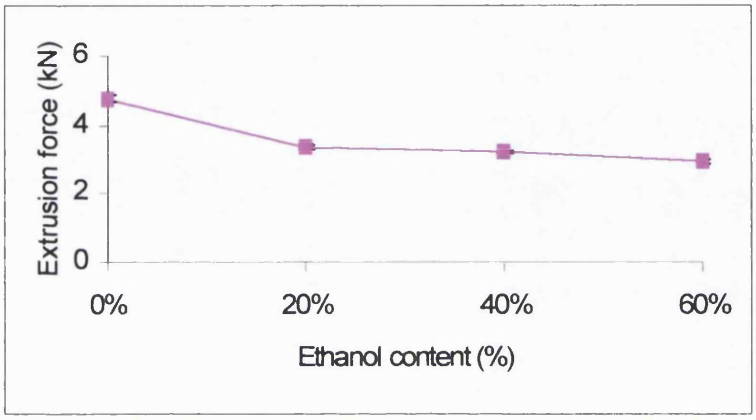


Fig-4.2.1 Extrusion force variation with the ethanol proportion in the water/ethanol liquid binder.

There was a consistent decrease in the median pellet size with an increase of ethanol content (Table-4.2.1). Moreover, there was a decrease in higher pellet size fraction with an increase of ethanol content. Ninety five percent of the pellets produced by 60%w/w ethanol content were collected in the sieve sizes of less than 1.18 mm aperture, while the population was 91% for 40%w/w ethanol, 84% for 20%w/w ethanol and only 63% for those prepared by 100% w/w water content as a liquid binder. This could probably be due to their fragmentation during spheronization process. Millili and Schwartz (1990) made a similar observation of pellet fragmentations. The range of the size distribution was, however, more or less the same as indicated by the interquartile range (Table-4.2.1).

The bulk and tapped density of the pellets were also significantly reduced with the increase of ethanol content (Table-4.2.1). This was not due to variation in their packing, as indicated by the similar values for the Hausner ratio, but the difference in their effective density (Table-4.2.1). The total porosity of the pellets, as calculated from the effective and apparent pellet density, increased with the increase of the ethanol content in the formulation (Table-4.2.1).

Structural and Mechanical Properties of Pellets	The proportion of ethanol in the binding liquid (%)			
	0%	20%	40%	60%
Mode* (%)	36.4	48.2	52.9	61.8
Median particle diameter (mm)	1.01	0.98	0.89	0.89
Interquartile range (mm)	0.34	0.18	0.35	0.34
Bulk Density (g/cc)	0.877(0.2)	0.833(0.1)	0.694(0.1)	0.602(0.1)
Tapped Density (g/cc)	0.935(0.2)	0.885(0.2)	0.769(0.1)	0.658(0.1)
Hausner ratio	1.066(0.1)	1.062(0.1)	1.108(0.1)	1.093(0.1)
Apparent pellet density (g/cc)	1.42(0.06)	1.34(0.07)	1.47(0.09)	1.52(0.10)
internal porosity (sealed) (%)	7.72(0.5)	12.85(0.1)	4.67(0.3)	1.16(0.1)
Effective pellet density (g/cc)	1.32(0.10)	1.15(0.10)	1.00(0.05)	0.86(0.03)
Total pellet porosity (%)	14.04(1.5)	25.13(1.7)	34.85(2.3)	44.12(3.4)
Surface area of pellets (sq.m/g)	0.0017(0.00)	0.018(0.00)	1.760(0.05)	5.809(0.03)
Pore volume (ml/g) for pore diameter range of 0-200 nm	0.00019 (0.0000)	0.000185 (0.0000)	0.00611 (0.0000)	0.01997 (0.0020)
Shape factore, e_R	0.62(0.07)	0.62(0.06)	0.65(0.07)	0.65(0.08)
Aspect ratio	1.083(0.2)	1.076(0.2)	1.064(0.2)	1.065(0.3)
Circularity	0.928(0.1)	0.931(0.1)	0.933(0.1)	0.919(0.2)
Projected sphericity	0.892(0.1)	0.895(0.1)	0.906(0.1)	0.895(0.2)

Table-4.2.1:- Structural characteristics of MCC pellets of 1.0-1.18 mm size fraction, prepared from different proportions of ethanol/water mixtures as liquid binders. The values in the parenthesis indicates the standard deviation.

**- The mode was the 1.0 mm - 1.18 mm size fraction.*

The results on porosity were similar to that reported by Millil and Schwartz (1990) and Johansson et al. (1995). The apparent density, however, had the opposite trend. An increase in ethanol content was observed to increase the apparent density of the pellets (Table-4.2.1) and reduce the percentage of the sealed pores. However, the open pore volume (for pore diameter range of 0-200 nm) of the pellets produced with a higher proportion of ethanol was

found to be higher (Fig-4.2.2). In pellets from 20% ethanol content, the total pore volume was approximately equal to those pellets produced with only water, while the surface area was 10 fold higher. However, the values for surface area of these two batches of pellets were below the equipment measurement limit, which was indicated by the a correlation factor of less than 0.5 in the linear portion of the BET equation (18). For pellets produced with 40% and 60% ethanol content, where the correlation coefficient was 1.00, the surface area and the total pore volume of the latter was more than three fold that of the former (Table-4.2.1). This illustrates the accessibility of helium molecules (see 2.2.2.3) deep into the open pores, hence reduced the proportion of the sealed pores to approximate the apparent density of pellets from higher (eg. 60%) ethanol content formulations to that of apparent particle density of MCC powder. The variation in the distribution of the volume of the open pores in pellets was also considerable (Fig-4.2.3). At higher ethanol content (40%, and 60% of the liquid binder), more than 60% of the pore volume was in pore diameter above 20 nm, while it was only 20% in those pellets from lower (0% and 20%) ethanol content. Moreover, only 10% of the pore volume of the former formulations was in pore diameter range of less than 6 nm, while for those produced with less ethanol content (0% & 20%) it was about 30%. In terms of absolute value of pore volume, the values for those produced with higher ethanol content were higher at all pore diameter ranges (Fig-4.2.2).

All the pellets were nearly spherical. They had a shape factor (Podczeck and Newton, 1994) from nearly 0.6 up to 0.66 (Table-4.2.1). Since this was above the limit for acceptable sphericity, according to Podczeck et al. (1999a), the effect of shape on measuring all the properties of the pellets based on their diameter could be assumed unaffected, including the determination of effective pellet density. Even though they did not provide quantified value of shape Millili and Schwartz (1990) stated that the size uniformity and sphericity of the pellets decreased with an increase of ethanol content. However the reverse was observed here. There was a gradual increase in pellets sphericity with increase of ethanol content. This could be due to the softness of the pellets, which enabled them to deform easily to provide a more round shape during spheronization. The packing and flowing property of the pellets could also be noted to have been less affected by the surface roughness and sphericity of the pellets, for this measuring technique put both sphericity and surface nature in consideration.

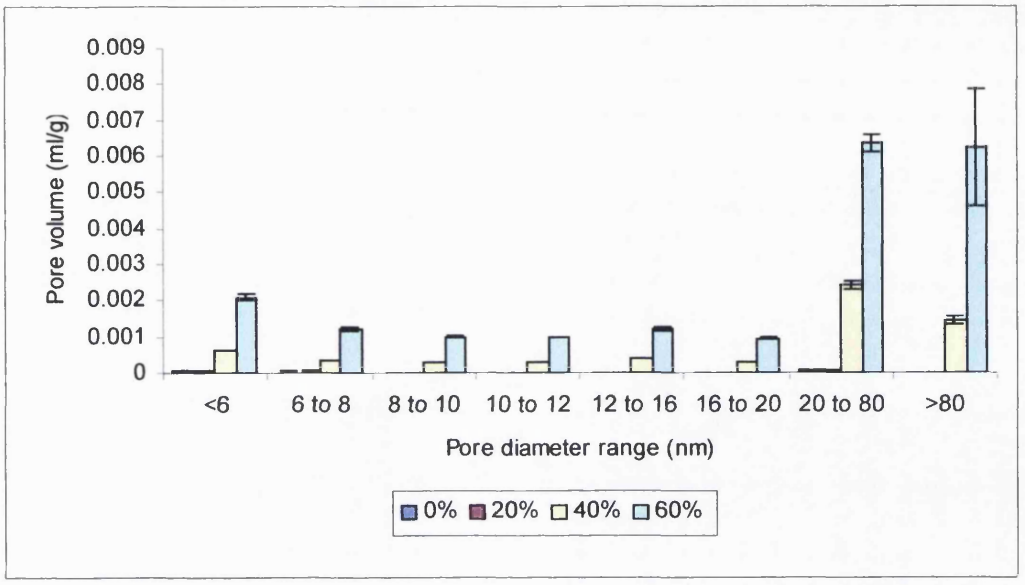


Fig:4.2.2:- The volume of pores of different diameter range measured form MCC pellets of 1.0 -1.18 mm size fraction produced from different ethanol proportion in the ethanol/water mixture as liquid binders.

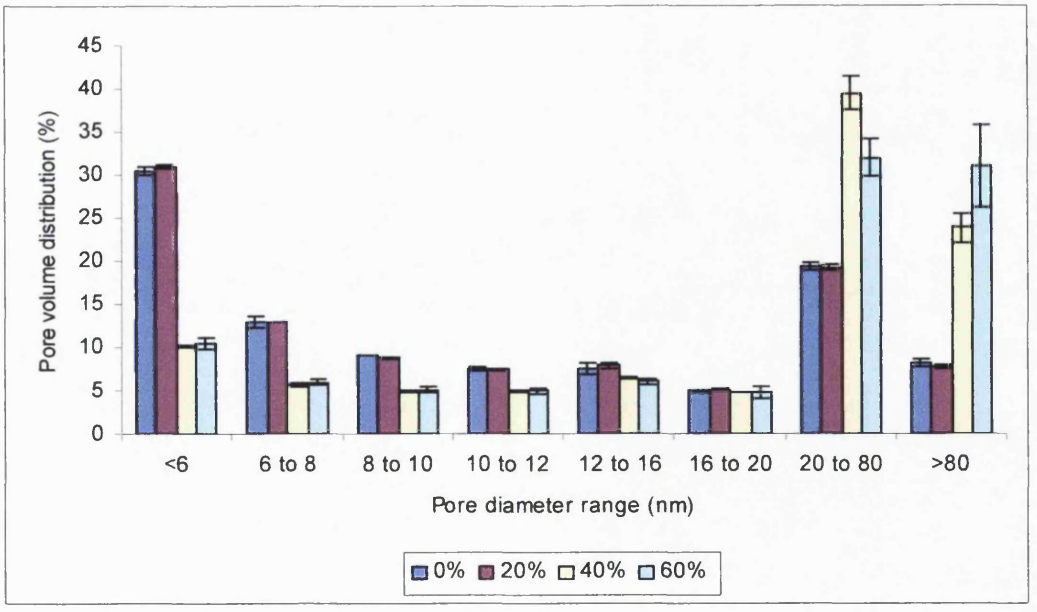


Fig- 4.2.3:- The distribution of pore volume of MCC pellets of 1.0 -1.18 mm size fraction produced from different ethanol proportion in the ethanol/water mixture as liquid binders

The tensile strength of the MCC pellets was reduced with the increase of the amount of ethanol proportion in the liquid mixture (Fig-4.2.4). With a higher ethanol content the pellets snapped instantly during compression and the platen returned automatically. For pellets produced with only water or 20% ethanol, however, a first peak was recorded before the pellets were further strained during diametral compression.

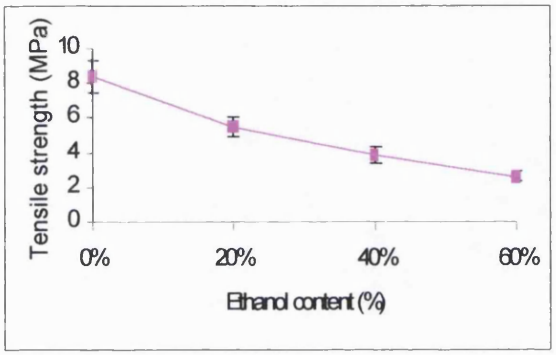


Fig-4.2.4

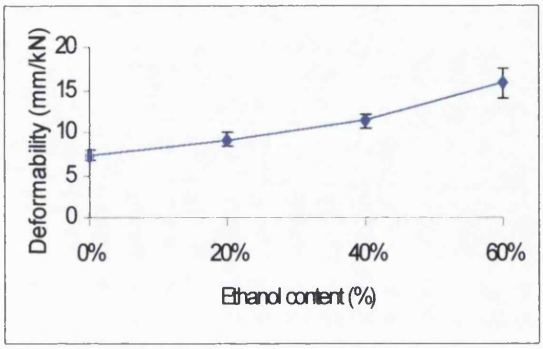


Fig-4.2.5

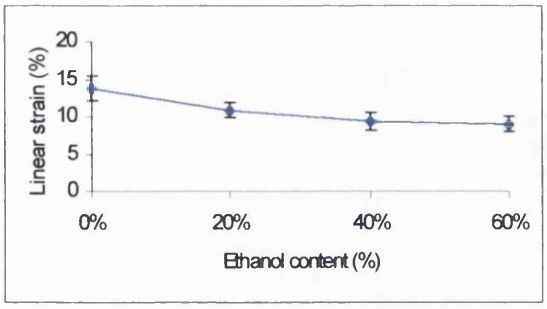


Fig-4.2.6

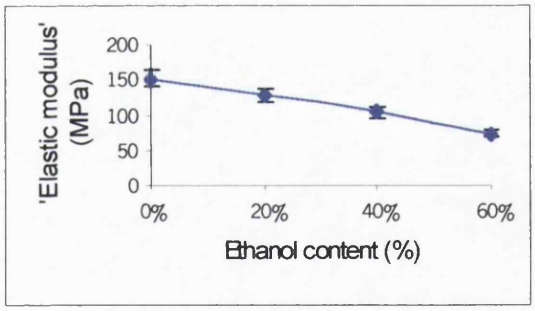


Fig-4.2.7

Fig-4.2.2,3,4&5:- The effect of increase in ethanol proportion in the water/ethanol mixture binding liquid, on tensile strength(4.2.4), deformability (4.2.5), linear strain (4.2.6) and 'elastic modulus' (4.2.7) of pellets of 1.0-1.18 mm size fraction.

The variation in tensile strength was statistically analysed by ANOVA and the difference was significant ($p < 0.001$) compared to those pellets produced with 100% water (Table-4.2.2).

Ethanol content	Mean Tensile strength MPa	Standard Deviation	MS	F	P
0%	8.37	0.98	-	-	-
20%	5.51	0.60	122.9	184.4	< 0.001
40%	3.81	0.45	312.6	529.9	< 0.001
60%	2.61	0.24	497.9	964.8	< 0.001

Table-4.2.2:- Result and ANOVA of the effect of ethanol on tensile strength of pellet from 1.0-1.18 mm size fraction.

Different reasons can be given to the effect of ethanol in reducing the strength of pellets. The increase in porosity, which might act as a flaw to initiate and easily propagate the cracks may be considered the most important. Millili and Schwartz (1990) noticed that an increase in friability of pellets in almost linear way with the increase of the mole fraction of ethanol when ethanol/water mixtures were used as binding liquids. They assumed that it was due to the change in a bonding mechanism with the change of binding liquid composition. In a further study Millili et al. (1990) referred to this effect as a change in autohesion, a term which they used to describe the strong bonds formed by the interdiffusion of free cellulose chain ends across particle-particle interface Millili et al. (1990).

Some Mechanical Properties of Pellets	The proportion of ethanol in the liquid binder (%)			
	0%	20%	40%	60%
Weibull-modulus	9.14	5.84	4.09	2.81
Weibull-constant (MPa)	7.29	8.02	7.37	8.54
Shear Strength (MPa)	2.44±0.12	2.42±0.12	2.97±0.13	3.14±0.14

Table-4.2.3:- The change in physico-mechanical properties of MCC pellets of 1.0 -1.18 mm size fraction with the change in the proportion of ethanol in ethanol/water mixture as liquid binders.

The shear strength was observed to increase with the increase of the ethanol content, although to very small extent, showing an increase in the resistance to fail by shear, while their tensile strength was significantly reduced. This indicated the increase in the brittleness of the pellets with the increase of the ethanol proportion. The decrease in the Weibull-modulus with the

increase of ethanol agrees with this interpretation (Table-4.2.3).

The deformability of the MCC pellets, as determined from the inverse of the force/ displacement curve slope, was also observed to increase with the increase of ethanol content in the formulations (Fig-4.2.5). The space in the porous pellets may have enabled the primary particles to rearrange themselves and to make the specimen to further deform before it broke as suggested by Johansson et al. (1995). Moreover, with the increase in ethanol content, there was a concurrent decrease in the linear strain (Fig-4.2.6) and 'elastic modulus' (Fig-4.2.7) of the pellets. The porous, weak pellets produced with higher ethanol content could not be strained significantly, as they were brittle. The stiffness of the MCC pellets could also have been reduced by the increase in porosity, hence reduce the rigidity of the specimen.

4.2.2 COMPACTION OF PELLETS

The pressure needed to compress 600 mg pellets from the different formulations to tablets of approximately the same dimensions as explained in (section 2.2.4A) was different. With the increase of the ethanol content in the formulations, the pressure increased (Fig-4.2.8).

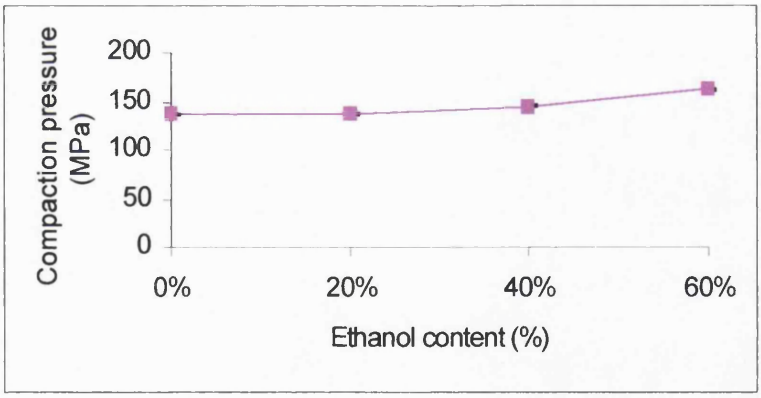


Fig-4.2.8:- The effect of ethanol proportion in water/ethanol mixture as a binding liquid, on the pressure needed to compress 600 mg of MCC pellets to the same tablet thickness

This had a direct relation to the porosity of the pellets as well as to the compressibility of the pellet-beds. The porous, compressible pellet-beds needed a higher compaction pressure. Pellets produced from wet mass of higher ethanol content had lower bulk density. They had to be compressed to a greater extent to reach to the predetermined tablet thickness. This might need more work and pressure to overcome the friction and to crush the pellet

structures. From the pressure/displacement curve (Fig-4.2.9) one can easily estimate the work of compaction (the area under the curve) which was higher for those pellets produced form the higher proportion of ethanol, in other words more porous pellets.

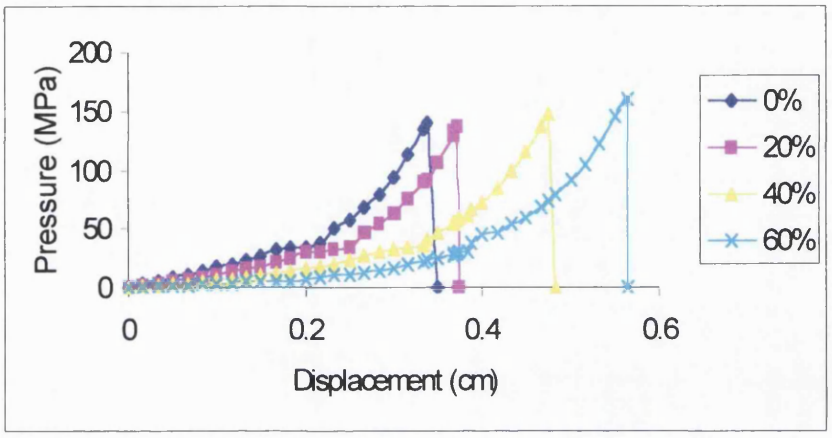


Fig-4.2.9:- The effect of ethanol proportion in water/ethanol mixture on the pressure/ displacement profile of the compaction of 600 mg MCC pellets to same tablet thickness

The detection of compaction pressure started for pellets from a higher ethanol content at a greater tablet thickness. This reflected the lower tapped density of the pellets. The rearrangement of pellets could be carried out only until they reached to the tapped density above which pressure was needed either to deform or to fragment the pellets. The Heckel plot of these formulations (Fig-4.2.10) indicated that the final dried pellets were made up of the same material (MCC) as the slopes of the curves were approximately the same.

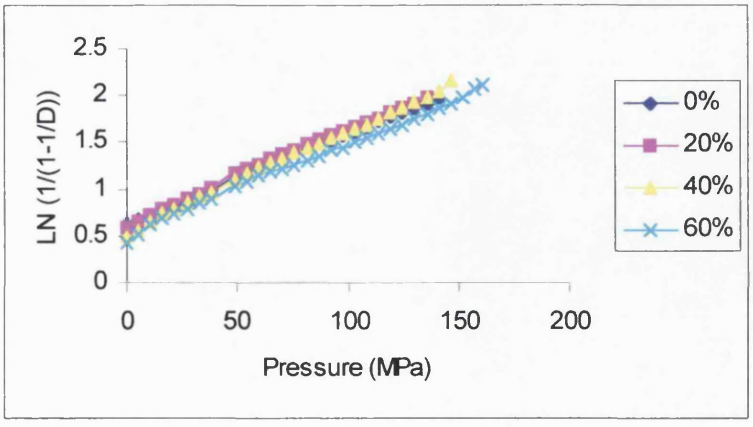


Fig-4.2.10:- Fig-4.2.7:- The effect of ethanol proportion in water/ethanol mixture as binding liquids on the Heckel plot MCC pellets of 1.0-1.18mm size fraction.

In a test to determine the failure of the pellets during compression, a curve was plotted

between the relative density of the tablets versus the logarithm of the pressure. In the presence of ethanol of any proportions, the point at which the linear curves broke seems at approximately the same point. It occurred at compaction pressure of about 20MPa. Therefore, using this technique, it was not possible to find a variation with the increase in ethanol content in the binding liquid.

Tablets could not be produced by compaction of pellets formed with 100% water or 20% ethanol in the binding liquid. The tensile strength (2.2.4.2.2) of the compacts from pellets of 60% ethanol content was higher than those pellets from 40% ethanol content (Fig-4.2.11).

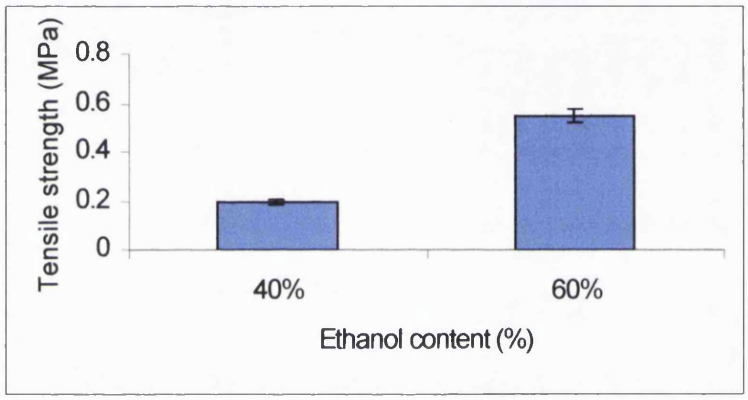


Fig-4.2.11:- The effect of increase in ethanol proportion in water/ethanol mixture as binding liquids, on the tensile strength of tablets produced from pellet of 1.0-1.18 mm size fraction.

The boundaries between the pellets was faint in the compacts of highest ethanol content (Plate-4.1, see p-212). This shows the extent to which these porous pellets were compressed. The variation in the compressing forces was also reflected in the tensile strength of the compacts. Those which were highly compressed were observed to be stronger. The effect of ethanol content in volumetric elastic recovery of the tablets was, however, marginal. This shows the permanent deformation/fragmentation of the pellets in the compacts.

4.2.4 CONCLUSION

The increase in the proportion of ethanol in the ethanol/water mixture as binding liquids in the production of pellets (MCC pellets) reduced the pellet strength, linear strain, and 'elastic modulus', while it increases the deformability of the pellets. The main reason for such effects could presumably be due to its ability to increase the porosity of the pellets with increase in ethanol content. This affected the mechanism and extent of rearrangement of the primary

particles in the pellets during diametral compression. In addition the bonding mechanism and autohesion between the MCC fibres, as suggested by Millili et al. (1990), could have been affected by the different binding liquids for MCC swells in the presence of water while not affected by ethanol. The mechanism of compaction of the pellets and their compacts property was also affected by the percentage of ethanol in the binding liquid mixture. With the increase of ethanol, a higher compaction pressure was needed to compress the same mass of pellets to the same tablet dimensions. The tablet strength was also increased with the increase of ethanol content. The surface nature of the pellets, which enabled the pellets to cohere with each other to form a rigid compact seems to have been affected by the addition of ethanol.

4.3 THE EFFECTS OF GLYCEROL AS A LIQUID BINDER

In this section, glycerol was used as a binding liquid by mixing it with water in different proportions. The produced MCC pellets, however, needed to be stored in tight plastic bag as glycerol is a hygroscopic material. The higher the glycerol content, the more sticky the pellets became when they were left in the open air. In these formulations, glycerol was retained within the pellets after the drying process due to its higher boiling point (above 200^0C) relative to the drying temperature (60^0C). Therefore the pellets were made up of MCC and glycerol. In this work, it was possible to produce MCC: Glycerol (10:9) pellets without using water, although the pellets produced were of a relatively lager size compared to the die diameter. When MCC: Glycerol 1:1 ratio was used, the pellets agglomerated inside a spheroniser, when it was changed to 5:4 ratio, it had an excessive extrusion force (35kN), and the rigid extrudates could not be rounded by spheronization. Thus, in this project, MCC pellets were produced by a standard extrusion and spheronization process having different water /glycerol mixture (0%, 20%, 40%, 60%, and 80%w/w glycerol) as binding liquids. With the increase of glycerol content in the formulations, longer spheronization times were required to produced pellets of acceptable sphericity. All pellets produced had a shape factor about 0.53.

4.3.1 THE PROPERTIES OF PELLETS

The force needed to extrude the wet mass through the 1.0mm diameter and 5mm long die increased steadily with an increase of glycerol content (Fig-4.3.1).

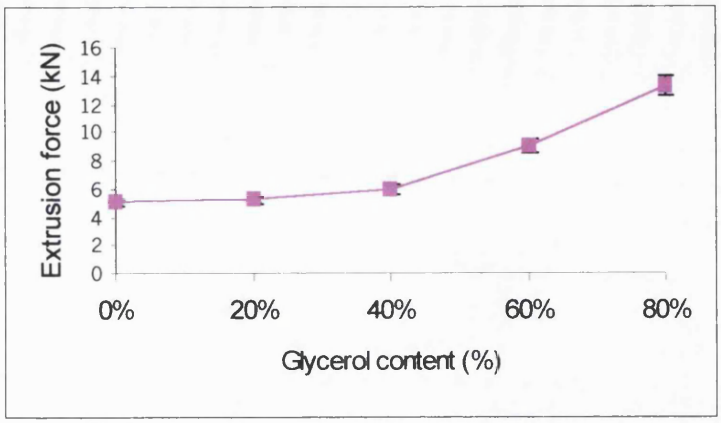


Fig-4.3.1 The effect of increase in glycerol proportion in the water/glycerol mixture binding liquid, on extrusion force.

Glycerol is a viscous solvent. It may have increased the viscosity of the wet mass so that it needed a greater force to converge the wet mass from the wider barrel into the die to extrude. Moreover, glycerol increased the adhesiveness of the wet mass, hence the upstream force, as was proven by the greater force needed to remove the slug from the barrel at the end of the extrusion process. The extrudates produced had no surface defects. Those produced by 80% w/w glycerol as a binding liquid were very long and coiled.

The median pellet size was directly proportional to glycerol content, while the size range was not significantly different (Table-4.3.1) as shown by the inter-quartile range. Specially with 80%w/w glycerol content only less than 2% of the pellets were obtained at size fraction of 1.0-1.18mm. The reason was not due to agglomeration or greater diameter of the extrudate, but the greater length to which the extrudates were cut, which rounded to spheres of a larger size without fragmentation. The apparent, bulk and tapped densities of the pellets decreased with an increase of glycerol content (Table-4.3.1). This was mainly due to the lower apparent density of the glycerol compared to MCC. With the increase of the weight to weight percent of the glycerol, the overall density was expected to decrease as the proportion of the MCC was reduced. That was because glycerol was retained in these formulations. The porosity of the pellets (closed pores) as determined by helium pycnometer, was observed to decrease with the increase of glycerol content (Table-4.3.1). This shows that glycerol was able to fill the internal pores.

Structural and Mechanical Properties of Pellets	The proportion of glycerol in the binding liquid (%)				
	0%	20%	40%	60%	80%
Mode (%)	36.4*	40.8*	37.1**	27**	48**
Median particle diameter (mm)	1.01	1.04	1.25	1.25	1.49
Interquartile range (mm)	0.34	0.28	0.31	0.29	0.28
Bulk Density (g/cc)	0.87(0.10)	0.84(0.10)	0.80(0.06)	0.76(0.08)	***
Tapped Density (g/cc)	0.93(0.05)	0.92(0.01)	0.86(0.02)	0.80(0.02)	***
Hausner ratio	1.07(0.1)	1.09(0.1)	1.07(0.1)	1.06(0.1)	***
Apparent pellet density (g/cc)	1.42(0.1)	1.41(0.1)	1.37(0.1)	1.33(0.1)	1.34(0.1)
Internal porosity (sealed) (%)	7.7(0.6)	6.34(0.5)	2.34(0.2)	0.9(0.1)	0.5(0.0)

Table-4.3.1:- Structural characteristics of MCC/glycerol pellets of 1.0-1.18 mm size fraction, prepared from glycerol/water mixture as liquid binders. The values in the parenthesis indicate the standard deviation.

** -modal size fraction was 1.0 - 1.18 mm size fraction;*

*** - modal size fraction was 1.4 - 1.7 mm size fraction;*

**** - no measurement was made due to insufficient pellets on the 1.0 -1.18 mm size fraction.*

The tensile strength of the pellets reduced substantially (Table-4.3.2) with an increase in the glycerol proportion (Fig-4.3.2). It was difficult to find the breaking point of the pellets which contained 80%w/w glycerol. They continued to deform without reduction in compressing force which could be detected by the CT-5. However, it was possible to determine the value of the first peak from the magnified force time curve recorded with the plotter.

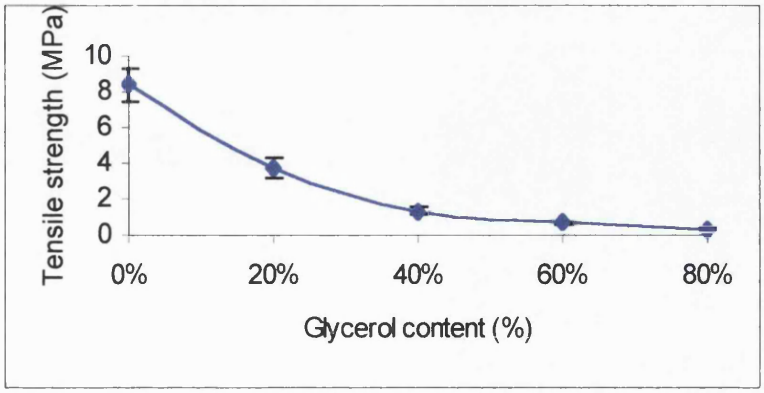


Fig-4.3.2 The effect of glycerol proportion in the water/glycerol mixture binding liquid, on tensile strength of pellets of 1.0-1.18 mm size fraction.

It was also difficult to identify the presence of a crack on the pellets of 80%w/w glycerol content after diametral compression. So an internal failure could be a possible reason. The presence of glycerol changed the rigidity of the pellets too. They became soft.

Glycerol content	Mean Tensile strength MPa	Standard Deviation	MS	F	P
0%	8.37	0.98	-	-	-
20%	3.71	0.54	326.3	513.9	<0.001
40%	1.35	0.19	737.7	1461.0	<0.001
60%	0.65	0.09	895.2	1823.3	<0.001
80%	0.33	0.05	969.5	1986.2	<0.001

Table-4.3.2:- Result and ANOVA of the effect of glycerol on the tensile strength of pellet from 1.0-1.18 mm size fraction.

The shear strength (Table-4.3.3) of the pellets was observed to decrease significantly with the increase of glycerol content. The procedure used (2.2.3.1) may not be suitable for such pellets, which have fluid like flowing properties rather than failing by shearing. Furthermore, the variability of the tensile strength of the pellets was increased with increase in glycerol content as shown by increase in the coefficient of variance (highest was for 80%w/w glycerol, i.e. 15%).

Some Mechanical Properties of Pellets	The proportion of glycerol in the liquid binder (%)				
	0%	20%	40%	60%	80%
Weibull-constant	9.14	4.14	1.48	0.70	0.36
Weibull-modulus	7.29	6.43	5.84	6.3	5.32
Shear Strength (kPa)	$(2.44\pm0.1)\times10^3$	126±11	80.7±7.9	44.8±3.6	0.046±00

Table-4.3.3:-The change in physico-mechanical properties of MCC pellets of 1.0 -1.18mm size fraction with the change in the proportion of glycerol in glycerol/water mixture as liquid binder.

Pellets produced by higher amount of glycerol were more deformable (Fig-4.3.3). Although

the crushing force was small, they were compressed (displaced) to a greater extent, as a result a higher reduction in the slope of the force /displacement curve was obtained. Especially at the highest glycerol content, these pellets could be considered to be semisolid in nature, where the MCC particles were 'dispersed' in the viscous glycerol medium.

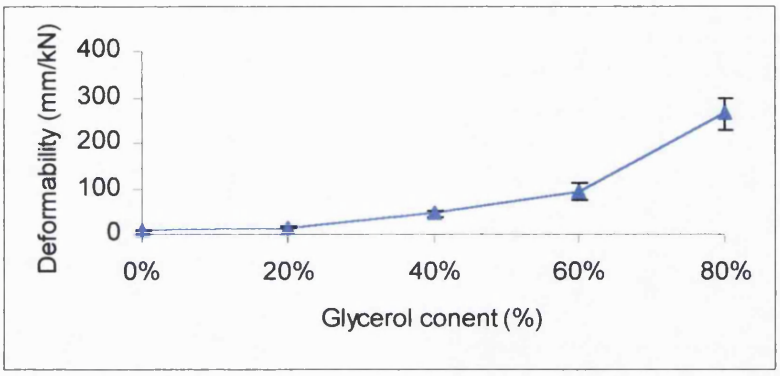


Fig-4.3.3 The effect of glycerol proportion in the water/glycerol mixture binding liquid, on deformability of pellets of 1.0-1.18 mm size fraction.

The pellets had a slight increase in linear strain (Fig-4.3.4). The strength of the "glycerol-pellets" was determinantal in the linear strain value, for an early failure with a higher glycerol content undermined the ability of the specimen to further strain.

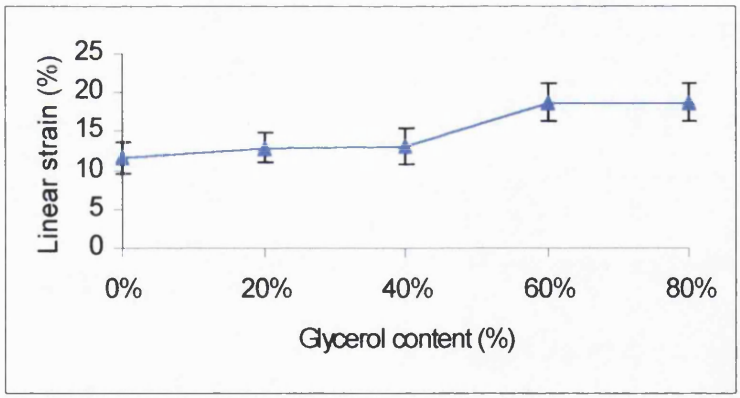


Fig-4.3.4 The effect of glycerol proportion in the water/glycerol mixture binding liquid, on linear strain of pellets of 1.0-1.18 mm size fraction.

There was a decrease in the 'elastic modulus' of the pellets with the increase of the proportion of glycerol (Fig-4.3.5). This indicates the decrease in the rigidity of the pellets, which agrees with the change in the nature of the pellets towards semisolid type of materials with the increase in glycerol content. Moreover, this indicates that the significant strength difference

between the pellets dominated the slight linear strength difference to produce pellets with considerable decrease in 'elastic modulus' with the increase of glycerol content, since the 'elastic modulus' was determined as a ratio of the pressure to a linear strain (Dyer et al. 1994).

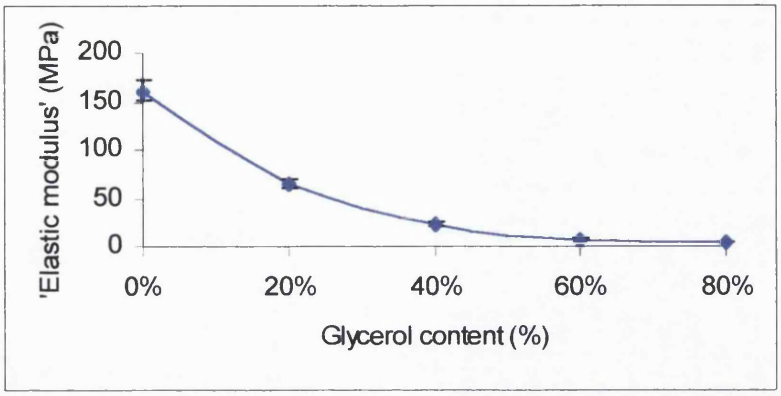


Fig-4.3.5 The effect of glycerol proportion in the water/glycerol mixture binding liquid, on 'elastic modulus' of pellets of 1.0-1.18 mm size fraction.

4.3.2 COMPACTION OF GLYCEROL CONTAINING PELLETS

Six hundred milligram of MCC/glycerol pellets produced with different glycerol content were compacted to the same tablet thickness (2.2.4.1 A). Generally these pellets needed less compaction pressure than those of pellets produced by the same ratio of water/ethanol mixture. This was presumably due to the higher deformability of the pellets containing glycerol.

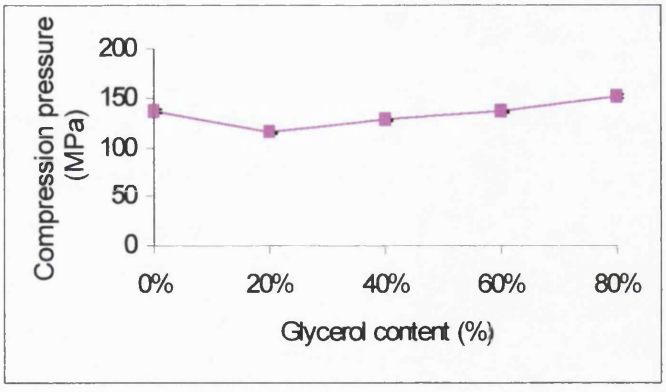


Fig-4.3.6:- The effect of glycerol proportion in the water/glycerol mixture binding liquid, on pressure needed to compress 600mg of pellets to the same dimensions.

There was an increase in compaction pressure with an increase in the glycerol content (Fig-4.3.6). The main reason is assumed to be the difference in the density of the pellets. The higher the glycerol content the lower was the density of the pellets. The force needed to

compress the same mass of a less dense material to a predetermined equal thickness of tablets is expected to be greater, for there is a higher rate of compressibility (change in volume during compaction). This compelled them to deform to a greater extent, which could include elastic deformation. These materials had also to be pressed to a lower final porosity, which could induce more friction between the pellets.

The pressure/displacement curve (Fig-4.3.7) had two distinct sections. In early stages, all the formulations containing the glycerol had different curves. This reflected the variation in deformability of the pellets. Those with higher amount of glycerol had the lowest rate of increase in compaction pressure. It shows that after the early rearrangement of the pellets in the die, deformation occurred in a manner observed in separate pellets (Fig-4.3.3).

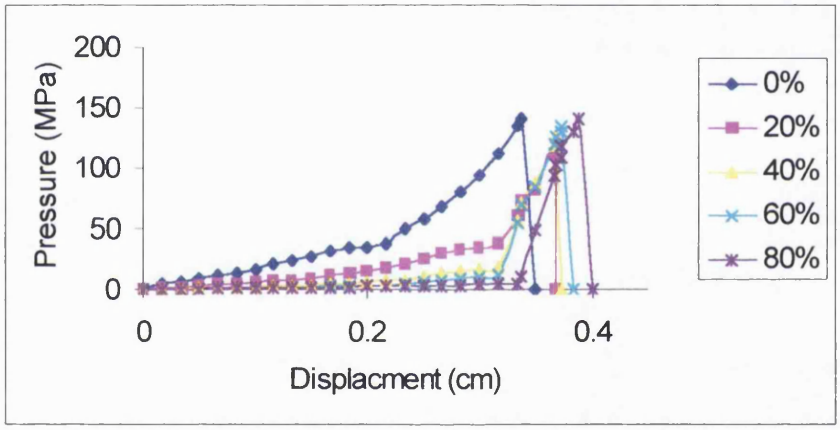


Fig-4.3.7:- The effect of glycerol proportion in the water/glycerol mixture binding liquid, on pressure/displacement profile needed to compress 600mg of pellets of 1.0-1.18 mm size fraction.

In the second section of the curve, all those containing glycerol had the same extent of pressure increase with displacement. In a very short distance, the pressure increase was very large. This could be assumed to be the elastic deformation of the compact, which was later reflected in their volumetric elastic expansion. The area under the curve was slightly higher for those pellets having a greater tensile strength and less deformability. The marginal difference arouse mainly from the first part of the plot. This could be due to the higher pressure needed to deform the bulk pellet-bed to the same level.

The Heckel plot of these formulations is illustrated on (Fig-4.3.8). Deviation from linearity of the curves was increased with the increase of the glycerol content. This could mainly be

due to the ability of the glycerol to fill void space with increase in its amount and results in elastic deformation with increase in further pressure. A slight increase in the slope of Heckel plot was observed indicating the decrease in yield stress of the specimen, as easily deformable structures were formed. There was no a clear breaking point in the relative density versus logarithm graph derived form the compaction of the "glycerol-pellets". All had a reasonably linear curve with correlation factor more than 0.9, indicating the propensity of the pellets to deformation rather than fracturing as confirmed by the images in (Plate-4.2, see p-212).

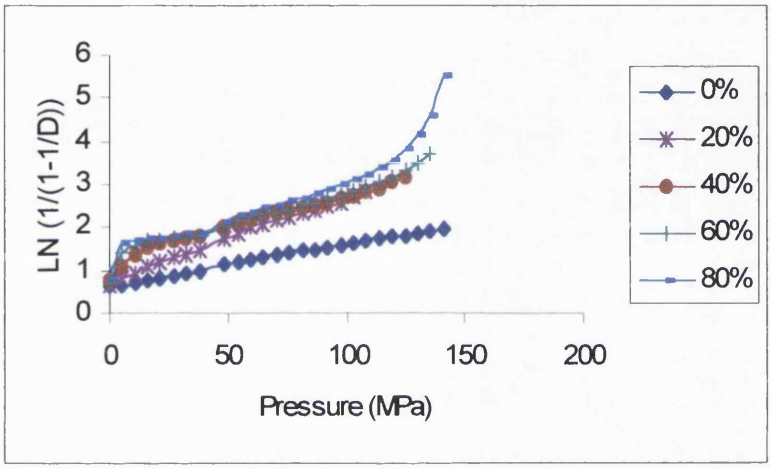


Fig-4.3.8:- The effect of glycerol proportion in the water/glycerol mixture on Heckel plot obtained during the compaction of 600 mg pellets of 1.0-1.18 mm size fraction

The tablets produced had a small but steady increase in thickness with increase in the amount of glycerol, showing an instant elastic recovery during decompression. The tensile strength of the compacts reduced significantly with increase in the glycerol content (Fig-4.3.9).

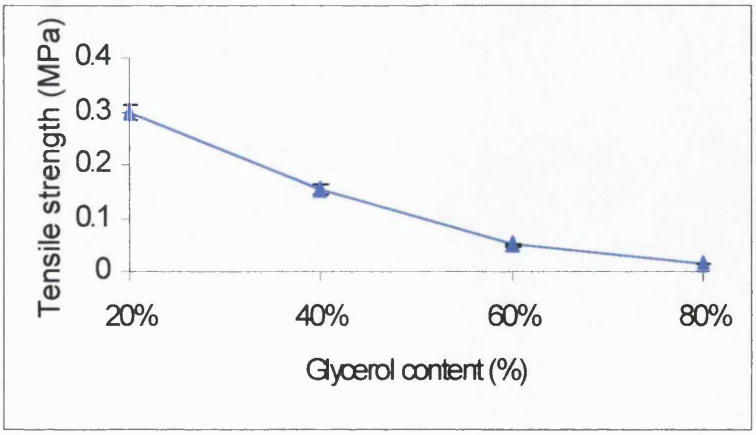


Fig-4.3.9 The effect of glycerol proportion in water/glycerol mixture as binding liquids, on the tensile strength of tablets produced from pellet of 1.0-1.18 mm size fraction.

This could presumably be due to the effect of glycerol in reducing the intergranular coherence. Another reason could be the disruption of the connections formed during the volumetric elastic expansion of the tablets, for tablets having more glycerol showed a high extent of elastic recovery (Fig-4.3.10), presumably due to the stored reversible elastic deformation, for the pellets with high glycerol content were observed to have lower density and to be highly compressed to tablets of equal tablet thickness.

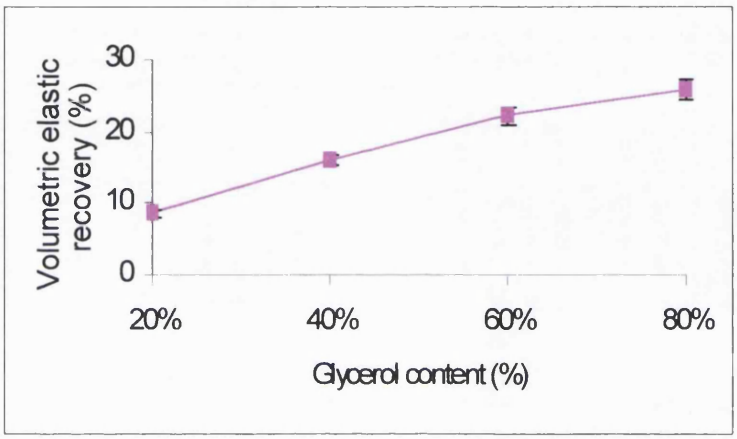


Fig-4.3.10:- The effect of increase in glycerol proportion in water/glycerol mixture as binding liquids, on the volumetric elastic recovery of tablets produced from pellet of 1.0-1.18 mm size fraction.

4.3.3 CONCLUSION

This work showed that MCC pellets could be produced by incorporation of a wide range of water/glycerol mixtures. Unlike the previous pellets, glycerol is retained into the pellets after the drying process. This affected the nature of the pellets significantly. With the increase of glycerol content, the strength of the pellets, densities, and 'elastic modulus' were reduced, while their deformability and linear strain increased. This could be due to the lower relative density of glycerol and its ability to change the nature of the pellets to 'viscous' type of specimen. The strength of the tablets produced from the pellets was reduced significantly with the increase of glycerol content. This could be due to the disruptive effect of the reversibly elastic deformation which was proved by the excessive volumetric expansion of the compacts.

4.4 THE EFFECT OF TERNARY MIXTURE OF LIQUID BINDERS

There are several comparison procedures in pharmaceutical formulations. One of which is the procedure that consists of preparing a series of formulations by varying the concentrations of the formulation ingredients in some systemic manner. These formulations are then evaluated according to one or more attributes. Based on the results of these tests, particular formulation (or series of formulations) may be predicted to be optimal. In this work, to compare the effect of the different binding liquids on the properties of the pellets, such as tensile strength, deformability, linear strain, and 'elastic modulus', 18 formulations were designed based on the different proportion of water, ethanol, and glycerol as binding liquids (Table-4.4.1). The ratio between the dry mass (MCC powder) to the total solvent mass was, however, kept constant at 1:1 in all cases.

№	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
W	8	8	6	6	6	4	4	4	4	2	2	2	2	2	0	0	0	0
E	2	0	2	4	0	6	4	2	0	8	6	4	2	0	8	6	4	2
G	0	2	2	0	4	0	2	4	6	0	2	4	6	8	2	4	6	8

Table-4.4.1: The ratio of the binding liquids (W-water; E-ethanol; R-Glycerol) in the tertiary liquid mixture in production of MCC pellets.

