# THE FORMULATION TECHNOLOGY OF DISPERSIBLE TABLETS.

**BY**
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# ABSTRACT

This thesis describes generic technology for the formulation of dispersible tablets using wet granulation and conventional tableting. Tablet dispersion was measured using a disintegration tester with sieve apertures of 2000, 1700, 1400, 1180 and 710μm. Testing was carried out in distilled water at 19-20°C to simulate dispersion in practice. The use of the super disintegrants sodium starch glycollate (Explotab™), croscarmellose sodium (Ac-Di-Sol™), crospovidone (Kollidon-CL™) and polacrin potassium (Amberlite IRP88™) was investigated.

Paracetamol was used as a model, high dose, poorly compressible drug with low aqueous solubility. The influence of granule size and intragranular disintegrant type on tablet properties, particularly dispersion, was investigated. When disintegration of tablets from granule sieve cuts was monitored through 710μm, intragranular disintegrant had a greater effect on tablet dispersion than granule size and compression force, but the relationship depended upon type. Where disintegrant efficiency was low, the influence of granule size was greater and disintegration times tended to increase with granule size. Ac-Di-Sol was superior to the other disintegrants and the non-fractionated granulation gave adequate dispersion. Kollidon CL performed poorest. The efficiency of intragranular Amberlite IRP88 was highly dependent on granule size and performance was highest in an unfractionated granulation of small particle size.

Deaggregation down to 710μm was more dependent on the type of disintegrant used intragranularly than extragranularly. With Ac-Di-Sol, the rate of dispersion was not improved by the addition of extragranular disintegrant and in some cases was reduced. With intragranular Amberlite IRP88 it was only slightly increased. Greatest improvement in tablet dispersion with the addition of extragranular disintegrant, occurred in tablets containing intragranular Kollidon CL. The effectiveness of Amberlite IRP88, Ac-Di-Sol and Kollidon-CL as extragranular disintegrants was similar at low and intermediate compression forces. Amberlite IRP88 tended to be better at high compression forces, whereas Explotab was poor.

Disintegrant poisoning of Ac-Di-Sol by dissolved and recrystallised paracetamol during the wet granulation process was investigated. Disintegrant was slurried with ethanol : water mixtures of different saturated paracetamol concentrations, to cause varying levels of drug to be drawn into the disintegrant during the hydration process and deposited on drying. "Poisoned" disintegrant was incorporated into a direct compression system and compared to untreated and solvent treated Ac-Di-Sol. Disintegrant poisoning occurred due to solvent stress and deposition of paracetamol. However, disintegrant efficiency of Ac-Di-Sol remained high.

Na-p-aminosalicylate provided a very aqueous soluble, high dose model. Citric acid and Na-dihydrogen orthophosphate dihydrate were incorporated into the tablet to lower the microenvironmental pH at granule surfaces below drug pKa to suppress drug solubility and therefore the rate at which porosity and viscosity develop. In theory this should give better disintegrant function. Unfortunately, the addition of acid failed to lower pH sufficiently to convert a dissolving matrix into a dispersing tablet. In this highly aqueous soluble model, Amberlite IRP88 was a better disintegrant than Ac-Di-Sol, and omitting a binder increased dispersion, while still achieving mechanically acceptable tablets.

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# 1. INTRODUCTION.

## 1.1 The dispersible tablet as a dosage form.

Solid medicinal preparations have been used since antiquity (Griffenhagen, 1980). The earliest reference to a dosage form resembling a tablet can be found in Arabic medical literature, in which drug particles were compressed between ebony rods, the force applied by a hammer. Details of the tableting process were first published in 1843 when Thomas Brockendon was granted a patent for "manufacturing pills and medicinal lozenges by causing materials when in a state of granulation, dust or powder, to be made into form and solidified by pressure in dies."

In