These pellets were produced by a standard extrusion spheronisation procedure (2.2.1-4), and a size fraction of 1.0-1.18 was separated and used in all the analysis. It was not possible to produce pellets by mixing 60%w/w ethanol in the presence glycerol as a binding liquid. The liquid was squeezed out during extrusion and left a rigid dry mass in the barrel. The other 15 formulation were able to produce pellets of varying properties.

The tensile strength of the pellets decreased with an increase of the percentage of ethanol and/or glycerol as liquid binders (Fig-4.4.1). The effects of ethanol and glycerol on the tensile strength of pellets seems additive compared to their binary mixture with water (Section 4.2 and 4.3). With the increase of both factors the decrease in strength was significant. Pellets with no water content had the lowest tensile strength (less than 0.25 MPa), while pellets produced from 100% water as a binding liquid were the strongest (8.4 MPa).

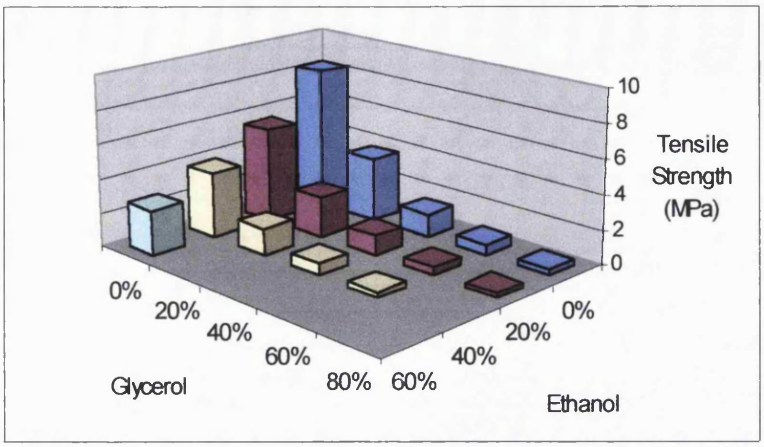


Fig-4.4.1:- The effect of binding liquids on the tensile strength of MCC pellets of 1.0-1.18mm size fraction.

The deformability of the pellets was also similar to the effect of each of the binding liquids` effect separately. There was an increase in this property of the pellets with the increase of the proportion of ethanol and/or glycerol in the formulations (Fig-4.4.2).

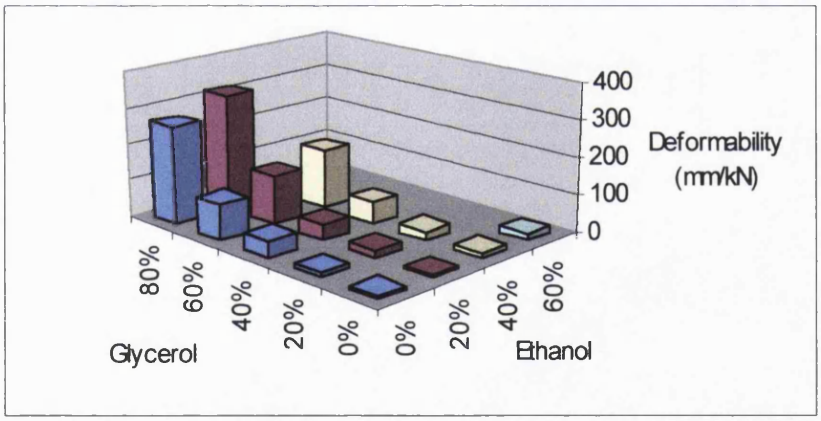


Fig-4.4.2:- The effect of binding liquids the deformability of MCC pellets of 1.0-1.18mm size fraction.

The increase in the deformability of pellets with the increase of glycerol was in the same proportion at all constant ethanol contents. Similarly, the increase in the deformability of pellets with the increase of ethanol was in the same proportion at all constant glycerol contents. The relative effect of the factors was however to a different extent. Pellets were 10 times more deformable for the same increase of glycerol content rather than with ethanol content.

The effect on the linear strain of these pellets was again similar to that of the separate factors.

With an increase in glycerol content, the linear strain of the pellets increased at all levels of ethanol content, while it decreased with the increase of ethanol content at all constant levels of glycerol (Fig-4.4.3).

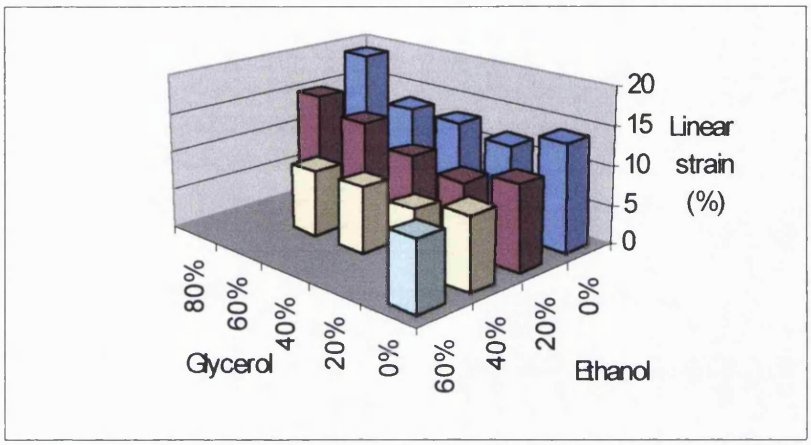


Fig-4.4.3:- The effects of biding liquids on the linear strain of MCC pellets of 1.0-1.18mm size fraction.

The increase in the linear strain with the increase of glycerol content, however, started at 20%w/w of glycerol. In all formulations containing the same amount of ethanol, the strain at 0%w/w glycerol was higher than at 20%w/w glycerol presumably due to the higher strength of the MCC pellets, hence their ability to accommodate an extended strain.

The effect of these formulations on the 'elastic modulus' of the pellets was also consistent with their separate results (Fig-4.4.4). Increase in ethanol and/or glycerol percentage as liquid binders reduced it considerably.

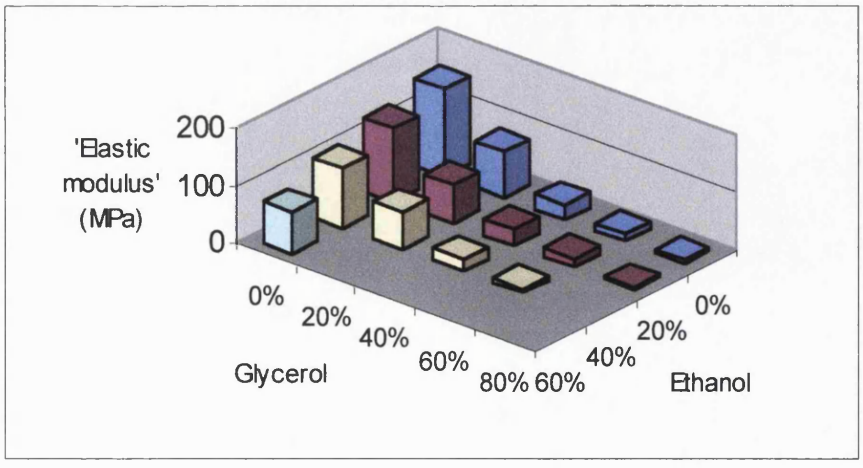


Fig-4.4.4:- The effect of binding liquids on the 'elastic modulus' of MCC pellets of 1.0-1.18mm size fraction.

As these values were determined from the ratio of the compressing pressure to linear strain, the effect of glycerol was further reduced, as the force was decreased while linear strain was increased with increase of glycerol content at higher ethanol levels. In pellets of different ethanol content, likewise, the significant reduction in compressing force followed by a moderate reduction in linear strain produced pellets of less 'elastic modulus' with the increase of ethanol percentage in the binding liquid at higher glycerol levels.

Six hundred milligrams of the pellets from each formulation were compacted to the same pre-determined tablet dimensions as explained in (section 2.2.4.1 A). The effects of these different formulation factors on the property of their pellet compacts was analysed in terms of compression force, tablet strength, and volumetric expansion of the tablets (section 2.2.5) after 7 days of storage at ambient temperature and humidity.

The pressure needed to compress the pellets to the same tablet dimensions increased with the increase of the percentage of ethanol and/or glycerol in the binding liquid mixture (Fig-4.4.5).

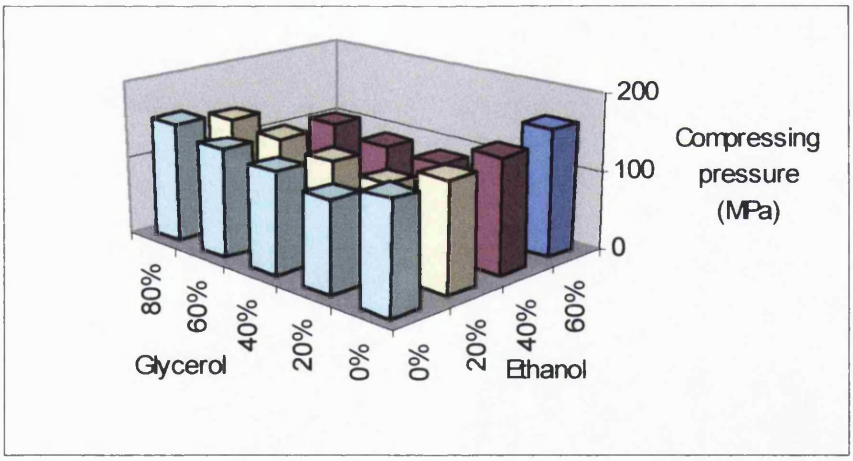


Fig-4.4.5:- The effect of binding liquids on the pressure needed to compress 600 mg pellets to tablets of 12 mm diameter and 4 mm thickness.

The difference in this effects was not as apparent as the other properties. This could be due to the relatively small strength differences of the individual pellets compared to the compaction pressure. Nevertheless, it was related to the density of the pellets. The less dense pellets needed a high compressing pressure due to a larger reduction in volume needed for these pellets to ensure an equal tablet dimension. An extra force may be needed to deform/fragment the pellets so that tablets of lower porosity from the less dense pellets can

be produced. The higher compressing pressure which occurred with the increase in glycerol content, however, did not produce stronger compacts. Fig-4.4.6 illustrates the increase in tablet tensile strength with the increase of ethanol content and the decrease of strength with increase of glycerol content.

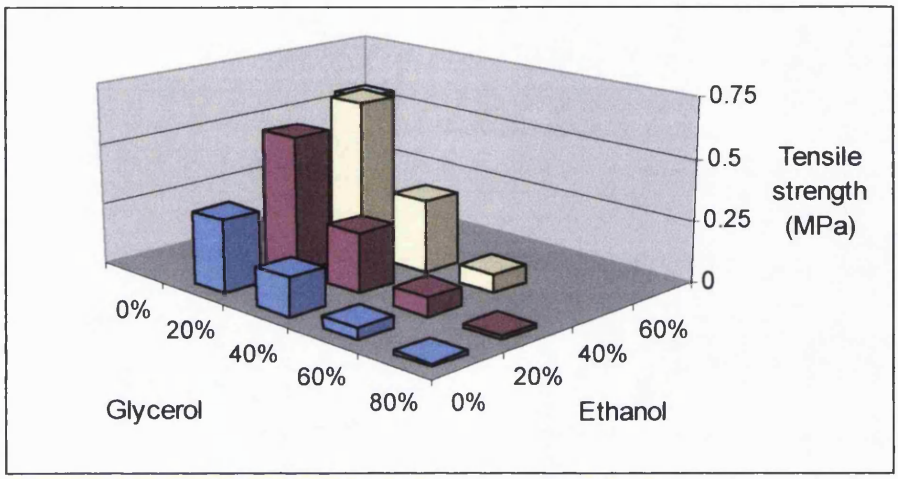


Fig-4.4.6:-The effect of binding liquids on the tensile strength of tablets having a mean diameter of 12 mm and 4 mm thickness.

This indicates the decrease in inter pellet attachment to form rigid MCC pellet compacts in the presence of more glycerol. In pellets produced with higher ethanol content, however, only MCC remained after drying. The higher porosity, greater extent of compressibility and higher compaction pressure, enabled the pellets to deform and bring the surfaces to closer proximity and form rigid structures. In addition, the exposure of new surfaces during fracture could enhance the formation of connection sites. The high pressure needed to produce tablets from pellets of a higher glycerol content was observed to have been stored as reversible elastic deformation. (Fig-4.4.7) indicates the increase in the volumetric elastic recovery of the compacts with the increase of glycerol content and decrease of ethanol content.

The compacted pellets of higher ethanol content were observed to have been deformed and fragmented after the de-aggregation. This could be the reason for the reduction in their volumetric elastic recovery. The SEM in (Plate-4.2, see p-212) shows the fracture and deformation of the pellets form higher ethanol content and the reduced connectivity between glycerol rich pellets by the prominent gap between the pellets.

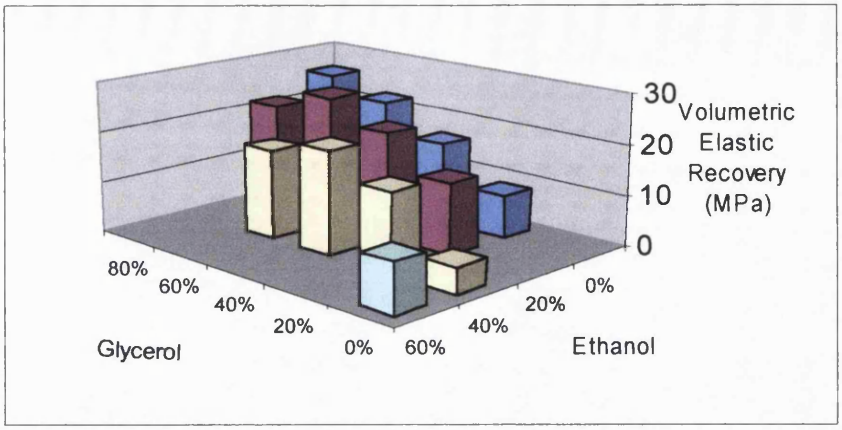


Fig-4.4.7:- The effect of binding liquid on the volumetric elastic recovery of the tablets as measured after 7 days of production.

4.5 FACTORIAL ANALYSIS

In an attempt to assess the overall effects of the three liquid binders on the properties of the pellets and the properties of their compacts, a factorial designed experiment was also performed (similar to that explained in chapter-3). However, here the factors were, water, ethanol and glycerol. Water: Ethanol: Glycerol had (3:1:1) proportion as a starting or lower level of composition, while one part was added to each factor at its higher level (Table-4.4.2).

S/N	Formula	MCC Content	Binding liquid		
			Water	Ethanol	Glycerol
1	weg	5	3	1	1
2	Weg	6	4	1	1
3	wEg	6	3	2	1
4	WEg	7	4	2	1
5	weG	6	3	1	2
6	WeG	7	4	1	2
7	wEG	7	3	2	2
8	WEG	8	4	2	2

Table-4.4.2:- The ratio of each liquid binder incorporated in the wet mix of the factorial designed experiment to produce MCC pellets. The three factors were , Water content (w/W), Ethanol content (e/E), and Glycerol content (g/G), the lower case standing for the lower level of the factors while the upper case indicates the higher level of the factors.

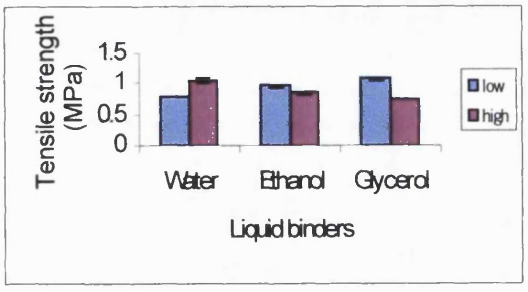
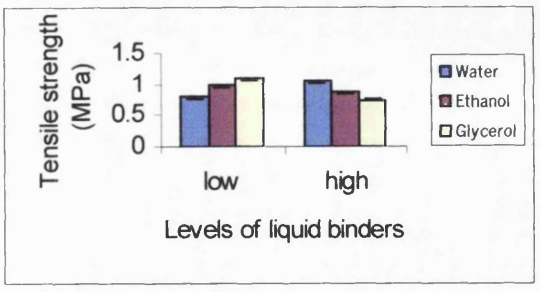


Fig-4.4.8 a



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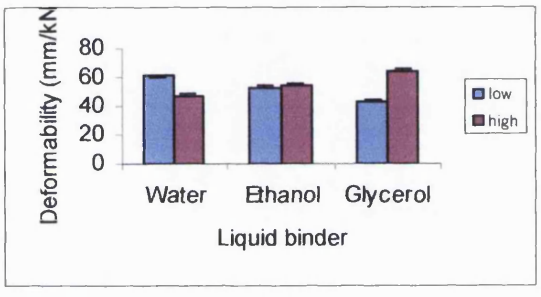

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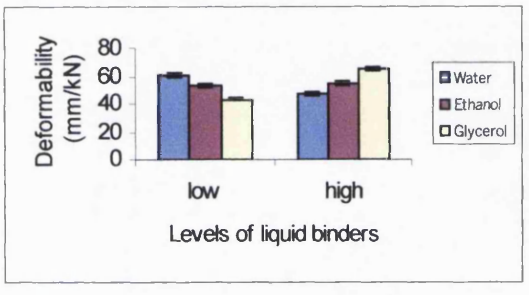

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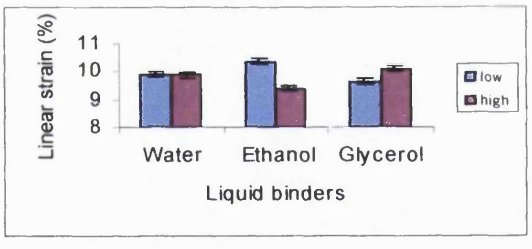
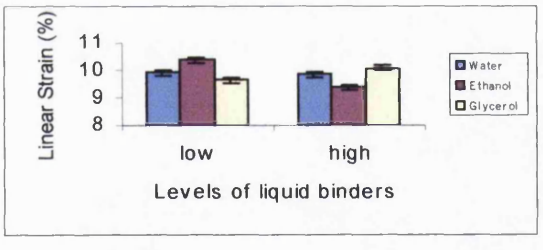


Fig-4.4.10a



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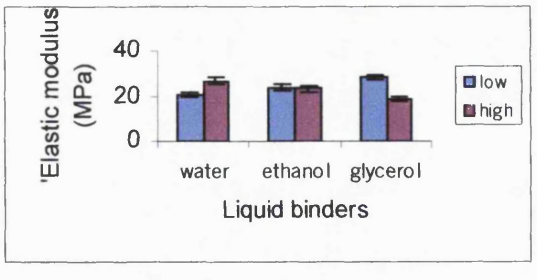


Fig-4.4.11 a

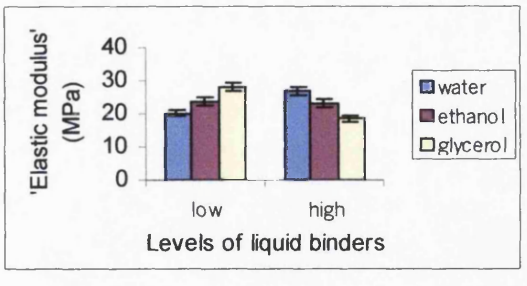


Fig-4.4.11 b

Fig-4.4.8-11:- The effect of the liquid binders levels (upper case for higher level, and lower case for lower level) on the tensile strength (8a&b), deformability (9a&b), linear strain (10a&b), and 'elastic modulus' (11a&b) of the pellets of 1.0-1.18 mm size fraction, produced by 2^3 factorial designed experiment.

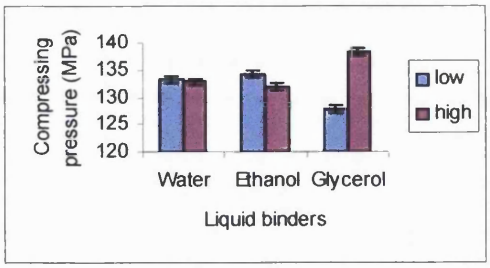
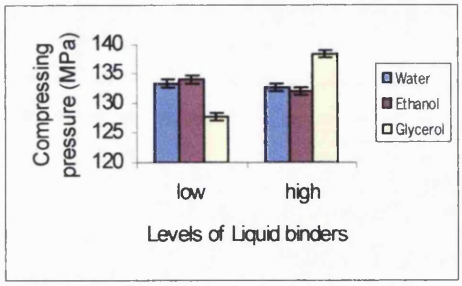


Fig-4.4.12 a



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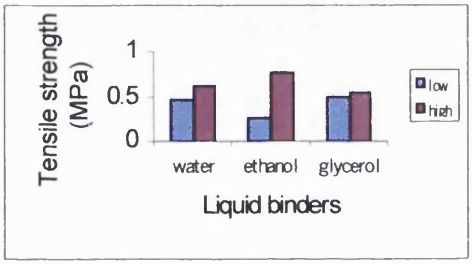


Fig-4.4.13 a

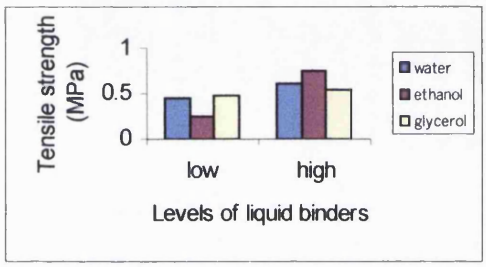


Fig-4.4.13b

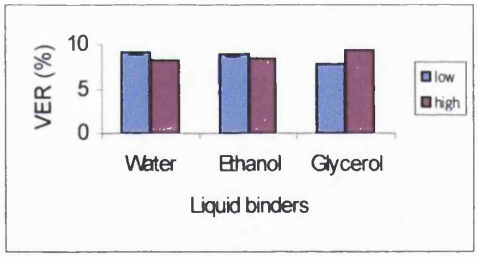


Fig-4.4.14 a

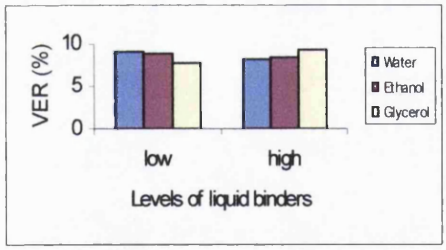


Fig-4.4.14 b

Fig-4.4.12-14:- The effect of the liquid binders levels (upper case for higher level, and lower case for lower level) on the pressure needed to compress 600 mg pellets (12a&b), tensile strength (13a&b), and volumetric elastic recovery (14a&b) of the compacts from pellets of 1.0-1.18 mm size fraction, produced by 2^3 factorial designed experiment.

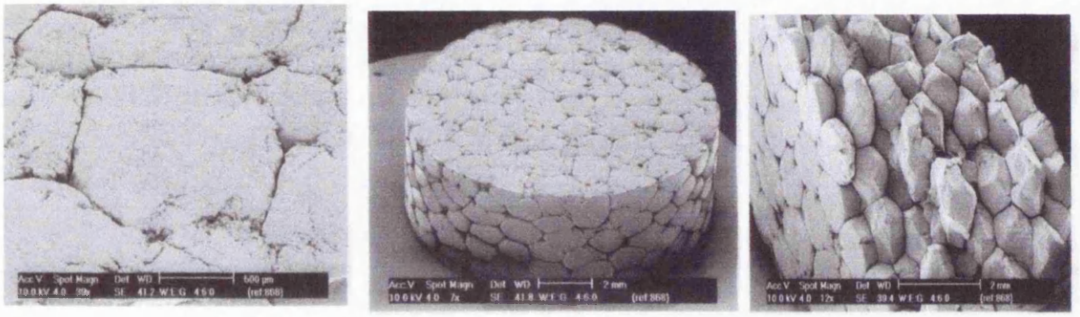
The average effect of each factor in the eight formulations, as assessed in terms of pellet properties and tablet properties have been summarized in (Fig-4.4.8-12) and (Fig-4.4.13-15) respectively.

ANOVA established the significant variation in the tensile strength, deformability, and 'elastic modulus' of the pellets produced from all formulation compared to that of the starting formula (weg) with the exception of wEg and wEG ($P<0.01$). In linear strain, however, four formulation, namely, Weg, wEg, weG, and wEG had no significant variation while the rest had ($P<0.01$). The Yates algorithm was able to establish the significant effects of some factors on the properties of the pellets and their compacts ($P<0.05$). For instance, the effects of water in increasing the pellet strength and 'elastic modulus' and decrease in the pellet deformability was significant. The effect of ethanol in increasing the pellet deformability and decreasing the pellet linear strain was substantial. Glycerol effect in increasing the pellet deformability and linear strain, as well as its decreasing effect in strength and 'elastic modulus' of the pellets was significant. Moreover, glycerol had a significant effect in increasing the compression pressure to produced tablets of the same dimensions, while the tensile strength of tablets was significantly increased by the incorporation of ethanol at its higher level.

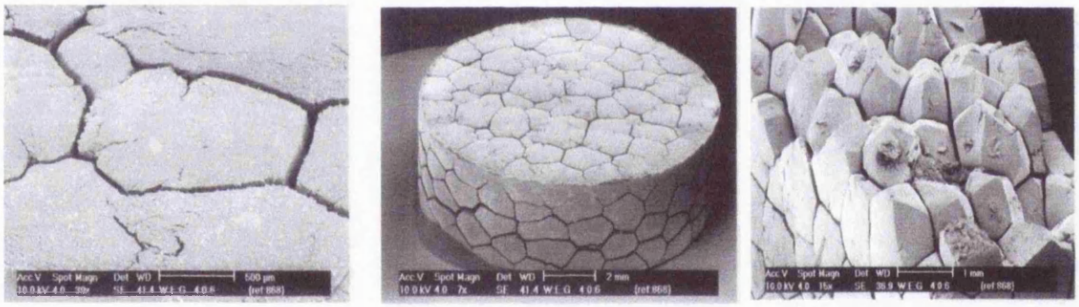
4.6 CONCLUSION

This work evaluated the effect of water, ethanol and glycerol content as liquid binders in the preparation and properties of MCC pellets and their compacts. MCC pellets could only be produced with certain limit of water as a liquid binder. A wet MCC mass with less than 80%w/w water had insufficient plasticity to be extruded and rounded in a spheronizer, while with water above 100% w/w, it was very wet and agglomerated during spheronization. Within these limit, the increase in moisture as a liquid binder reduced the porosity and deformability of the pellets, while it increased the strength, linear strain, 'elastic modulus', sphericity, size and size distribution of the pellets. Although all the formulation did not produce compacts, their compaction mechanism was approximately similar as noted on the Heckel plot and pressure/displacement curves. The increase in the proportion of ethanol in the ethanol/water mixture as binding liquids in the production of MCC pellets decreased the pellet strength, linear strain, and 'elastic modulus', while it increases the deformability of the pellets as well as the strength of the compacts. Unlike the other liquid binders, glycerol was retained in the MCC pellets after the drying process. This affected the nature of the pellets considerably. With the increase of glycerol content, the strength of the pellets, densities, and 'elastic modulus' and the strength of the pellet compacts were reduced, while their deformability and linear strain increased. The effect of each liquid at different levels of the other liquids in the

ternary liquid binders mixture was the same as that of the binary mixture of ethanol or glycerol with water in all pellet and compact properties studied. No interaction was observed between the factors for they had additive effect on all their attributes.



1(a) 1(b) 1(c)



2(a) 2(b) 2(c)

Plate-4:- The SEM of pellet compacts produced with 60%w/w (1) ethanol and (2) glycerol. (a) shows the magnified surface of the tablets, (b) shows the whole tablet, while (c) shows a magnified cross-section of the tablets

CHAPTER-FIVE

THE EFFECTS OF DRYING PROCESS AND PELLET SIZE

5.1 THE EFFECT OF DRYING TECHNIQUES

5.1.1 INTRODUCTION

The objective of this section was not to compare the efficiency of the techniques, but to study the effects of the drying process on the mechanical properties of pellets, their compaction mechanism and the properties of their compacts. Wet MCC pellets, containing water/ethanol (6:4) mixture as liquid binders, were produced by a standard extrusion and spheronization process (2.2.1-3). These wet pellets were dried by four different techniques (see 2.2.1.4), which utilize different means of heat and mass (moisture) transfer. The drying process was continued until the final moisture content of the pellets was less than 5%w/w, which is equivalent to the moisture content specified for MCC (Avicel®PH101). Therefore, the drying time was different for the different techniques as described on (Section 2.2.1.4). The dried pellets were stored in a sealed container for 48 hours, and their moisture content before further analysis was determined by Thermogravimetric analysis (TGA) at three temperatures consecutively in an increasing order (Table-5.1.1). The structural (2.2.2), mechanical (2.2.3) properties of the pellets as well as their compaction mechanism and properties of the compacts(2.2.4.1-2) were analysed.

TGA Temperature	Drying methods			
	oven	silica-gel	freeze	fluid-bed
90°C	0.275%	0.245%	2.601%	0.957%
110°C	0.419%	0.350%	2.758%	1.579%
200°C	1.896%	1.616%	3.023%	4.525%

Table-5.1.1:-The weight by weight percentage (%w/w) of moisture released in TGA at different temperatures from MCC pellets dried by different methods. N.B. The variation in the values between samples (n=3) of the same batch (standard deviation) was negligible.

The total water content of the pellets dried by desiccation with silica-gel and oven drying technique was the lowest. This could be due to the longer time these pellets were exposed to

the drying process. The very small difference in water loss at the three different temperatures (Table-5.1.1) shows that the remaining water was distributed evenly throughout the structure of the pellets. In freeze dried pellets, however, most of the water loss was before 90^0C, showing that it was on the surface of the pellets or simply condensed in the 'open' pores. Their relatively higher water content shows the propensity of such pellets to adsorb water from their surroundings. The efficient drying technique of fluid-bed drier needed only 30 minutes to produce pellets of less than 5%w/w moisture content. However, pellets dried by this technique had relatively higher water content. Since most of the weight loss during the TGA was above 110^0C, the moisture content was not likely to be due to adsorption on the surface. The very short drying time may not have been sufficient to further dry the moisture from the capillaries or narrow cavities of the pellets.

5.1.2 THE PROPERTIES OF THE PELLETS

The drying technique had a profound effect on the median pellet size (Table-5.1.2.). The median pellet diameter increased in an ascending order form oven drying, dessication with silica-gel, fluid bed drying to freeze drying. There had been a substantial difference between the first two and the last two. The pellets, however, had a more or less similar value for the inter quartile range.

The greater median pellet size of freeze-dried pellets may be due to the suppression of shrinkage or even swelling of the pellets for water expands on freezing. Moreover, there is no liquid involvement, which could contract the pellets, as the ice directly changed to vapour without passing through the liquid state. Oven dried and those pellets dried by desiccation with silica-gel attained a similar median pellet diameter. This could be due to their static and slow water removal mechanism which could allow the solid material to shrink by capillary pressure due to the significant surface tension of water. The constant collision among pellets themselves as well as against the vessel might be expected to reduce the median diameter of fluid bed dried pellets. However, there was no such abrasion and breakage of the pellets by the violent agitation since the pellets were cushioned from each other by the gas stream. The overall difference in pellet size was mainly due to the difference in the rate of shrinkage of the pellets during drying. That is because the median pellet diameter was less than 1.0 mm (die diameter) in all cases.

Kleinebudde et al. (1994a) had a similar observation with his 20 different formulations. He observed a decrease in width and length of his pellets by 23-41% when they were oven dried, but only 2-12% when freeze dried. This decreased the surface area by 54-93% when dried in an oven while it was only 2-20% decrease in surface area when dried by freeze drying. Similarly in this work, the surface area of oven dried pellets was only about 1.5 fold that of pellets dried by desiccation with silica-gel, while those of fluid-bed dried and freeze dried were about 6 and 20 fold higher respectively (Table-5.1.2). The main reason for such variation, however, was not the difference in size. It was the difference in the 'open' pores volume (Fig-5.1.1) the surface of which was measured by the monolayer adsorption of nitrogen molecules.

Structural and Mechanical Properties of Pellets	Drying techniques			
	Freeze drier	Fluid-bed drier	Hot air oven	Desiccation with silica-gel
Median pellet diameter (mm)	0.9	0.89	0.63	0.63
Interquartile range (mm)	0.34	0.35	0.32	0.31
(%) by weight of the Modal fraction	48.28**	50.91**	78.72*	81.12*
Bulk Density (g/cc)	0.56(0.06)	0.74(0.06)	0.81(0.05)	0.79(0.06)
Tapped Density (g/cc)	0.60(0.02)	0.77(0.03)	0.82(0.02)	0.85(0.01)
Hausner ratio	1.07(0.08)	1.04(0.06)	1.01(0.02)	1.07(0.04)
Total porosity (%)	31.6(0.9)	16.4(0.8)	12.5(0.4)	13.8(0.5)
Apparent pellet density (g/cc)	1.49(0.01)	1.47(0.01)	1.40(0.02)	1.36(0.01)
porosity (sealed) (%)	2(0.01)	3.3(0.02)	7.9(0.6)	10.5(0.09)
Effective density (g/cc)	1.04(0.03)	1.27(0.04)	1.33(0.02)	1.31(0.01)
Pore volume (ml/g) for pore diameter range of 0-200 nm	0.0216 (0.0038)	0.00589 (0.0005)	0.0016 (0.0000)	0.0011 (0.0000)
Surface area(sq. m/g)	6.177(0.03)	1.572(0.01)	0.371(0.01)	0.269(0.004)

Table-5.1.2.:- The structural properties of MCC pellets, 1.0-1.18mm size fraction, produced by different dying techniques. The modal size fraction for (*) was 0.71-1.0 mm and for (**) was 1.0-1.18mm. The values in the parenthesis indicate standard deviation.

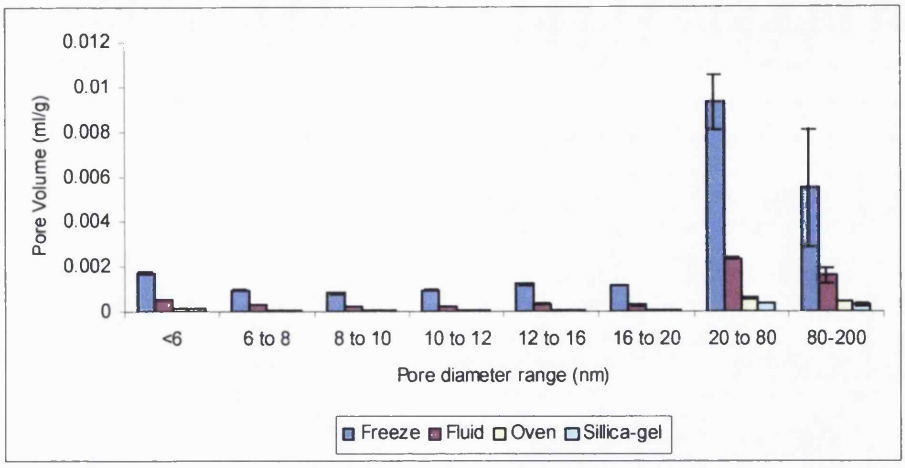


Fig:5.1.1:- The volume of pores of different diameter range measured form MCC pellets of 1.0 -1.18 mm size fraction produced by different drying techniques.

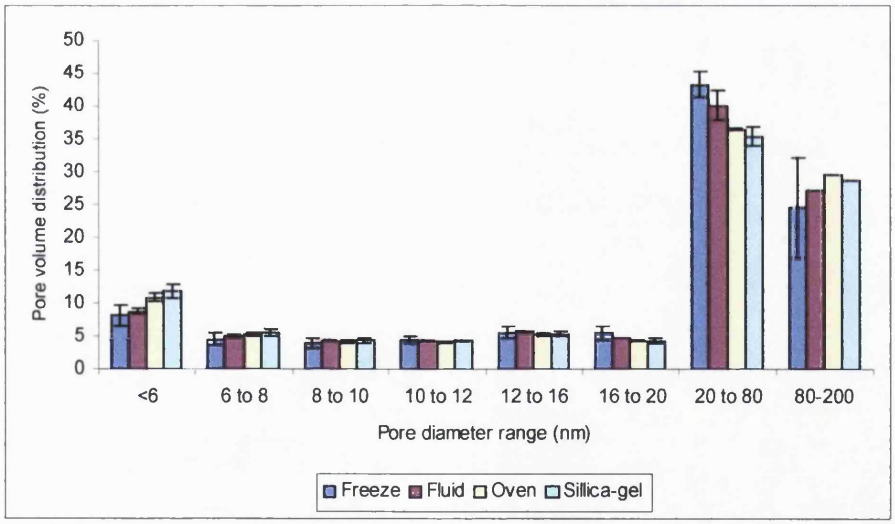


Fig- 5.1.2:- The distribution of pore volume of MCC pellets of 1.0 -1.18 mm size fraction produced by the different drying techniques.

The total porosity of the pellets increased in a similar way to increase in the median pellet diameter (Table-5.1.2.), while their effective density decreased in the same order. This again indicates the occurrence of shrinkage and densification as reported by Berggren and Alderborn, (2001a&b) during drying, but to a different extent based on the drying techniques.

Freeze dried pellets had the highest porosity, while oven dried pellets were the least porous. Kleinebudde et al. (1994a) made a similar observation. He noted the freeze dried pellets were more porous than fluid-bed dried pellets by at least a factor of three in the eight different formulations, while their pore size determined by mercury porositymeter was even higher by a greater factor. In this work, however, the pellet volume distribution was relatively similar in the pore diameter range of 0-200 nm (Fig-5.1.2).

The apparent pellet density was, however, in the reverse order (Table-5.1.2.). Pellets dried by freeze drying had the highest density while pellets dried by desiccation with silica-gel had the lowest density. This could presumably be due to the difference in the distribution of pores, indicating the presence of more open pores in the freeze dried pellets (Table-5.1.2). The helium gas was therefore able to access to the open pores and the value of the apparent density of these pellets became higher. These pellets had closed pores as well, although to a smaller extent. This could be proved by the lower apparent density of these pellets compared with the MCC powder. Desiccated and oven dried pellets had the lowest apparent density. This was in agreement with their lower size distribution due to their shrinkage. These pellets were able to have a greater part of their pores in closed forms relative to the fluid-bed or freeze dried pellets (Table-5.1.2.).

Bataille et al (1993) studied the effect of two drying technique on the porosity of pellets made from a binary Avicel and lactose (20/80) mixture. They dried all their pellets until the weight was constant (12 hrs in ventilated 40^0C oven, 30 minutes in micro wave oven). They reported that the degree of porosity of the pellets dried by microwave was higher than those of pellets dried in an oven by 50%, and the average diameter of the pores was almost doubled as measured by mercury porosimetery.

Determination of the bulk densities (Bulk and tapped) reflected the porosity of the pellets (Table-5.1.2.). Pellets with greater total porosity and lower effective density had a lower bulk densities. It increased in the ascending order from freeze dried, fluid-bed dried, oven dried, to those dried by desiccation with silica-gel. A similar experiment with a larger size fraction of pellets (1.18-1.4mm) was performed, and the results were of the same order and range.

The tensile and shear strength of the pellets increased with the decrease of total porosity of

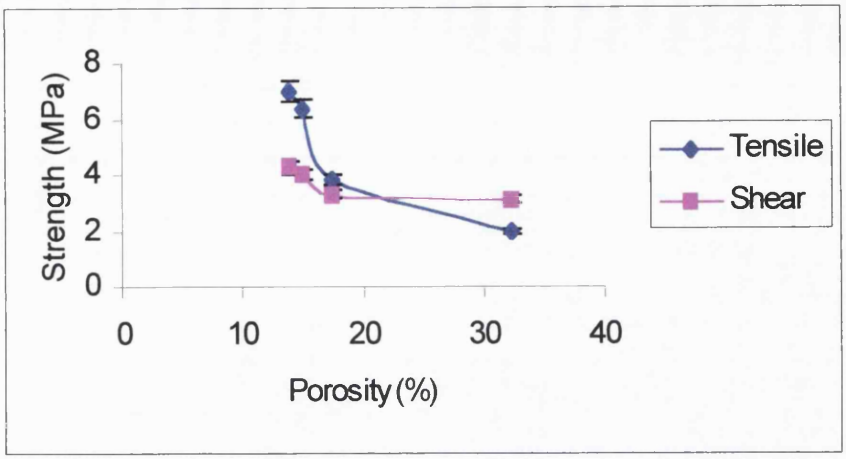
the pellets (Fig-5-1.3a). The agreement in the order of tensile and shear strength of the pellets shows that the validity of prediction of the strength of the pellets from the confined uniaxial compaction technique as Adams et al. (1994) suggested. The relatively weaker shear strength indicates the susceptibility of the pellets to fail by shearing during compression.

The order of increase in pellet strength starting from the weakest was, freeze dried, fluid bed dried, then oven dried to those pellets dried by desiccation with silica-gel having the highest strength (Fig-5.1.3 b&c). The arrangement of the pellets in their strength was in reverse order to their porosity. The more porous the pellets, the weaker they became. The increase in porosity of the pellets, therefore, can be explained with the consequence of a weakening in the inter-particular links translated by a decrease in the strength of the pellets. Dyer et al. (1994) made a similar observation. They concluded that the drying technique for a given uncoated pellet formulation had a significant effect on the mechanical properties of pellets prepared by extrusion/spheronization after noting that pellets dried by tray drying to have required a significantly greater crushing force than those of fluid bed dried pellets. Bataille et al. (1993) had also found that the less porous pellets produced by oven drying to have a higher strength than the porous microwave dried pellets.

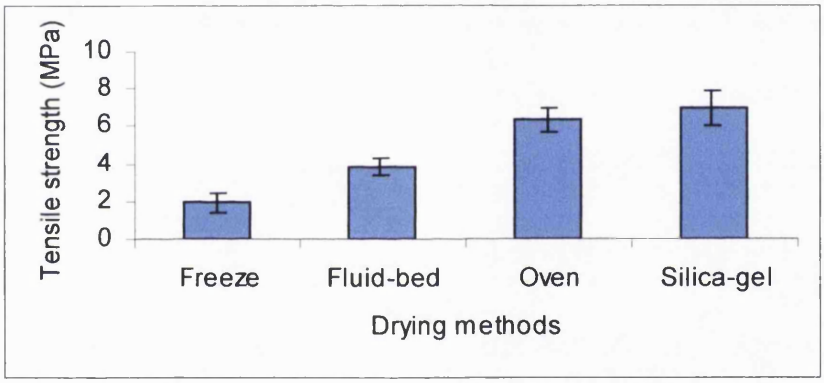
Some Mechanical Properties of Pellets	Drying techniques			
	Freeze drier	Fluid-bed drier	Hot air oven	Desiccation with silica-gel
Weibull-modulus	3.809	7.352	8.732	6.815
Weibull-constant (MPa)	2.209	4.091	6.813	7.514

Table-5.1.3:- Weibull statistics for the strength of MCC pellets, 1.0-1.18mm size fraction, produced by different dying techniques.

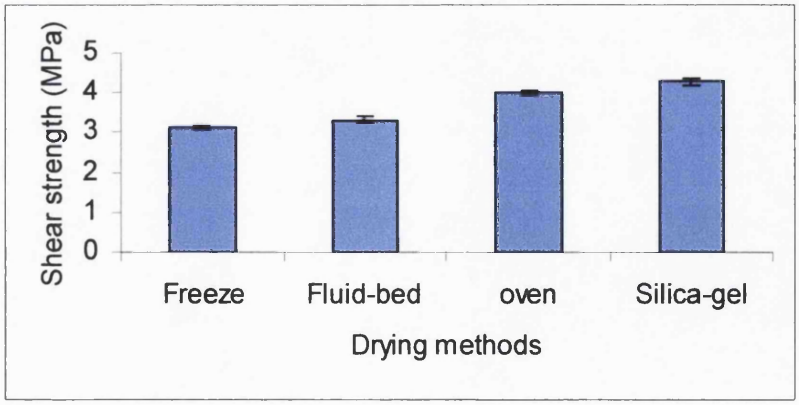
Weibull modulus (Table-5.1.3) illustrats the increase in the relative brittleness of the pellets with increase in their porosity, with the exception of the those dried by desiccation with silica-gel. The reason for this is not readily apparent. However, all the pellets could be considered as brittle for the values were low (less than 10) in all cases. As previously mentioned, the pores may have been used as crack initiators and propagators. The values for the Weibull-



(a)



(b)



(c)

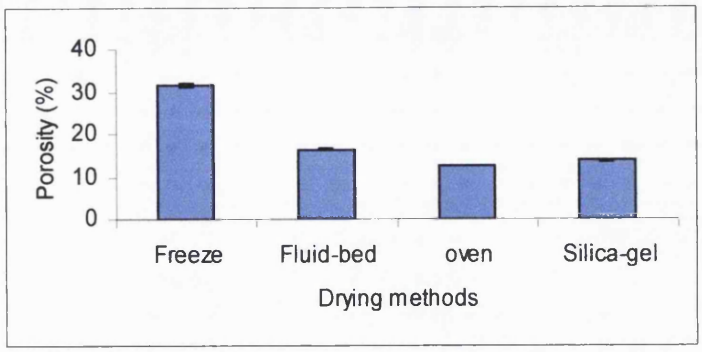
Fig-5.1.3:- The effect of porosity (a) and drying techniques on the tensile (b) and shear (c) strength of MCC pellet from 1.0-1.18 mm size fraction

constant, was in the same order to the tensile strength with a small increase in magnitude. This was mainly due to the absence of normal distribution of the data, and elimination of the smallest value to improve the correction factor (Erck,1994).

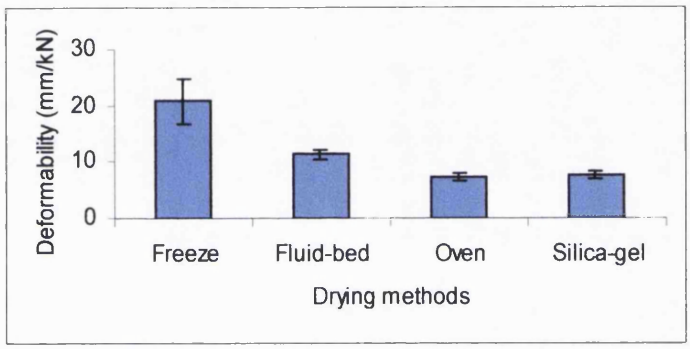
The deformability of the pellets increased in order starting from oven dried, to pellets dried by desiccation with silica-gel, then the fluid bed dried and to the freeze dried pellets, which were the most deformable (fig-5.1.4). The difference in deformability between the oven and silica-gel dried pellets was insignificant. This difference had the same magnitude as that of variation in the porosity of the pellets (Fig-5.1.4a), showing the more porous pellets were more deformable. It was also related to the strength of the pellets. The stronger pellets were less deformable. The linear strain of the pellets was in the reverse order to the deformability, although the difference was less (Fig-5.1.4c). The increase in porosity and decrease in strength was associated with a decrease in the linear strain of the pellets. This could be due to the early failure of the porous and weak pellets before they were strained to a greater extent. Dyer at el. (1994) observed a similar result. In their work on comparing the effect of oven and fluid-bed drying techniques on linear strain of pellets of two different formulations, they found that tray dried pellets exhibited greater displacement prior to fracture than the fluid-bed dried pellets. Moreover, (Figure-5.1.4d) shows the increase in the 'elastic modulus' of the pellets with the decrease of the porosity and deformability of the pellets. It had, however, a concurrent increase with the increase in the tensile strength and linear strain of the pellets.

As the 'elastic modulus' is determined form the pressure to linear strain ratio, a concurrent increase in both terms might be expected to result in a comparable 'elastic modulus'. However, the magnitude of the increase in pressure was considerably higher and dominated the increase in the linear strain of the pellets. This result had an order which is the reverse of the porosity of the pellets, showing the decrease in stiffness of the pellets with porosity. The results of Dyer el al. (1994) were in agreement with this observation. Their fluid bed dried pellets demonstrated greater elasticity as indicated by the relatively low 'elastic modulus' values obtained when compared to those of oven dried pellets.

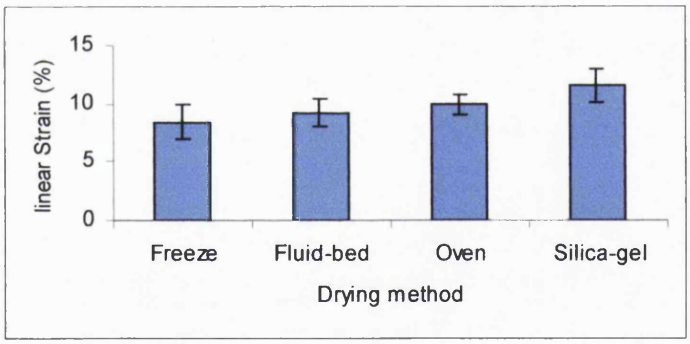
From these observation, it is possible to conclude that, based on the different rate of moisture removal, means of heat and mass transfer, and static or dynamic nature of the bed, these



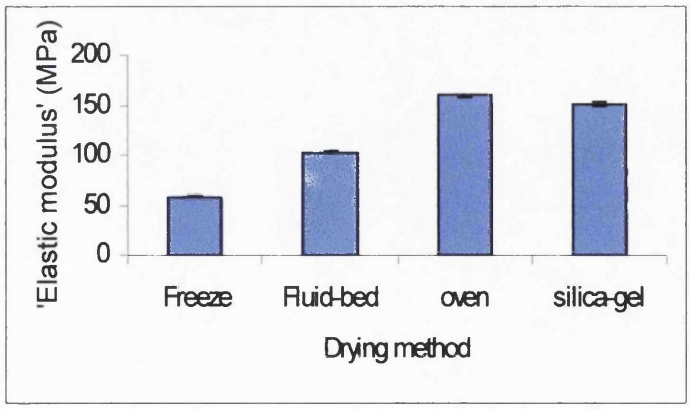
(a)



(b)



(c)



(d)

Fig-5.1.4:- The effect of drying techniques on the (a) porosity, (b) deformability, (c) Linear strain, and 'elastic modulus' of pellets from 1.0-1.18 mm size fraction.

different drying techniques produced pellets with different structural and mechanical properties. The most crucial of which was the porosity as a result of the different extent of shrinkage and expansion (in the case of freeze drying) of the pellets. The rapid evaporation of water as a result of the turbulent motion of the fluidized pellets (fluid-bed) and the sublimation of the expanded ice (freeze drying) suppressed the shrinkage of the pellets during drying to produce pellets of higher porosity and of greater mean diameter. On the other hand, the evaporation of the fluid takes place in very slow and less drastic way when drying by the oven or desiccation with silica-gel. This could be the reason for the highest shrinkage and lower porosity of the pellets in these latter techniques. As a result, the strength, deformability, stainability, and stiffness of the pellets varied.

5.1.3 COMPACTION OF THE PELLETS

Different compaction pressures (Fig-5.1.5) were needed to compress a bed of pellets of the same set of masses (600, 700, and 750 mg) produced by the different drying techniques to approximately the same tablet thickness (2.2.4 A).

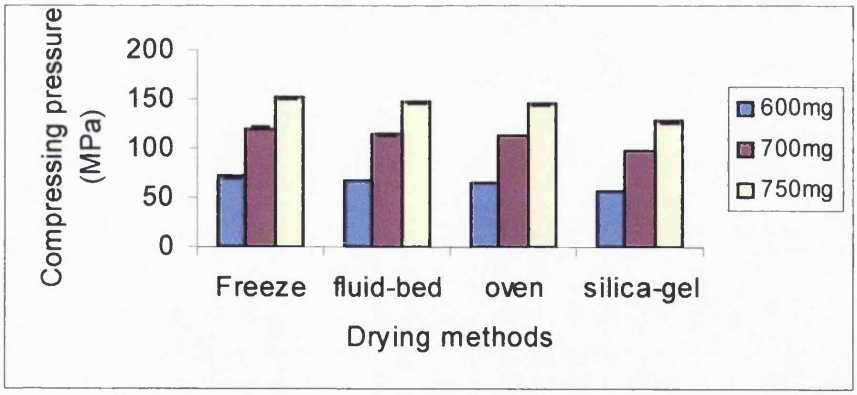


Fig-5.1.5:- The effect of drying technique on compaction pressure needed to compress the three different weight of MCC pellet beds to the same tablet thickness.

A lower pressure was recorded for a lower bed mass (600 mg). This was because the pellet bed was compressed to a lower solid fraction (a higher in die tablet porosity). The compressing pressure was, however, different for the pellets from different drying techniques although they had the same mass. An increase in compressing pressure was noted in all the different set of weights in an increasing order from those dried by desiccation with silica-gel, to those oven dried, the fluid-bed dried, and freeze dried pellets. This may be again confirmed

by the comparison of the work done to compress the pellets to tablets from pressure/displacement curves (Fig-5.1.6).

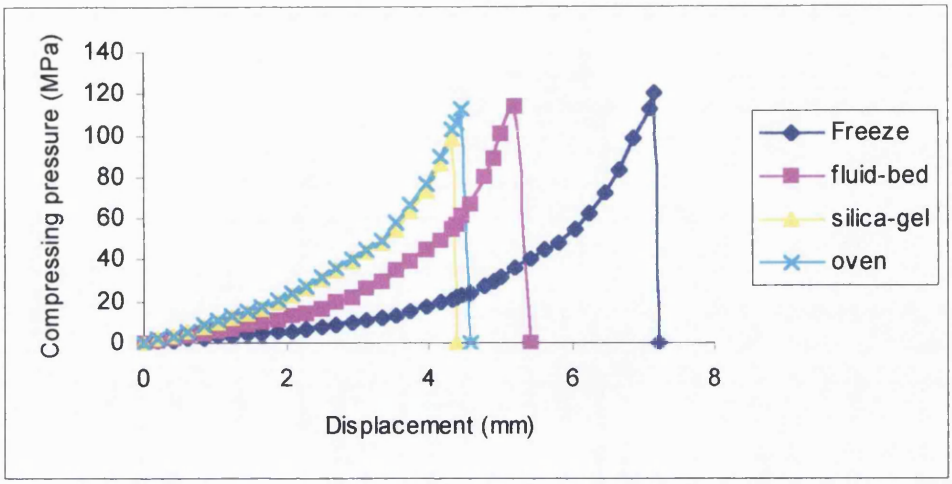


Fig-5.1.6:- The effect of different drying techniques on compaction mechanism of 700 mg of MCC pellets from 1.0-1.18 mm size fraction

Freeze dried pellets had the largest area under the pressure/displacement curve followed by fluid bed dried, oven dried, and those dried by desiccation with silica-gel in decreasing order. The extent to which the tablets compressed (compressibility) was related to the pressure and porosity of the pellets. The more porous were more compressible and needed a greater compaction pressure. An in die determination of the compressing pressure and platen displacement enabled the determination of the in die porosity of the tablets at different pressures. From these it was possible to draw Heckel plot (Fig-5.1.7).

The pellets seemed to have more or less the same slope, from which the yield strength was found to be approximately the same. This could be due to the fact that the same material remained after drying, although different techniques were involved. The curves however did not overlap with each other showing different initial packing mechanism. The pellets from different drying techniques had different porosities at the same compressing pressure. This was in agreement with the work of compaction discussed previously. Freeze-dried pellets required a higher pressure for the same porosity while fluid-bed dried pellets needed the lowest pressure for the same porosity.

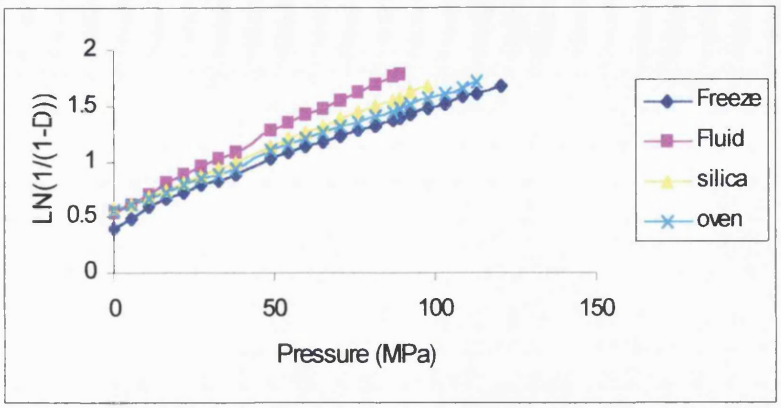


Fig-5.1.7:- The effect of different drying techniques on the Heckel plot produced form the compaction of 700 mg of MCC pellets form 1.0-1.18 mm size fraction

The out of die thickness of the tablets of different weights and produced by different drying techniques was measured using a micrometer. Although, they were supposed to be compressed to the same thickness, the values increased with the amount of pellets in the die. This shows, the presence of an instant elastic recovery of the tablets during decompression. Those tablets from a higher mass and greater compressing pressure were thicker than those of lower mass pellets produced by the same drying techniques. After storage of these tablets at ambient temperature and humidity from one to three days, the dimensions of the tablets were measured again (2.2.5). The tablets from 600 mg of oven dried pellets and those desiccated with silica-gel were very weak, so no further analysis could be made. From an immediate out die dimension measurements of the other tablets and measurements taken after a day from the 700 mg, as well as the measurements taken after 3 days from the 600 mg, 700 mg and 750mg tablets, comparison of the volumetric elastic expansion of the tablets was possible.

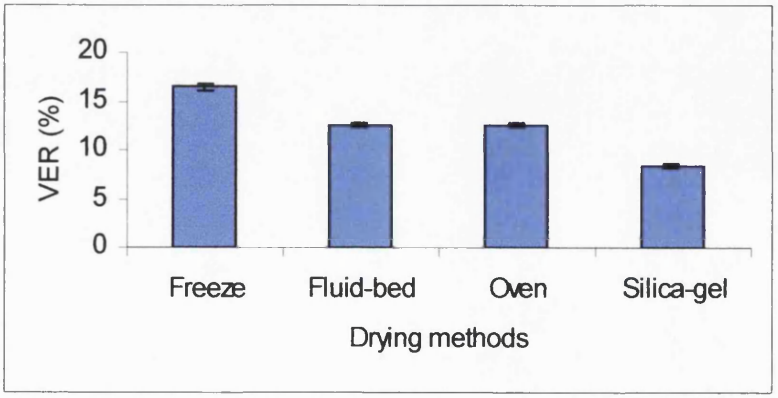
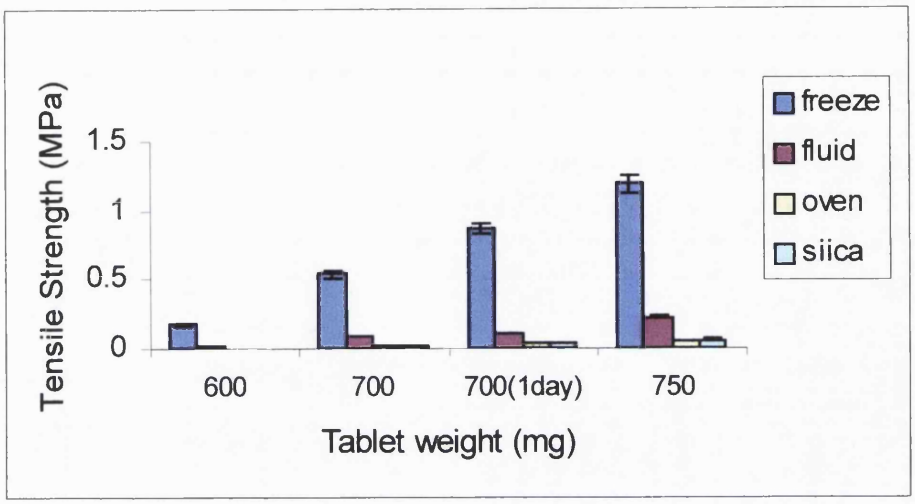


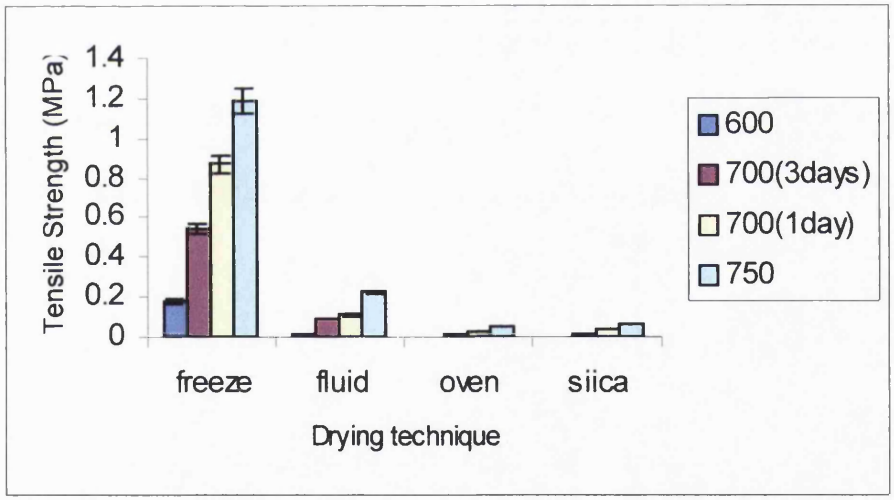
Fig-5.1.8:- The effect of different drying techniques on the volumetric elastic recovery of tablets produced from pellets of 1.0-1.18 mm size fraction

In all cases tablets of higher weight expanded to a greater extent. This was due to the greater elastic deformation for they were compressed to a higher solid fraction and by a higher compressing pressure. Tablets which were stored for a longer time expanded more presumably due to time dependent elastic recovery. The comparison after three days was, however, very difficult for some of the tablets were laminated (those from the freeze dried pellets) mainly due to excessive compressing pressure. Comparison of the expansion of 700 mg pellet compacts after one day showed pellets dried by freeze-drying expanded to the highest extent followed by fluid-bed dried, then oven dried, and at last those desiccated with silica-gel (Fig-5.1.8). This was in reverse order of the 'elastic modulus' of the pellets, showing that once the stiff pellets yielded, the occurrence of irreversible structural change such as cracks (Plate-5, see p228) hindered the volumetric elastic recovery of the compacts.

The tensile strength of the tablets (2.2.5) compacted from the different pellet weights and dried by different techniques were measured at different storage times (Fig-5.1.9 a&b). Tablets of higher weight had greater strength. This could be again due to the higher solid fraction (lower porosity) which enabled the surfaces to come to closer proximity, hence, cohere to form more rigid structures. The strength of the tablets measured after one day of their production was greater than those measured after three days, showing the structural disruptive effects of the reversible elastic deformation (Fig-5.1.9 a). In some cases, they were laminated. The strength of these tablets was also related to the way the pellets were dried. Tablets prepared from pellets of freeze-drying technique had the greatest strength for all weight and storage time categories. They were followed by fluid-bed dried, then oven dried, and finally those desiccated with silica-gel had the lowest strength (Fig-5.1.9 b). The difference between the oven and silica gel dried pellet compacts was actually marginal. This result was related to the deformability, porosity and strength of the pellets. The more porous pellets had higher deformability and lower pellet strength. Compacts of higher tensile strength were formed from pellets having lower strength but higher deformability and porosity. Although these pellets had the same formulation, the different drying techniques enabled them to have the above three different pellet properties. Pellets of weaker strength were easily crushed, while porous pellets were easily deformed to enable the surfaces of the pellets to come into contact and form rigid compacts of higher strength (Plate-5, see p-228).



(a)



(b)

Fig-5.1.9:- The effect of different drying techniques (a&b) on the tensile strength of tablets of different weight produced from MCC pellets of 1.0-1.18mm size fraction and tested after storage of different times (see p-224)

5.1.4 CONCLUSION

This work revealed that different drying techniques affected the property of the pellets, their compaction mechanism and the properties of their compacts. The oven drying technique produces, through thermal conduction, an evaporation of the fluid in the mono-molecular

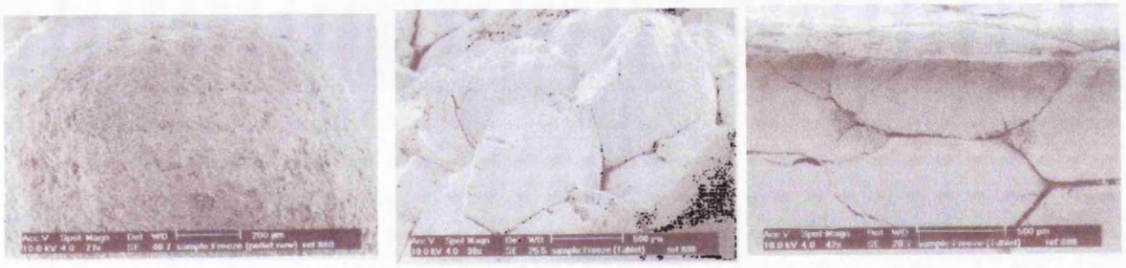
layers. The migration of the water to the surface of the pellets, by capillarity, produced through a slow and less drastic process. This could be the reason for the highest shrinkage and less elastic and strongest pellets production. As a result of these factors, their compacts were weak and had a lower elastic recovery.

The freeze drying technique which converted the water to expanded ice (about -200 ^{0}C by the liquid nitrogen) followed by their sublimation produced the most porous, deformable, weakest pellets. This helped the pellets to produce stronger compacts as the pellet surfaces came to closer proximity during compaction (Plate-5, see p-228)

In most cases the property of the pellets produced by desiccation with silica-gel was similar to those of oven dried. Nevertheless, the water molecules needed a lower temperature for their latent heat of vaporization in the low vapour pressure atmosphere of the sealed desiccator due to water absorbing nature of the silica-gel. The static and long lasting nature of the drying process was, however, similar to enable them to produce pellets of approximately similar properties.

The process of fluid bed drying technique was proved to be very effective for it was possible to dry the pellets in only 30 minutes to a comparable water content. This rapid process was observed to reduce the shrinkage of the pellets, produced relatively porous and deformable pellets. As a result their compacts were strong and had less volumetric expansion.

Finally, it should be noted that the values of the strength of the compacts were related to the drying techniques of the pellets. The techniques which produced porous, deformable and weak pellets had stronger compacts. The volumetric elastic recovery of the compacts was also observed to be affected by the different drying methods. In addition to many processing variables which are capable of significantly influencing the nature and quality of the final product, the drying technique employed as a pelletization process variable could also influence the surface characteristics of pellets (Plate-5, see p-228) and this may have consequences in respect of suitability of such material for film coat application and the dissolution of the incorporated drug.



(a) (b) (c)

Freeze drier pellets and pellet compacts

(a) (b) (c)

Fluid-bed dried pellets and their compacts

(a) (b) (c)

Hot air oven dried pellets and their compacts

(a) (b) (c)

Pellets dried by desiccation with silica-gel and their compacts

Plate-5: (a) surface of a pellet, (b) cross-section of a pellet compact, and (c) an edge of a pellet compact, produced from pellets dried by different techniques.

5.2 THE EFFECTS OF PELLET SIZE

5.2.1 INTRODUCTION

The effect of composition (chapter 3&4) and a processing factor (Section 5.1) on the mechanical properties of the pellets had been investigated. Another factor which had a profound effect on the properties of the pellets is their morphology. Chopra et al. (2001) illustrated the effect of the shape of pellets on the other properties, while Johansson et al. (1998) observed the effects of pellet size on their compaction mechanism and strength of their compacts. Moreover, the relationship between agglomerate size (diameter) to their strength (Section 1.2.4) and deformability (1.2.6) as well as the effects of pellet size on the strength of their compacts were reviewed with citation of some equations (1.2.1). In this section, the effect of MCC pellets size of a broader range (0.71-1.0, 1.0-1.18, 1.18-1.4, 1.4-1.7, 1.7-2.0, 2.0-2.36 mm) on the structural and mechanical properties of the pellets in terms of strength, deformability, linear strain and 'elastic modulus', as well as their compaction mechanism and the properties of their compacts has been investigated. To improve the compressibility, water/ethanol (80/20) was used as a binding liquid. Pellets of the same formulation were also produced by different die diameters (1.5 and 2mm), however, their property was approximately the same as those having the same size produced by smaller die diameter. Thus pellets produced from only the 1.0mm die diameter, which were sieved (2.2.2.1) to different size fractions, have been considered here. Furthermore, the effects of different size distribution, obtained by mixing the various size fraction, have been examined in terms of the compaction mechanism and properties of the compacts.

5.2.2 THE PROPERTIES OF PELLETS

Despite the fact that all the pellets were spherical, from the same material, and produced by the same procedure, they had variations in packing property as was illustrated in their bulk and tapped densities (Table-5.2.1). Moreover, the apparent density of the pellets was also influenced by the increase in the pellets size. With the increase of the mean pellet size, these three density terms were observed to decrease, although by a very small magnitude (Fig-5.2.1). These results indicate that when the same mass of pellets are placed in the same die diameter, the bigger sized pellets will have a greater pellet-bed height, hence will be compressed to a greater extent (greater compressibility) to produce tablets of the same thickness. The apparent pellet density revealed the presence of a higher "sealed pores" in pellets of greatest diameter (14.6%) compared to the smallest diameter (5.9%), for they had

a relatively lower apparent pellet density. This was because the helium gas could not access the sealed space.

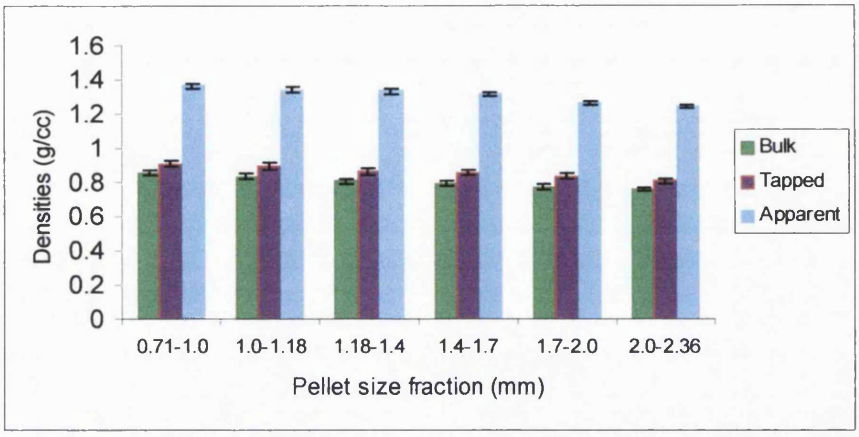
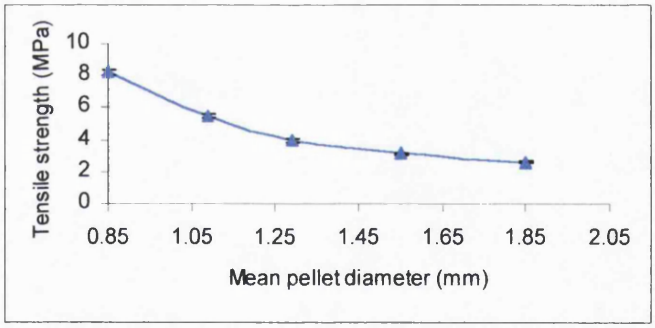


Fig-5.2.1:- The effect of pellet size on the bulk, tapped and apparent densities of MCC pellets

A decrease in pellet size resulted in increase of the shear strength and tensile strength of pellets as was measured from surface failure according to Shipway and Hutchings (1993) (Fig-5.2.2 a&b).

(a)



(b)

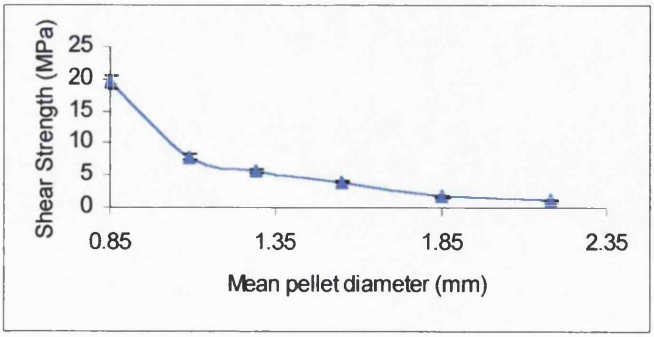


Fig-5.2.2:- The effect of size on the (a) tensile and (b) shear strength of MCC pellets

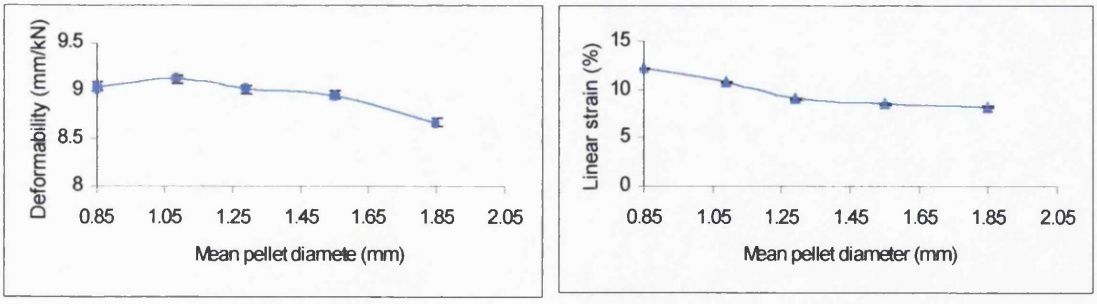
The underlying reason for the increase in tensile strength with decrease in particle size was generally attributed to a reduced probability of the existence of defects in the structure (Stanley, 2001). These defects can act as sites at which a crack could be initiated and

propagated during a fracture. This was supported by the higher probability of brittleness of the bigger pellets as determined form the Weibull-modulus although the difference was not of considerable (Table-5.2.1).

Some Mechanical Properties of Pellets	Mean pellet size				
	0.85mm	1.09mm	1.29mm	1.55mm	1.85mm
Weibull-modulus	8.703	8.047	8.956	7.927	6.809
Weibull-constant (MPa)	8.766	5.845	4.232	3.303	2.795

Table-5.2.1:- Some mechanical properties of MCC pellets of different mean diameter.

The different mechanisms by which these pellets failed during compression was observed by comparing the force/displacement curves of the pellets during diametral crushing. An increase in slope or decrease in deformability was observed with an increase in pellet size (Fig-5.2.3 a). The result complements the observed brittleness of the pellets. The bigger and brittle pellets had lower deformability. The rank order of this observation was concurrent with that of strength value with the exception of lower deformability of pellets from 0.85mm mean diameter compared to those of 1.09mm mean diameter. Moreover, the linear strain of the pellets was observed to decrease with the increase of the mean pellet diameter (Fig-5.2.3b).



(a) (b)

Fig-5.2.3:- The effect of particle size on the (a) deformability and (b) linear strain of MCC pellets

The difference in absolute displacement of the pellets was not as significant as the strain in percentage. However, for the same diametral compressing force, the absolute displacement increased steadily with the decrease in mean pellet size, although to a very small extent. This

shows that the deformability of the pellets occurred locally, mainly on the contact area of the pellets with the platen as they had, approximately, the same absolute displacements.

The 'elastic modulus' of the pellets was also found to be related to the mean size of the pellets (Fig-5.2.4). There was a consistent decrease in 'elastic modulus' with the increase of the mean pellet size. The decrease in stiffness with increase in size could presumably be due to the presence of more porous structures which could absorb the stress by slippage of the primary particles into the available spaces.

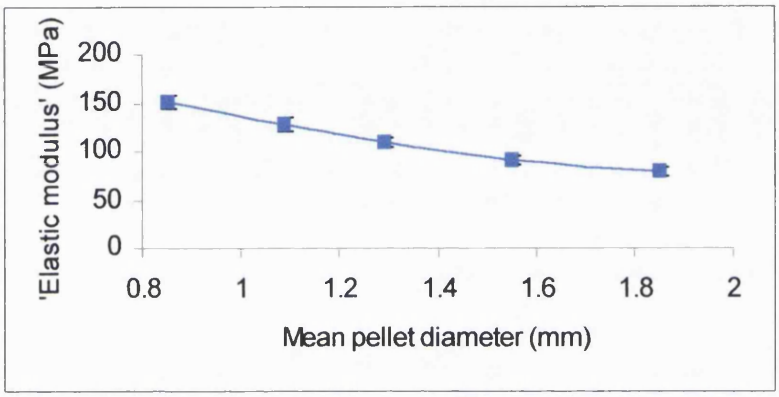


Fig-5.2.4:- The effect of pellet size on the 'elastic modulus' of MCC pellets

5.2.3 COMPACTION OF THE PELLETS

The force needed to compact 600 mg of pellets to the same tablet thickness as explained on (section 2.2.4 A) was approximately of the same magnitude, except on the lowest pellet size fraction as discussed below. The compaction pressure versus tablet thickness of the compact in the die is illustrated on (Fig-5.2.5). The pellets appear to be compacted by the same mechanism from about 6.5 mm in die tablet thickness up to the final tablet thickness (about 3.85mm). This reflects that the composition of the pellets was identical , i.e. MCC, although of different size fractions.

The compaction pressure was expected to start after the pellets were rearranged to the highest packing density (tapped density). However, in this work, pressure started to be registered at far lowest densities than the tapped density of each size fraction of the pellets. This shows that rearrangement of the pellets was not complete before the onset of pellet deformation/fracture. In pellets of the largest diameter, the pressure started at 9.6mm in die tablet thickness. This was about 0.55g/ml in density. For pellets of the smallest size fraction (0.85mm in diameter),

pressure started at 7.6mm tablet thickness. This was about 0.7g/ml in density. This shows an earlier compression pressure for pellets of greater size and a consistent delay of pressure with decrease in pellet size confirming the variation in compressibility (Fig-5.2.6).

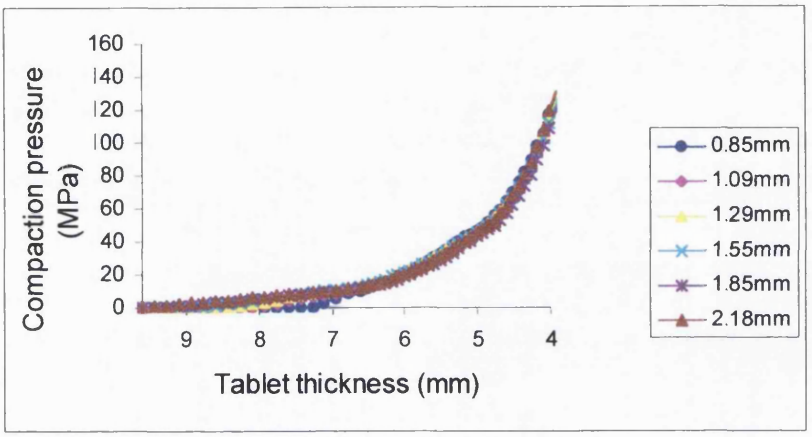


Fig-5.2.5 :- The effects of pellet size on the compaction mechanism of MCC pellets

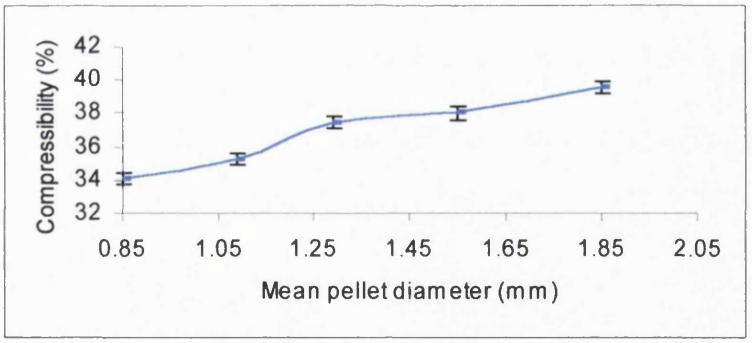


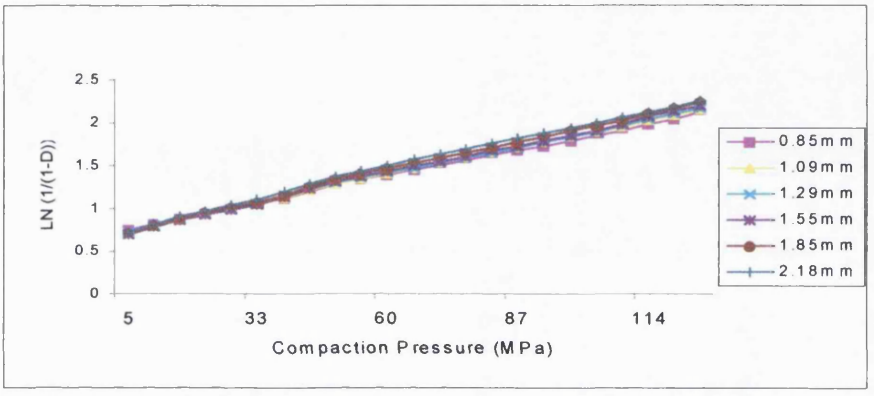
Fig-5.2.6 :- The effect of pellet size on the compressibility of MCC pellets

From this observation it can be concluded that none of the pellets reached their densest packing at the time of initial pressure detection. Moreover, the rearrangement of the smaller pellets was relatively better or to a higher packing density before a compression pressure was recorded. As the smaller pellets had a greater surface area, more contact area was expected to produce higher friction and lower packing. However, the rougher surface of the larger pellets could be the reason for less rearrangement and earlier recording of compression pressure. Fig-5.2.5 illustrates a relatively greater area under the pressure/displacement curve for the bigger pellet sizes. The possible explanation for this observation could be, the extra work needed to rearrange the bigger pellets and to break them so that to fill the space

between them by the fragments.

Duberg and Nystrom (1982) suggested that the effect of particle size on volume reduction behaviour of powder could be assessed primarily by studying the relationship between applied pressure and volume of the pellet-bed during the actual compression phase by Heckel profile. Based on this, the Heckel plots of the six different size fractions were drawn and are shown on (Fig-5.2.7 a&b).

(a)



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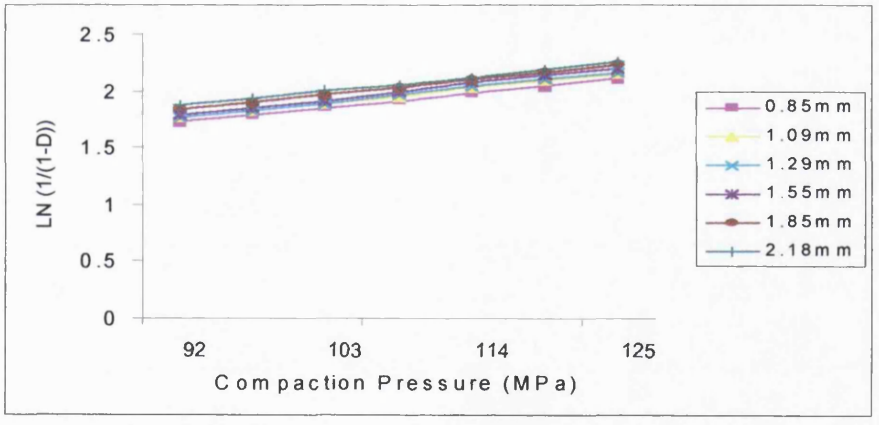


Fig-5.2.7 :- The Heckel plot derived from an in die compaction of pellets of different sizes (a) the whole plot and (b) the upper part.

The upper part of the plot shows almost parallel lines (Fig-5.2.7 b). This indicates the presence of the same slope, reciprocal of which is proportional to the yield pressure of the material. Since all pellets were made by the same material, the yield pressures were almost the same. Although these plots were not drawn to zero pressure, there was a trend of deviation of the lines from the linearity at the beginning as the pellet size increased. This was in agreement with the observation made by Duberg and Nystrom (1982). They found that the

linearity of the Heckel profiles increased with the decrease in particle size during compaction of a series of materials. They argued that this can be interpreted as a reduced degree of fragmentation of the particles during compaction with a decrease in particle size.

Each size fraction of the pellets were compressed to approximately the same tablet thickness. The two smallest size fractions (0.85 mm and 1.09 mm in diameter) did not produce strong pellet compacts which could be handled and analysed in terms of tablet dimensions and strength. The remaining four sets produced compacts that had almost the same tablet thickness (about 3.85 mm). The compression pressure of the larger four fraction sizes was similar (approximately 130 MPa) (Fig-5.2.8). There was a slight decrease in pressure with increase of pellet size.

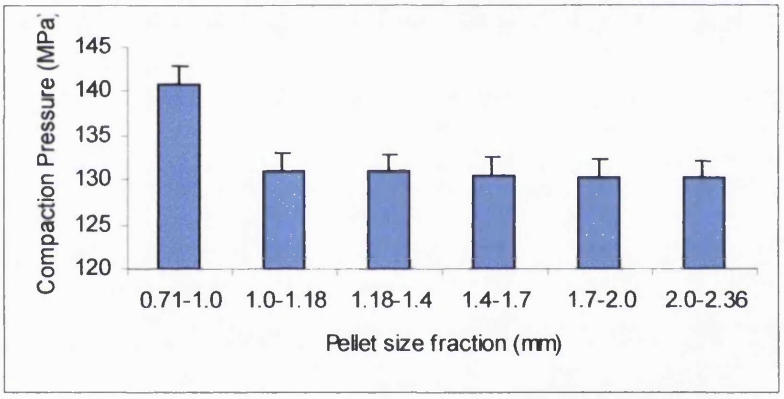


Fig-5.2.8:- The pressure needed to compress the 600 mg pellets of different size to the same tablet thickness.

This appears to be related to the ease of shearing and lower tensile strength of the pellets. The bigger the pellets, the smaller was the tensile strength. This may not be a straight forward relation for in the compaction of the pellets in a confined space, each pellet is in contact with the neighbouring pellets or laterally with the wall of the die, while during diametral compression to determine pellets tensile strength there is no any lateral support which could help in resisting the failure of the pellet from the induced tensile force.

Pellets of the two smallest size fractions did not produce tablets although their compaction pressure was relatively higher than the rest. They had also the greatest pellet tensile strength which could have helped them to resist the fracture that would produce new connection surfaces. The rest size fractions produced compacts of almost the same dimensions, but

different tensile strength as measured by diametral compression (Fig-5.2.9)

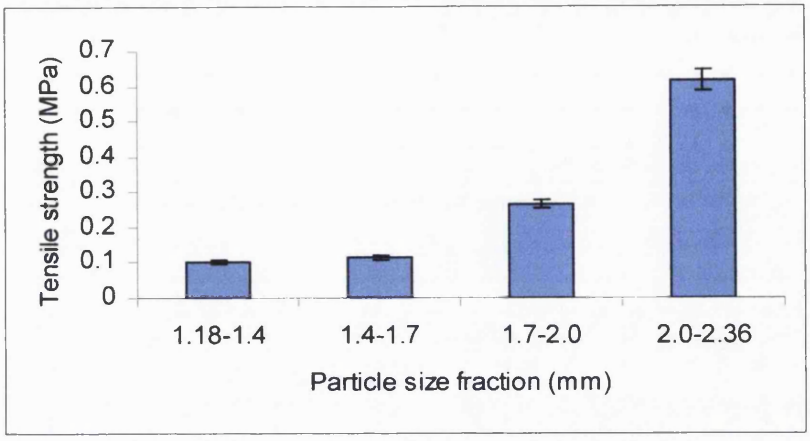


Fig-5.2.9 :- The tensile strength of the tablets produced by different pellet sizes.

The tensile strength of the compacts increased with the increase in pellet size. In other words, the compact strength increased with the decrease of the pellet tensile strength. The possible reason is due to the more fragmentation of the bigger pellets, hence formation of new and clean surfaces which increased the inter-granular interaction sites for the formation of rigid structures.

In their investigation on compression behaviour of MCC pellets having different porosity Johansson et al. (1995) and Johansson and Alderborn (1996) reported that the relevant compression mechanism was permanent deformation (i.e. a change in the shape of the individual pellets) and densification (i.e. contraction or porosity reduction of individual pellets) and that fragmentation of pellets was minute. This could be due to their very porous pellets produced from 70%w/w ethanol as a liquid binder. A detailed characterisation of the pellets in this work (produced with 20%w/w ethanol), however, showed a decrease in the linear strain of the pellets with an increase in mean pellet size before they broke to form new surfaces. Moreover, the compacts here were de-aggregated in an absolute ethanol (a solvent which does not dissolve or swell MCC) and water (which swells the MCC and magnifies the structure). The de-aggregated pellets were dried in an oven and studied visually to identify whether they had variation in structural change which could be related with their size variations. This revealed a grater fragmentation of the larger sized pellets. Moreover, the visual observation on the disappearance of pellet boundaries of the compacts was by itself an indication of this structural change. As a result, it was possible to conclude that fragmentation

was more likely to happen with pellets of larger mean diameter.

The occurrence of fragmentation with increase of pellet size to produce new surfaces and the ability of the new surfaces to form inter granular connection was illustrated by covering the surface of the pellets by a lubricant film and compressing them to tablets to observe the effect of particle size on fragmentation and rupturing of the film, as a result formation of new surfaces and strong compacts. In a similar experiment where Avicel was mixed with 10% of magnesium stearate before it was compressed to tablets, Van der Watt (1987) observed that the disintegration time and the crushing strength decreased with a decrease of particle size of Avicel in the ranges of (80-180, 180-250, 250-350 μm). They noted that the crushing strength of tablets decreased with increased mixing time of all Avicel size fraction with magnesium stearate up to a limiting value where a complete film formation occurred. For bigger particles, however, they noted a higher strength due to the fragmentation and rupturing of the coating film.

There was almost no volumetric expansion of the tablets produced by different pellet size fractions after storage. The individual elasticity difference of the pellets which was shown by 'elastic modulus' was not reflected here. This could be due to the excessive force used to compact the pellets which resulted to permanent deformation and/or fragmentation.

5.2.4 PELLETS SIZE DISTRIBUTION

Pellets of different size fractions were mixed to produce a range of different size distribution. The median and the inter-quartile range of mixed pellets for the one, three and five component size fractions are presented in Table-5.2.2.

No.	Number of size fractions	Median pellet size (mm)	Inter Quartile Range (mm)
1	one	1.29	0.11
2	three	1.31	0.55
3	five	1.32	0.61

Table-5.2.2:- The size and size distribution of MCC pellet of mixed fraction sizes

The increase in size distribution was made by adding an equal weight of pellets from the lower and upper size fractions of the pellets to the starting size fraction (1.18-1.4mm). That was why the pellets had a similar median size, which assisted in excluding the effect of the difference in the median pellet size. It was very difficult to determine the bulk and tapped densities of these pellet mixtures due to their segregation. The results which include the apparent density is presented in Fig-5.2.10.

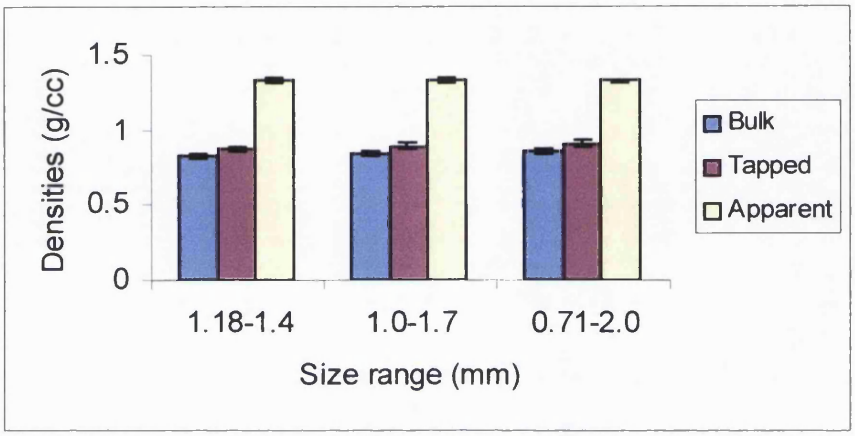


Fig-5.2.10 :- The bulk, tapped , and apparent densities of pellets of different size distribution

There was very little difference in the bulk density values, which could be within the error of measurement. The values in the apparent density of the pellets was also approximately the same. A theoretical calculation, from the results (Fig-5.2.1) and proportion of each size fraction (Table-5.2.2), indicated approximately the same porosity. This was reflected in a similar compressibility of the pellet beds, and force/displacement profile.

The mixed pellets containing three and five size fractions did not produce compacts which could be retrieved from the die. That was why no further analysis was done on the dimensions and strength of their compacts. That was because of the incorporation of the incompactible size fractions (i.e. 0.71-1.0mm and 1.0-1.18mm size fraction) as noted in section 5.2.3. However, the size distribution of the pellets had an effect on the maximum compression pressure of the pellets in a die (Fig-5.2.11).

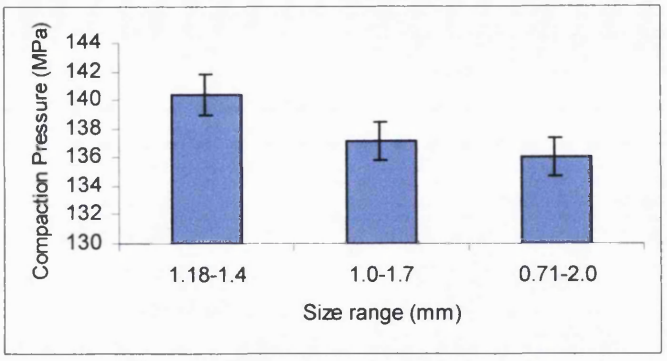


Fig-5.2.11:- The pressure needed to compress 600 mg pellets of different size distribution to the same tablet thickness.

The magnitude of the compression force decreased with an increase in the size distribution of the pellets. This again is related with the rearrangement of the pellets during compression. In a wider size distribution, the smaller pellets were able to fill the void between the larger pellets during the first phase of the compression to result in a reduction in the compressing pressure. For the mono dispersed pellets, however, the deformation and/or fracture of the pellets was the only possible volume reduction mechanisms, hence, expenditure of extra force was inevitable.

5.2.5 CONCLUSION

This work showed the effect of pellet size on their other properties. Their porosity, strength, deformability, linear strain, and 'elastic modulus' was observed to decrease with an increase of the mean pellet size. This could be due to the more closed pores and higher probability of the existence of defects on the surface which could be crack initiators.

The compaction of pellets of different sizes resulted in approximately the same in die compaction pressure and the same slope for the higher portion of the Heckel plot. However, there was a trend of deviation of the lines from the linearity at the beginning of the Heckel plot with an increase of the pellet size. The tensile strength of the compacts increased with an increase of pellet size. This was presumably due to the fracture of the bigger pellets, which enabled them to produce new clean surfaces that can cohere and form rigid structures. This fracture was observed from the de-aggregated pellets as it was more apparent with the increase of the pellet size. The lowest volumetric elastic recovery of the compacts also

indicates a none reversible deformation and fracture of the pellets in the compacts. Finally, this work provided an evidence on the effect of the size distribution of the pellets on their compaction force. This was mainly due to the difference in the mode of packing. The denser arrangement of the poly dispersed pellets reduced the pressure exerted due to the reduction in compressibility.

PART - III

CHAPTER-SIX

DRUG PELLETS

6.1 UNCOATED DRUG PELLETS

A detailed study of the effects of different proportions of excipients (Chapter-3), liquid binders (Chapter-4), drying techniques and pellet morphology (Chapter-5) on the mechanical properties of the placebo pellets, their compaction mechanism, and the properties of their compacts have been discussed previously. The objective of this chapter is, to investigate the comparative effect of the formulation factors on the mechanical properties and compactability of the pellets containing 10%w/w paracetamol. The pellets were produced by a standard extrusion and spheronization procedure and were dried by fluid bed drier. A size fraction of 1.0 -1.18mm was separated for all further analysis. Table-6.1.1 shows the formulae of the five different drug pellets.

Formula		Constituents in the wet mass						
name	Symbol	MCC	Paracetamol	Lactose	GMS	Water	Ethanol	Glycerol
MCC	M	9	1	0	0	9	0	0
Lactose	L	9	2	9	0	10	0	0
GMS	G	9	2	0	9	10	0	0
Ethanol	E	9	1	0	0	4	4	0
Glycerol	R	18	2	0	0	9	0	9

Table-6.1.1:- The ingredients in the wet mass of the five drug formulations.

6.1.1 THE PROPERTIES OF THE PELLETS

The formulae, M, L, E, G, and R needed different forces, 4.0, 4.2, 3.8, 4.5, and 5.8 kN, respectively to extrude them through a die of 1mm diameter and 5 mm in length. All had a smooth surfaced extrudates, while those containing glycerol had a very long, unbroken and coiled extrudates. The spheronization time for lactose or glycerol containing formulations was five minutes more than the other formulations, yet the shape of these pellets was less spherical (Table-6.1.2). The longer cut size of the glycerol extrudate, produced pellets of relatively greater median size and wider size distribution (Table-6.1.2), their modal size fraction was

1.18-1.4mm, which was 44.88% of the total weight. The porosity of the pellets was reflected on the bulk densities, while the proportion of "sealed pores" was insignificant in all formulations except in MCC pellets (Table-6.1.2). To determine the proportion of the open-pores, these pellets were coated by 5%w/w of ethyl cellulose and a helium pycnometer was used to determine the apparent density, from which the total porosity was determined. Pellets produced with ethanol in the liquid binders had approximately 30% porosity, while all the other formulations had less than 10%.

Structural Properties of the Pellets	Formulae				
	MCC	Lactose	Ethanol	GMS	Glycerol
Median pellet diameter (mm)	1.07	1.12	1.08	1.09	1.25
Interquartile range (mm)	0.16	0.12	0.2	0.11	0.24
Modal size fraction,1.0-1.18mm (%)	59.10	68.44	50.58	71.18	30.07
Bulk Density (g/cc)	0.82(0.05)	0.83(0.06)	0.67 (0.04)	0.73 (0.05)	0.82(0.06)
Tapped Density (g/cc)	0.87(0.05)	0.87(0.06)	0.68(0.03)	0.74(0.04)	0.87(0.05)
Hausner ratio	1.057	1.038	1.015	1.017	1.057
Apparent pellet density (g/cc)	1.35(0.05)	1.48(0.06)	1.50(0.07)	1.21(0.05)	1.33(0.04)
internal (sealed) porosity (%)	9.32(0.50)	1.18(0.01)	0.64(0.01)	0.59(0.01)	2.91(0.01)
Shape factore, e_R	0.56(0.02)	0.49(0.01)	0.53(0.02)	0.55(0.03)	0.49(0.01)
Aspect ratio	1.09(0.1)	1.11(0.2)	1.11(0.2)	1.08(0.1)	1.11(0.1)
Circularity	0.83(0.04)	0.77(0.03)	0.86(0.04)	0.78(0.04)	0.74(0.03)
Projected sphericity	0.87(0.04)	0.85(0.04)	0.86(0.04)	0.87(0.04)	0.84(0.04)

Table 6.1.2:- The structural properties of the drug pellets in the1.0-1.18 mm size fraction, produced from a wet mass of different composition. The values in the parenthesis indicate the standard deviation.

The mechanical properties of the pellets from the five formulations were studied. In order to examine the change in properties with time, the pellets were stored at ambient temperature and humidity for three and six months and were mechanically characterized as described in (section 2.2.3). Fig-6.1.1 to Fig-6.1.4 depicts the tensile strength, deformability, linear strain, and 'elastic modulus' of the pellets immediate after production, after three and six

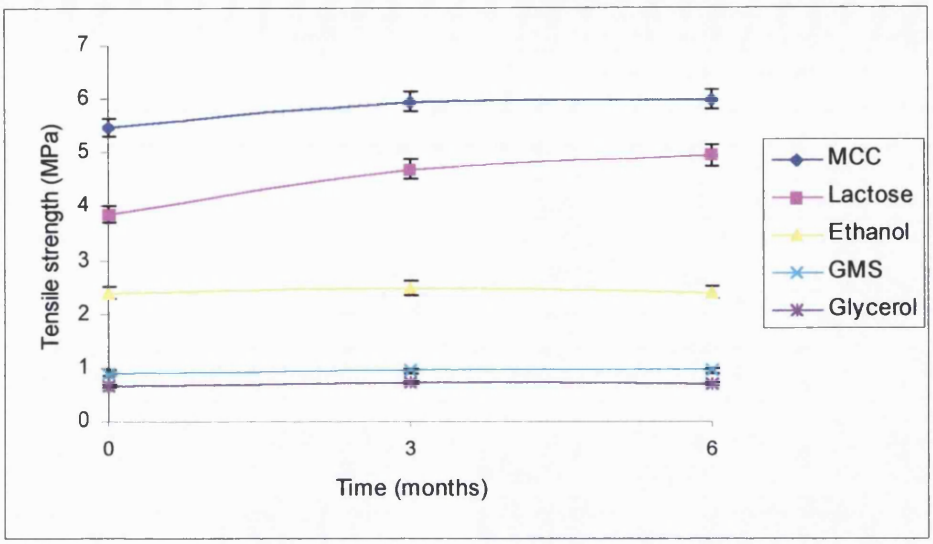


Fig-6.1.1 The tensile strength of drug pellets of 1.0-1.18 mm size fraction measured at three different times.

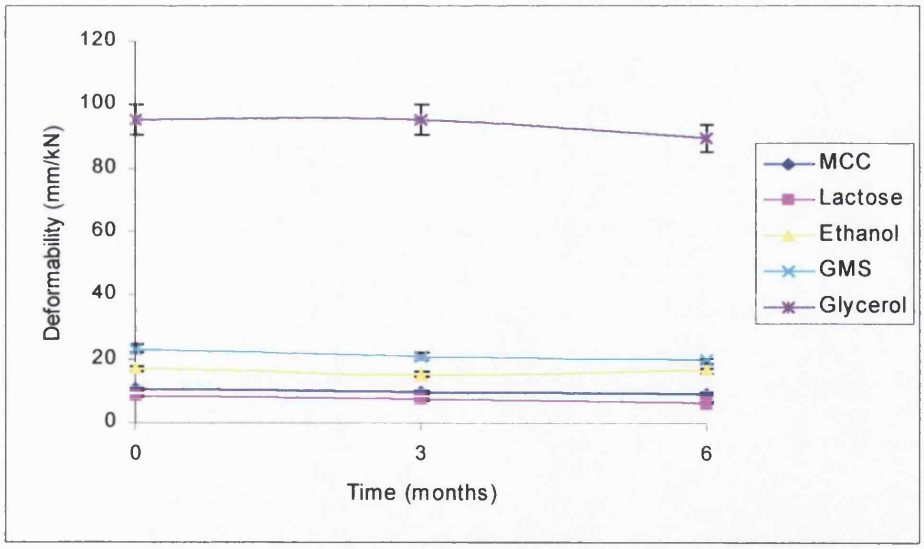


Fig-6.1.2 The deformability of drug pellets of 1.0-1.18 mm size fraction measured at three different times.

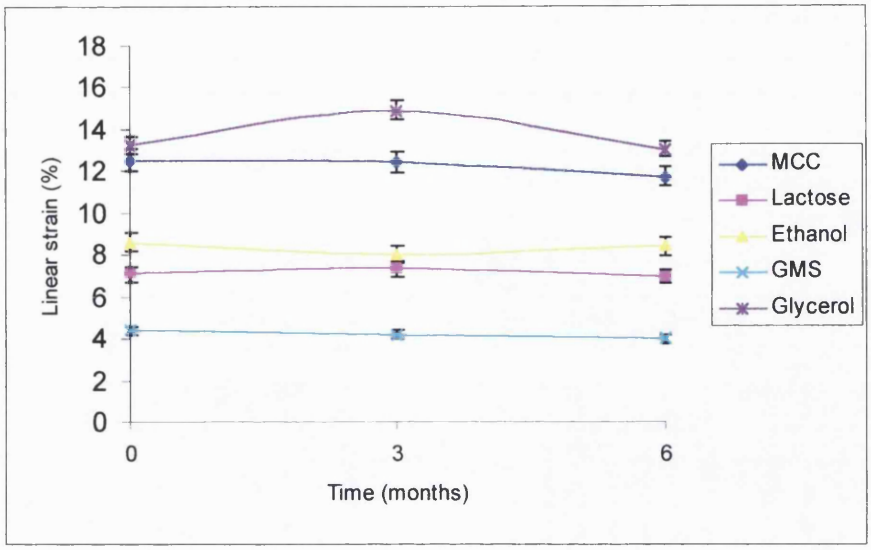


Fig-6.1.3 The linear strain of drug pellets of 1.0-1.18 mm size fraction measured at three different times.

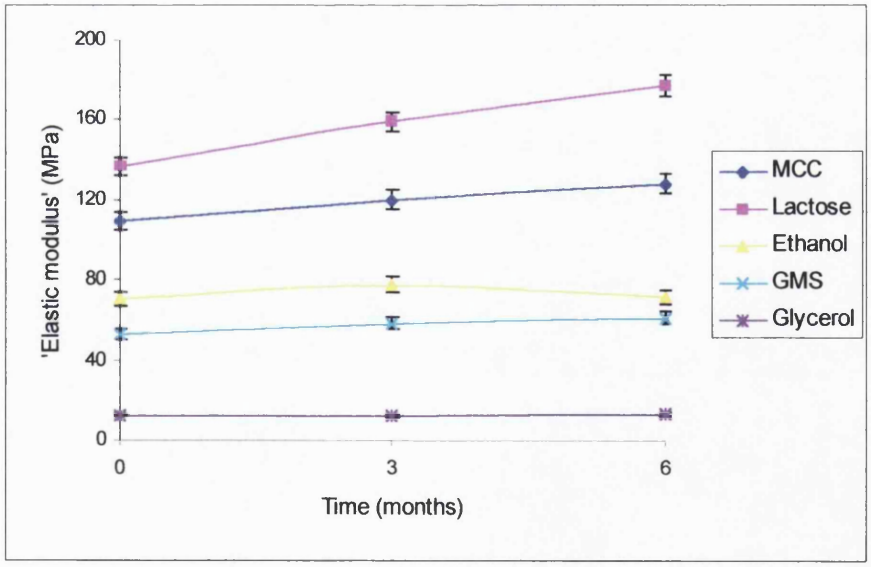


Fig-6.1.4 The 'elastic modulus' of drug pellets of 1.0-1.18 mm size fraction measured at three different times.

months of storage. There was a statistically significant difference in the tensile strength between the pellets of the five formulations at all time intervals. The strength of MCC and those containing lactose pellets significantly increased in the first three months ($P<0.05$), while it had only a slightly increase in the following three months. Pellets containing GMS or glycerol and those produced with ethanol in the liquid binder had virtually a constant strength at all the times. The shear strength of the pellets, measured immediately after production, was lower than the corresponding tensile strengths of the pellets (Table-6.1.3). The difference in the values of MCC and lactose containing pellets as well as pellets containing GMS and those produced with ethanol was only marginal.

Some Mechanical Properties of Pellets	Formulae				
	MCC	Lactose	Ethanol	GMS	Glycerol
Weibull-constant	5.790	4.246	2.616	0.997	0.724
Weibull-modulus	8.207	4.730	5.946	4.820	5.690
Shear Strength (MPa)	1.67±0.06	1.68±0.03	0.47±0.02	0.43±0.02	0.011±0.01
Tensile/Shear Strength ratio	3.27	2.29	5.15	2.14	60.00

Table-6.1.3:- Mechanical properties of the drug pellets of 10-1.18 mm size fraction.

The Weibull-modulus (Table-6.1.3) of the pellets indicate that all the pellets could be considered as brittle for the values are less than 10. The variation between the formulations, however, indicated a greater relative brittleness of pellets containing lactose or GMS. This was supported with the lower tensile to shear strength ratio of these two formulations. The lower melting point of GMS could be the reason for the formation of a hard and brittle crust on the pellets during drying, while the relative brittleness of lactose containing MCC compacts is a well documented observation (eg. Newton et al. 1993).

The deformability of the pellets increased in an ascending order from lactose, MCC, ethanol, GMS, to glycerol containing pellets for all time intervals. This was the reverse order of the tensile strength of the pellets. All the formulations had a reduced deformability with time, except those formed with ethanol in the liquid binder (Fig-6.1.2). However, all the differences were statistically insignificant. The order of the linear strain of the pellets increased in an

ascending order from GMS, lactose, ethanol, MCC to glycerol (Fig-6.1.3). MCC and GMS containing pellets showed a slight decrease in linear strain with time, while ethanol, lactose, or glycerol containing pellets had a higher strain after three months, while pellets which had ethanol as a liquid binder had a lower strain after three months. The variation in the linear strain of the formulations with time was not statistically significant. Between the formulations, however, it was significant ($P<0.05$).

The 'elastic modulus' of the pellets, was observed to increase in an ascending order from glycerol, GMS, ethanol, MCC to lactose containing pellets (Fig-6.1.4). The 'elastic modulus' of the pellets had a similar order to that of the shear and tensile strength of the pellets, with the exception of MCC pellets which had the greatest tensile strength. The relatively higher linear strain could have reduced the 'elastic modulus' of the MCC pellets compared to those containing lactose, as the 'elastic modulus' was calculated as a ratio of the compressing pressure to the linear strain (Dyer et al. 1994). The 'elastic modulus' increased with storage time for all formulations. The rank order in increase proportion after six months in ascending order was from ethanol (2%), glycerol (5%), GMS (17%), MCC (18%), to lactose (30%).

The study of the effects of the formulation factors of the placebo pellets (Part-II) was reflected here in the drug pellets. The strength, deformability, and strainability effects of the factors were in the same rank order. However, the effect of factors on the mechanical properties of the pellets varied with time to different extent. This could be presumably due to variation in the change in forms of the excipients in time (eg. re-crystallization).

6.1.2 COMPACTION OF THE PELLETS

Tablets of the same thickness were produced from 600 mg of pellets from all the formulations according to the procedure given in (section 2.2.4.1A). Due to the different bulk densities (Table-6.1.2), the pellets had to be compressed to different extent i.e compressibility. The porous pellets produced with ethanol in the liquid binder had the greatest compressibility, while lactose containing pellets, which had a higher bulk density were compressed to the lowest extent. The Kawakita compressibility constant, b, however had a different rank order (Table-6.1.4). The rank order was the same as the ease of deformability of the pellets and to the reverse order of the strength of the pellets, indicating that less deformable and strong

pellets were difficult to compress. The compaction pressure required for the same mass of the pellets from the different formulations to the same tablet thickness was different, ranking in ascending order from glycerol, MCC, ethanol, lactose to GMS containing pellets. The ease of deformability of glycerol containing pellets reduced the compaction pressure, while the need for the higher volume reduction in the porous MCC pellets produced with ethanol increased the compaction pressure. GMS containing pellets had the lowest apparent density which resulted in tablets of the lowest final in die porosity. This could be the main reason for the considerable increase in compaction pressure required for the pellets from this formulation.

Compaction Properties of Pellets	Formulae				
	MCC	Lactose	Ethanol	GMS	Glycerol
Compressibility (%)	38.6±0.06	38.0±0.04	48.3±0.05	40.8±0.08	38.6±0.06
Compaction pressure (MPa)	114.23±0.5	135.38±0.9	121.28±0.9	214.8±4.1	76.6±2.9
Tablet tensile strength (MPa)	-	0.25±0.04	0.23±0.02	0.60±0.08	-
Volumetric Elastic Recovery (%)	-	1.46±0.8	2.63±0.9	0.46±0.3	-
Yield Pressure, 1/k, (MPa)	43.1 ±2.1	49.5 ±2.4	65.4 ±3.2	24.7 ±1.2	18.4 ±0.9
Kawakita compressibility constant ,b, (MPa^{-1})	0.034 ±0.002	0.039 ±0.002	0.046 ±0.003	0.068 ±0.003	0.196 ±0.010

Table-6.1.4:- Compaction properties of the drug pellets of 1.0-1.18mm size fraction produced form the different formulations.

Fig-6.1.5 depicts the compaction process of the pellets, which indicates the variation in compressing pressures (vertical component) and compressibility (horizontal component) of the formulations. The area under the curve, the work of compaction had a rank in an ascending order from, glycerol, MCC, lactose, ethanol to GMS. This was the same order as the compressing pressure with the exception of ethanol, which required a greater work than lactose, due to a higher compressibility.

The Yield pressure of the formulation had the same rank order as the 'elastic modulus' of the pellets with the exception of the pellets produced with ethanol in the liquid binder. This confirms the rigidity of the pellets. Specially, glycerol or GMS containing pellets resulted in a very low pressure (Table-6.1.4). These two formulations produced a reasonably linear

curve, with correction factor of 0.98 and 0.99 respectively, when the in die relative density of the compact was plotted against the natural logarithm of the compressing pressure (Fig-6.1.6). This indicates the absence of fracture as proposed by Messing et al. (1982). The retrieved pellets from the compacts supported this assumption. The curves for pellets of the other three formulations, however, had a break at approximately the same compression pressure, (27 MPa.). This pressure was higher than the value for the strength of each pellet in the different formulations. Nevertheless, in a confined condition, the lateral forces from the neighbouring pellets might have helped the pellets to withstand a greater compression pressure before failure.

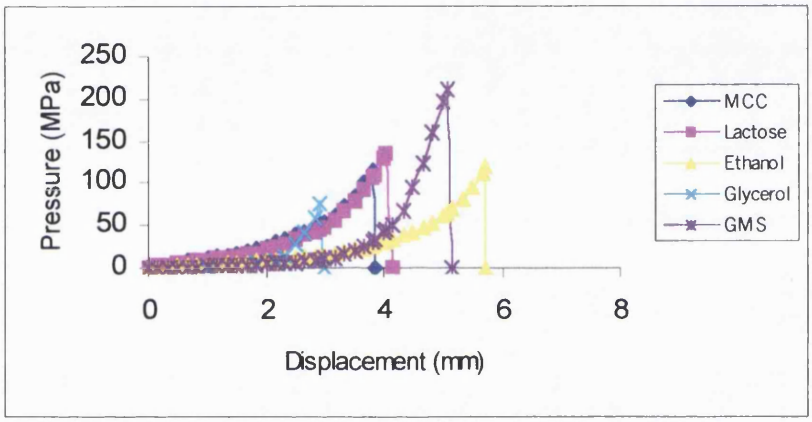


Fig-6.1.5 The pressure/displacement curves of drug pellets obtained during compaction of 600 mg of pellets from the 1.0-1.18 mm size fraction.

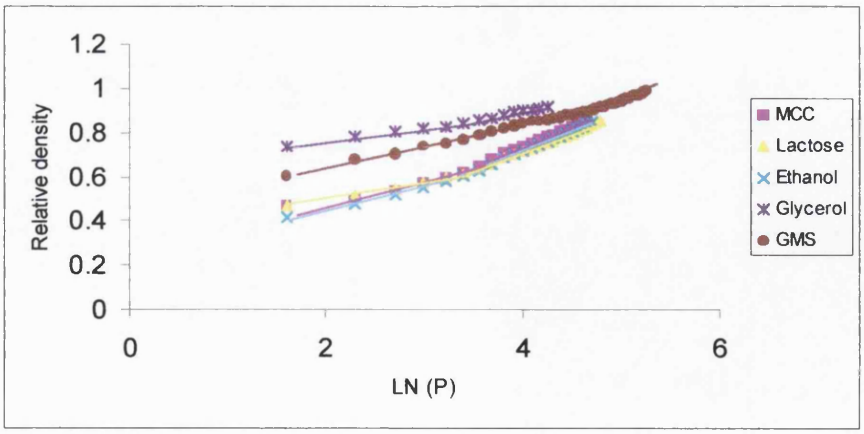


Fig-6.1.5 The relationship of relative density of drug pellets and natural logarithm of pressure obtained during compaction of 600 mg of pellets from the 1.0-1.18 mm size fraction.

At the pressures applied, tablets could only be produced form the pellets produced with ethanol, lactose or GMS. These were the three formulations which had a higher compressing pressure and greater work of compaction. The connectivity of glycerol containing or MCC pellets was poor, the compressed pellets did not cohere to produce rigid compacts. In addition to the lower compaction pressure, the change in the surface nature of the pellets could be another possible reason for their reduced connectivity. The values of the tensile strength of the tablets (Table-6.1.4) increased in the same order as that of compaction pressure. The volumetric elastic recovery (VER) of the compacted pellets was very low (Table-6.1.4), indicating the permanent deformability of GMS containing and pellets produced with ethanol, while the structural failure could be the possible reason for the low elastic recovery of lactose containing pellets. The values of VER of the GMS containing pellets was the lowest. GMS containing pellets produced thicker tablets, which indicates a considerable expansion during decompressing, as all tablets form the different formulations were compacted to the same tablet thickness.

6.2 COATED DRUG PELLETS

Coating the drug pellets (6.1) with a different weight by weight percentage of ethyl cellulose film affected the mechanical properties of the pellets. The values of the tensile strength of GMS or glycerol containing pellets increased, while those of lactose containing pellets or those of pellets produced with ethanol reduced (Fig-6.2.1). The slight increase in the value of the tensile strength of MCC pellets was not statistically significant. In the soft pellets (GMS and glycerol containing pellets) the coating film formed a rigid crust, which resisted the compression, while in the porous pellets produced with ethanol, the filling of the flaws (pores) may not have reduced the initiation of cracks. The shear strength of the pellets was reduced with increase in the coating material in all formulations except with glycerol containing pellets (Fig-6.2.2). These pellets had the least shear strength, the highest deformability (6.1), coating them with the polymer produced a hard crust which again resisted the shearing up to a certain degree. The increase in the value of shear strength of pellets produced with ethanol was statistically significant between the 5%w/w to 20%w/w coating levels ($P<0.01$), however, it had a similar shear strength at 0%w/w coating with those of MCC or lactose containing pellets.

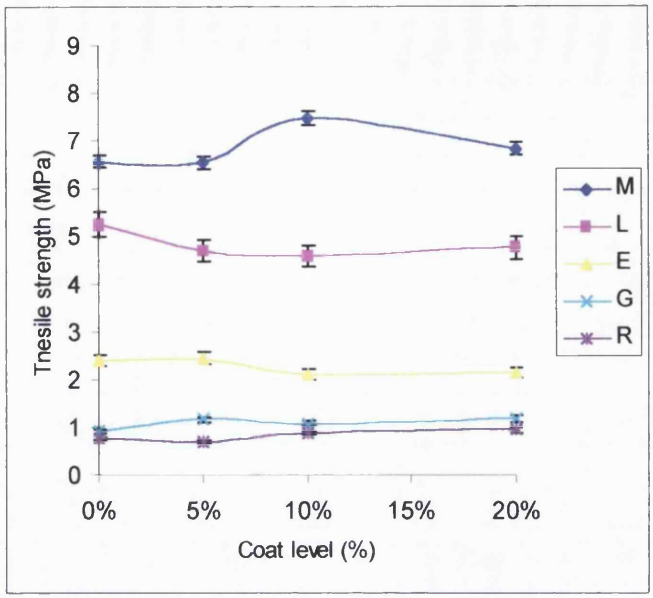


Fig-6.2.1 The influence of coat thickness (%w/w) on the tensile strength of coated drug pellets of 1.0-1.18 mm size fraction.

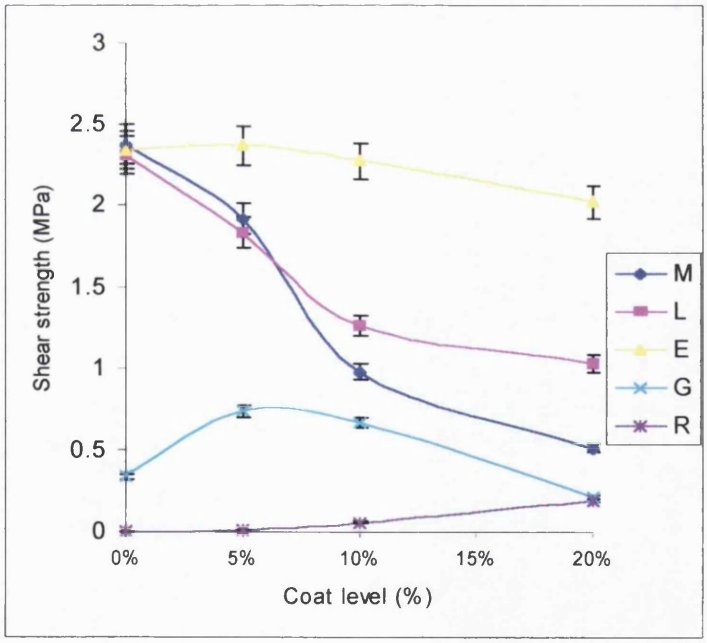


Fig-6.2.2 The influence of coat thickness (%w/w) on the shear strength of coated drug pellets of 1.0-1.18 mm size fraction.

The deformability of the pellets increased with the increase of the coating material, but to different extent (Fig-6.2.3). Lactose containing pellets had the greatest change in this

property, at 20%w/w coating the deformability was increased by 70%. Pellets produced with ethanol, GMS and glycerol showed a slight increase in this property, presumably due to the similarity in deformability of the core pellets to that of coating material. The linear strain of all the pellets increased with the exception of pellets produced with ethanol (Fig-6.2.4). These pellets showed a reduction of 5% in linear strain, while pellets containing GMS or lactose showed an increase of 55% when coated by 20%w/w ethyl cellulose. Increase in the strength produced by coating may have helped GMS containing pellets to be strained to a greater extent, while in lactose pellets the slope of the force/displacement curve was markedly reduced, mainly due to the absorption of some compression force by the deformable coating material. In pellets produced with ethanol, presumably there was little room for the primary particles to rearrange themselves with compression for the open pores could have been filled by the coating material. The 'elastic modulus' of the pellets was reduced with the increase in coating material (Fig-6.2.5). The uncoated pellets with the higher 'elastic modulus' had the greatest reduction. The order of reduction was : lactose (40%), MCC (22%), ethanol (17%), GMS (6%) and glycerol pellets (2%). This indicated the plasticity of the coating polymer.

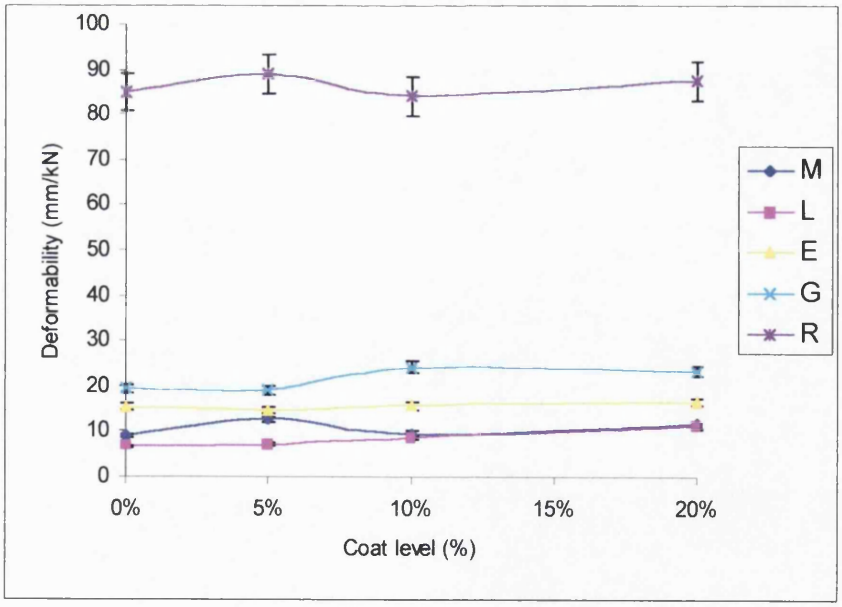


Fig-6.2.3:- The influence of coat thickness (%w/w) on the deformability of coated drug pellets of 1.0-1.18 mm size fraction

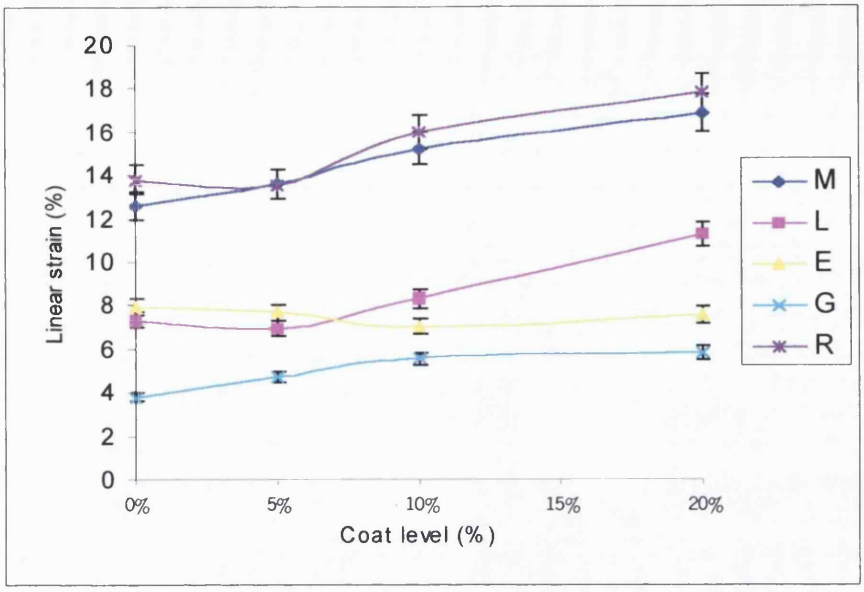


Fig-6.2.4:- The influence of coat thickness (%w/w) on the linear strain of coated drug pellets of 1.0-1.18 mm size fraction.

Using a helium pycnometer, it was possible to determine the apparent density of the pellets. The only source of errors were the closed pores which could not be accessed by the helium. In this work, the employment of the helium pycnometer to film coated pellets was used to approximate the total porosity (Fig-6.2.6) and the effective density of the pellets. Once a 5%w/w coating level was applied, the change in porosity of all the pellets was marginal. Compared with uncoated ones, however, pellets produced with ethanol had a considerable increase in porosity, while lactose or GMS containing pellets had a modest increase. Comparing these result with the apparent density of the pellets (Table 6.1.2) the distribution of the pores between the closed and open compartments can be observed. In pellets produced with ethanol, the increase in porosity with coating indicates the closure of the open pores, which were no longer accessible to helium molecules, showing that these pellets had the highest proportion of open pores.

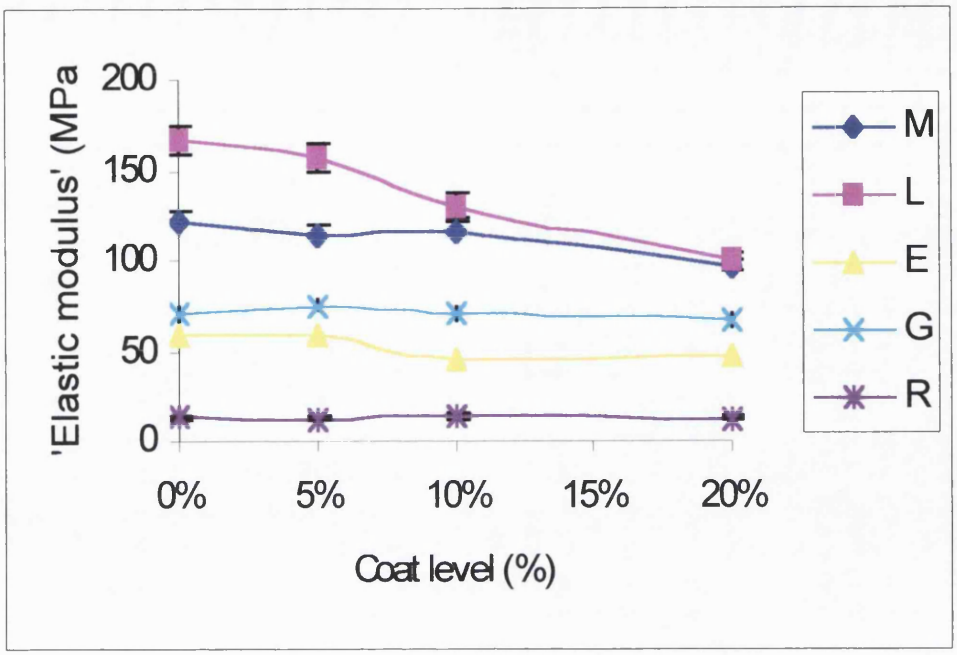


Fig-6.2.5:- The influence of coat thickness (%w/w) on the 'elastic modulus' of coated drug pellets of 1.0-1.18 mm size fraction.

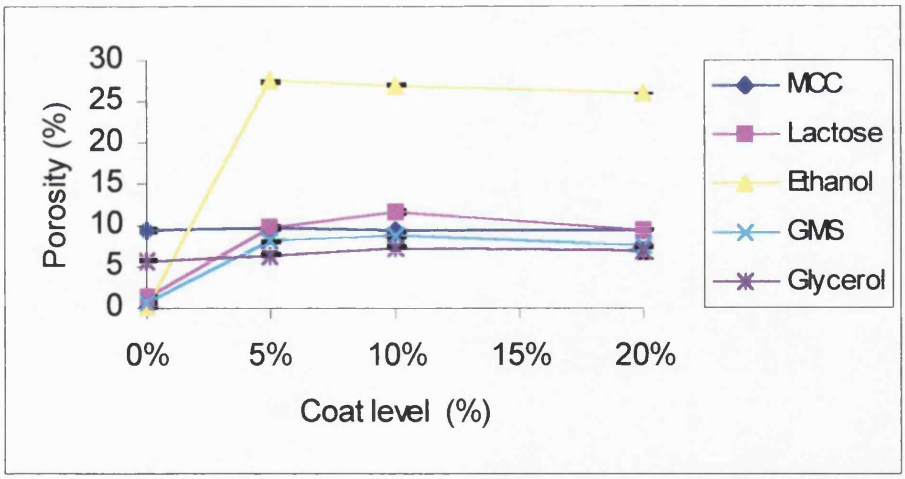


Fig-6.2.6:- The influence of coat thickness (%w/w) on the porosity of coated drug pellets of 1.0-1.18 mm size fraction.

The pressure needed to compact the same amount (weight) of pellets to the same tablet dimensions (see 2.2.4.1A), slightly increased with the increase of the coating material (Fig-6.2.7). A considerable effect of the coating materials was only observed with pellets

containing glycerol, while those of MCC and lactose formulations showed a decrease in pressure when they were coated by 5%w/w compared to those of uncoated. The main reason appears to be the variation in the density, for the same pellet amount were compacted to the same final tablet dimensions. The coating material had a lower density (1.13 g/ml) than the average density of the pellets in all formulation. In addition, the increase in the strength of the pellets, eg. pellets containing glycerol, could be another reason for increase in compaction pressure.

The compressibility of the pellets increased with the increase in the amount of the coating material added. The pressure/displacement curve obtained during the compaction of the pellets (eg. Fig-6.2.8) illustrated that the pellets containing glycerol were compressed to a greater extent with an increase of the coating level. The difference in compaction pressure started from the onset of the curve (eg. Fig-6.2.9). The pressure development was rapid in uncoated pellets while this was to greater displacement with increase in the amount of coating material applied. There was not as such significant difference in the Heckel plot. (Fig-6.2.10 a &b) depicts the curves at 5% and 20%w/w coating of the pellets. This shows that the property of the core pellet is dominant on this case or removal of the coating material during compaction can be another reason (eg. MCC pellets, See Plate-6, p-263). Nevertheless, the coating material protected the pellets from crushing during compaction as the improvement of the linearity of the curve in Fig-6.2.11 indicates. MCC or lactose containing pellets had a noticeable break in linearity of the curve when compacted without coat (Fig-6.1.6). The correlation of the curve increased form the R^2 value of 0.962 in uncoated pellets to 0.985 in coated MCC pellets, likewise it increased from 0.966 to 0.989 in lactose containing pellets. Moreover, the cross-section of the tablets in SEM (Plate-6, see p-263) illustrates the cushioning of the pellet core by coating material.

The increase in coating levels increased the tensile strength of the compacts produced from all types of pellets (Fig-6.2.12). Uncoated pellets from MCC and those containing glycerol were unable to form tablets. In the presence of as less as 5%w/w of coating material, however, they were able to produced compacts that could be handled and further analysed. The polymer seems to have served as a matrix forming material (Plate-6, see p-263). There

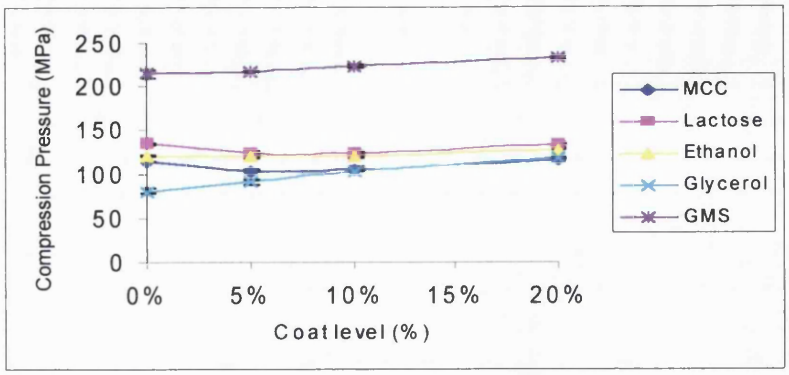


Fig-6.2.7:- The influence of coat thickness (%w/w) on the compaction pressure needed to produce tablets of the same dimensions from coated drug pellets of 1.0-1.18 mm size fraction.

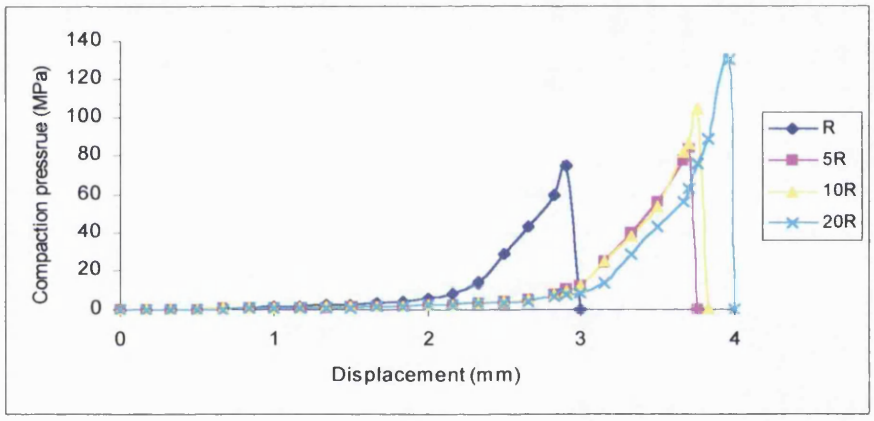


Fig-6.2.8:- The pressure/displacement curve of glycerol containing drug pellets coated with different % w/w of Surelease® obtained during compaction of 600 mg of the pellets.

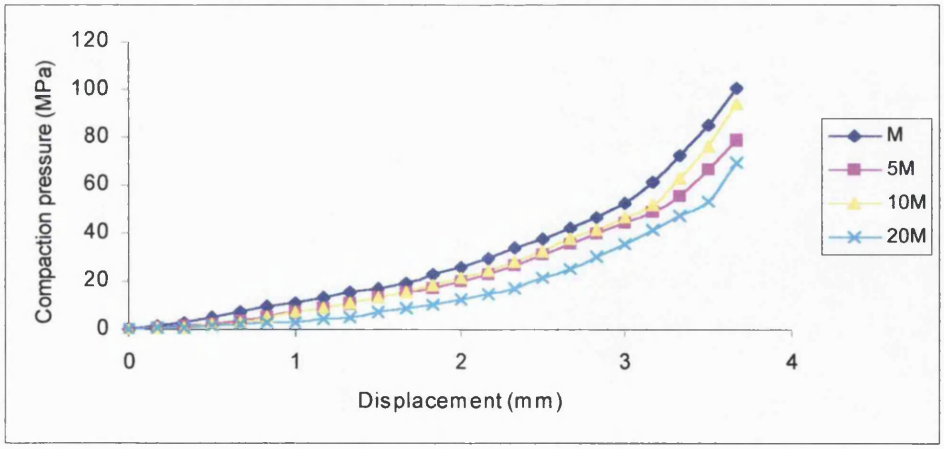
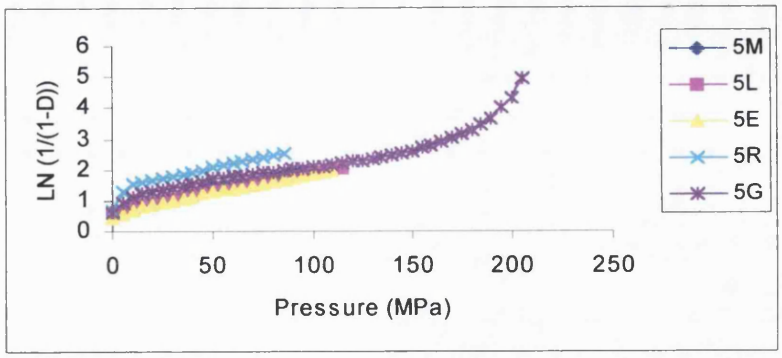


Fig-6.2.9:- The early stage of the pressure/displacement curve of MCC pellets (M) coated with different % w/w of Surelease® obtained during compaction of 600 mg of the pellets.

(a)



(b)

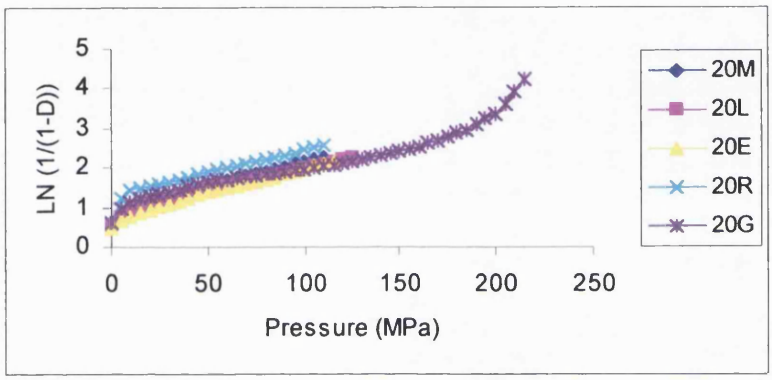


Fig-6.2.10 The Heckel plot obtained during compaction of 600 mg of drug pellets form the different formulations coated with (a) 5% and (b) 20%w/w Surelease®.

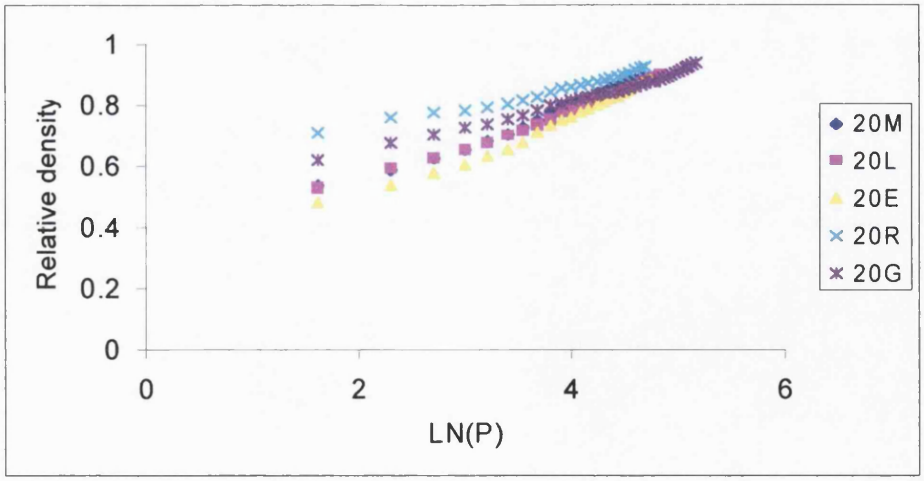


Fig-6.2.11:-The relationship of relative density of drug pellets and natural logarithm of pressure obtained during compaction of 600mg of pellets coated with 20%w/w Surelease®

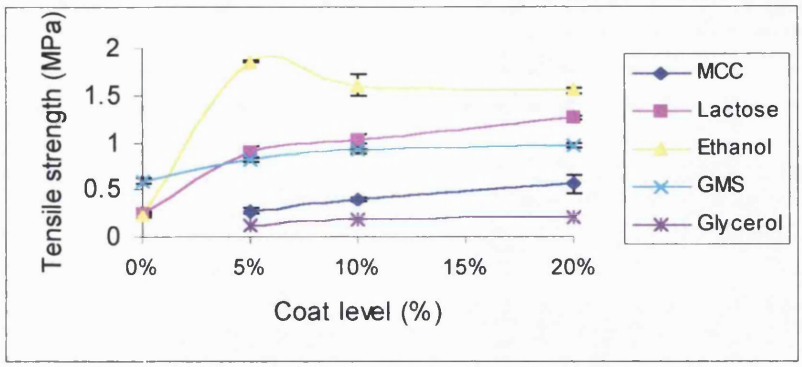


Fig-6.2.12:- The influence of coat thickness (%w/w) on the tensile strength of tablets produced from 600 mg coated drug pellets produced form the different formulations.

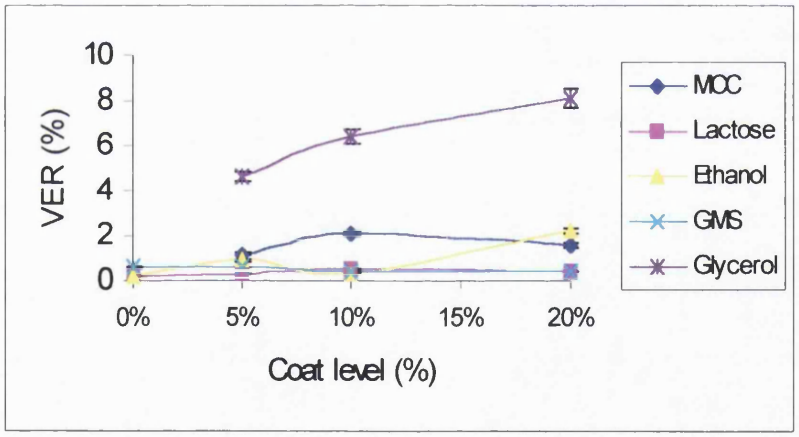


Fig-6.2.13:- The influence of coat thickness (%w/w) on the volumetric elastic recovery (VER) of tablets produced from 600 mg coated drug pellets produced form the different formulations.

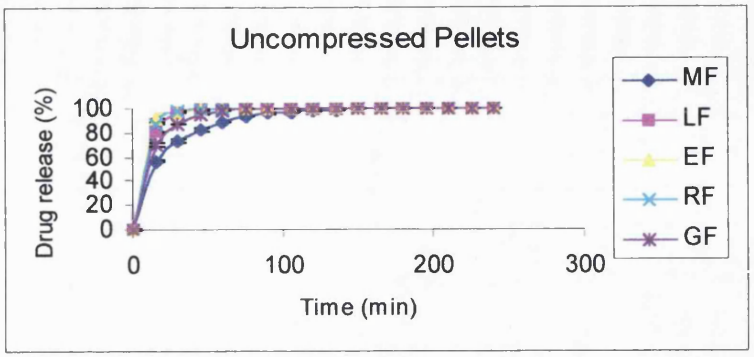
was a gradual increase in strength of compacts from all formulations with the increase of the coating material with the exception of compacts form pellets produced with ethanol. These pellet-compacts had the greatest strength at 5%w/w coating, after which the value reduced with the increase of the coating material. The effect of the coating material on the volumetric elastic recovery of the compacts was minimal except for glycerol containing pellets (Fig-6.2.13). These pellets had a considerable increase in compaction pressure, some of which could have been stored to recover with time.

6.3 DISSOLUTION TEST

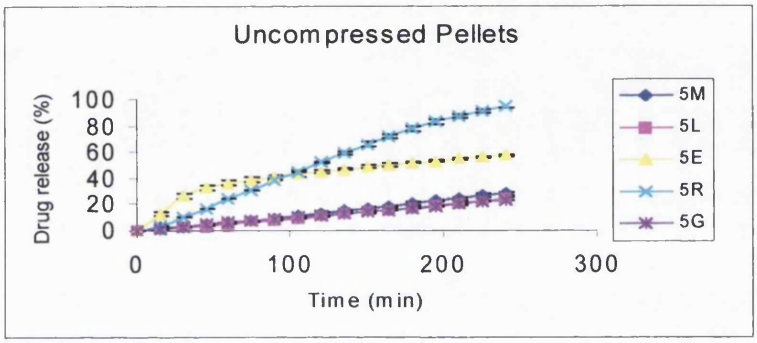
Fig-6.3.1 shows the percentage of drug release with time when the pellets were coated with different levels of the plasticized ethyl cellulose from the pseudo latex dispersion, Surelease®, where (a) is for uncoated pellets while the other pellets had (b) 5%w/w , (c) 10% w/w and (d) 20% w/w coating levels. For the uncoated pellets, the drug release was completed in the first hour of dissolution test for all formulations with the except of MCC-pellets which needed a further half an hour. This could be considered as a base line for the test on the effect of the coating material and film integrity during compaction. After 5% weight gain, pellets produced with ethanol or glycerol were not completely coated. More coating materials were needed to fill the open-pores in pellets produced with ethanol, while the coating film on pellets containing glycerol seemed to have some pores or flaws, hence 50% and 90% of the drug was released in four hours time from both formulations respectively. At the higher coating levels, however, the drug release rate was almost the same in all formulation, where less than 20% and 10% of the drug was released in the 10%w/w and 20%w/w coating levels of all formulations respectively (Fig-6.3.1 c&d).

Compaction pressure affected the drug release rate differently for the different formulations coated by 20%w/w level (Fig-6.3.2a-d). The change in pressure from 33 MPa to 100 MPa did not have any influence on the drug release of pellets prepared with ethanol or glycerol. In the first half an hour about 98% of the drug was released from pellets prepared with ethanol, while for glycerol containing pellets it was 85% at the end of the second hour and 98% after four hours. In lactose or MCC pellets, the drug release rate reduced with the increase of the compaction pressure. After two hours, lactose containing pellets released 65%, 52%, and 50% of the drug when compacted by 33.3 MPa, 66.7 MPa, and 100 MPa. respectively, while 80%, 68%, and 62% of the drug was released when the same pressures were applied to MCC pellets. For GMS containing pellets, however, the drug release rate was lowest at 66.7 MPa, while it was higher at 33 MPa than that of 100 MPa. After two hours, 50%, 43%, and 45% of the drug was released form the GMS containing pellets compacted by 33.3 MPa, 66.7 MPa, and 100 MPa respectively, while only 74%, 67%, and 69% of the drug was released after four hours. The rate of drug release form the various formulations at the different compaction pressures had the same rank order (Fig-6.3.2a-d).

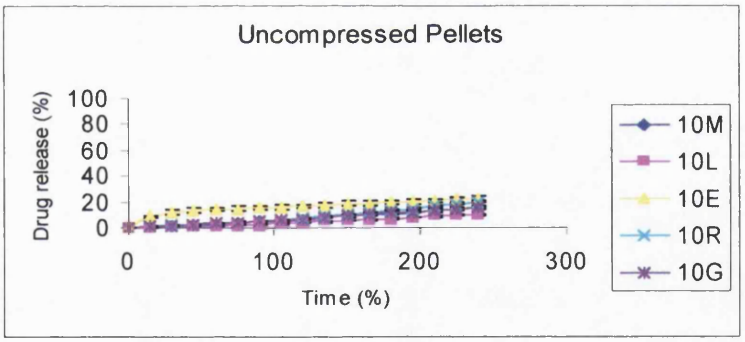
(a)



(b)



(c)



(d)

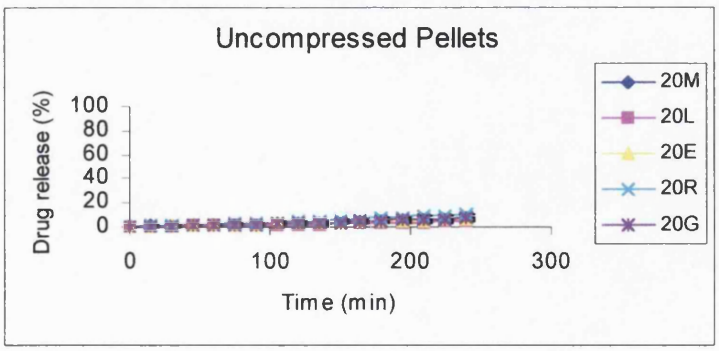
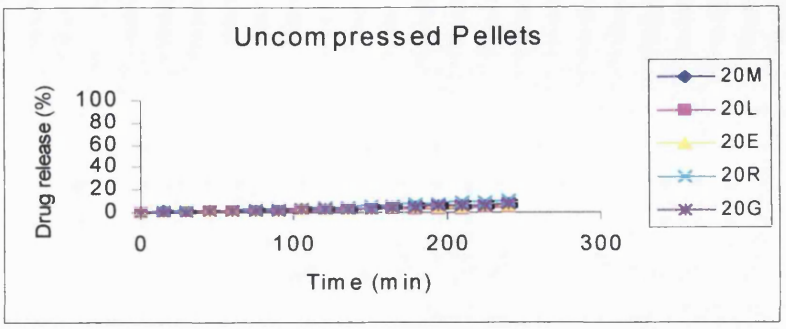
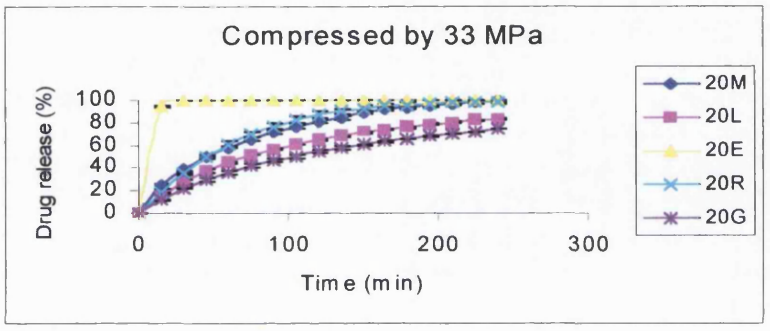


Fig-6.3.1:- The drug release from pellets of different formulations coated by (a) 0%, (b) 5%, (c) 10%, and (d) 20% w/w Surelease®.

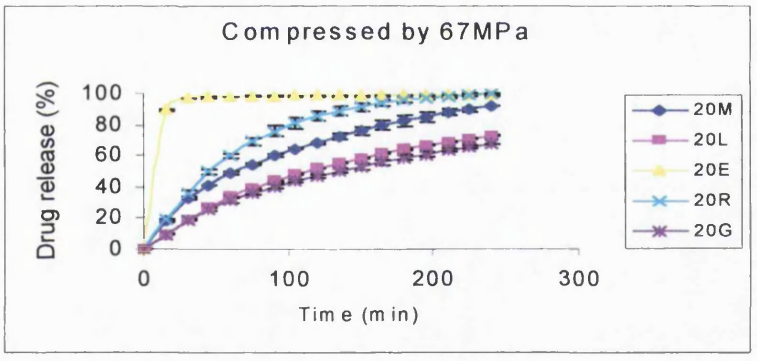
(a)



(b)



(c)



(d)

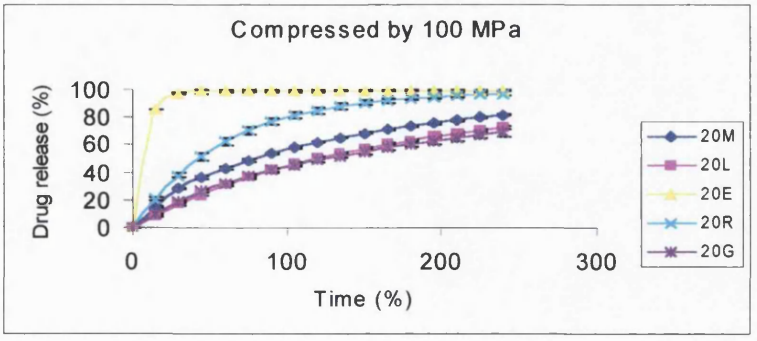
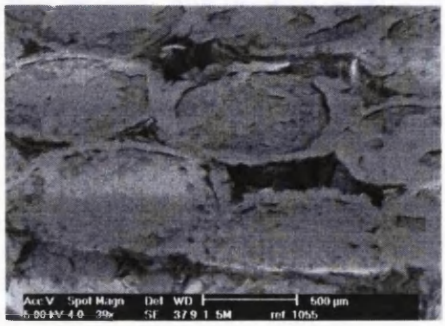


Fig-6.3.2:- The drug release from pellets of different formulations coated with various % w/w Surelease® and compacted by (a) 0 MPa, (b) 33 MPa, (c) 67MPa, and (d) 100 MPa.

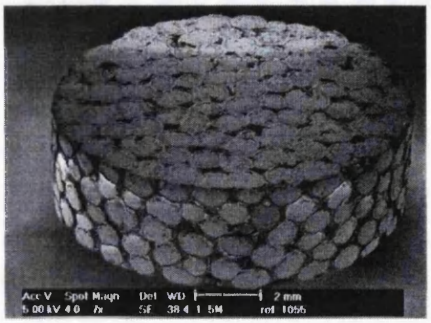
The drug release rate in an ascending order was, GMS < lactose < MCC < Glycerol < ethanol. In all cases it was higher in the first two hours, which could be caused by the damage of the coating film of pellets on the surface of the tablets. The rupture of the film when interacted with the punch and the die surfaces has been indicated on the SEM (Plate-6, see p-263). Moreover, the structural change of pellets at the edges of the compacts was the greatest, which could result in cracking of the coating film. Due to the higher porosity, the pellets produced with ethanol had to be compressed to the greatest extent (Table-6.1) which was observed to flatten the pellets and possibly rupture the coat, hence release much of the drug in the first half an hour. Similarly, the greatest deformability of glycerol containing pellets may have ruptured the film coating. During compaction, all the coated pellets (20%w/w) fused together and were intact during the whole dissolution test time with the exception of those pellets containing glycerol and produced with ethanol which disintegrated after 120 and 90 minutes respectively when compressed by 33MPa. Thus this test can be considered as dissolution test of the intact tablets compacted by different pressures although drug release rate was less affected by the pressure. GMS-pellet compacts, had the lowest drug release rate mainly due to the insolubility of GMS in water and formation of the tightest compacts with greatest strength.

From these observations it is possible to conclude that the mechanical properties of the core pellets greatly affected the integrity of the coating film. In GMS containing pellets, which had the lowest variation in mechanical properties with different coating levels (section 6.2), increase in coating levels had relatively reduced drug release rates at all compaction pressures indicating the reduction in film rupture. Moreover, the ethyl cellulose was observed to serve as a cushion to reduce the fracture of pellets during compaction in all formulations. Furthermore, the fusion of the pellets in the presence of the coat helped some formulations to form rigid compacts.

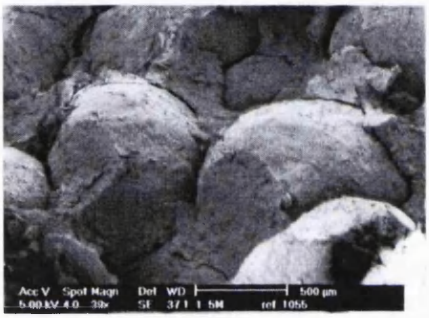
Plate-6 (following pages) :- Scanning Electron micrograph of 5% and 20% w/w coated drug pellets: The numbers indicated the level of coating in percentage weight by weight; the upper case letters represent the formulas, where M is for MCC, L for lactose, G for GMS, R for glycerol containing pellets while E for pellets produced with ethanol: (a) the magnified top face of the compacts, (b) the top surface of the edge of the compacts, (c) the magnified cross-section of the compacts, and (d) the whole crosse-section of the compacts:



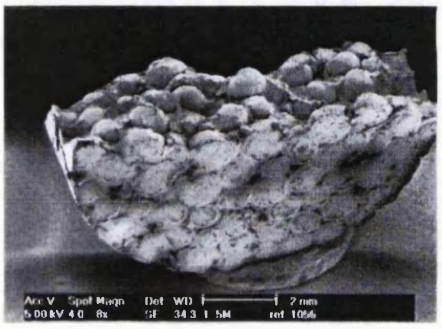
5M-a



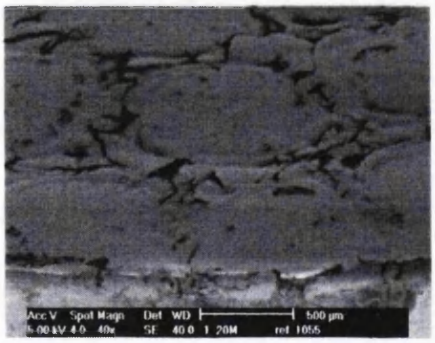
5M-b



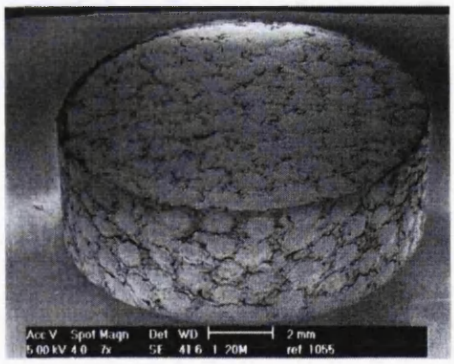
5M-c



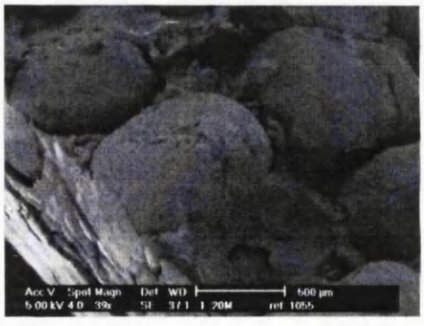
5M-d



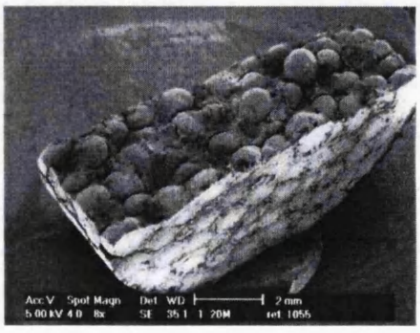
20M-a



20M-b



20M-c



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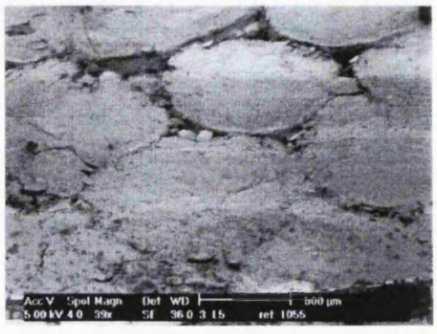
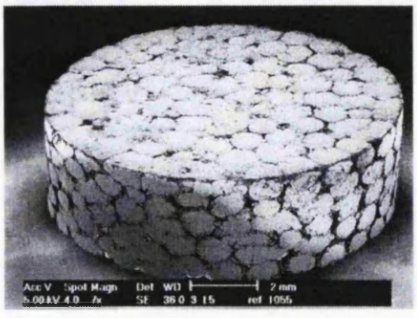
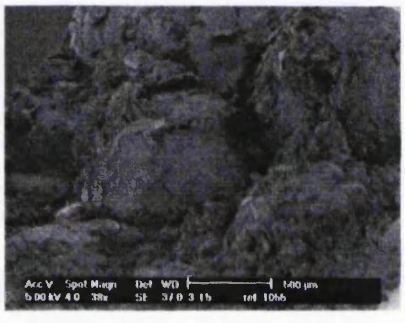


5L-1



5L-b



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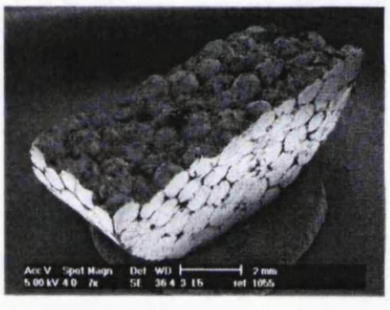
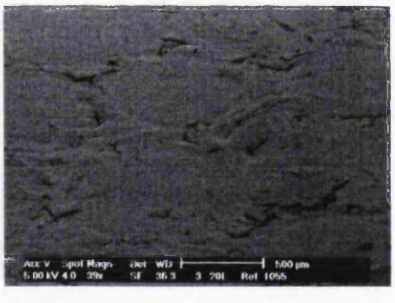


5L-d



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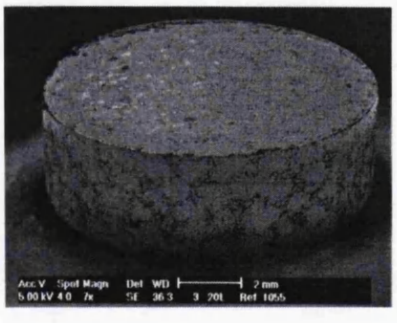

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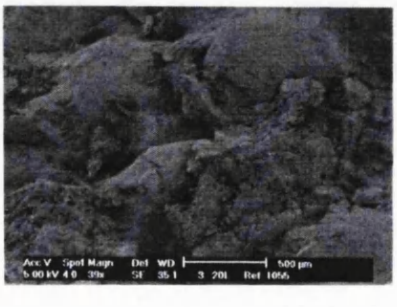

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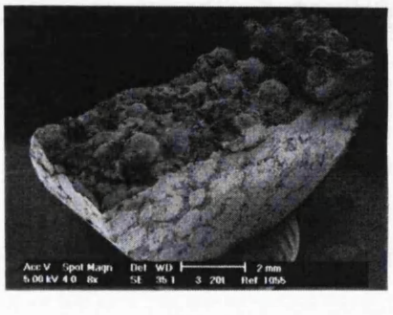

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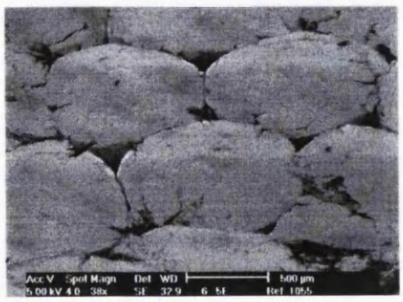

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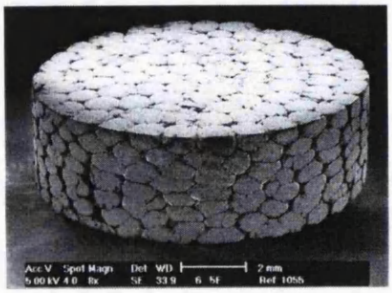

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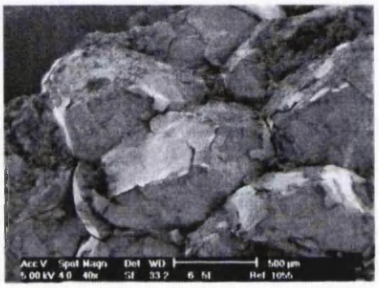

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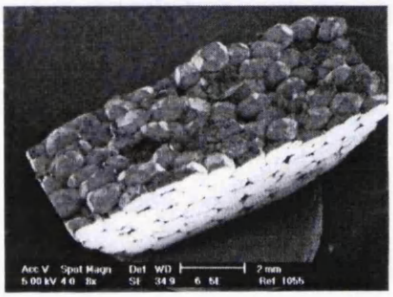

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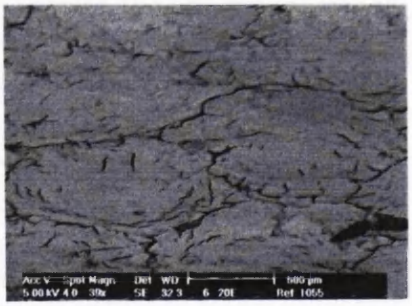

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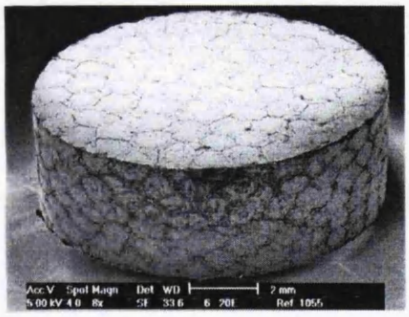

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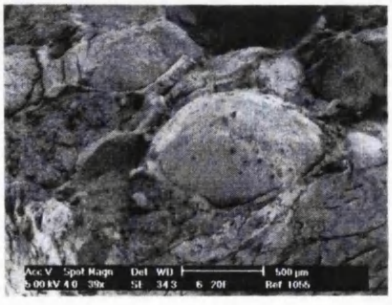

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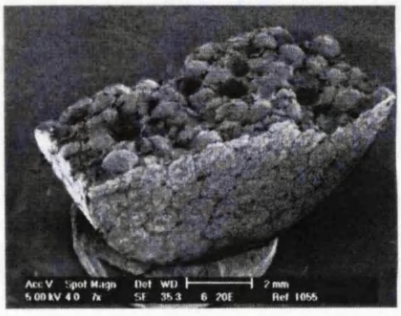

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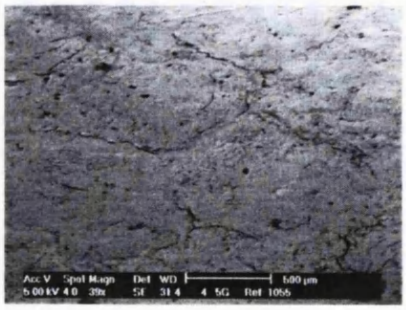

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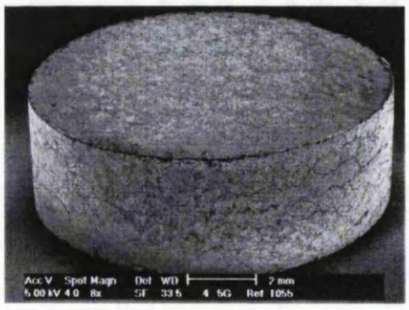

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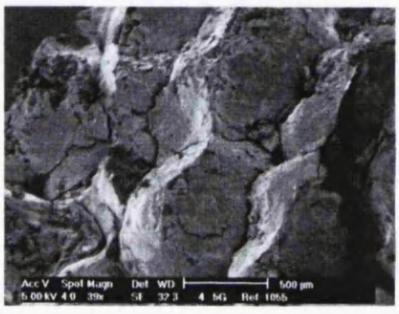

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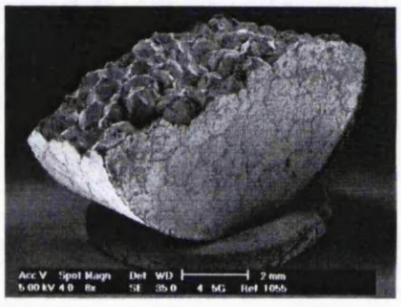

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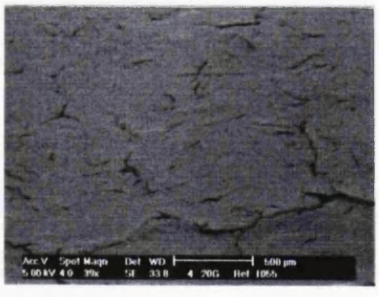

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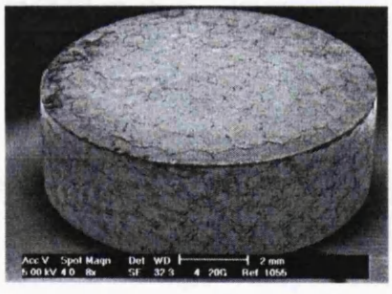

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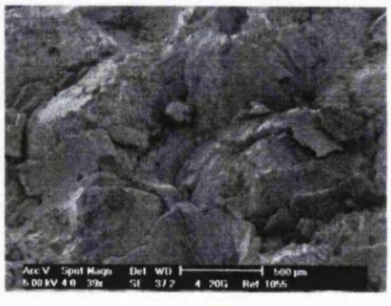

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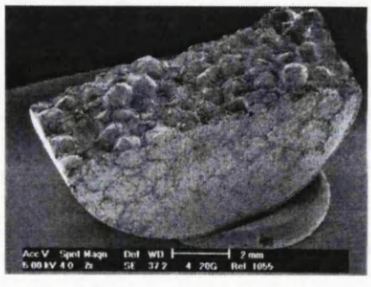

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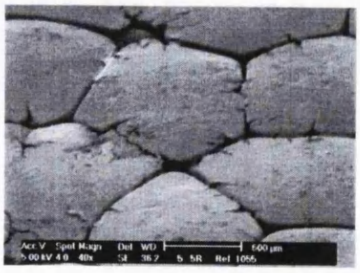

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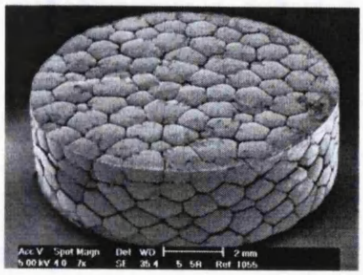

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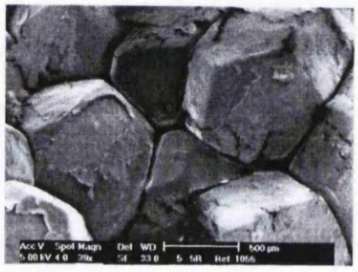

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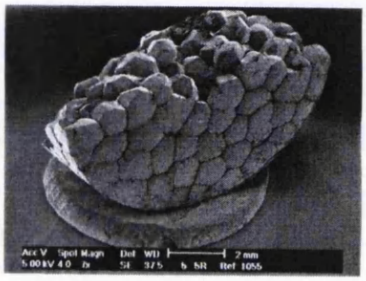

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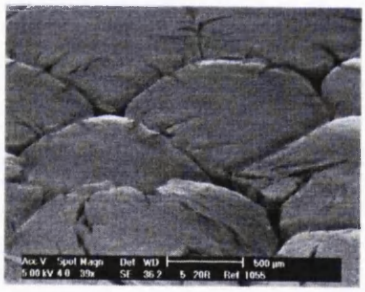

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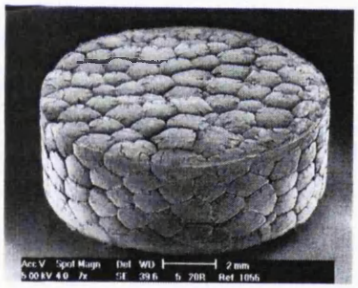

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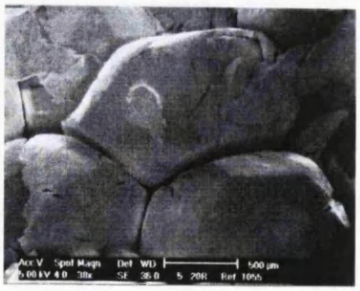

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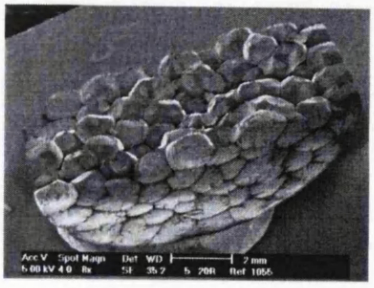


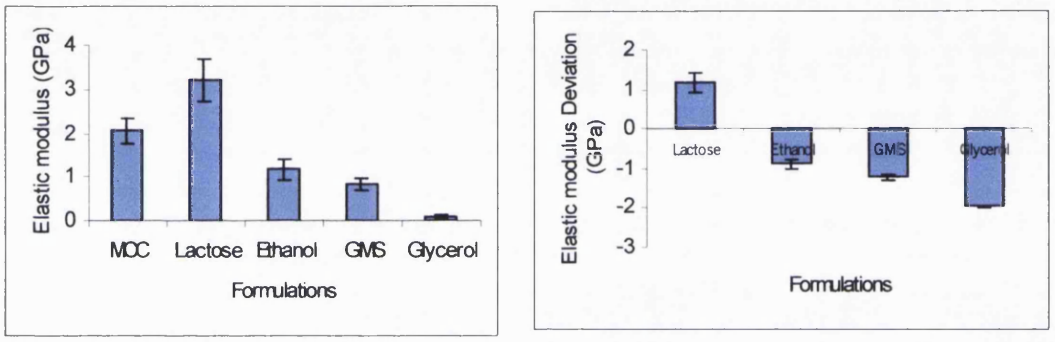
20R-d

CHAPTER -SEVEN

DYNAMIC MECHANICAL ANALYSIS (DMA)

7.1 UNCOATED DRUG PELLETS

The Young's modulus of elasticity of the uncoated drug pellets described in (section 6.1) was calculated from the slope of the linear portion of the stress-strain curve obtained form the static scan (eg. Fig-7a, see p-271) using a DMA. (Fig-7.1a) depicts the values of the elastic modulus of the pellets. The variation of the values from that of the starting formula (MCC:Water) with the incorporation of different excipients or liquid binders is presented in (Fig-7.1b).



(a) (b)

Fig-7.1:-(a) the Elastic modulus of the drug pellets of 1.0-1.18 mm size fraction, determined by DMA, (b) the deviation of the elastic modulus of the MCC pellets with addition of other ingredients.

The values of Young's modulus was increased by lactose, reduced by GMS, glycerol and inclusion of ethanol in the preparation of the pellets. All the factors had a statistically significant effect (Table-7.1).

No.	Formula	Elastic modulus (GPa)		MS	F	P
		Mean	STD			
1	MCC	2.044	0.29	-	-	-
2	Lactose	3.208	0.47	1353.5	87.33	<0.001
3	Ethanol	1.173	0.23	759.2	108.93	<0.001
4	GMS	0.835	0.14	1462.3	280.88	<0.001
5	Glycerol	0.106	0.04	3779.1	878.31	<0.001

Table-7.1:- ANOVA of the elastic modulus of uncoated drug pellet of 1.0-1.18 mm size fraction produced from five different formulations

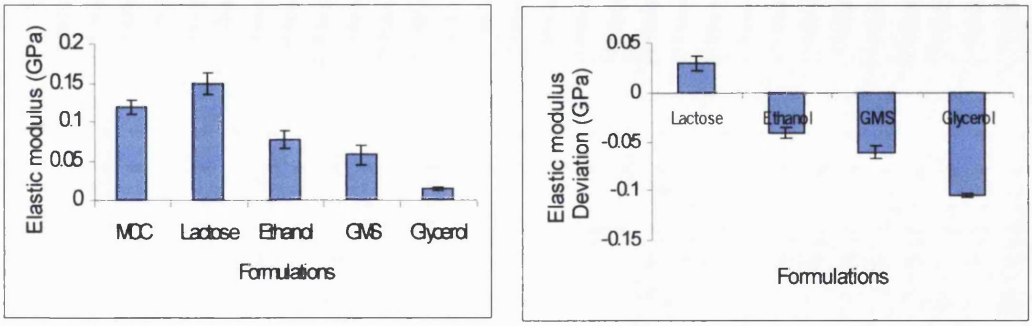
This was the reflection of the rigidity of the individual ingredient in the pellets. Substitution of 50%w/w of the MCC by lactose, increased the elastic modulus of the pellets for lactose, which has a Young's modulus of 24.1 GPa (Robert et al. 1991), is more rigid than the MCC, whose value is 10.3 GPa MCC (Mashadi and Newton, 1987b). GMS is a soft solid, while glycerol is a viscous liquid, and their presence reduced the stiffness of the pellets.

In prediction of the elastic properties of composite materials, a generalized modulus equation known as the 'rule of mixtures' has been proposed by Radebaugh et al. (1989). A composite, which is also referred to as a filled system, is defined as materials with a continuous matrix phase and a discontinuous filler phase. The filler phase can be solid, liquid or gas. This relation is denoted by equation (41) (Radebaugh et al. 1989).:

$$G' = G'_1 \phi_1 + G'_2 \phi_2 \qquad \text{.....(41)}$$

where G' is the elastic modulus of the filled system, G'_1 is the elastic modulus of the pure matrix phase, G'_2 is the elastic modulus of the filler phase, while ϕ_1 and ϕ_2 are the volume fractions of the matrix phase and the filler phase respectively. For compacted polymeric materials where the filler is gaseous void space, ϕ_2, is equal to the porosity and $G'_2 \phi_2$ is equal to zero, since G' of air is zero. Hence the elastic modulus of the composite decreases with increase in porosity. Radebaugh et al. (1989) observed a 6-fold increase in elastic modulus of MCC from 0.55 to 0.88 solid fraction as a result of reduction in porosity. Similarity, the values obtained in this work, illustrated the reduction of the elastic modulus of MCC pellets produced with ethanol in the liquid binder by 43%.

Dyer et al. (1994) determined the 'elastic modulus' of the pellets form the ratio of pressure to the linear strain obtained during the diametral compression of the pellets. A similar procedure was used in (chapter-6) for pellets of the same formulation. The results obtained have been presented (Fig-7.2a) and their deviation form that of the starting formula has been illustrated (Fig-7.2b). These two techniques had a similar rank order and comparable proportion in deviation of the factors effect on elastic modulus. However, the absolute value of the elastic modulus determined by DMA was about 20-fold higher than that from the CT-5. The results from the static scan using a DMA is accurate, for the slope is determined form the real elastic region, about 5% of strain in most cases, and from a nearly linear portion of the curve, in a range of about 0.5-1% of the linear strain (Fig-7a).



(a) (b)

Fig-7.2:-(a) The elastic modulus of pellets of 1.0-1.18 mm size fraction, determined from the force/displacement curve obtained during diametral compression of the pellets (b) the deviation of the elastic modulus of the MCC pellets with the addition of other ingredients.

In the diametral compression using CT-5, however, the slope was determined from the whole range of the stain, up to 15% in some cases, and the whole region was assumed as linear, hence the range of the strain was more than 10% in most cases. At the higher region of compression, plastic deformation of the pellets might have occurred to strain the pellets to a greater extent without significant increase in pressure, as a result the elastic modulus may have been underestimated.

From the dynamic scan, the storage modulus was initially observed to change as a function of dynamic force applied i.e. at low dynamic force values the storage modulus reduced rapidly in a non-linear fashion (Fig-7b). At higher dynamic forces, this function became linear. The onset of the linear portion i.e. the dynamic force for this to occur was determined. In addition, the storage modulus at the maximum dynamic force (600 mN) and the slope of the linear portion of the function were obtained. Moreover, the phase angle as function of the dynamic force employed increased steadily with increasing dynamic force (Fig-7b). The phase angle at the onset of the linear portion of the storage modulus-dynamic force curve was read after smoothing of the phase angle curve using standard algorithms and a window size of 300 points. Furthermore, the phase angle at the maximum dynamic fore (600 mN) was determined in the same way, the difference between the two measured phase angles was also calculated (Fig-7.3 to Fig7.8).

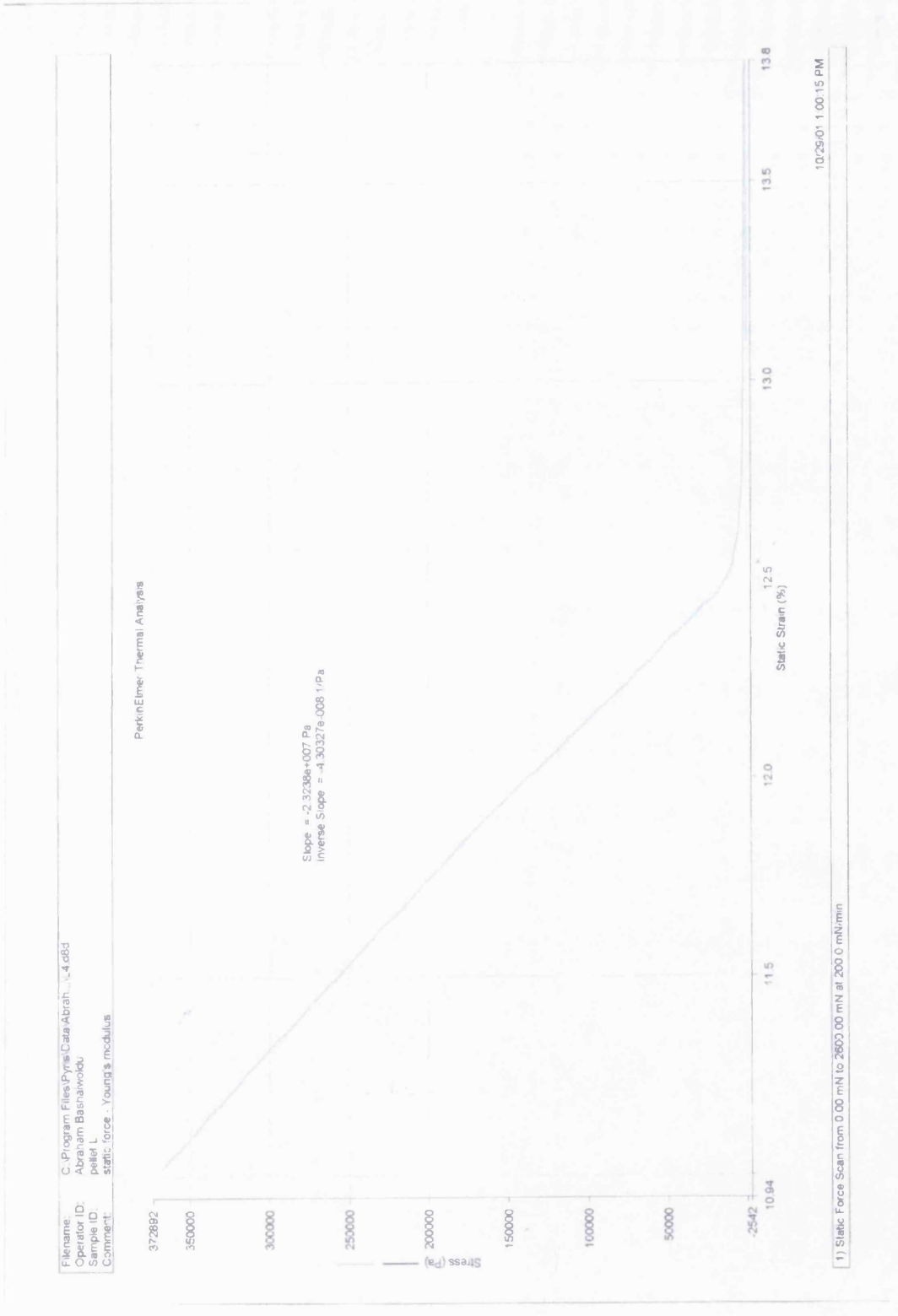


Fig-7a:- A typical static scan of a pellet containing lactose.

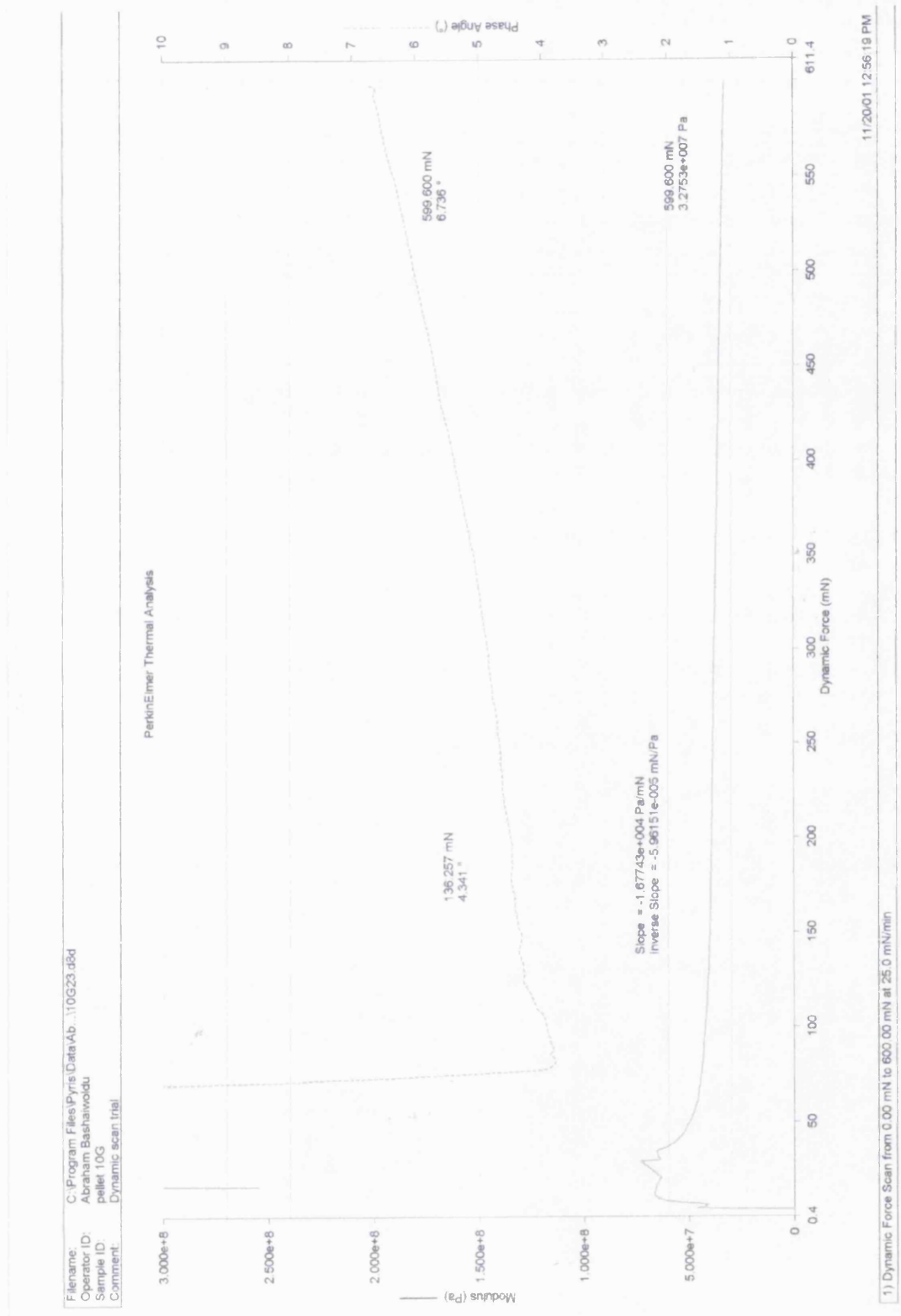


Fig-7b:- A typical dynamic scan of a pellet containing glyceryl monostreate and coated by ethyl cellulose at 10%w/w level.

The effect of the factors on the storage modulus measured at the fixed dynamic force (Fig-7.3) was proportional to that of elastic modulus determined by the static scan. This shows that in both cases the measured parameter was the reversible elastic deformation. The values of elastic modulus was, however, about 50-fold higher than that of storage modulus, indicating the variation in the force range at which these values were determined. Moreover, the storage modulus indicated the presence of a reversible force, although small, even after the pellets had deformed plastically. The storage modulus-dynamic force curve, started to be linear at different dynamic forces for pellets of different formulations. The difference from that of the starting formula was only significant ($P<0.01$) in the pellets containing glycerol or those produced with ethanol(Table-7.2).

No.	Formulae	DF	MS	F	P
1	M	1	-	-	-
2	L	1	2216	3.30	0.077
3	E	1	7406	12.90	0.001
4	G	1	2233	4.45	0.042
5	R	1	18857	29.93	<0.001

Table:-7.2:- ANOVA of the dynamic force at the beginning of a linear storage modulus-dynamic force curve for drug pellet, 1.0-1.18 mm size fraction from various formulations

Lactose pellets needed a relatively higher dynamic force, while all the other pellets needed a lower dynamic force to produce a linear storage modulus-dynamic force curve, when compared to that of MCC pellets (Fig-7.4). The storage modulus of all the pellets increased in a linear manner with the increase of the dynamic force. However, it was to different extent. The slope of the curve for lactose containing pellets was higher than that of MCC pellets, while the rest pellets had a lower slope than that for MCC pellets (Fig-7.5). Nevertheless, the effect of lactose was statistically insignificant, while that of GMS and glycerol was significant at ($P<0.05$) and pellets produced with ethanol at ($P<0.01$).

The phase angle results from the time necessary for the molecular rearrangements and is associated with relaxation phenomena. It indicates the dissipation of energy as a result of

permanent plastic deformation of the material (Radebaugh and Simonelli, 1983; Jones,1999).

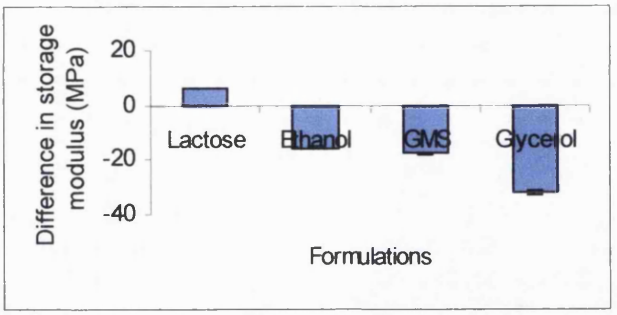


Fig-7.3:- The effect of each formulation factor on the storage modulus of the MCC pellets of 1.0-1.18 mm size fraction determined at dynamic force of 600 mN

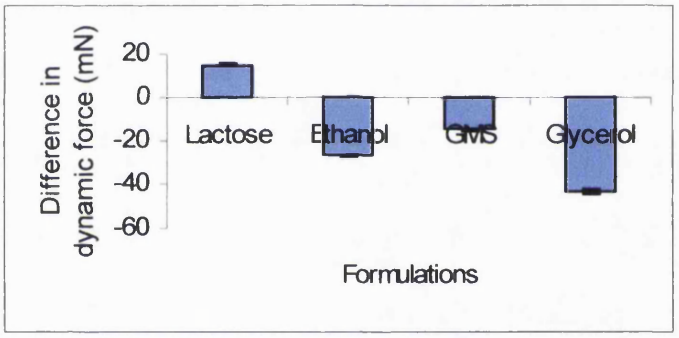


Fig-7.4:- The effect of each formulation factor on the dynamic forces of the MCC pellets of 1.0-1.18 mm size fraction determined at the beginning of the linear portion of the storage modulus-dynamic force curve.

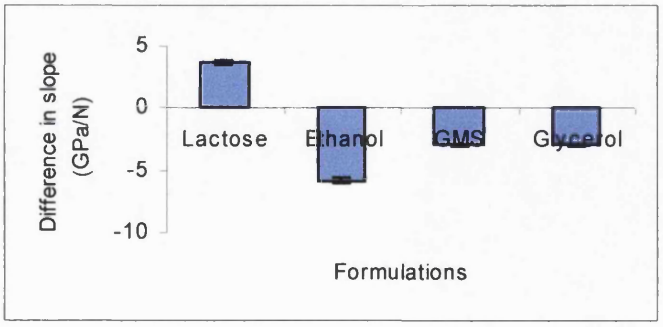


Fig-7.5:-The effect of each formulation factor on the slope of the linear portion of the storage modulus-dynamic force curve of MCC pellet of 1.0-1.18 mm size fraction.

In this work, the phase angle was determined at the start of the linear portion of the storage modulus-dynamic force curve and at a fixed dynamic force (600 mN). Lactose reduced the value of the phase angle, while the other factors increased the value when compared to MCC pellets at both measured phase angles (Fig-7.6 and Fig-7.7). The effect of each factor was significant in both cases. This was in agreement with the rank order of deformability of pellets determined from diametral compression (Fig-6.1.2). In all cases the phase angle increased with the increase of the dynamic force, but in non-linear way. The difference of the two phase angles taken (at 600mN of dynamic force and at the start of the linear curve of the storage modulus-dynamic force) varied for the different formulation factors, however, it was higher in all factors than that of MCC-pellets (Fig-7.8). Nevertheless, the difference was insignificant in the lactose containing pellets and pellets produced with ethanol, while those of GMS or glycerol containing pellets were significant ($P<0.01$).

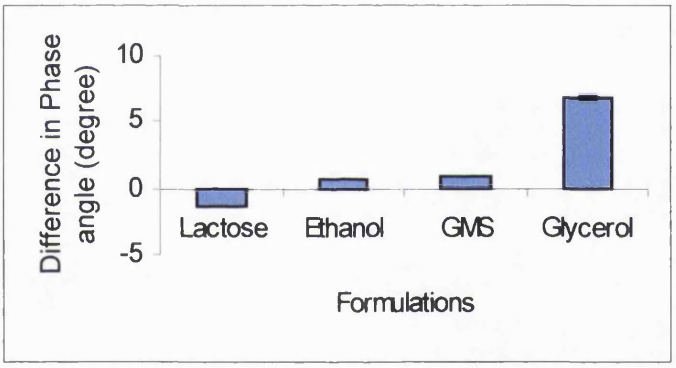


Fig-7.6:--The effect of each formulation factor on the phase angle at the beginning of the linear portion of the storage modulus-dynamic force curve of MCC pellets of 1.0-1.18 mm size fraction.

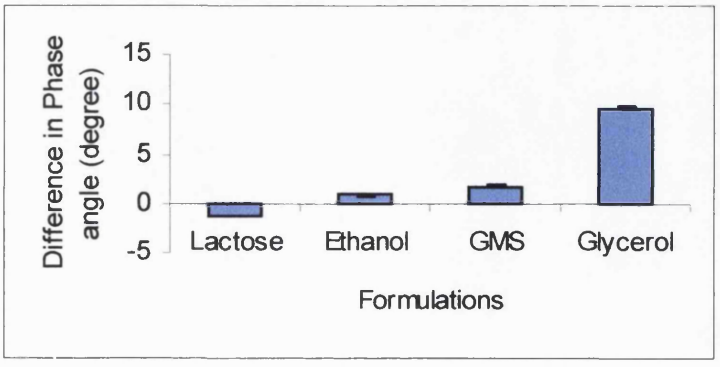


Fig-7.7:- The effect of each formulation factor on the phase angle at dynamic force of 600 mN of MCC pellets of 1.0-1.18 mm size fraction.

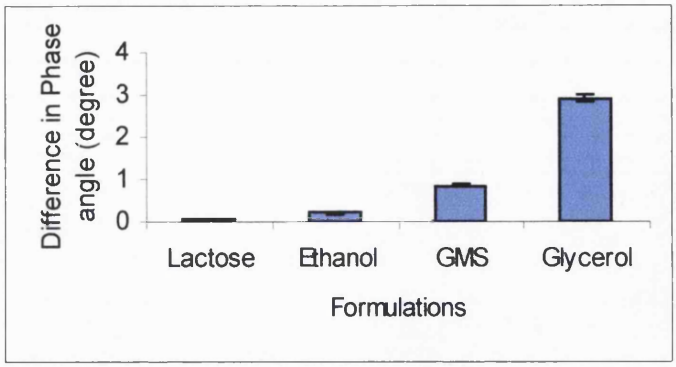


Fig-7.8:- The effect of each formulation factor on the increase in Phase angle at 600 mN of dynamic force from the force at the beginning of the linear portion of the storage modulus-dynamic force curve of MCC pellets of 1.0-1.18 mm size fraction.

7.2 COATED DRUG PELLETS

The dynamic force at which the storage modulus-dynamic force curve started to be linear was smaller for pellets produced with glycerol, GMS and ethanol than those of MCC pellets for all coating systems, while it was greater for lactose containing pellets except at 10%w/w coating levels (Fig-7.9). These results corresponds to the stiffness of the core pellets. At all coating thickness the rank order for the dynamic force at the start of the linear curve was the same. However, the effect of lactose was statistically insignificant at all coating levels, while the rest factors' effect was significant ($P<0.01$). With the increase in the coating thickness, there was a general trend to increase the dynamic force at the start of the linear curve, however, it was statistically insignificant for all pellets produced with ethanol, glycerol or GMS. Nevertheless increasing the coating thickness significantly increased ($P<0.05$) the dynamic force at which the linear curve occurred for MCC and lactose containing pellets.

The storage modulus of the pellets at the 600 mN dynamic force had the same rank order for all pellets from the different formulations regardless of the coating thickness (Fig-7.10). The change of formulations reduced the storage modulus of MCC pellets at corresponding coating thickness with the exception of lactose. This finding was statistically significant ($P<0.05$) except for lactose pellets coated by 5%w/w. Here again, the effect of the core material still influenced the elastic properties of the coated pellets.

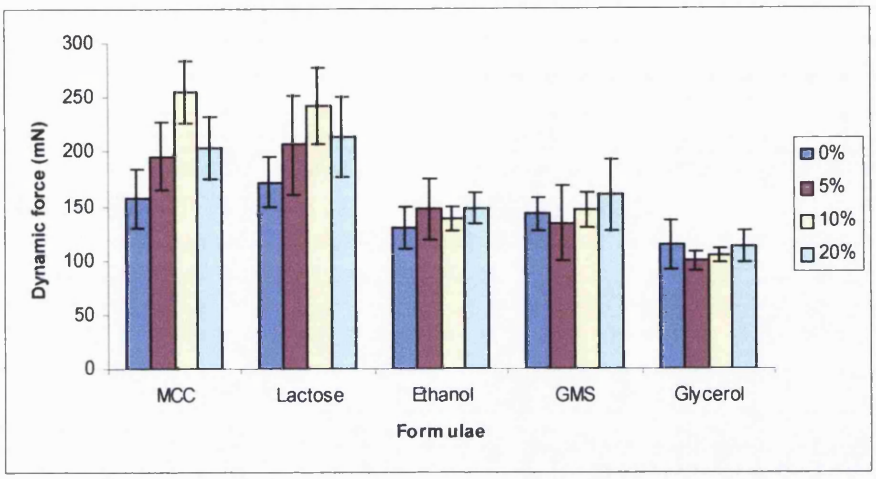


Fig-7.9:-The dynamic forces, determined at the beginning of the linear portion of the storage modulus-dynamic force slope, of the pellets (1.0-1.18 mm size fraction) from different formulations and coated at different coating levels (i.e. 0%, 5%, 10% and 20%w/w)

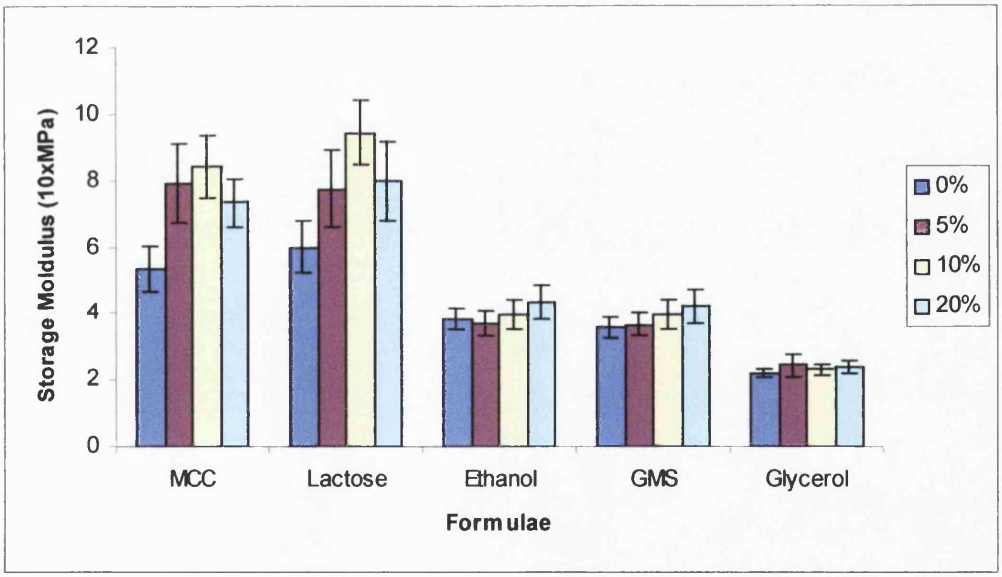


Fig-7.10:-The storage modulus, determined at dynamic force of 600 mN, of the pellets (1.0-1.18 mm size fraction) from different formulations and coated at different coating levels (i.e. 0%, 5%, 10% and 20%w/w)

With the increase of the coating material, the storage modulus of each pellet of the different formulations increased with the exception of a slight decrease at 20%w/w of coating from that of 10%w/w coat level for formulations of lactose and MCC. However, the effect of increase in coating material was insignificant in pellets produced with ethanol and GMS.

The rank of the mean slope of the linear portion of the storage modulus-dynamic force curve in descending order was: lactose, MCC, GMS, glycerol to pellets produced with ethanol. There was a considerable variations within a batch, as is indicated by standard deviation in the (Fig-7.11). This indicated the approximately similar change in response of the latter three formulations to the sinusoidal stimuli of various magnitude, and also the similarity of the former two formulations in terms of response.

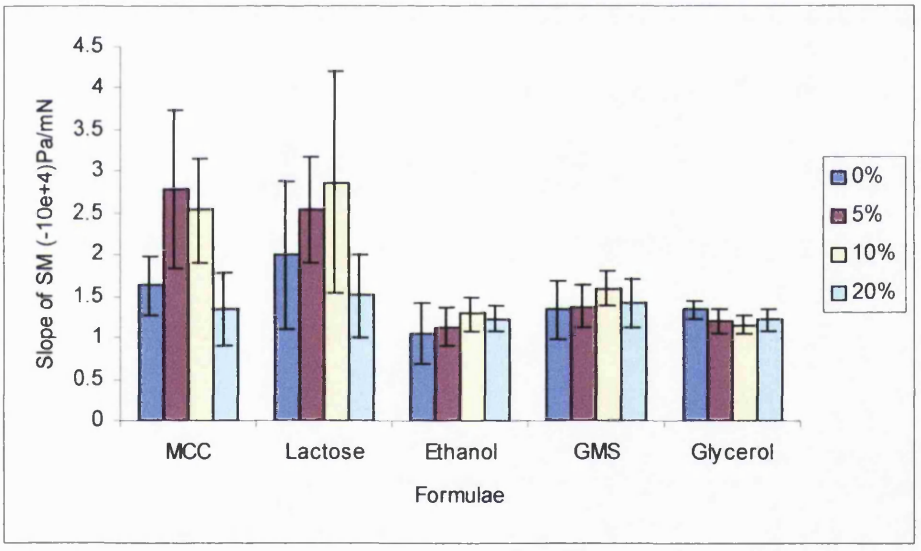


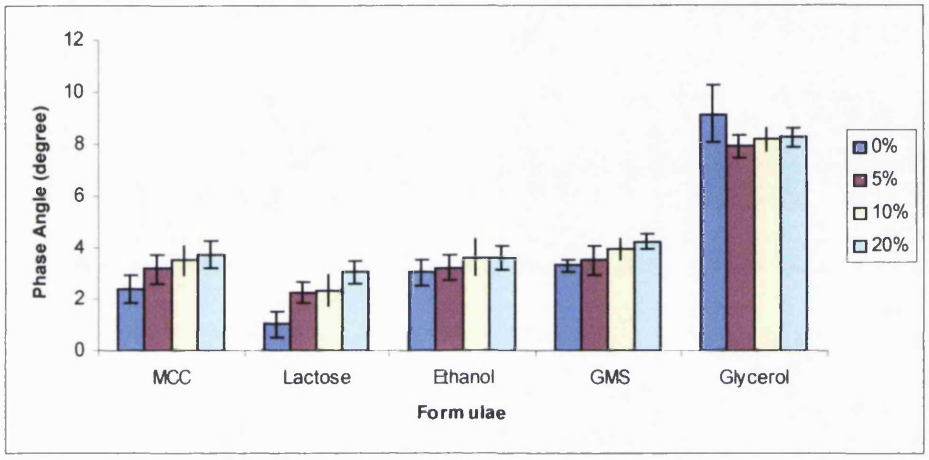
Fig-7.11:- -The slope of the linear portion of the storage modulus-dynamic force curve of pellet (1.0-1.18 mm size fraction) from the different formulations and coated at different coating levels (i.e. 0%, 5%, 10% and 20%w/w).

The effect of the coating materials seems to be minimal. Lactose, ethanol, and GMS containing pellets showed an increase in values up to their 10%w/w coating levels. All formulations coated by 20%w/w had a lower slope than that of 10%w/w indicating the presence of a threshold. Uncoated glycerol containing pellets, however, had the greater slope compared to the coated ones.

Generally, it is possible to conclude that, comparison of the formulation in terms of their

storage modulus has a similar rank order to that of Young's modulus of elasticity determined by static scan. Moreover, the coating material (ethyl cellulose) seems to have increased the elasticity of the materials, as the storage modulus was observed to increase with increase in coating levels. The slope of the curves, however, had marginal difference with considerable variability, hence it was not possible to draw a conclusion as to the effect of the formulations or coating material on the storage modulus sensitivity to increasing dynamic force.

(a)



(b)

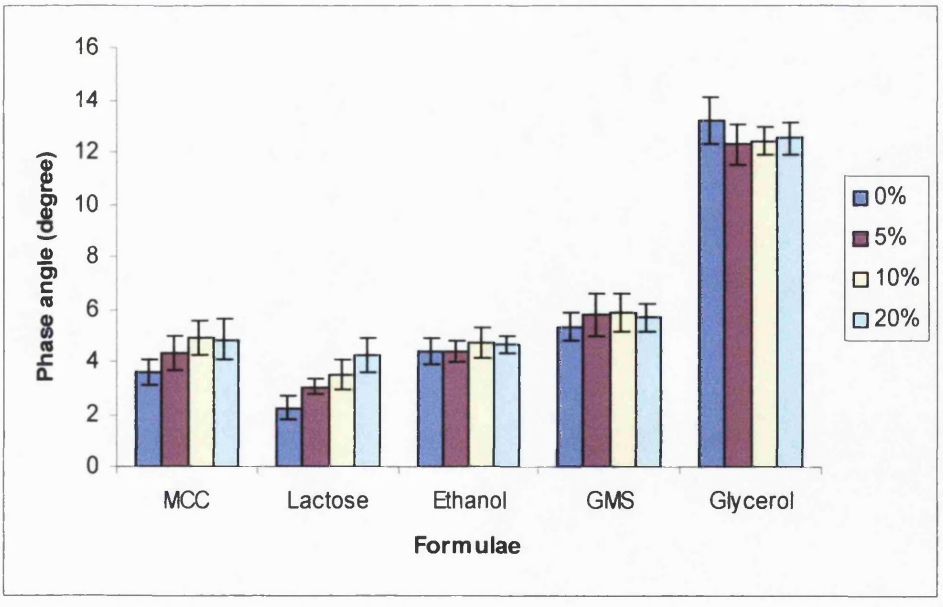


Fig-7.12:--The phase angle, determined (a) at the beginning of the linear portion of the storage modulus-dynamic force curve (b) at dynamic force of 600 mN, of the pellets (1.0-1.18 mm size fraction) from the different formulations and coated at different coating levels (i.e. 0%, 5%, 10% and 20%w/w)

The phase angle of the formulations measured at both positions (see 2.2.3.3) had the same rank order which increased form lactose, MCC, ethanol, GMS to glycerol (Fig-7.12a&b). This was in the reverse order of the storage modulus and Young's modulus. In both cases there was an increase in phase angle value with the increase of the coating levels. This again indicates the plasticity of the polymer (ethyl cellulose). The effect of the coating material was, however, significant ($P<0.05$) only in pellets containing lactose or only MCC. For GMS and glycerol containing pellets, the effect of the coating material was small, presumably due to the comparable plasticity of the core pellets and the coating material. Moreover, the effect of coating material on the phase angle of pellets produced with ethanol was very slight.

In all formulations, the phase angle increased with the increase of the dynamic force, although to different extents (Fig-7.13). This indicates the different proportion of dissipated energy with variation in formulations. Glycerol containing pellets, showed the highest increase in phase angle followed by GMS containing pellets, while the remaining formulations had approximately the same increment value. The effect of the coating material was not appreciable in these cases, in fact, in pellets produced with ethanol and those containing GMS, there was a slight reduction in the rate of increase of phase angle with increase in coating levels.

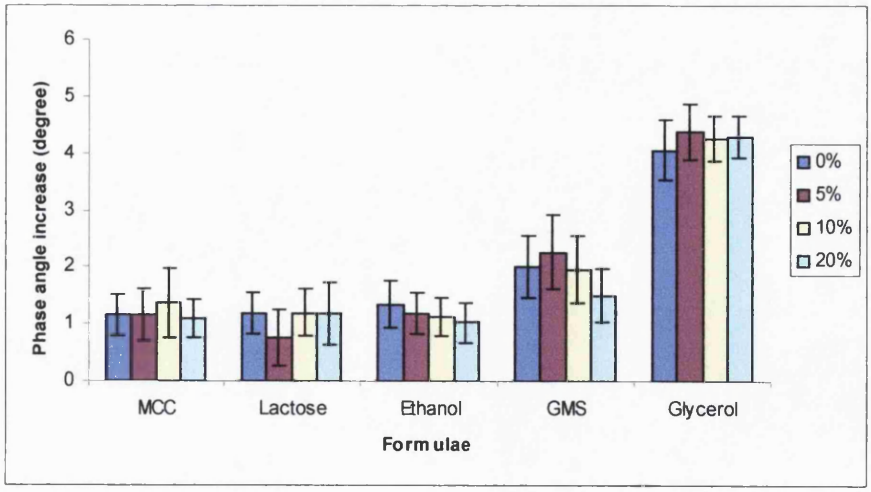


Fig-7.13:-The increase in phase angle at 600 mN of dynamic force from the force at the beginning of the linear portion of the storage modulus-dynamic force curve, of pellets (1.0-1.18 mm size fraction) from the different formulations and coated at different coating levels (i.e. 0%, 5%, 10% and 20%w/w)

Generally, it was possible to identify the relatively greater plastic deformability of pellets containing glycerol or GMS by determining the phase angle at the same constant dynamic force or at the point where the storage modulus-dynamic force function started to relate linearly. Moreover, the least plastic deformability of lactose containing pellets was illustrated. Increase in coating material, ethyl cellulose, was observed to increase the plasticity of mainly lactose or MCC pellets, however, its effect on pellets of the other formulations was not appreciable. This could be due to the variation of the properties of the core pellets i.e. GMS or glycerol containing pellets had a comparable plasticity to that of coating material as illustrated by the minimal change in the phase angle with increase in coating levels.

7.3 CONCLUSION

This work has shown that the determination of the Young's modulus of elasticity of pellets from the diametral compression tests using conventional tablet crushing equipments is insufficiently sensitive for the production and accurately evaluation of the elastic portion of the deformation, hence the results obtained underestimated the actual elastic modulus when compared to that determined by dynamic mechanical analysis. Moreover, the plastic deformation of the pellets could only be determined from dynamic scan using the dynamic mechanical analyser. The 'deformability' value calculated form the force/displacement curve obtained during diametral compression of the pellets do not reflect the plastic property of the pellet for it does not identify the possible structural recovery. The only feasible technique is the one which subject the specimen to a stress/relaxation cycle and could determine the dissipated energy, like loss modulus or phase lag (i.e. DMA). For a screening purpose of materials of a considerable variation in viscoelastic property, however, it could be used as a brittle material would snap after a very limited strain.

CHAPTER - 8

SURFACE ROUGHNESS OF COMPACTED PELLETS BY NON-CONTACT LASER PROFILOMETRY

8.1 PLACEBO PELLET COMPACTS

On Part-II, the deformability of the pellets produced from different excipients (chapter-3), liquid binders (chapter-4) and produced by different drying techniques (chapter-5) were determined from the force displacement curves obtained during diametral compression. These values were assumed to include the plastic and elastic deformations, the latter of which could be determined from the stress/strain analysis of a static scan of the DMA (chapter-7). The plastic component of the deformation could also be indicated by the phase angle from the dynamic scan. Moreover, in this chapter the extent of the expansion of the individual pellets during 48 hours storage after compaction were analysed in terms of the surface roughness parameters. This could be explained as a measure of plastic deformation, for the extent of permanent structural change is determined.

A fixed amount of pellets containing or produced with 40%w/w or 60%w/w of the four formulation factors (lactose, GMS, ethanol, or glycerol) taken from the respective chapters of 3 and 4 (Part-II) were compressed by a constant 130 MPa compaction pressure, a value which produced strong compacts. The same amount of pellets containing 60%w/w of the factors were again compacted by another constant pressure of 86.7 MPa, a value 2/3 of the previous pressure. The upper surfaces of all the pellet-compacts, and the bottom surface of the compacts form 40%w/w of the factors were scanned by the non-contact laser profilometer (Plate-8) as described in (section-2.2.4.2.3).

Table-8.1 presents the mean and standard deviation of the values of the R_a, R_q, R_{tm}, and FD (defined in 1.9) of five tablets from each set of experiment. With the increase of the compaction pressure, the rugosity value produced (Fig-8.1), as well as R_q, and R_{tm} values (Table-8.1) of all the pellet-compacts reduced in all cases except for the glycerol-containing pellets. GMS containing pellets had the lowest values in all the surface roughness parameters, indicating their greatest deformability. From a visual observation of the scanning electro-micrograph it was difficult to identify the boundaries of the GMS containing pellets on the surface of the compact (Plate-3.2a, see p-178).

Material		Lactose				GMS				Ethanol				Glycerol			
content (%)		40%		60%		40%		60%		40%		60%		40%		60%	
Press/ tab-surf		HPT	HPB	LPT	HPT	HPT	HPB	LPT	HPT	HPT	HPB	LPT	HPT	HPT	HPB	LPT	HPT
R_a	Mean	6.16	4.99	4.04	3.59	3.15	2.89	2.01	1.74	7.28	5.82	5.59	4.99	18.94	14.44	22.08	22.75
	STD	0.48	0.22	0.168	0.36	0.30	0.26	0.24	0.13	0.69	0.58	0.11	0.27	0.91	0.79	1.33	0.52
R_q	Mean	7.84	6.42	5.2	4.63	4.00	3.67	2.63	2.34	9.26	7.82	7.10	6.36	23.70	18.42	27.85	28.60
	STD	0.61	0.29	0.20	0.48	0.41	0.27	0.36	0.15	0.85	1.27	0.23	0.39	0.78	1.27	1.22	1.04
R_{tm}	Mean	42.71	42.34	32.62	29.37	19.26	18.37	15.45	15.38	48.52	46.15	34.73	32.11	94.52	79.36	104.8	104.1
	STD	1.21	4.71	1.81	2.15	2.08	0.63	2.74	1.23	4.34	5.59	0.72	2.02	2.77	8.61	6.40	10.44
FD	Mean	2.34	2.34	2.33	2.33	2.41	2.42	2.38	2.33	-	-	-	-	-	-	-	-
	STD	0.02	0.05	0.02	0.03	0.04	0.03	0.06	0.17	-	-	-	-	-	-	-	-

Table-8.1:- The surface roughness parameters (R_a, R_q, R_{tm}, and FD) obtained form the placebo pellet compacts of different formulations.

Where: 40% or 60% stands for the percentage of the formulation factors in the dry mass for GMS and lactose, and in the liquid binder for ethanol or glycerol.

The HPT stands fo the High Pressure applied (130 MPa) and the Top of the tablet surface

The LPT stands for the Low Pressure applied (86.7 MPa.) and the Top of the table surface

The HPB stands for the High Pressure applied (130 MPa) and the Bottom of the tablet surface

The LPB stands for the Low Pressure applied (86.7 MPa) and the Bottom of the tablet surface

The pellets seemed to be flattened and fully merged with each other to produce the smoothest surface profile. The range between the peak and valley was only about 20 μm, indicating the absence of gap between the pellets.

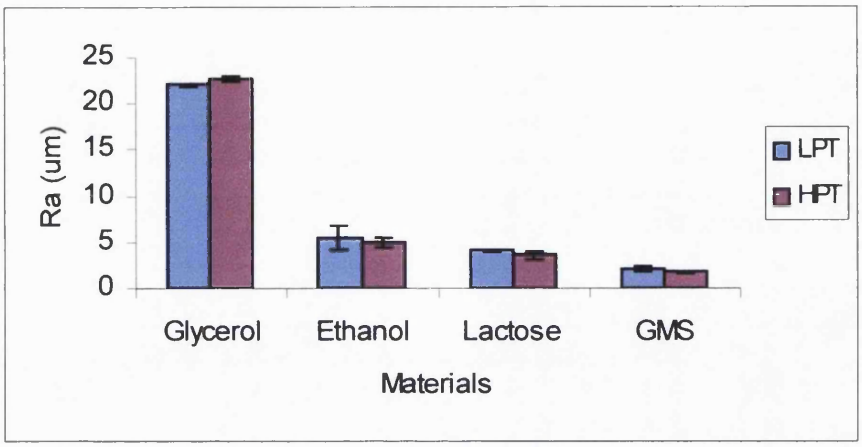


Fig-8.1-The rugosity of the upper surface of the tablets produced form pellets containing 60%w/w of the different formulation factors and compacted by 86.7 MPa (LPT) and 130MPa (HPT).

A similar observation was noted from the comparison of pellet-compacts containing 40%w/w and 60%w/w of the aforementioned ingredients (Table-8.1 and Fig-8.2). Pellets containing glycerol did not cohere with each other, the space between them was distinct and deep which resulted in R_{tm} values of more than 100μm (Table-8.1). Thus, the considerable deformability of these pellets (chapter-4) was dominated by the prominent grooves between the pellets. This was increased with the increase of glycerol content from 40% to 60%w/w, and compaction pressure from 86.7 MPa to 130 MPa.

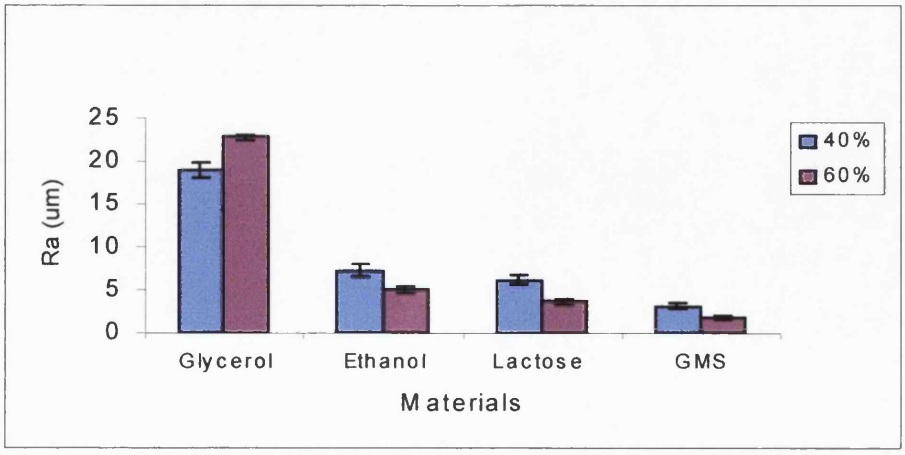


Fig-8.2:-The rugosity of the upper surfaces of the tablets produced form pellets containing 40%w/w and 60%w/w of the different formulation factors and compacted by 130 MPa.

In all cases, the bottom surface of the pellets had a lower rugosity (Fig-8.3). This could not be due to the excessive pressure on the upper surface, as an intermediate pressure was indicated to produce the least rugosity by (Riippi et al. 1998). Because, on the 60%w/w content of the factors a similar pressure was observed to reduce the rugosity compared to that of lower pressure (Fig-8.1). The possible explanation could be, the instant relaxation (expansion) of the upper surface during the decompression as the upper punch returns. Moreover, during ejection of the tablets by pushing from the bottom of the die, the upper surface could have been subjected to lateral deformation (relaxation) while leaving the edge of the restricted die wall first.

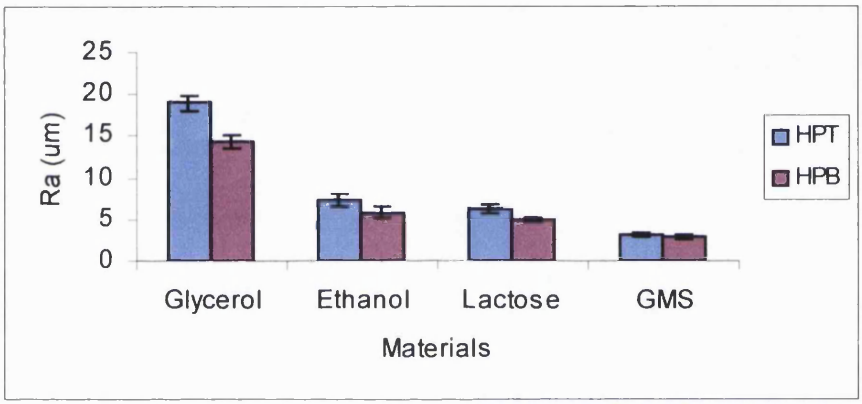


Fig-8.3:-The rugosity of the top (HPT) and bottom (HPB) surfaces of the tablets produced form pellet containing 40%w/w of the different formulation factors and compacted by 130 MPa.

The ratio between the rugosity of the upper surface to the lower surface of tablets produced with 40%w/w of the GMS, lactose, ethanol, and glycerol was 1.09, 1.23, 1.25, 1.31 respectively, while the ratio between the rugosity of the upper surfaces of compacts produced from pellets which had 40%w/w to 60%w/w of the same formulation was 1.81, 1.72, 1.46, and 0.83 respectively, as well as the ratio of the rugosity of the upper surface of the compacts having 60%w/w content of the formulations compacted by 86.7 MPa to 130 MPa. was 1.16, 1.13, 1.12, and 0.97 respectively. This shows that the formulations had the same rank order in the different surface roughness parameters, in addition to the similar order in their response to increase in the compaction pressure, change in content proportion, and variation in their upper and lower faces roughness. GMS had the least difference in the upper and lower surfaces roughness, indicating again less expansion during decompression, while glycerol-containing pellets were with the greatest value. The values for lactose and pellets produced with ethanol was comparative with a slight decrease in lactose containing pellets presumably

due to greater fracture propensity of these pellets as was noted on (Plate-3.1b).

The mean ratio between the R_p and R_t (where, R_p is the distance between an asperity tip and the centre line of the roughness profile and R_t is maximum peak-to-valley height) of the compacts from the 40%HPT was determined to be 0.46, 0.48, 0.55, and 0.56 for the formulations containing GMS, glycerol, ethanol, and lactose respectively. This indicates that the shape of the irregular part of the surface was low and broad based wavelike structure rather than sharply protruded asperity. This supports the concept of determining the plastic deformability of the pellets from the surface of the compacts using the profilometry. Had the values of the ratio of R_p to R_t approached unity, the variation in the surface profile would merely be due to the difference in surface finish of the pellets rather than the macroscopic structure of the pellet due to deformation. The relatively low ratio value of R_p to R_t for glycerol containing pellets indicate the flatness of the pellets surface in the compacts due to their permanent deformation. However, the high values of the rugosity and other parameters were mainly due to the prominent valleys between the pellets as a result of the lack of their coherence. The higher deformability of the GMS and glycerol containing pellets relative to those produced by ethanol and lactose containing pellets was supported by the phase angle values obtained on (chapter-7) and deformability (part-II).

The surface profile of MCC pellet-compacts produced with 40%w/w ethanol as a liquid binder and dried by the four different techniques (chapter-5) were also analysed in terms of R_a, R_q, R_{tm} and FD. All the surface roughness parameters increased in the same order from freeze dried, fluid bed dried, desiccated with silica-gel, to oven dried pellets (Fig-8.4).

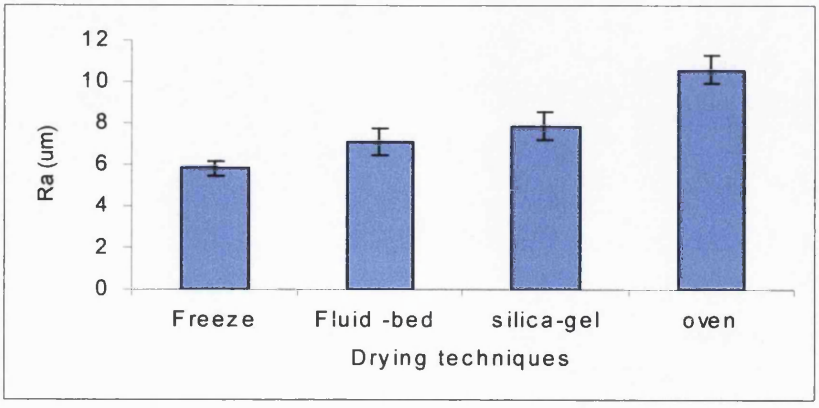


Fig-8.4:-The rugosity of the upper surfaces of the tablets produced form MCC pellets containing 20%w/w ethanol and compacted by 130 MPa.

A similar order of pellet deformability was observed on (chapter-5). The compacts from the pellets dried by the latter two techniques were very soft (chapter-5) and were susceptible to fragmentations during handling due to poor inter-pellet connection, hence a wider surface roughness variability, R_q, and greater mean peak to valley distance, R_{tm}, were noted. Freeze dried pellets produced the lowest surface roughness parameter. The coherence of the pellets (Plate-5, see p-228) and the permanent repositioning of the primary particles after compaction due to the highest porosity of the pellets (chapter-5) are considered to be the reasons of such findings.

It is possible to conclude from these results that non-contact laser profilometry provides a reasonable estimation of the permanent structural change or plastic deformability of the pellets after compaction. The surface irregularity was observed as to have a broader and rounded ends and the rugosity increased with the decrease of the deformability of the pellets. However, the clefts between pellets were the main source of variation, which could underestimate the plastic behaviour of cracked pellet compacts such as glycerol containing pellets. The surface roughness values in this work were found to be comparable to the deformability values obtained form the pressure/displacement profiles during diametrical compression, however, the surface roughness parameters could be considered more reliable as they are determined after 48 hours to give time for the elastic expansion of the pellet, while the previous technique included elastic deformability of the pellets as well.

8.2 COATED AND UNCOATED DRUG PELLETS

The values of all surface roughness parameters of the drug pellet compacts were observed to vary with the formulations. All parameters were observed to decrease in value in a descending order from glycerol, MCC, ethanol, lactose to GMS containing pellets (Table-8.2). These results coincided with those of placebo pellet compacts (Section-8.1). The main reason for such variation is presumably due to the ability of the pellets to deform and form flat and smooth faced tablets as well as their ability to cohere and form structures without grooves between them. The same rank order of the values of the strength of these tablets (chapter-6) supports the latter argument. The flatness of the pellets after compaction, as indicated with the decrease in K_p/K_t ratio, had a rank in a descending order from lactose, MCC, ethanol, glycerol, to GMS. This was a real indication of the permanent structural change or plastic deformation of the pellets. The rank order was the same to that of phase angle determined

from the dynamic scan by DMA (chpater-7) with the exception of the glycerol pellets position in respect to those of GMS containing pellets. This could again be related to inter-pellet gap variation as illustrated on (Plate-6, see p-263).

The increase in coating material affected the surface profile of the tables of the various formulations in different ways (Table-8.2) and (Plate-8, see p-296). The rugosity of the uncoated and 20%w/w coated drug pellet-compacts is illustrated as an overall findings (Fig-8.5).

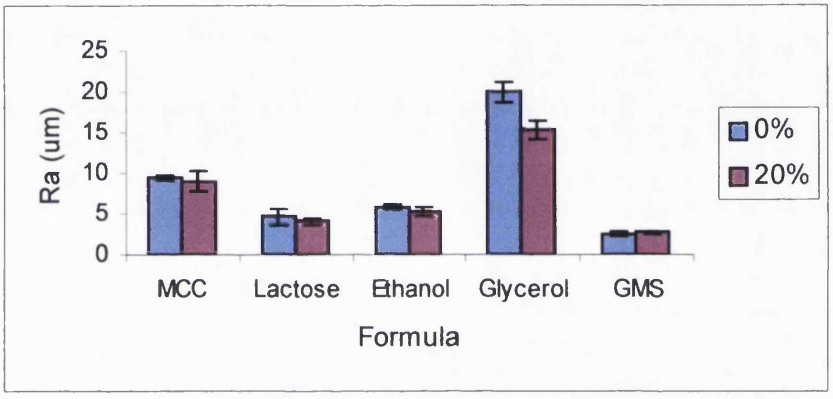


Fig-8.5:-The rugosity of the upper surfaces of the tablets produced form uncoated and 20%w/w coated pellets form the different formulations.

The rugosity reduced for all the pellet compacts after coating, except in those GMS containing pellets. (Plate-8, see p-296) depicts the reflection of sample surface profiles. In glycerol or only MCC containing formulations the gap between the pellets after compaction was filled with the coating material (Plate-6, see p-263). This reduced the R_{tm} considerably and the rugosity marginally. In formulations with ethanol or lactose, however, it was merely change in the surfaces as the pellets and their coats were crushed to smoother and cohered tablet surface. In pellets containing GMS, the rugosity increased after coating. The relative increase in R_p/R_t ratio from 0.4 to 0.48 with 20%w/w coating indicates the presence of protruding asperities. Moreover, the peaks of the profile could be seen to be situated on the centre of the pellets when uncoated pellets were compacted, while it was on the periphery of the pellets when coated pellets were compacted, showing squeezing out of the coating material above the surface of the pellets to increase the rugosity (Plate-8, see p-296).

The results for the surface roughness parameter in (Table-8.2) indicates that there was no linear relation between the values of surface parameters and the coating levels. This illustrates

the sensitivity of the technique to some other structural defects beside to the deformability of the pellets. For instance, the removal of the coat during compression (at least in some formulation) as well as the squeezing out of the coating materials form the soft pellets (Plate-6, see p-263) increased the magnitude of variability considerable. However, from the overall trends and comparison of the uncoated with those coated by 20%w/w level, it is possible to conclude that the coating material increased the deformability of the pellets as this technique has illustrated in a similar order to that noted by the phase angle (chapter-7) with the exception of GMS containing pellets, where the coat was protruded between the pellets during compaction process to increase the rugosity.

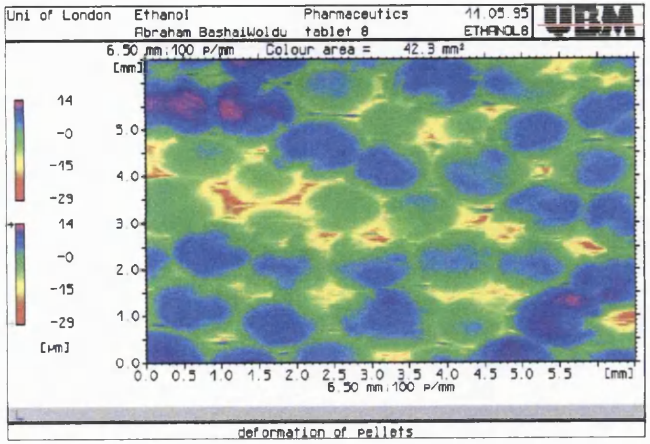
	M		5M		10M		20M	
	Mean	STD	Mean	STD	Mean	STD	Mean	STD
Ra	9.40	0.28	9.94	0.74	10.36	1.31	8.98	1.15
Rq	12.00	0.42	13.22	1.12	13.07	1.89	11.22	1.45
Rtm	62.80	0.85	56.84	3.51	51.91	4.72	41.27	1.25
FD	2.29	0.03	2.29	0.03	2.34	0.03	2.35	0.03
	L		5L		10L		20L	
	Mean	STD	Mean	STD	Mean	STD	Mean	STD
Ra	4.60	0.95	3.91	0.54	4.90	0.65	4.08	0.44
Rq	5.93	1.22	5.01	0.64	6.27	0.99	5.20	0.60
Rtm	30.82	2.75	27.28	4.93	26.76	3.36	26.61	2.83
FD	2.30	0.03	2.32	0.02	2.35	0.03	2.39	0.03
	E		5E		10E		20E	
	Mean	STD	Mean	STD	Mean	STD	Mean	STD
Ra	5.75	0.30	5.03	0.26	5.41	0.27	5.19	0.54
Rq	7.35	0.30	6.32	0.37	6.76	0.28	6.66	0.64
Rtm	32.68	0.98	28.61	0.93	29.28	0.67	28.80	1.44
FD	2.30	0.01	2.32	0.02	2.31	0.01	2.32	0.02
	R		5R		10R		20R	
	Mean	STD	Mean	STD	Mean	STD	Mean	STD
Ra	19.90	1.27	15.92	1.31	19.00	2.38	15.24	1.02
Rq	24.70	2.12	20.10	1.67	23.98	3.15	21.52	4.36
Rtm	89.65	6.43	79.14	8.45	85.80	11.70	82.52	3.14
FD	2.25	0.01	2.26	0.01	2.29	0.02	2.28	0.03
	G		5G		10G		20G	
	Mean	STD	Mean	STD	Mean	STD	Mean	STD
Ra	2.44	0.25	1.92	0.16	2.18	0.13	2.65	0.23
Rq	3.23	0.40	2.46	0.18	2.65	0.30	3.46	0.27
Rtm	16.64	2.30	13.44	1.75	14.83	0.42	20.31	0.86
FD	2.35	0.05	2.40	0.03	2.41	0.01	2.46	0.02

Table-8.2:- The surface roughness parameters (R_a, R_q, R_{tm}, and FD) obtained form the uncoated and 5%, 10%, and 20%w/w coated drug pellet compacts of different formulations. M stands for MCC, L for lactose, G for GMS, R for glycerol containing pellets while E for those pellets prepared with ethanol.

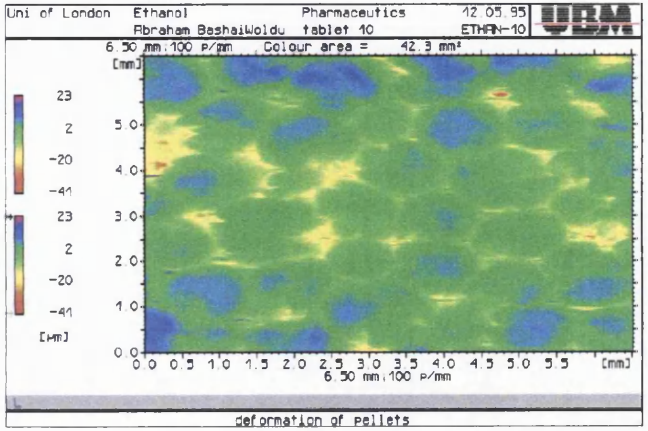
8.3 CONCLUSION

The increase in deformability of the pellets with the increase of the contents of GMS, lactose, ethanol, or glycerol form 40% to 60%w/w in the formulation was illustrated by the reduction of the surface roughness parameters. Moreover, the increase in compaction pressure enhanced the deformability of the pellets. The rank order of the formulation factors was not similar to that deformability determined from the pressure/displacement curve during diametral compression for glycerol containing pellets produced the roughest surfaces. That was because the prominent grooves created between the less coherent pellets. The flatness of the pellets on the tablet surface was, however, a better indication of the deformability of the pellets as was determined as a ratio of R_p to R_t. GMS or glycerol containing pellets were very flat, while those formulated with ethanol or lactose containing pellets were relatively less flat. This corresponded to the results from the previous techniques, however, the extent of variation between the formulations was marginal (small) in this technique. Because the structural change due to pellet failure (eg. lactose containing pellets) was included. This resulted in the reduction of the difference between the formulations. In the previous technique (Part-II), the inclusion of the elastic deformation overestimated the difference between the formulations. Thus, the deformability of the pellets determined from pressure/displacement curve obtained during diametral compression could be considered as "complex-deformation" which includes the elastic as well as the plastic deformation, and had to be resolved between them to quantify the plasticity of the pellets. In coated and uncoated drug pellets, the results obtained were reasonably comparable to those obtained in terms of phase angle from dynamic scan by using DMA. The separation of the coat from the core pellets, such as in GMS, might explain the slight discrepancy observed. Therefore, this technique can be recommended as a feasible pellet structural change assessing procedure.

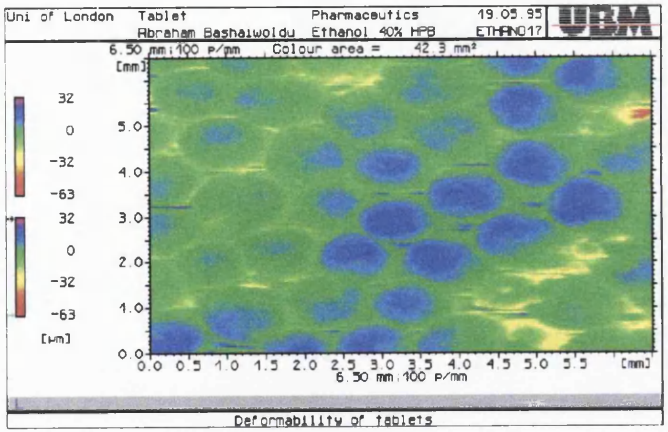
Plate-8 (following pages) :- The reflection of the profile of the compacts surfaces obtained form the non-contact laser profilometer.



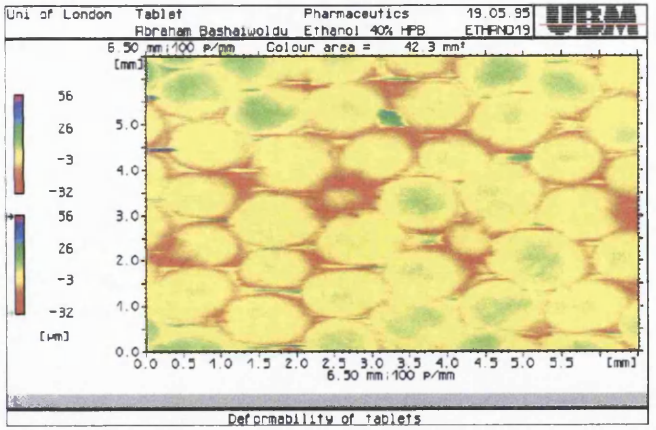
E-1



E-2



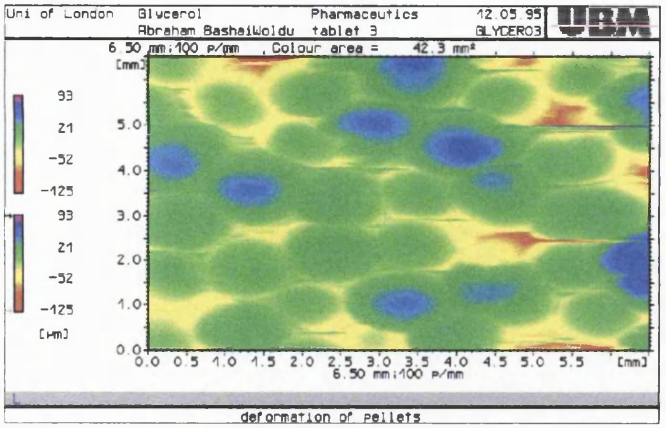
E-3



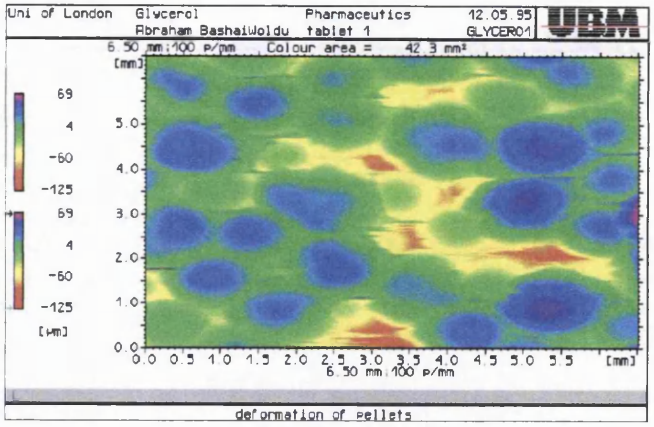
E-4

The upper surface of compacts produced with 60%w/w ethanol and compacted by (1) 130MPa, (2) 86.7 MPa;

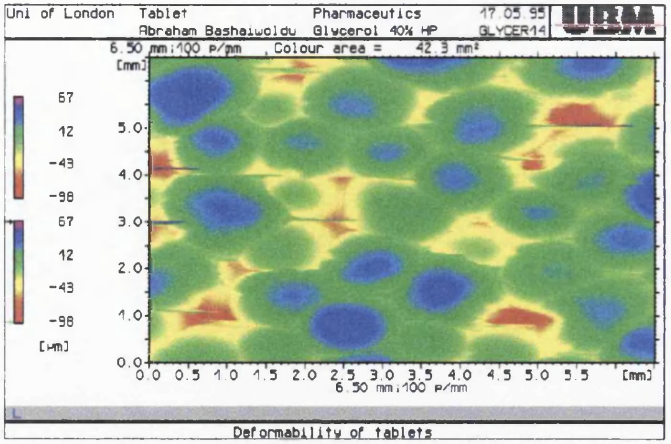
The surfaces of the compacts produced with 40%w/w ethanol and compacted by 86.7 MPa (3) upper and (4) bottom surfaces



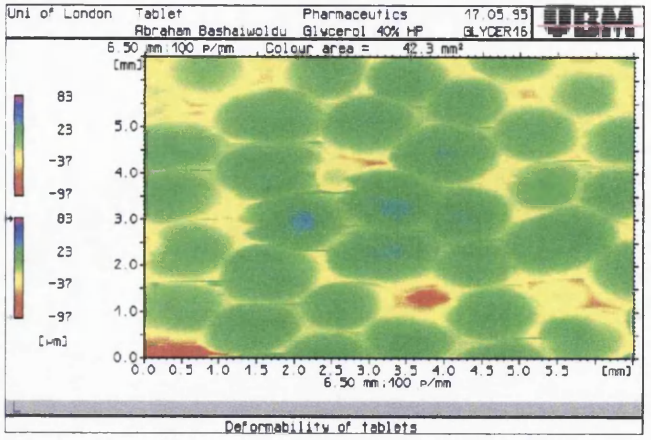
R-1



R-2



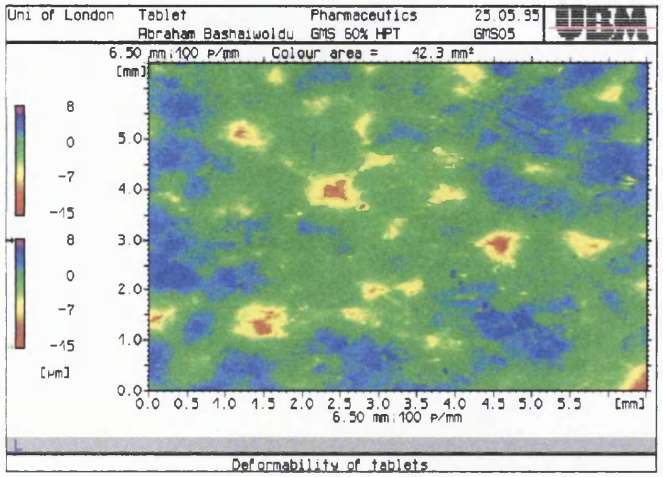
R-3



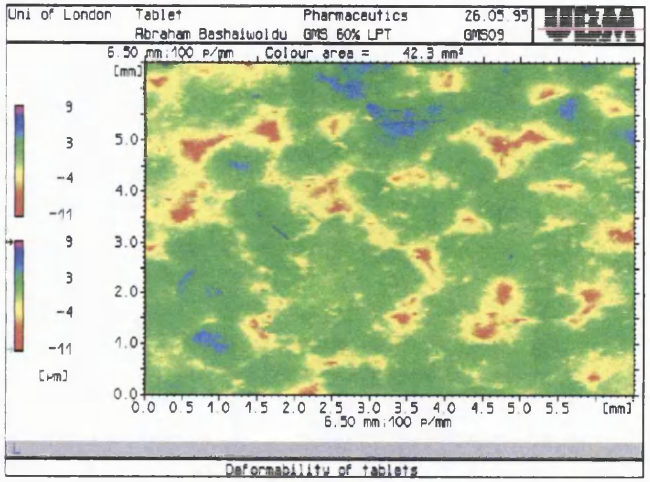
R-4

The upper surface of compacts containing 60%w/w glycerol and compacted by (1) 130MPa, (2) 86.7 MPa;

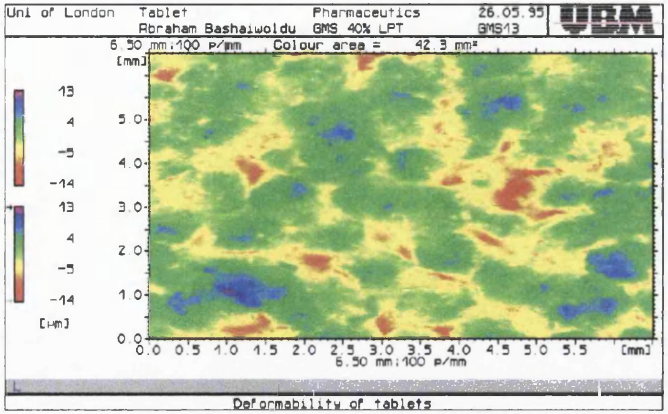
The surfaces of the compacts containing 40%w/w glycerol and compacted by 86.7 MPa (3) upper and (4) bottom surfaces



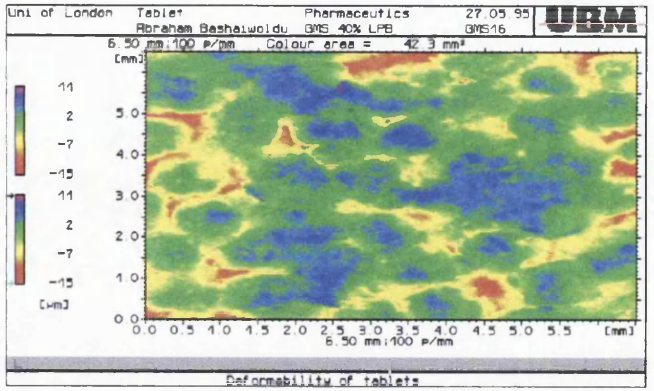
G-1



G-2



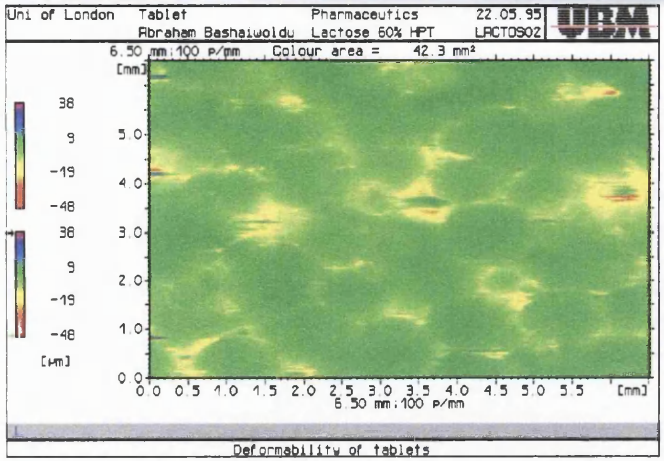
G-3



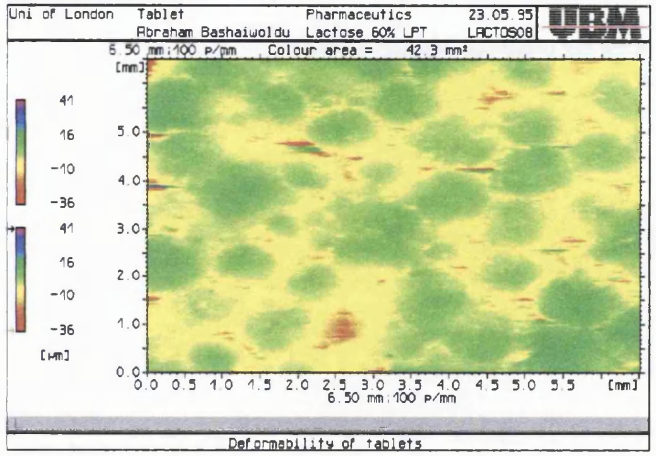
G-4

The upper surface of compacts containing 60%w/w GMS and compacted by (1) 130MPa, (2) 86.7 MPa;

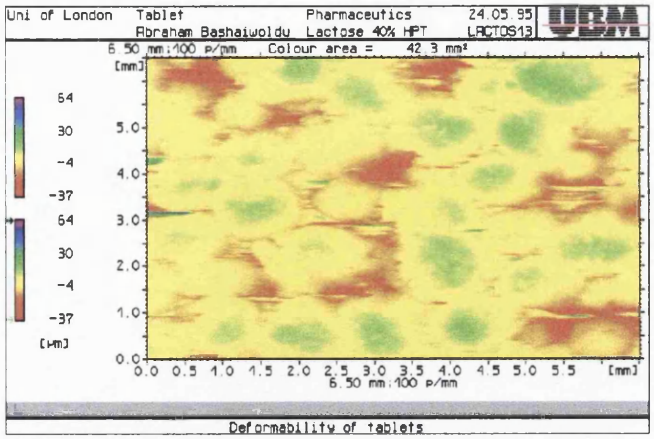
The surfaces of the compacts containing 40%w/w GMS and compacted by 86.7 MPa (3) upper and (4) bottom surfaces



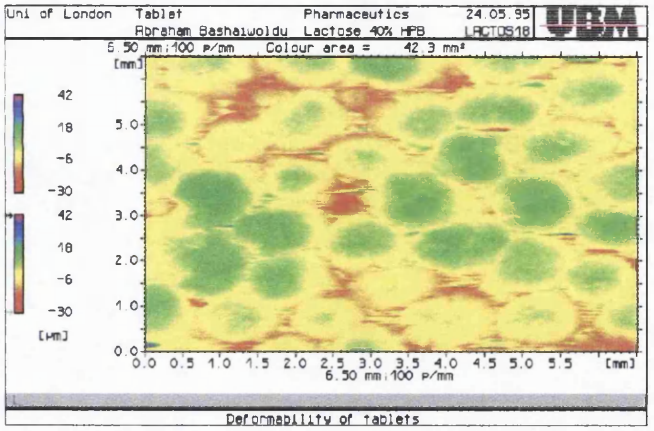
L-1



L-2



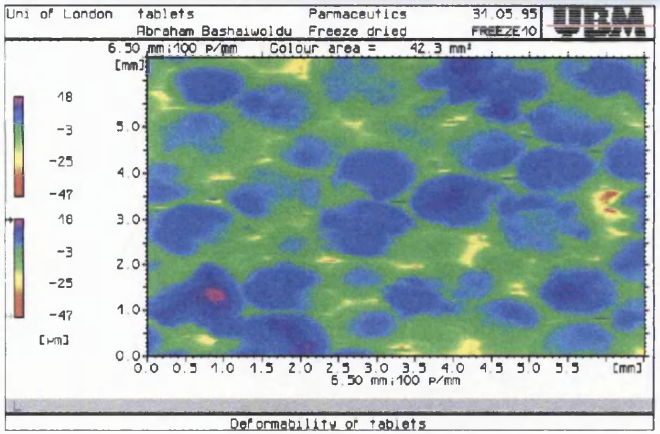
L-3



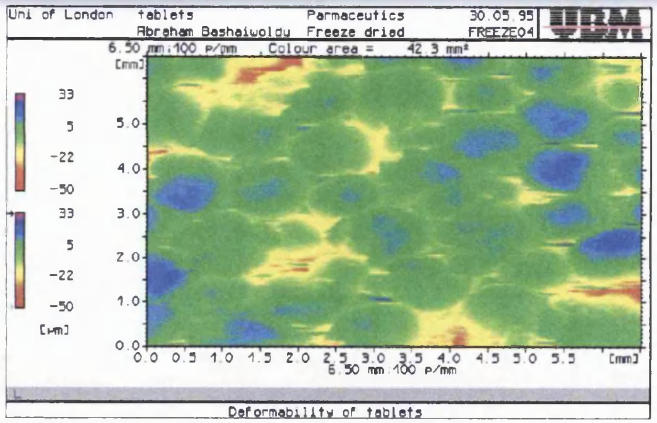
L-4

The upper surface of compacts containing 60%w/w lactose and compacted by (1) 130MPa, (2) 86.7 MPa;

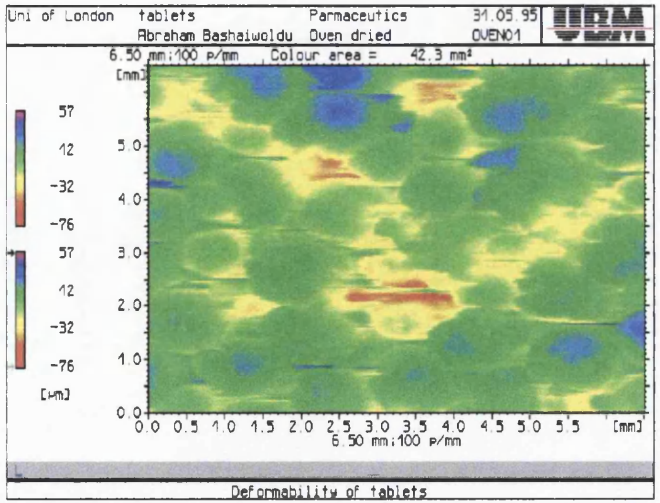
The surfaces of the compacts containing 40%w/w lactose and compacted by 86.7 MPa (3) upper and (4) bottom surfaces



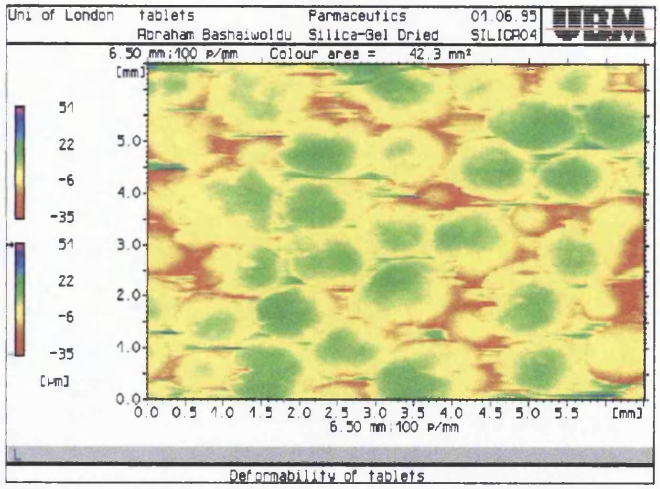
Freeze dried



Fluid-bed dried

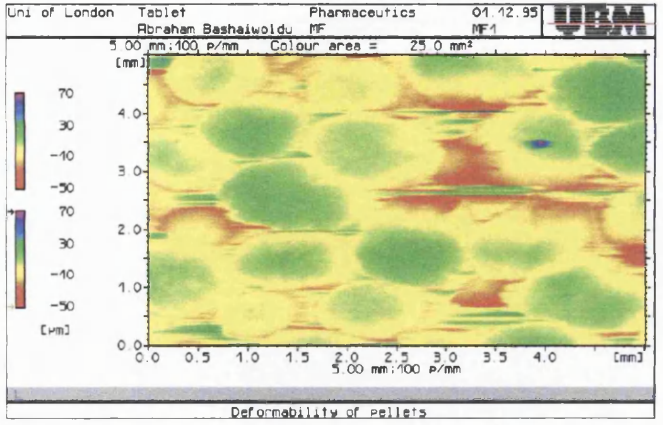


Oven-dried

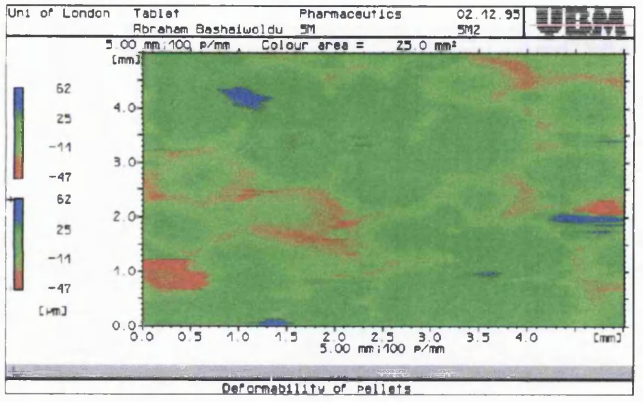


Desiccated with Silica-gel

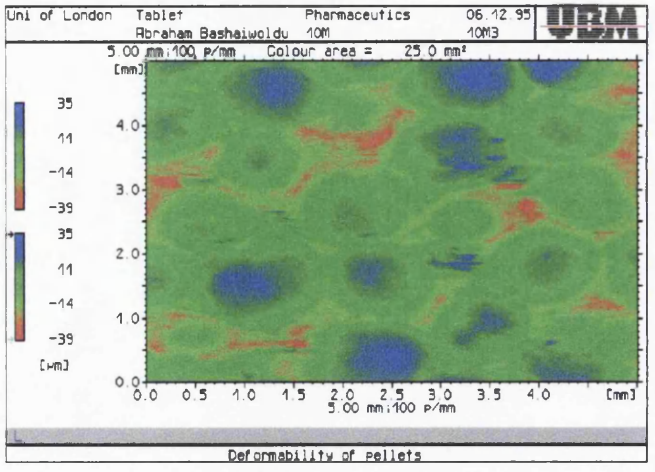
The upper surface of the MCC pellets compacts dried by (a) freeze drier, (b) fluid bed-drier, (c) hot air oven, and (d) desiccated with silica-gel.



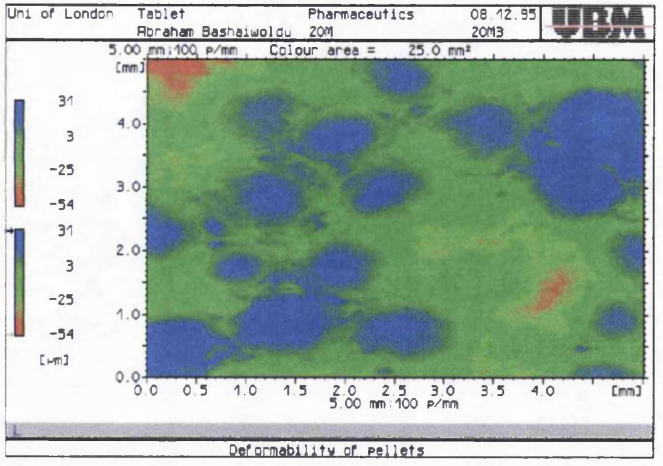
0M



5M

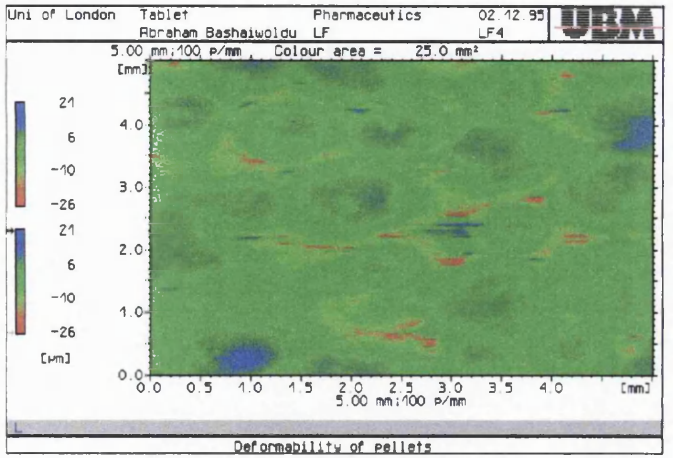


10M

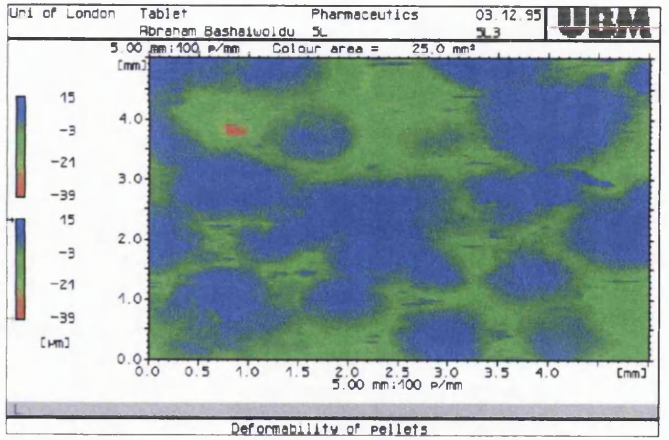


20M

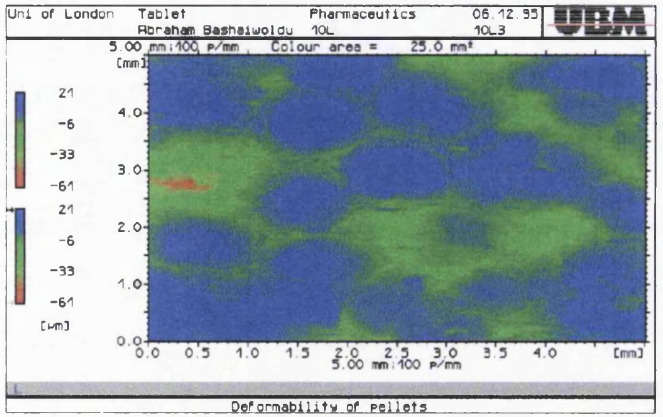
The upper surface of drug containing MCC pellet-compacts coated with 0%, 5%, 10%, and 20%w/w Surelease®.



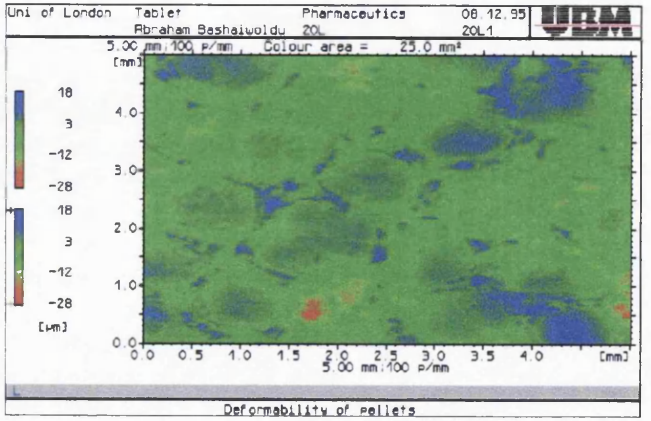
0L



5L

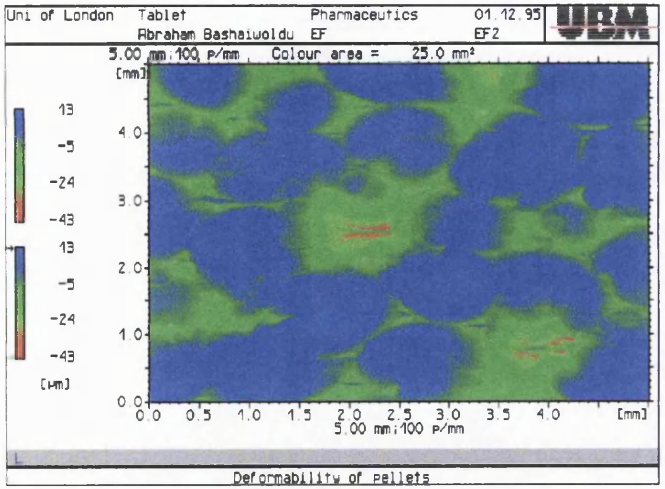


10L

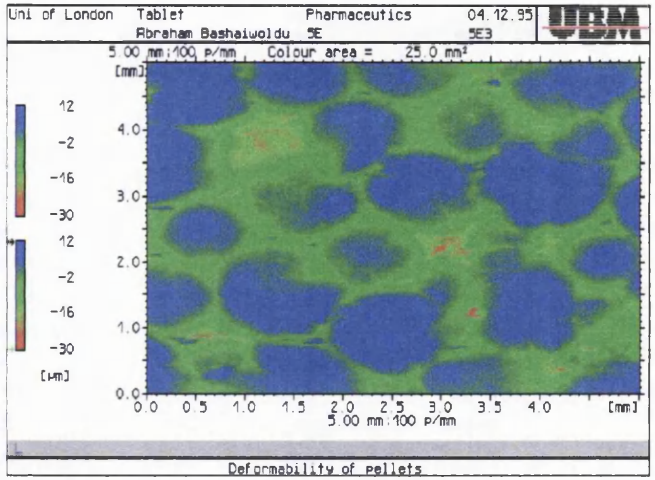


20L

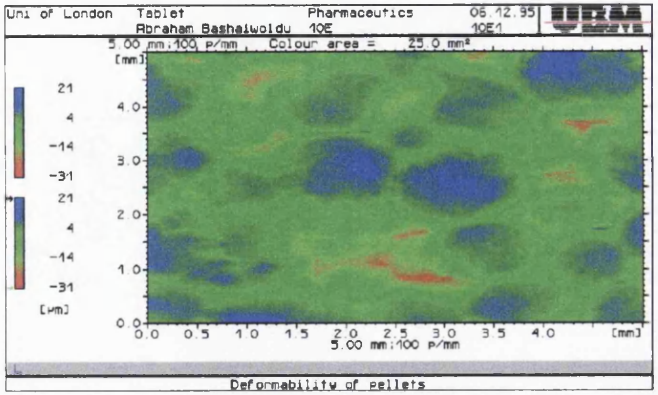
The upper surface of drug containing MCC/lactose (1:1) pellet-compacts coated with 0%, 5%, 10%, and 20%w/w Surelease®.



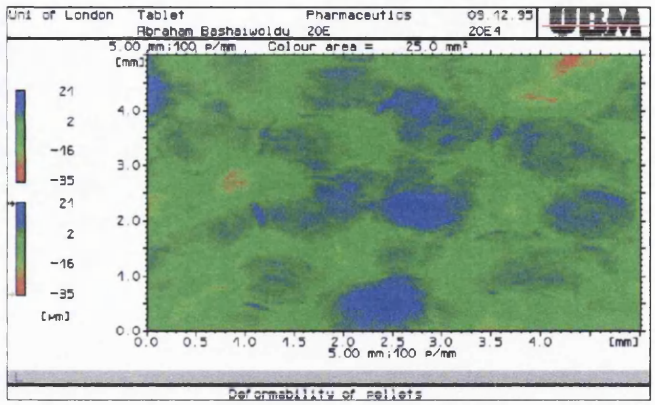
0E



5E

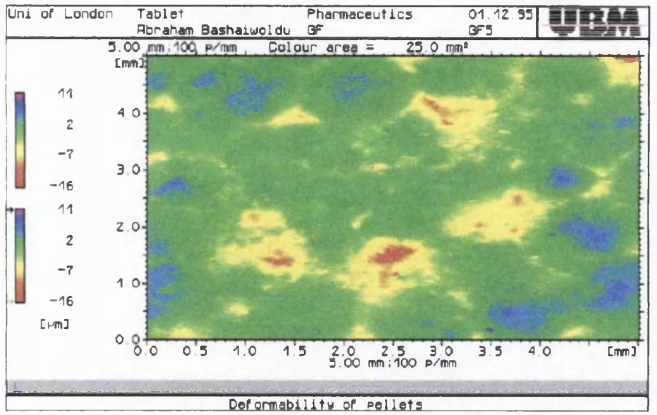


10E

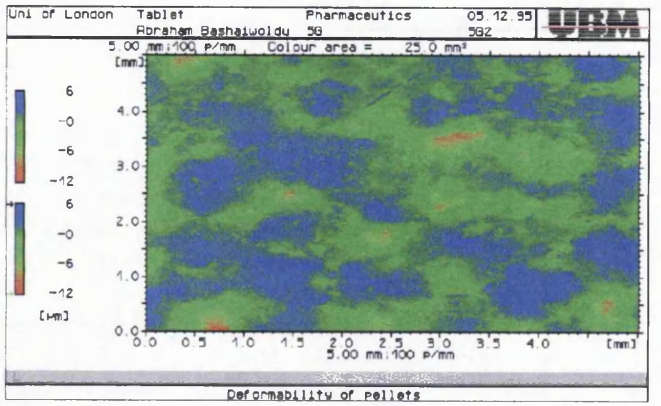


20E

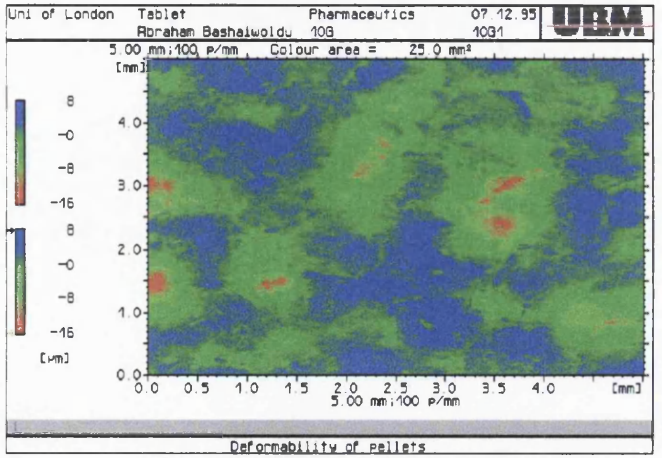
The upper surface of drug containing MCC pellet-compacts produced with 50%w/w ethanol and coated with 0%, 5%, 10%, and 20%w/w Surelease®.



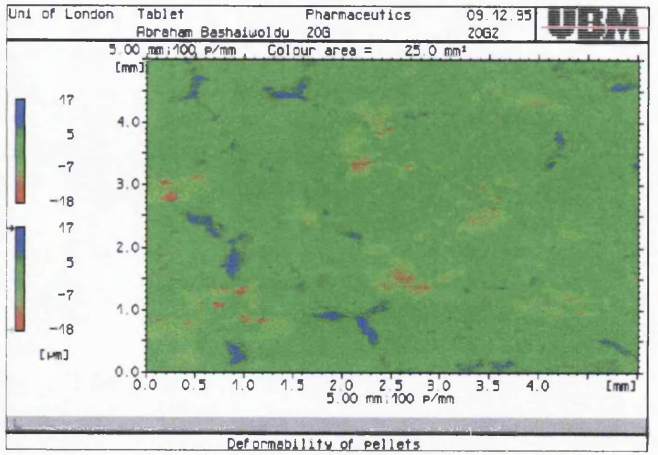
0G



5G

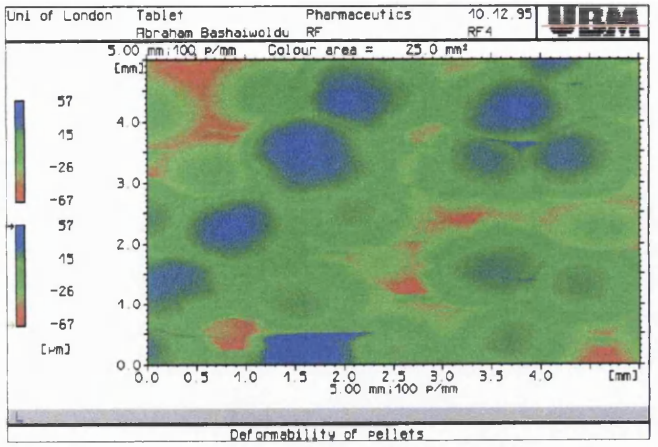


10G

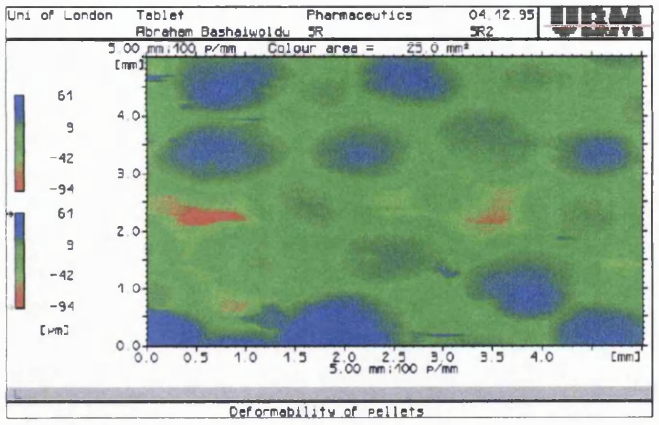


20G

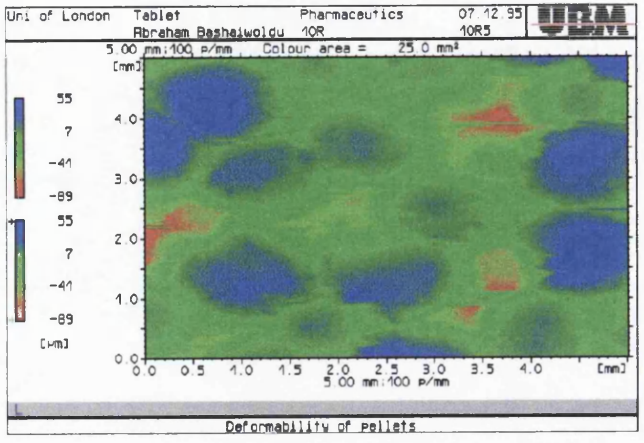
The upper surface of drug containing MCC/GMS (1:1) pellet-compacts coated with 0%, 5%, 10%, and 20%w/w Surelease®.



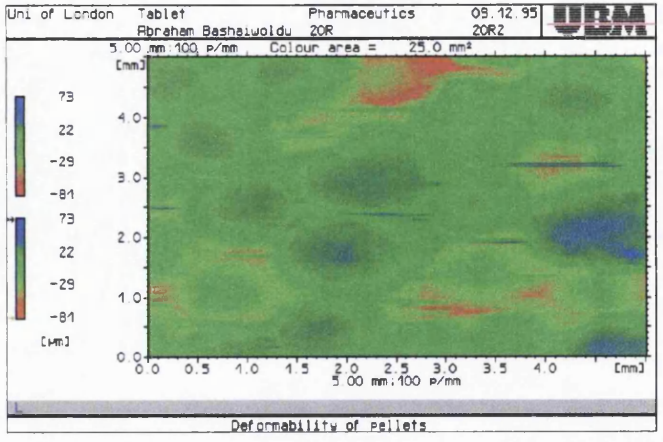
0R



5R



10R



20R

The upper surface of drug and glycerol containing MCC pellet-compacts coated with 0%, 5%, 10%, and 20%w/w Surelease®.

CHAPTER - NINE

GENERAL CONCLUSION

From the binary mixture of the excipients and the factorial designed experiment reported in chapter 3, it was possible to establish the effects of each of the formulation factors on the mechanical properties of the pellets, their compaction mechanism, as well as the properties of their compacts. A stepwise addition of lactose to MCC : water in the formulations reduced the values of shear strength, tensile strength and linear strain of the pellets, while it increased the extrusion force, 'elastic modulus', and deformability of the pellets to small extent. Likewise, the effect of a stepwise addition of GMS had the same trend but the values were of a greater magnitude with the exception of a reduction in the 'elastic modulus' of the pellets. The sequential interdependence of the effects of GMS or lactose on deformability, porosity, compressibility, compaction pressure and work of compaction was one of the novel observations of this work. As a result, incorporation of GMS in the formulations increased the compaction pressure required and produced compacts of a greater strength and higher volumetric elastic recovery. The lactose-rich pellets were observed to have moderately high compaction pressures due to the relatively lower deformability of the pellets. The failure of these pellets during compaction was the main reason for the least volumetric elastic recovery of their compacts. Moreover, the exposure of new surfaces enabled the pellets to form inter-pellet connection network to produce stronger tablets. GMS containing pellets and powder mixture exhibited a similar mechanism of compaction, volumetric elastic recovery and final tablet porosity. This was attributed to the inherent and unchanged deformability of GMS. The difference in the strength was, however, presumably due to the effect of the pelletization process on the surface nature of the pellets mainly on the MCC part of the mixture. This was supported by the observation that failure of the pellet compacts occurred through the boundaries of the pellets during diametrical compression. The lower compressibility, the change in the surface nature during the pelletization process, lower and smooth surface area, as well as the higher volumetric elastic recovery were the main reasons for the reduction of the values of the strength of lactose containing pellet compacts compared to those of powder compacts of the same formulation. Moreover, the wider particle size distribution of powder particles may have reduced the inter-particle voids, hence, increased contact area that may have enhanced the formation of rigid structure.

In chapter 4, the effects of moisture content upon the properties of MCC pellets produced by extrusion and spheronisation process were observed to be considerable. With the increase of water content, the mean pellet size and size distribution, tensile strength, 'elastic modulus' and linear stain of the pellets increased, while the deformability, and "sealed" porosity decreased. The difference in compaction mechanism of such pellets was, however, marginal as was noted by the similarity in force/displacement curves and Heckel plots. The increase in the proportion of ethanol in the ethanol/water mixture as binding liquids in the production of MCC pellets reduced the pellet strength, linear strain, and 'elastic modulus', while it increases the deformability of the pellets. It also increased the compaction pressure and tablet strength. The main reason for such effects could be its ability to increase the porosity of the pellets with increase in ethanol content in the liquid binder. With the increase of glycerol content in the glycerol/water mixture as a liquid binder, the strength of the pellets, densities, and 'elastic modulus' were reduced, while their deformability and linear strain were increased.

Based on the different rate of moisture removal, means of heat and mass transfer, and static or dynamic nature of the bed, the different drying techniques produced pellets of different structural and mechanical properties (chapter 5). The most crucial of these was the porosity as a result of the different extent of shrinkage of the pellets. The rapid evaporation of water as a result of the turbulent motion of the fluidized pellets (fluid-bed) and the direct evaporation of the expanded ice (freeze drying) suppressed the shrinkage of the pellets during drying to produce pellets of higher porosity and of greater mean diameter. On the other hand, the evaporation of the fluid in mono-molecular layer, followed by the migration of the water to the surface of the pellets, through capillarity, took place through a slow and less drastic process in drying by the oven or desiccation with silica-gel. This could be the reason for the highest shrinkage and lower porosity of the pellets in these latter techniques. The porous pellets became weak, deformable, less strainable, and with lower 'elastic modulus'. The porous pellets again needed a higher compaction pressure and work of compaction to produce tablets of the same mass and dimensions. This indicated their compressibility, which helped them to produce stronger compacts with the a slightly higher volumetric elastic recovery. Also shown by the results in chapter 5 are the effects of pellet size on their mechanical properties. Their strength, deformability, linear strain, and 'elastic modulus' were observed to decrease with an increase of the mean pellet size. Their compaction mechanism, however,

seems to be similar as illustrated by the same in die compaction pressures and the same slopes for the upper portion of the Heckel plot. The tensile strength of the compacts increased with an increase of pellet size, while the volumetric elastic recovery decreased.

The application of an aqueous dispersion of ethyl cellulose coating (chapter 6) demonstrated that with the increase of the coating levels the values of the tensile strength of GMS or glycerol containing pellets increased, while those of lactose containing pellets or those pellets produced with ethanol reduced. The deformability of the pellets increased with the increase of the coating material applied, but to different extent based on the nature of the core pellet. The compressibility of the pellets increased with the increase in the amount of the coating material added. The increase in coating levels was also observed to increase the tensile strength of the compacts produced from all types of pellets. From the dissolution test of the different coated drug pellets and compressed by different pressure, it was possible to learn that the mechanical properties of the core pellets greatly affected the integrity of the coating film after compaction. In GMS containing pellets, which had the least variation in mechanical properties with different coating levels, increase in coating levels had relatively reduced drug release rates at all compaction pressures indicating the restriction of film rupture. Moreover, the ethyl cellulose was observed to serve as a cushion to reduce the fracture of pellets during compaction in all formulations and the fusion of the pellets in the presence of the coat helped some formulations to form rigid compacts.

This work has shown that the determination of Young's modulus of elasticity of the pellets from the diametral compression tests using conventional tablet crushing equipments was insufficiently sensitive for the production and accurately evaluation of the elastic portion of the deformation (chapter 3). This resulted in an underestimated value of the actual elastic modulus when the values are compared to those determined by dynamic mechanical analysis (chapter 7). These two techniques had a similar rank order and comparable proportion in deviation of the factors effect on elastic modulus. However, the absolute value of the elastic modulus determined by DMA was about 20-fold higher than that from the CT-5. The results from the static scan using a DMA is accurate, for the slope is determined from the real elastic region (less than 5% strain) and the stress/strain curve formed was nearly linear. In the diametral compression test using CT-5, however, the slope was determined from the whole range of the stress/stain curve. At the higher region of compression, plastic deformation of

the pellets might have occurred to strain the pellets to a greater extent without significant increase in pressure, as a result the elastic modulus might have been underestimated. The effect of the factors on the storage modulus measured at the fixed dynamic force during dynamic scan was proportional to that of elastic modulus determined by the static scan. The values of elastic modulus was, however, about 50-fold higher than that of storage modulus, indicating the variation in the force range at which these values were determined. From the dynamic scan, increase in the values of storage modulus and the decrease in phase angle were obtained with the same rank order starting from pellets containing lactose, only MCC, produced with ethanol, containing GMS to those containing glycerol. This indicates an increase in the visco-elasticity of the pellets in the same order. Lactose containing pellets needed a high dynamic force to produce a linear relation between the storage modulus and dynamic force. The same pellets also had the greatest change in storage modulus per unit dynamic force. These observations may be related to the greatest yield strength and highest rigidity of pellets produced with lactose. At all coating thickness the rank order for the dynamic force at the start of the linear curve had the same value to that of uncoated pellets. With the increase in the coating thickness, there was a general trend to increase the dynamic force at the start of the linear curve between the storage modulus and dynamic force. The storage modulus of the coated pellets at 600 mN dynamic force had the same rank order to those of uncoated. With the increase of the coating material up to 10%w/w, the storage modulus of the pellet from the different formulations increased. At 20w/w coating thickness, however, all the formulation factors had the same values suggesting that at this high level of coating, the observed property could have been that of the coating material itself. From these results it is possible to conclude that the plastic deformation of the pellets could only be determined from the dynamic scan using the dynamic mechanical analyser. The 'deformability' value calculated form the force/displacement curve obtained during diametral compression of the pellets does not reflect the plastic property of the pellets for it does not identify the possible structural recovery. The only feasible technique is the one which subjects the specimen to a stress/relaxation cycle and could determine the dissipated energy in terms of loss modulus or phase angle, that is DMA. For a screening purpose of materials of a considerable variation in viscoelastic property, however, the 'deformability' value form the diametral compression test could be used as brittle materials would snap after a very limited strain.

With the increase of the compaction pressure, the surface roughness parameters measured in chapter 8, it was found that the mean rugosity values of the compacts reduced for pellets containing GMS, lactose and those produced with ethanol. This provides evidence of an increase in deformability. GMS containing pellets had the lowest values, which was in agreement with the smoothest compact surface observed on the electron micrograph. Glycerol containing pellets, however, had the highest mean rugosity value at all levels and pressures used. This could be because these pellets did not cohere with each other, resulting in the space between them being distinct and deep. Thus, the plasticity of these pellets, as was indicated by the phase angle, was dominated by the prominent grooves due to lack of coherence. The lower mean R_p/R_t ratio of these pellet compacts, compared to those pellet compacts produced with ethanol or lactose, illustrated the flatness of the pellets containing glycerol as a result of plastic flow. The results were consistent at all compaction pressures and formulation factor proportions as well as tablet sides. The mean rugosity values for all pellet compacts was reduced after coating, except for the GMS containing pellets, which produced the smoothest compact before coating. In glycerol containing formulations, the gap between the pellets was filled with the coating material and the rugosity value reduced to the greatest extent. In GMS pellets, however, the surface roughness increased due to protrusion of some asperities with coating as was illustrated by the increase in R_p/R_t ratio. From these results, it is possible to conclude that non-contact laser profilometry provides a useful estimation of the permanent structural change or plastic deformability of the pellets after compaction. The surface roughness values were found to be comparable to the deformability values obtained form the pressure/displacement profiles during diametrical compression, however, the surface roughness parameters could be considered more reliable as they were determined after 48 hours of compaction to give time for the elastic expansion of the pellet, while the previous technique includes elastic deformability of the pellets as well. The values obtained for the coated and uncoated drug pellets were reasonably comparable to those obtained in terms of phase angle from dynamic scan of the DMA. The R_p/R_t ratio values of all the pellet compacts ranged from 0.40 to 0.56 indicating that the shape of the irregular part of the surface was low and broad based wavelike structure rather than sharp protrusions. This supports the concept of determining the plastic deformability of the pellets from the surface roughness parameters obtained using the profilometer.

In general, this work provided an evidence on the importance of an in-depth understanding

of the mechanical properties of the pellets in accurately predicting the tablet's behaviour and its optimization. The factors which produced porous, deformable and weak pellets had stronger tablets with lower volumetric elastic recovery. In methodological consideration, the application of DMA for determining the visco-elastic properties and the application of non-contact laser profilometer in determining the permanent structural change of the pellets after compaction have been established.

CHAPTER - TEN

FUTURE WORK

The role that pellet strength plays during the development of high-quality compacts has been investigated. A number of procedures that attempt to evaluate the mechanical properties of pellets have been reviewed. In addition, various theoretical and mathematical expression designed to explain the strength of the pellets has been utilised. However, this work has left some unanswered questions. In an attempt to complete the picture, a thorough study needs to be made to understand and explain the fundamental structural changes that influence the mechanical strength of these pellets. Moreover, the following brief suggestion for future works can be proposed.

The characterization of the surface nature of the pellets form the different formulations in terms of surface free energy could allow one to explain the consolidation behaviour of the compacts. For this reason, the spreading coefficient of the materials over each other could be investigated based on the work of adhesion and cohesion.

Pellets of known mechanical properties can be arranged in some designed way (eg. cubic or rhombohedral arrangements) inside a die and the change in shape of the pellets as well as lateral transmission of the pressure can be monitored against the axial pressure. Moreover, the change in pellet contact area, hence pressure concentration can be compared against the strength of the compacts as well as the axial pressure.

The work presented here has achieved a goal to investigate the effects of a coating material in the form of an aqueous polymer dispersion (Surelease®) on the mechanical properties of the pellets. However, an extensive study on the mechanical properties of different coating films formed from solutions, plus the influence of the presence and types of plasticizers and their suitability to pellets of different mechanical properties also needs more attention.

BIBLIOGRAPHY

Abdullah, E. C., and Geldart, D. (1999) The use of bulk density measurements as flowability indicators. Powder Technol. **102**, 151-165.

Adams, M. J., Mullier, M. A., and Seville, J. P. K. (1994) Agglomerate strength measurement using a uniaxial confined compression test. Powder Technol. **78**, 5-13.

Adeyeye, C. M., and Price, J. C. (1994) Development and evaluation of Sustained-Release Ibuprofen-Wax Microspheres. II. In Vitro Dissolution Studies. Pharm. Res. **11**, 575-579.

Ahange G., Schwrtz, G.B. and Schnaare R.L. (1990) Effects of spheronization technique on drug release from uncoated beads. Drug Dev. Ind. Pharm. **16**, 1171-1184.

Ahuja, S. K. (1977) The critical stresses of brittle and ductile polymeric particles. Powder Technol. **16**, 17-22.

Alderborn, G. And Nystrom, C.(1996) Nomenclature. In: Pharmaceutical Powder Compaction Technology. Eds. G. Alderborn, and C. Nystrom, Marcel Dekker, New York. pp vii-viii.

Alderborn, G. and Wikberg, M. (1996) Granule property. In: Pharmaceutical Powder Compaction Technology. Eds. G. Alderborn, and C. Nystrom, Marcel Dekker , New York. pp. 326-334.

Allen, M., Brown, G. J., and Miles, N. J.(1995) Measurement of boundary fractal dimensions: review of current techniques. Powder Technol. **84**, 1-14.

Andronis, V. and Zografi, G.(1997) Molecular modulity of supercooled amorphous indomethacin, determined by dynamic mechanical analysis. Pharm. Res. **14**, 410-414.

Armstrong, N. A., and Haines-Nutt, R. F. (1972) Elastic recovery and surface area changes in compacted powder system. J. Pharm. Pharmacol. **24** (Suppl.), 135P-136P.

Arwidsson, H., Johansson, B.(1991) Application of intrinsic viscosity and interaction constant as a formulation tool for film coating. Part 3. Mechanical study on free ethyl cellulose films, cast from organic solvents. Int. J. Pharm. **76**, 91- 97.

Aulton, M.E., Dyer, A.M., and Khan K.A. (1994) The strength and compaction of millispheres: The design of a controlled-release drug delivery system for ibuprofen in the form a tablet comprising compacted polymer-coated millispheres. Drug Dev. Ind. Pharm. **20**, 3069-3104.

Baert, L., and Down, G. R. B. (1994) Comparison of two mechods of instrumenting a small-scale basket extruder. Int. J. Pharm. **107**, 209-212.

Baert, I., and Remon, J. P.(1993) Influence of amount of granulation liquid on the drug release from pellets made by extrusion-spheronization. Int. J. Pharm. **95**, 135-141.

Baert, L., Remon, J. P., Elbers, J. A. C. and Van Bommel, E. M. G.(1993) Comparison between gravity fed extruder and a twin screw extruder. Int. J. Pharm. **99**, 7-12.

Bagley, E. B. (1957) End correction in the capillary flow of poly ethylene. J. Appl. Physics. **28**, 624-627(through Harrison, 1982).

Bains, D., Boutell, S. L., and Newton, J. M.(1991) The influence of moisture content on the preparation of spherical granules of barium sulphate and microcrystalline cellulose. Int. J. Pharm. **69**, 233-237.

Bansal, P., Vasireddy, S., Plakogiannis, F., Parikh, D. (1993) Effect of compression on the release properties of polymer coated niacin granules. J. Control. Rel. **27**, 157-163.

Barrau, J. P., Bataille, B., and Jacob, M. (1993) Influence of spheronizer load in extrusion/spheronization process. Pharm. Tech. Int. **5** (9), 66-70.

Basit, A. W.(2000) Oral colon-specific drug delivery using Amylose-based film coating. Pharm. Technol. Eur. **21** (2), 30-36.

Basit, A. W., Newton, J. M., and Lacey, L. F.(1999) Formulation of ranitidine pellets by extrusion -spheronization with little or no microcrystalline cellulose. Pharm. Dev. Technol. **4**, 499-505.

Bassam, F., York, P., Rowe, R. C., and Roberts, R. J.(1988) Effect of particle size and source on variability of Young's modulus of microcrystalline cellulose powders. J. Pharm. Pharmacol. **40**, 68P.

Bassam, F., York, P., Rowe, R. C., and Roberts, R. J.(1990) Young's modulus of powder used as pharmaceutical excipients. Int J. Pharm. **64**, 55-60.

Bataille, B., Ligarski, K., Jacob, M., Thomas, C., and Duru, C. (1993) Study of the influence of spheronisation and drying conditions on the physico-chemical properties of neutral spheroids containing Avicel PH 101 and lactose. Drug Dev. Ind. Pharm. **19**, 653-671.

Bechagaard, H and Ladefoged, K. (1978) Distribution of pellets in the gastrointestinal tract. The influence of transit time exerted by the density or diameter of pellets. J. Pharm. Pharmacol. **30**, 690-692.

Bechagaard, H., and Nielson, G. H.(1978) Controlled release multiple units and sing-unit doses. Drug Dev. Ind. Pharm. **4**, 53-67.

Bechard, S. R., and Leroux, J. C. (1992) Coated pelletized dosage forms: Effect of compaction on drug release. Drug Dev. Ind. Pharm. **18**, 1927-1944.

Beckert, T. E., Lehmann, K., and Schmidt, P. C.(1996) Compression of enteric-coated pellets to disintegrating tablets. Int. J. Pharm. **143**, 13-23.

Beekman, W. J. (2000) Measurement of the mechanical strength of granules and agglomerates, PhD thesis, Delft University of Technology, Netherlands.

Belda, P. M., and Mielck, J. B.(1998) The tableting machine as an analytical instrument: qualification of the measurement devices for punch forces and validation of the calibration

procedures. Eur. J. Pharm. Biopharm. **46**, 381-395.

Benbow, J. J., and Bridgwater, J. (1993) Paste Flow and Extrusion, Clarendon press, Oxford.

Berggren, J., and Alderborn, G. (2001a) Drying behaviour of two sets of microcrystalline cellulose pellets. Int. J. Pharm. **219**,113-126.

Berggren, J., and Alderborn, G. (2001b) Effect of drying rate on porosity and tableting behaviour of cellulose pellet. Int. J. Pharm. **227**, 81-96.

Bianchini, R., Bruni, G., Gazzaniga, A., and Vecchio, C. (1992) Influence of extrusion-spheronization processing on the physical properties of d-indobufen pellets containing pH adjusters. Drug Dev. Ind. Pharm. **18**, 1485-1503.

BinBaie, S., Newton, J. M., and Podczeck, F.(1996) Characterization of the mechanical properties of pharmaceutical materials. Eur. J. Pharm. Biopharm. **43**, 138-141.

Bodmeier, R.(1997) Tableting of coated pellets. Eur. J. Pharm. Biopharm. **43**, 1-8.

Bodmeier, R.,and Paeratakul, O.(1994) Mechanical properties of dry and wet cellulosic and acrylic polymer films prepared from aqueous colloidal polymer dispersions. Pharm. Res. **11**, 882-888.

Bolton, S.(1990) Pharmaceutical Statistics. Practical and Clinical Applications, 2nd Ed. Marcel Dekker, New York. pp. 132-154.

Boutell, S. L. (1995) Factors influencing the preparation of spherical granules by extrusion/spheronisatoin, Ph. D. Thesis, University of London. UK.

British Standard 1134 (1972) Method for the assessment of surface texture. British Standard Institute, London.

Celik, M.(1994) Compaction of multiparticulate oral dosage forms. In: Multiparticulate Oral

Drug Delivery. Ed. I. Ghebre-Sellassie. Marcel Dekker, New York. pp. 181-215.

Celik, M., and Marshall, K.(1989) Use of compaction simulator system in tableting research. Part 1. Introduction to and initial experiment with the system. Drug Dev. Ind. Pharm. **15**, 759-800.

Chang, R. K., and Rudnic E. M. (1991) The effect of various polymeric coating systems on the dissolution and tableting properties of potassium chloride microcapsules. Int. J. Pharm. **70**, 261-270.

Chang, R. K., Hisiao, C. H., and Robinson, J. R.(1987) Review of aqueous coating techniques and preliminary data on release from a theophylline product. Pharm. Technol. **11** (3), 56-68.

Chapman, S. R. (1985) Influence of process variables on the production of spherical granules. PhD Thesis, University of London. UK.

Chapman, S. R., Rowe, R. C., and Newton J. M.(1988) Characterization of the sphericity of particles by the one plane critical stability. J. Pharm. Pharmacol. **40**, 503-505.

Chetty, D. J., and Dangor, C. M. (1994) Development of oral controlled release pellet formulation of diethylpropion hydrochloride. Drug Dev. Ind. Pharm. **20**, 993-1005.

Chohan, R. K., and Newton, J. M. (1996) Analysis of extrusion of some wet powder masses used in extrusion/spheronization. Int. J. Pharm. **131**, 201-207.

Chopra, R., Newton, J. M., Alderborn, G., and Podczeck, F.(2001), Preparation of pellets of diffeent shape and their characterisation. Pharm. Dev. Technol. **6**, 495-503.

Chuichi, M.(1993) Standardization of measuring methods of the strength of Agglomerates (JIS), 6th International symposium on agglomeration, Novermber 15-17, Nogoya, Japan. pp. 890-895.

Church, M., and Kennerley, J. W. (1983) A comparison of the mechanical properties of pharmaceutical materials obtained by flexure testing of compacted rectangular beams. J. Pharm. Pharmacol. **35**, 43P.

Cimicata, L. E. (1951) How the manufacture and polish smallest pan goods-nonpareil seeds, Confectioners J. 41-43 (through Ghebre-Selassie (1989).

Cole, G., Hogan, J., Aulton, M. (1995) Pharmaceutical Coating Technology, Taylor and Francis. London.

Conine, J. W., and Hadley, H. R. (1970) Preparation of solid pharmaceutical spheres. Drug Cosmetic Ind. **106**(4), 38-41.

Cutt, T., Fell, J. T., Rue, J. P., and Spring, M. S.(1986) Granulatoin and compaction of a model system I. Granule properties. Int. J. Pharm. **33**, 81-87.

Danielson, D. W., Morehead, W. T. and Rippie, E. G. (1983) Unloading and post compression viscoelastic stress versus strain behaviour of pharmaceutical solids. J. Pharm. Sci. **72**, 342- 345.

David, S. T., and Augsburger, L. L.(1974) Flexure test for determination of tablet tensile strength. J. Pharma. Sci. **63**, 933-937.

David, S. T., and Augsburger, L. L. (1977) Plastic flow during compression of directly compressible fillers and its effect on tablet strength. Int. J. Pharm. **66**, 155-159.

De Blaey, C. J. (1971)Measurement of the work involved in compression of pharmaceuticals. Ph. D. Thesis, University of Leiden, Netherlands.

Donbrow, M., and Friedman, M. (1975) Enhancement of permeability of ethyl cellulose films for drug penetration. J. Pharm. Pharmacol. **27**, 633-646.

Donbrow, M., and Samuelov, Y. (1980) Zero order drug delivery from double layered porous

films: release rate profiles from ethyl cellulose, hydroxy propyl cellulose and ploy ethylene glycol mixture. J. Pharm. Pharmacol. **32**, 463-470.

Duberg, M., and Nystrom, C. (1982) Studies on direct compression of tablets. Part VI. Evaluation of methods for the estimation of particle fragmentation during compaction. Acta Pharm. Suec. **19**, 421-436.

Duncan-Hewitt, W. C., and Weatherly, G. C. (1989) Evaluating the fracture toughness of sucrose crystals using microindenter techniques. Pharm. Res. **6**, 373-378.

Dyer A.M., Khan K.A., and Aulton M. E. (1994) Effects of the drying method on mechanical and release properties of pellets prepared by extrusion-spheronization, Drug Dev. Ind. Pharm **20**, 3045-3068.

Elbers, J. A. C. Bakkenes, H. W., and Folkens, J. G. (1992) Effect of amount and composition of granulation liquid on mixing, extrusion and spheronization. Drug Dev. Ind. Pharm. **18**, 501-517.

Erck., R. A. (1994) Pin-pull adhession measurements of copper film on ion-bombarded alumina. Thin Solid Films **253**, 362-366.

Eriksson, M., Alderborn, G., Nystrom, C., Podczeck, F., and Newton, J. M.(1997) Comparison between and evaluation of some methods for the assessment of the sphericity of pellets. Int. J. Pharm. **148**, 149-154.

Erkoboni, D. F.(1997) Extrusion-Spheronization as a granulation technology. In: Pharmaceutical Granulation Technology. Ed. Parikh, K. Marcel Dekker, New York. pp. 333-368.

Fell, J. T., Newton, J. M.(1970a) Determination of tablet strength by diametral compression test. J. Pharm. Sci.**59**, 688-691.

Fell, J. T., Newton, J. M., (1970b) The prediction of the tensile strength of tablets. J. Pharm.

Pharmacol. **22**, 249-248.

Fell, J. T., Newton J.M. (1971) Assessment of compression characteristics of powders. J. Pharm. Sci. **60**,1428-1429.

Fielden, K. E.(1987), Extruion and spheronization of Microcrystalline cellulose and lactose mixtures, PhD. Theses, University of London. UK.

Fielden, K. E., and Newton, J. M.(1992) Extrusion and extruders; In: Encyclopedia of Pharmaceutical Technology. Eds. J. E. Swarbrick, and J.C. Boylan. Marcel Dekker Inc. New York. Vol. 5, pp. 395-442.

Fielden, K. E., Newton, J. M., and Rowe, R. C.(1989) The effect of lactose particle size on the extrusion properties of microcrystalline cellulose-lactose mixtures. J. Pharm. Pharmacol. **41**, 217-221.

Fielden, K. E., Newton, J. M., and Rowe, R. C.(1992a) The influence of lactose particle size on spheronization of extrudate processed by a ram extruder. Int. J. Pharm. **81**, 205-224.

Fielden, K. E., Newton, J. M., and Rowe, R. C.(1992b) A comparison of the extrusion and spheronization behaviour of wet powder masses processed by a ram extruder and cylinder extruder. Int. J. Pharm. 81.225-233.

Fielden, K. E., Newton, J. M., and Rowe, R. C.(1993) The influence of moisture content on spheronization of extrudate processed by a ram extruder. Int. J. Pharm. **97**, 79-92.

Follonier, N., and Doelker, E. (1992) Biopharmaceutical comparison of oral multiple unit sustained-release dosage forms. STP Pharm. Sci. **2**, 141-158.

Fonner, D. E., Banker, G. S., and Swarbrick, J. (1966) Micromeritics of granular pharmaceutical solids II: Factors involved in the sieving of pharmaceutical granules. J. Pharm Sci. **55**, 576-583.

Fukumori, Y., (1994) Coating of multiparticulate using polymeric dispersions: formulation and processing considerations: In Multiparticulate Oral Drug Delivery. Ed. I. Ghebre-Sellassie. Marcel Dekker, New York. pp. 79-113.

Ghaly, E. S., and Ruiz, N. R.(1996) Compressibility characteristic of matrices prepared with ethyl cellulose aqueous dispersion. Drug Dev. Ind. Pharm. **22**, 91-95.

Ghebre-Sellassie, I., Gordon, R. H., Fawzi, M. B. and Nesbitt, R. U.(1985) Evaluation of a high-speed pelletization process and equipment. Drug Dev. Ind. Pharm. **11**, 1523-1541.

Ghebre-Sellassie, I. (1989) Pellets: a general overview. In: Pharmaceutical Pelletization Technology. Ed. I. Ghebre-Sellassie. Marcel Dekker Inc., New York. pp. 1-8.

Goodhart, F. W., Draper, J. R., and Ninger, F. C. (1973) Design and use of laboratory extruder for pharmaceutical granulation. J. Pharm. Sci. **62**, 133-136.

Gregg, S. T.,and Sing, K. S. W. (1982) Adsorption, Surface Area and Porosity, 2nd Edition. Harcourt Brace Jovanovich, London, England.

Habib, Y. S., Shangraw, R. F.(1997) Effect of different drying techniques on the physico-mechanical properties of beads containing microcrystalline cellulose produced by extrusion and spheronization. Pharm. Res. **14**, S14.

Harris, M. R., and Ghebre-Sellassie I.(1989) Formulaltion Variables: In Pharmaceutical Pelletization Technology. Ed. I Ghebre-Sellassie. Marcel Dekker Inc., New York. pp. 217-239.

Harrison, P. J. (1982) Extrusions of wet powder masses. Ph. D. Thesis, University of London.

Harrison, P. J., Newton, J. M., and Rowe, R.C. (1985a) The characterization of wet powder masses suitable for extrusion and spheronization, J. Pharm. Pharmacol. **37**, 686-691.

Harrison, P. J., Newton, J. M., and Rowe, R.C. (1985b) Flow defects in wet powder mass

extrusion; J. Pharm. Pharmacol. **37**, 81-83.

Harrison, P. J., Newton, J. M., and Rowe, R.C. (1987) The application of capillary rheometry to the extrusion of wet powder masses. Int. J. Pharm. **35**, 235-242.

Hasznos, L., Langer I., and Gyarmathy, M. (1992) Some factors influencing pellet characteristics made by extrusion-spheronization process Part I: effects on size characteristics and moisture content decrease of pellets. Drug Dev. Ind. Pharm. **18**, 409-437.

Hausner, H. H (1967) Friction conditions in a mass of metal powder. Int. Powder Met. **3**,7-13

Healy, A.M., Corrigan, O. I., and Allan, J. E. M. (1995) The effect of dissolution on the surface texture of model solid-dosage forms as assessed by non-contact laser profilometry, Pharm. Technol. Eur. 7 (9), 14-22.

Heckel, W. (1961a) An analysis of powder compaction phenomena. Trans. Metal. Soc. A.I.M.E. **221,** 671-675.

Heckel, W. (1961b) Density-pressure relationships in powder compaction. Trans. Metal. Soc. AIME. **221**, 1001-1008.

Helen, L. (1992). Evaluation of essential process variable of the NICA pelletising equipment, PhD. thesis, University of Helsinki, Finland.

Helen, L., and Yliruusi, J.(1993) Process variables of instant granulator and spheronizer. Part III: Shape and shape distributions of pellets. Int. J. Pharm **96**, 217-223

Helen, L., Yliruusi, J., Muttonen, E., and Kristoffersson, E. (1993a) Process variables of radial screen extruder. Part II. Size and size distribution of pellets, E., Pharm. Tech. Int. **5**(11) 44-53.

Helen, L., Yliruusi, J., Merkku, P., and Kristoffersson, E. (1993b) Process variables of instant granulator and spheronizer. Part I. Physical prperties of granules, extrudate and pellets. Int.

J. Pharm. **96**, 205-2216.

Hersey, J. A., Rees, J. E., Cole, E. T. (1973b) Density Changes in lactose tablets: J. Pharm. Sci. **62**, 2060-2063.

Hicks, D. C., and Freese, H. I. (1989) Extrusion and Spheronization Equipments. In: Pharmaceutical Pelletization Technology. Ed. I. Ghebre-Sellassie. Marcel Dekker, New York. pp.71-100.

Hiestand, E. N. (1989) The basis for practical applications of the tableting indices. Pharm. Tech. **13**(9), 54-66.

Hiestand, E. N. (1996) Rational for and the measurement of tablet indices. In: Pharmaceutical Powder Compaction Technology. Eds. G. Alderborn and C. Nystrom. Marcel Dekker, New York. pp. 219-245.

Hiestand, E. N., Bane, Jr., J. M., and Strzelinski, E. P. (1971) Impact test of hardness of compressed powder compacts. J. Pharm. Sci. **60**, 758-763.

Hiestand, E. N., and Peot, C. B. (1974) Tensile strength of compressed powders and an example of in compatibility as end point on shear yield locus. J. Pharm. Sci. **63**, 605-612.

Hiestand, E. N., and Smith , D. P. (1984) Indices of tableting perormance. Powder Technol. **38**, 145-159.

Hiramatsu, Y. and Oka, Y. (1966) Determination of the tensile strength of rock by compression test of an irregular test piece. Int. J. Rock Mech. Min. Sci. **3**, 89-99.

Horisawa, E., Komura, A., Danjo, K. and Otuska, A. (1995) Effect of granule strength of compressed tablet strength. Chem. Pharm. Bull. **43**, 2261-2263.

Houghton, G. W., Dennis, M. J., Rigler, E. D., and Parsons, R. L. (1984) Comparative pharmacokinetics of ketoprofen derived form single oral doses of ketoprofen capsules or a

novel sustained release pellet formulations. Biopharm. Drug Dispos. **5**, 203-209.

Hunter, B. M., and Ganderton, D.(1973), The influence of pharmaceutical granulation of the type of capacity of mixers. J. Pharm. Pharmacol. Suppl. **25**, 71P-78P.

Iley, W. J. (1991) Effect of particle size and porosity on particle film coatings. Powder Technol. **65**, 441-445.

Jalal, I. M., Malinowski, H. J., and Smith, W. E. (1972) Tablet granulations composed of spherical-shaped particles. J. Pharm. Sci. **61**, 1466-1468.

Jarosz, P., and Parrot, E. L.(1983) Comparison granule strength and tablet tensile strength. J. Pharm. Sci. **72**, 530-534.

Johansson, B., and Alderborn, G.(1996) Degree of pellet deformatin during compaction and its relationship to the tensile strength of tablets formed of microcrystalline cellulose pellets. Int. J. Pharm. **132**, 207-220.

Johansson, B. Alderbon, G.(1998) Effect of pellets size on degree of deformation and densification during compression and on compatibility of MCC pellets. Int. J. Pharm. **163**, 35-48.

Johansson, B., Wikberg, M., Ek, R., Alderborn, G. (1995), Compression behaviour and compactability of microcrystalline cellulose pellets in relationship to their pore structure and mechanical properties. Int. J. Pharm. **117**, 57-73.

Jones, D. M. (1994) Solution and Suspension layering. In: Multiparticulate Oral Drug Delivery. Ed. I. Ghebre-Sellassie. Marcel Dekker, New York. pp. 145-164.

Jones, D. S. (1999) Dynamic mechanical analysis of polymeric systems of pharmaceutical and biomedical significance. Int. J. Pharm. **179**, 167-178.

Juslin, M., Turakka, L., Puumalainen, P. (1980) Controlled release tablets. Pharm. Ind. **42,**

829-832.

Kawakita, K.(1956) Jpn. Science, in Japanese, **26** (3), 149-153, through Kawakita, K., and Ludde, K. H., Some consideration on powder compression equations. Powder Technol. **4,** (1970/1971) 61-68.

Kawakita, K., and Ludde, K. H. (1970/1971) Some consideration on powder compression equations. Powder Technol. **4**,61-68.

Kerridge, J. C., and Newton, J. M.(1986), The determination of the compressive Young's modulus of pharmaceutical materials. J. Pharm. Pharmacol. **38**: Suppl, 79P.

Khan, K. A. and Musikabhumma, P.(1981) Effect of slugging pressure on the properties of granules and tablets prepared form potassium phenethicillin. J. Pharm. Pharmacol. **33**, 627-631.

Kibbe, A. H. (2000) Lactose: In Handbook of Pharmaceutical Excipients. Ed. A. H. Kibbe. American Pharmaceutical Association and Pharmaceutics Press, London. pp. 276-285.

Kleinebudde, P. (1994a) , Shrinking and swelling properties of pellets containing MCC and low substituted hydroxy propyl cellulose. Part I. Shrinking properties. Int. J. Pharm. **109**, 209-219.

Kleinebudde, P. (1994b) , Shrinking and swelling properties of pellets containing MCC and low substituted hydroxy propyl cellulose. Part II. Swelling properties. Int. J. Pharm. **109**, 221-227.

Kristensen, H. G., and Schaefer, T. (1987) Granulation. A review of pharmaceutical wet-granulation. Drug Dev. Ind. Pharm. **13**, 803-827.

Krycer, I., Pope, D.G., and Hersey, J. A. (1982) An evaluation of techniques employed to investigate powder compaction behaviour. Int. J. Pharm. **12**, 113-134.

Kuno, H., Okada, J.(1982) The compaction Process and Deformability of Granules. Powder Technol. **33**, 73-79.

Leuenberger, H. (1982) Compressibility and compactability of powder system. Int. J. Pharm. **12**, 41-55.

Lahmann, K.and Steuernag, S.(1989), Chemistry and application properties of poly-methacrylate coating systems. In: Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms. Ed. J. W. McGinity. Marcel Dekker, New York. pp. 153-245.

Linder, H. and Klienbudde, P. (1994) Use of powdered cellulose for production of pellets by extrusion/spheronization. J. Pharm. Pharmacol. **46**, 2-7.

Lopez-Rodriguez, F. J., Torrado, J. J., Torrado, S., Escamilla, C., Cadorniga, R., Augsburger, L. L. (1993) Compression behaviour of acetyl salicylic acid pellets. Drug Dev. Ind. Pharm. **19**, 1369-1377.

Lovgren, K., and Lundberg, P. L. (1989) Determination of sphericity of pellets prepared by extrusion and spheronization and the impact of some processing parameters. Drug Dev. Ind. Pharm. **15**, 2375-2392.

Lundqvist, A. E. K., Podczeck, F., and Newton, J. M. (1997) Influence of disintegrant type and proportion on the properties of tablets produced from mixtures of pellets. Int. J. Pharm. **147**, 95-107.

Lundquvist, A. E. K., Podczeck, F., and Newton, J. M. (1998) Compaction of, and drug release from, coated drug pellets mixed with other pellets. Eur. J. Pharm. Biopharm. **46**, 369-379.

Maarschalk, K. V., Vromans, H., Bolhuis, G. K., and Lerk, C. F. (1996) The effect of viscoelasticity and tabletting speed on consolidation and relaxation of a viscoelastic material. Eur. J. Pharm. **42**, 49-55.

Maarschalk, K. V., Zuurman, K., Steenbegen, M. J. V., Hennink, W. E., Vromans, H., Bolhuis, G. K., and Lerk, C. F. (1997) Effect of compaction temperature on consolidation of amorphous copolymers with different grass transition temperature. Pharm. Res. **14**, 415-419.

Maganti, L., and Celik, M. (1993) Compaction studies on pellets: Part 1. Uncoated pellets. Int. J. Pharm. **95**, 29- 42.

Maganti, L., and Celik, M. (1994) Compaction studies on pellets: Part 2. Coated pellets. Int. J. Pharm. **103,** 55-67.

Malinowski, H. J., and Smith, W. E.(1974) Effects of spheronization process variables on selected tablet properties. J. Pharm. Sci. **63**, 285-288.

Malinowski, H. J., and Smith, W. E. (1975) Use of factorial design to evaluate granulations prepared by spheronization. J. Pharm. Sci. **64**, 1688-1692.

Marshall, K. (1986) In: Theory and Pratice of Industrial Pharmacy, 3rd ed. (l. Lachman, H. Lieberman, and J. Kanig, Eds.), Lea and Febiger, Philadelphia. pp 66-94.

Marvola, M., Rajamiemi, M., Marttila, E., Vahervuo, K., and Sothmann, A. (1983) Effect of dosage form and formulation factors on the adherence of drugs to the oesophagus, J. Pharm. Sci. **72,** 1034-1037.

Mashadi, A. B. (1988) Mechanical Properties of compacted powders, PhD Thesis, University fo London, UK.

Mashadi, A. B., Newton, J. M. (1987a) Assessment of the mechanical properties of compacted sorbitol instant. J. Pharm. Pharmacol. Suppl. **39**, 676P.

Mashadi, A. B., Newton, J. M. (1987b) Characterizing of mechanical properties of microcrystalline cellulose: a fracture mechanics approach. J. Pharm. Pharmacol. **39**, 961-965.

McGinity, J. W. (1989) Aqueous Polymeric Coating for Pharmaceutical Dosage Forms.

Marcel Dekker. New York.

Melia, C. D., Washington, N., and Wilson, C. G.(1994) Advantages and disadvantages: In Martiparticulate Oral Dosage Forms: Technology and biopharmaceutics,(Melia, C. D., Washington, N., and Wilson, C. G. Eds.), Scottish Academic Press Ltd., Edinburgh. pp. 135-142.

Messing, G. L., Markhoff, C. J., and McCoy, L. G. (1982) Characterisation of ceramic powder compaction. Am. Ceram. Soc. Bull. **61**, 857-860.

Millili, G.P., and Schwartz, J. B. (1990) The strength of microcrystalline cellulose pellets: The effect of granulating with water ethanol mixtures. Drug Dev. Ind. Pharm. **16**, 1411-1426.

Millili, G. P., Wigent, R. J., and Schwartz, J. B. (1990) Autohesion in pharmaceutical solids. Drug Dev. Ind. Pharm **16**, 1383-2407.

Mullier, M. A., Seville, J. P. K., and Adams, M. J.(1991) The effect of agglomerate strength on attrition during processing. Powder Technol. **65**, 321-333.

Narisawa, S., Yoshino, H., Harakawa, Y., and Noda, K. (1994) Porosity-controlled ethyl cellulose film coating. IV. Evaluation of Mechanical strength of the porous ethyl cellulose film. Chem. Pharm. Bull. **42**, 1491-1495.

Newton, J. M. (1994) Extrusion/Spheronization. In: Powder Technology and Pharmaceutical Processes. Eds. Chulia, D., Deleuil, M., and Pourcelot, Y. Elsevier, Amsterdam, pp. 391-401.

Newton, J. M.(1996) Spheronization; In: Swarbrick, J. E., Boylan, J.C. (Ed): Encyclopedia of Pharmaceutical Technology. Marcel Dekker Inc., Vol.14, New York. pp.181-205.

Newton J.M.(1999) New Development in Pellets, Progress in Pharmaceutical Technology and Biopharmaceutics, Stuttgart. pp. 39-45.

Newton, J. M. (2000) Progress in Pellets, Multipartulate, multipurpose dosage forms: Pharm.

Tech. Europe. p-40.

Newton, J.M., Alderborn, G., and Nystrom, C. (1993a) A method of evaluating the mechanical characteristics of powders from the determination of the strength of compacts. Powder Technol. **72**, 97-99.

Newton, J. M., Chapman, S. R., and Rowe, R. C.(1995a) The influence of process variables on the preparation and properties of spherical granules by the process of extrusion and spheronization. Int. J. Pharm. 120, 101-109.

Newton J. M., Chapman, S. R., and Rowe, R. C. (1995b) Assessment of the scale-up performance of extrusion/spheronization process. Int. J. Pharm. **120**, 95-99.

Newton, J. M., Chow, A. K., Jeewa, K. B. (1992b) Effect of excipient source on spherical granules made by extrusion/spheronization Pharm. Tech. Int. **4** (11) 52-58.

Newton, J. M., Ingham, S., and Onabajo, C. O. (1986) The effect of strain rate on the mechanical strength of tablets. Acta Pharm. Technol. **32**, 61-62.

Newton, J M., and Stanley, P. (1974) Characterization of the mechanical strength of tablets. J. Pharm. Pharmacol. **26** Suppl. 61P.

Nicklasson, F., and Alderborn, G. (1999) Modulation of the tableting behaviour of microcrystalline pellets by incorporation of polyethylene glycol. Eur. J. Pharm. Sci. **9**, 57-65.

Nicklasson, F., Johansson, B., and Alderborn, G. (1999a) Occurrence of fragmentation during compression of pellets prepared from a 4:1 mixture of dicalcium phosphate dihydrate and microcrystalline cellulose. Eur. J. Pharm. Sci. **7**, 221-229.

Nicklasson, F., Johansson, B., and Alderborn, G. (1999b) Tableting behaviour of pellets of a series of porosities-a comparison between pellets of two different compositions. Eur. J. Pharm. Sci. **8**, 11-17.

Niskanen, M., Niskanen, T., Ylirussi, J.K.; Kristoffersson, E. (1990) Pelletizaton in a centrifugal granulator, Part 1, Effects of binder-soldution: Pharm. Tech. Int. **2** (10), 22-28.

Nystrom, C., Malmquist, K., Mazur, J., Alex, W., and Holzer, A.W. (1978) Measurement of axial and radial tensile strength of tablets and their relation to capping, Acta Pharm. Suec., **15**, 226-232.

O'Connor, R. E., Holinez, J., and Schwartz, J. B. (1984) Spheronization I: Processing and evaluation of spheres prepared from commercially available excipients. Am. J. Pharm. **156**, 80-87.

O'Connor, R. E., and Schwartz, J. B. (1989) Extrusion and spheronization technology. In: Pharmaceutical Pelletization Technology. Ed. I.Ghebre-Sellasie. Marcel Dekker, New York. pp. 187-216.

Okhamafe, A. O., and York, P. (1988), Studies of interaction phenomena in aqueous-based film coatings containing soluble additives using thermal analysis technology. J. Pharm. Sci. **77,** 438-443.

Otsuka, M.; Gao, J.; Matsuda, Y. (1994) Effect of amount of added water during extrusion spheronization process on pharmaceutical properties of granules. Drug Dev. Ind. Pharm. **20**, 2977-2992.

Ozkan, N., and Briscoe, B. J. (1996) The surface topography of compacted agglomerates: a means to optimize compaction conditions. Powder Technol. **86,** 201-207.

Paronen, P. and Ilkka, J. (1996) Porosity-Pressure functions; In Pharmaceutical Powder Compaction Technology. Eds G. Alderborn and C. Nystrom. Marcel Dekker, New York. pp.55-77.

Peh, Kok-Khiang, and Yuen, Kah-Hay (1995) Development and in vitro evaluation of a novel multi particulate matrix controlled release formulation of theophylline. Drug Dev. Ind. Pharm. **21**, 1545-1555.

Pinto, J. F.(1992) Formulation and tableting of controlled release pellets produced by extrusion-spheronization, PhD. Thesis, University of London. UK.

Pinto, J. F., Buckton, G., Newton, J. M. (1993) The influence of four selected processing and formulation factors on the production of spheres by extrusion and spheronization. Int. J. Pharm **83**, 187-196.

Pitt, K. G., Newton, J. M. and Stanley, P. (1987) The effect of punch velocity on the tensile strength of aspirin tablets. J. Pharm. Pharmacol. **39**, 65P.

Podczeck, F. (1998a) Particle-particle Adhesion in Pharmaceutical Powder Handling, Imperial College Press, London. .

Podczeck, F. (1998b) Measurement of surface roughness of tablets made from polyethylene glycol powders of various molecular weight, Pharm. Pharmacol. Commun. **4**, 179-182.

Podczeck, F. (2001) , The end of Marathon?, Int. J. Pharm. **227**, 1-3.

Podczeck, F., and Newton, J.M. (1992a) Determination of the Young's modulus of different microcrystalline cellulose products, Pharmazie **47**, 387-388.

Podczeck, F., and Newton, J. M. (1992b) , Determination of the critical stress intensity factor and fracture toughness of different microcrystalline cellulose products, Pharmazie **47**, 462-463.

Podczeck, F., and Newton, J. M. (1994) Shape factor to characterize the quality of spheroids. J. Pharm. Pharmacol. **46**, 82-85.

Podczeck, F., and Newton, J. M. (1995) The evaluation of a three-dimensional shape factor for the quantitative assessment of the sphericity and surface roughness of pellets. Int. J. Pharm. **124**, 253-259.

Podczeck, F., Chopra, R., and Newton, J. M. (1995) The use of two- and three-dimensional

shape factor to characterize the sphericity of pellets. In Proc. 1st World Meeting APGI/APV, Budapest. pp. 351.

Podczeck, F., Rahman, S.R., Newton, J. M. (1999a) Evaluation of a standardised procedure to assess the shape of pellets using image analysis. Int. J. Pharm. **192**, 123-138.

Podczeck, F., Brown, S., Newton, J. M.(1999b) Monitoring film coating with surface profiometry. Pharm. Technol. Int. **23**(5) 48-56.

Podczeck, F., Brown, S., and Newton, J. M. (1999c), The influence of powder properties and tableting conditions on the surface roughness of tablets. Part. Part. Syst. Charact. **16**, 185-190

Porter, S. C. (1982) The practical significance of the permeability and mechanical properties of polymer films used for the coating of pharmaceutical solid dosage forms. Int. J. Pharm. & Prod. Mfr. **3**, 21-25.

Porter, S. C. (1989) Controlled-release film coatings based on ethyl cellulose. Drug Dev. Ind. Pharm. **15**, 1495-1521.

Price, J. C.(2000) Glycerin. In: Handbook of pharmaceutical excipients. Ed. Kibbe, A. H. American Pharmaceutical Association and Pharmaceutics Press, London. pp. 220-222.

Radebaugh, G. W., and Simonelli, A. P. (1983) Phenomenological viscoelasticity of Heterogenous pharmaceutical semisolids. J. Pharm. Sci. **72**, 415-422.

Radebaugh, G. W., Babu, S. R., and Bondi, J. N. (1989) Characterization of the viscoelastic properties of compacted pharmaceutical powders by a novel nondestructive technique. Int. J. Pharm. **57**, 95-105.

Ragnarsson, G., and Sjogren, J. (1985) Force displacement measurements in tableting. J. Pharm. Pharmacol. **37**, 145-150.

Ragnarsson, G., Sandberg, A., Jonsson, U. E., Sjogren, J.(1987) Development of a new

controlled release metoprolol product. Drug Dev. Ind. Pharm. **13**, 1495-1509

Ragnarsson, G., and Johansson, M. O. (1988) Coated drug cores in multiple unit preparations influenced of particle size. Drug Dev. Ind. Pharm. **14**, 2285-2297.

Raines, C. L., Newton. J. M.; Rowe, R. C. (1989), Extrusion of microcrystalline cellulose formulations; In: Rheology of Food, Pharmaceutical and Biological Materials with General Rheology. Carter, R.E. (Ed). Elsevier Applied Science. London. pp. 240-257.

Ramberger, R., and Buger, A. (1985) The application of the Heckel and Kawakita equations to powder compaction. Powder. Technol. **43**, 1-9.

Rees, J. E., and Rue, P. J. (1978) Work required to cause failure of tablets in diametral compression, Drug Dev. Ind. Pharm. 4, 131-156.

Reynolds, A. D. (1970) A new technique for the production of spherical particles, Manuf. Chem. Aerosol News. **41**(6) 40-44.

Ridgway, K., Aulton, M. E., and Rosser, P. H. (1970) The surface hardness of tablets, J. Pharm. Pharmacol. **22**, 70S-78S.

Riippi, M., Antikainen, O., Niskanen, T., Yliruusi, J. (1998) The effect of compression force on surface structure, crushing strength, friability and disintegration time of erythromycin acistrate tablets. Eur. J. Pharm. Biopharm. **46**, 339-345.

Rippie, E. G., and Danielson, D. W.(1981) Viscoelastic stress/strain behaviour in pharmaceutical tablets: Analysis during unloading and post compression periods. J. Pham. Sci. **70**, 476-482.

Roberts. R. J., and Rowe, R. C. (1985) Effect of punch velocity on compaction of a variety of materials. J. Pharm. Pharmacol. **37**, 377- 384.

Roberts, R. J., and Rowe, R. C. (1986) The effect of the relationship between punch velocity

and particle size on the compaction behaviour of materials with varying deformation mechanics. J. Pharm. Pharmacol. **38**, 567-571.

Roberts, R. J., and Rowe, R. C. (1987) The compaction of pharmaceutical and other model materials-a pragmatic approach., Chem. Eng. Sci. **42**, 903-911.

Roberts, R. J., and Rowe, R. C.(1989) Determination of the critical stress factor (KIC) of microcrystalline cellulose using radially edge-cracked tablets. Int. J. Pharm. **52**, 213-219.

Roberts, R. J., Rowe, R. C., York, P. (1991) The relationship between Young's modulus of elasticity of organic solids and their molecular structure. Powder Technol. **65**, 139-146.

Roberts, R. J., and Rowe, R. C., York, P. (1993) Measurement of the critical stress intensity factor (KIC) of pharmaceutical powders using three point single edge notched beam (SENB) testing. Int. J. Pharm. **91**, 173-182.

Rowe, R.C. (1977) Adhesion of film coating to tablet surfaces-the effect of some direct compression excipients and lubricants. J. Pharm. Pharmacol. **29**, 723-236.

Rowe, R.C. (1978a) The measurement of the adhesion of film coatings to tablet surfaces: the effect of tablet porosity, surface roughness and film thickness. J. Pharm. Pharmacol. **30**, 343-346.

Rowe, R.C. (1978b) The effect of some formulation and processing variables on the surface roughness of film- coated tablets. J. Pharm. Pharmacol. **30**, 669-672.

Rowe, R.C. (1979) Surface roughness measurements on both uncoated and film-coated tablets. J. Pharm. Pharmacol. **31**, 473-474.

Rowe, R. C. (1981a) The crack of film coatings on film-coated tablets: a theoretical approach with practical implications. J. Pharm. Pharmacol. **33**, 423-427.

Rowe, R.C. (1981b), The effect of the particle size of an inert additive on the surface

roughness of a film-coated tablets. J. Pharm. Pharmacol. **33**, 1-4

Rowe, R. C. (1985) Spheronization: a novel pill-making process? Pharm. Int. **6**(5), 119-123.

Rowe, R. C. (1986), The effect of molecular weight of ethyl cellulose on drug release properties of mixed films of ethyl cellulose and hydroxy propyl methyl cellulose. Int. J. Pharm. **29,** 37-41.

Rowe, R. C. (2001), Strategies for formulation using intelligent software: in 4th International Symposium on Solid Oral Dosage Forms, May 13-15, 2001. Malmo, Sweden.

Rowe, R. C., Roberts, R. J. (1996), Mechanical properties; In Pharmaceutical Powder Compaction Technology. Eds G. Alderborn and C. Nystrom. Marcel Dekker, New York. pp.283-323.

Rudnic, E., and Schwartz, J. B. (1990), Oral solid dosage forms. In: Remington's Pharmaceutical Sciences, 8th Ed. pp. 1633-1665.

Rue, J., and Rees, J. E. (1978) Limitation of the Heckel relation for predicting powder compaction mechanism. J. Pharm. Pharmacol. **30**, 642-643.

Rumpf, H.(1962) The strength of granules and agglomerates. In: Int. Symposium on Agglomeration (W. A. Knepper, ed.), Interscience, New York. pp. 379-418.

Salako, M., Podczeck, F., and Newton, J. M. (1998) Investigations into the deformability and tensile strength of pellets. Int. J. Pharm. **168**, 49-57.

Sandberg, A., Ragnarsson, G., Jonsson, U.E., and Sjogren, J. (1988) Design of a new multiple-unit controled-release formulation of metoprolol CR. Eur. J. Clin. Pharmacol, **33** Suppl., 53-57.

Sarisuta, N., Punpreuk, K. (1994) In vitro properties of film-coated diltiazem hydrochloride pellets compressed into tablets. J. Control. Rel. **31**, 215-222.

Schubert, H. (1975) Tensile strength of agglomerates. Powder Technol. **11**, 107-119.

Schubert, H., Hermann, W., and Rumpf, H.(1975) Deformation behaviour of agglomerates under tensile stress. Powder Technol. **11**, 121-131.

Schultz, P. and Kleinbudde, P. (1995) Determination of pellet friability by use of an air stream apparatus. Pharm. Ind. **57**, 323-328.

Schwartz, J. B., Nguyen, N. H.,, Schanaare, R. L. (1994) Compaction studies on beads: compression and consolidation parameters. Drug Dev. Ind. Pharm. **20**, 3105-3129.

Scott, M.W., Lieberman, H.A,. Rankell,A.S.,Chow, F.S., and. Hohanston G.W (1963) Drying as a unit operation in the pharmaceutical industry I.: Drying of tablet granulations in fluidized beds. J. Pharm Sci. **52**, 284-291.

Seitz, J.A., and Flessland, G. M.(1965) Evaluation of the physical properties of compressed tablets. J. Pharm. Sci. **55**, 1553-1557.

Selkirk, A. B. and Ganderton. D. (1970) An investigation of the pore structure of tables of sucrose and lactose by mercury porositmetry. J. Pharm. Pharmacol. **22**, 79S-85S.

Shaefer, T., Holm, P. Kristensen, H.G. (1990) Melt granulation in a laboratory scale high shear mixer. Drug Dev. Ind. Pharm. **16**, 1249-1277.

Shipway, P., H. and Hutchings, I. M. (1993) Attrition of brittle spheres by fracture under compression and impact loading. Powder Technol.**76**, 23-30.

Shotton, E., and Edwards, N. J. (1974), The effects of binding agents on granule and tablet strength. J. Pharm. Pharmacol. Suppl. **26**, 107P.

Shotton, E., and Ganderton, D. (1961), The strength of compressed tablets: III. The relationship of particle size, bonding and capping in tablets of sodium chloride, aspirin and

hexamine. J. Pharm. Pharmacol. Suppl. **13**, 144T.

Siew, L. F., Basit, A. W. and Newton, J. M (1999) Properties of amylose-ethylcellulose film cast from organic based solvents as potential coating for colonic drug delivery. Eur. J. Pharm. Sci. **11**, 133-139.

Silkong, L.; Hashimoto, H. and Yashima, S. (1990) Breakage behaviour of fine particles of brittle materials and coals. Powder Technol. **61**, 51-57.

Silvennoinen, R., Peiponen, K., Hyvarinen, V., Raatikainen, P., and Paronen, P.(1999) Optical surface rouhness study of starch acetate compacts. Int. J. Pharm. **182**, 213-220.

Stanley, P.,(2001) Mechanical strength testing of compacted powders. Int. J. Pharm. **227**, 27-38.

Stanley, P., and Newton, J. M. (1977) Variability in the strength of powder compacts. J. Powder & Bulk Solids Technol. **1**, 13-19.

Stanley, P., and Newton, J. M. (1980), The tensile fracture stress of capsule-shaped tablets. J. Pharm. Pharmacol. **32**, 852-854.

Taylor, A. K. (2000) Glyceryl monostearate. In: Handbook of pharmaceutical excipients 3rd ed. (Kibbe, A. H. ed.) American pharmaceutical association and pharmaceutical press, London. pp. 225-227.

Thomsen, L. J., Schaefer, T., Sonnergaard, J. M., and Kristensen, H. G.(1993), Prolonged release matrix pellets prepared by melt pelletization. I. Process variables. Drug Dev. Ind. Pharm. **19**, 1867-1887.

Thomsen, L. J., Schaefer, T., and Kristensen, H.G. (1994) Prolonged release matrix pellets prepared by melt pelletization. II. Hydrophobic substances as meltable binders. Drug Dev. Ind. Pharm. **20**, 1179-1197.

Tojo, K., Miyanami, K., and Fan, L. T. (1983), Mathematical simulation of membrane-moderated controlled release. Powder Technol. **35**, 89-96.

Tomer, G.and Newton, J. M. (1999) Water movement evaluation during extrusion of wet powder masses by collecting extrudate fractions. Int. J. Pharm. **182**, 71-77.

Torrado, J. J. and Augsburger, L.L. (1994) Effect of different excipients on the tableting of coated particles. Int. J. Pharm. **106**, 149-155.

Toyoshima, K., Yasumura, M., Ohnishi, N., and Ueda, Y. (1988), Quantitative evaluation of tablet sticking by surface roughness measurement. Int. J. Pharm. **46**, 211-215.

UBM Messtechnik GmbH, Microfocus Measurement System Manual,, Ettlingen, (1995).

van der Watt, J. G. (1987) Effect of particle size of MCC on tablet properties of in mixture with magnesium stearate. Int J. Pharm. **36**, 51-54.

Varshosaz, J.; Kennedy, R. A. and Gipps, E.M. (1997) Effect of binder level and granulating liquid on phenyl butazone pellets prepared by extrusions-spheronisation. Drug Dev. Ind. Pharm. **23**, 611-618.

Vertommen, J., and Kinget, R. (1997) The influence of five selected processing and formulation variables on the particle size, particle size distribution, and friability of pellets produced in a rotary processor. Drug Dev. Ind. Pharm. **23**, 39-46.

Vervaet, C., Baert, L., and Remon, J. P. (1995) Extrusion and Spheronization a literature review. Int. J. Pharm. **116**, 131-146.

Wade, A., and Weller, P.J. (1994) Glyceryl Monostrearate. In: Handbook of Pharmaceutical Excipients, 2nd Ed. (Kibbe, A. H. ed.), American Pharmaceutical Association and Pharmaceutics Press, London. pp. 99-103.

Wagner, G., Krumme, M., and Schmidt, P. C. (1999) , Investigation of the pellet-distribution

in single tablets via image analysis, Eur. J. Pharm. Biopharm., **47**, 79-85.

Wagner, K. G., Krumme, M., and Schmidt, P. C. (2000) Pellet-containing tablets: Examination of distribution and deformation behaviour. S.T.P. Pharm. Sci. **10**, 327-334.

Wan, D. S., and Jeyabalan, T. (1987) A simple apparatus for measuring the crushing strength of pellets. Acta. Pharm. Technol. **32**, 197-199.

Wang, L S. C., Heng, P. W. S., and Liew, C. V. (1993) Spheronization conditions on spheroid shape and size. Int. J. Pharm. **96**, 205-216.

Wang, C., Zhang, G. Shah, N.H., Infeld, M. H., Malick, A. W., McGinity, H. W. (1995) Compaction properties of spheronized binary granular mixtures. Drug Dev. Ind. Pharm. **21**, 753-779.

Wang, C., Zhang, G., Shah, N. H., Infeld, M. H., Malick, A. W., and McGinity, J. W. (1996) Mechanical properties of pellets containing acrylic polymers. Pharm. Dev. Technol. **1**, 213-222.

Wang, C., Zhang, G., Shah, N. H., Infeld, M. H., Malick, A. W., and McGinity, J. W. (1997), Influence of plasticizers on the mechanical properties of pellets containing Eudragit RS 30 D. Int. J. Pharm. **152**, 153-163.

Watanabe, Y., Kogoshi, T., Amagai, Y. Matsumoto, M. (1990) Preparation and evaluation of enteric granules of aspirin prepared by acylglycerols. Int. J. Pharm. **64**, 147-154.

Weibull, W., (1951) A statistical distribution function of wide applicability. J. Appl. Mech. **18**, 293-297.

Wells, J. J., and Walker, C. V. (1983) The influence of granulating fluids upon granule and tablet properties: the role of secondary binding. Int. J. Pharm. **15**, 97-111.

Wheatley, T. A.(2000): Cellulose, Microcrystalline Cellulose: InHandbook of Pharmaceutical

Excipients 2nd ed. (Ed. Kibbe, A.H.)American Pharmaceutical Association and Pharmaceutics Press, London. pp. 225-227.

Wieland, M., Hanggi, P., Hotz, W., Textor, M., Keller, B. A., and Spencer, N. D.(2000), Wavelength-dependent measurement and evaluation of surface topographies: application of a new concept of window roughness and surface transfer function. Wear. **237**, 231-252.

Wikberg, M., and Alderborn, G. (1990a) Compression characteristics of granulated materials. II. Evaluation of granule fragmentation during compression by tablet permeability and porosity measurements. Int. J. Pharm. **62**, 229-241.

Wikberg, M., and Alderborn, G. (1990b) Compression characteristics of granulated materials. III. The relationship between air permeability and mechanical strength of tablets of some lactose granulatios. Int. J. Pharm. **63**, 23-27.

Wikberg, M., and Alderborn, G. (1991) Compression characteristics of granulated materials. IV. The effect of granule porosity on the fragmentation propensity and the compactibility of some granulations. Int. J. Pharm. **69**, 239-253.

Wikberg, M., and Alderborn, G. (1992), Compression characteristics of granulated materials. V. Mechanical properties of individual granules, assessed by diametral compression, in granulation of different volume reduction behaviour, STP Pharma. Sci. **2**, 313-319.

Woodruff, C. W. and Nuessle, N. O. (1972) Effect of processing variables on particles obtained by extrusion-spheronization processing. J. Pharm. Sci. **61**, 787-790.

Wong, L. W., and Pilpel, N. (1990a) Effect of particle shape on the mixing of powders. J. Pharm. Pharmacol. **42**, 1-6.

Wong, L. W., and Pilpel, N. (1990b) Effect of particle shape on the mechanical properties of powders. Int. J. Pharm. **59**, 145-154.

Yang, S. T., and Ghebre-Sellassie, I. (1990) Effect of product bed temperature on the

microstructure of Aquacoat-based controlled release coating. Int J. Pharm. 60, 109-124.

York, P. (1978) Particle slippage and rearrangement during compression of pharmaceutical powders. J. Pharm. Pharmacol. **30**, 6-10.

York, P. (1979) Consideration of experimental variables in the analysis of powder compaction behaviour. J. Pharm. Pharmacol. **31**, 244-246.

York, P. (1992) Crystal engineering and particle design for the powder compaction process, Drug Dev. Ind. Pharm. **18**, 677-721.

York, P., Bassam, F., Rowe, R. C., and Roberts, R. J. (1990) Fracture mechanics of microcrystalline cellulose powder, Int. J. Pharm. **66**, 143-148.

York, P., and Pilpel, N. (1973) Tensile strength and compression behaviour of lactose, four fatty acids, and their mixture in relation to tableting J. Pharm. Pharmacol. **25** (Suppl.), 1P-11P.

Yuen, K. H., Deshmukh, A. A., and Newton, J. M., (1993) Development and in vitro evaluation of a multiparticulate sustained release theophylline formulation. Drug Dev. Ind. Pharm. **19**, 855-874.

Zang, G., Schwartz, J. B., Schnaare, R. L., Wigent, R. J., and Sugita, E. T. (1991) Bead coating: II. Effect of spheronization technique on drug release from coated spheres. Drug Dev. Ind. Pharm. **17**, 817-830.

SYMBOLS

ABBREVIATIONS

ANOVA - Analysis of variance

APC - Average Power of Consumption

APPIE - Association of Powder Process Industry and Engineering

BET - Brunauer, Emmett and Telller

BFI - Brittle fracture index

BI - Bonding index

BI_b - best-bonding index

BI_w -worst-bonding index

BP - British pharmacopoeia

BS - British Standard

DCP - Dicalcium phosphate dihydrate

DF - Degree of freedom

DMA - Dynamic mechanical analysis

FD - Fractal Dimension

GMS - Glyceryl monostearate

HPMC - Hydroxy propyl methyl cellulose

JIS - Japan Industrial Standards

MCC - Microcrystalline cellulose

OPCS - One plane critical stability

PTFE - Polytetrafluoroethylene

PVA - polyvinyl acetate

PVP - Polyvinyl pyrrolidone

RIM - Repeated Impact Machine

SEM - Scanning electron micrograph

SKF - Smith Kline & French

TGA - Thermogravimetric analyzer

TWC - Total work of compaction

SYMBOLS AND CONSTANTS

a - constant on Kawakita equation (equation -23)

A - a constant or an intercept on Heckel plot (equation -24)

A_M (m^2) - Molecular cross-section area

b (MPa^{-1}) - Kawakita compressibility constant (equation-23)

B - a constant on modified Heckel plot (equation- 27)

b (m) - Breadth

c (m) - crack length

C (%) - degree of volume reduction

d or D (m) - Diameter

d_g (m^{-1}) - Deformation modulus of a granule

E (MPa) - Elastic modulus

e_r - Shape factor

F (N) - Force

F_0 (N) - Agglomerate crushing force

G" (MPa) - Loss (imaginary or viscous) modulus

G'(MPa) - Storage (real or elastic) modulus

G** (MPa) - Complex modulus

h or H (m) - Height

k- coordination number or number of contacts (equation - 3)

K (MPa^{-1})- Slope for the Heckel plot

K_I ($MPam^{1/2}$) - Stress intensity factor

K_{IC} ($MPam^{1/2}$) - Critical stress intensity factor

l or L (m) - Length

m - Weibull modulus

M_V (m^3) - Molar volume

N_A - Avogadro's number

P (MPa) - Pressure

P_0 (Pa) - Saturation pressure

P(x) - Probability of failure

P_{dh} (MPa) - Deformation hardness

P_m (m) - Perimeter

P_y, (MPa) - Yield stress or strength

r or R (m) - Radius

R^2 - Correlation coefficient determinant

R_a (m) - Average roughness value

R_K (m) - Kelvin pore radius

R_q (m) - Root mean square deviation of surface roughness

R_t (m) - Maximum peak-to-valley height

S_{BET} (m^3/g) - BET surface area

S_g (%) - Linear shrinkage of a granule

SRS (%) - Strain rate sensitivity

V (m^3) - Volume

V_{ADS} (m^3) volume of adsorbed molecules

VER (%)- Volumetric Elastic Recovery

VSR (%)- Volumetric Strain Recover

W (g) - Weight

X_o (MPa)- Weibull-constant

X_u (MPa) - correction factor (equation - 8)

GREEK SYMBOLS

γ (Nm^{-1}) - surface tension

ϵ (%)- Strain

θ (degree) - Contact angle

ξ (%) - Total Porosity

ξ_{intra} (%) - Porosity within a pellet

ξ_{inter} (%) - Porosity between pellets

ρ_t (g/cm^3)- True density

ρ_g (g/cm^3)- Granule density

ρ_b (g/cm^3)- Bulk density

σ (MPa)- Tensile strength

σ_f (MPa)- Agglomerate Tensile strength

τ'_0 (MPa)- Shear Strength

Υ - Compression susceptibility.

ϕ (%)- Volume fraction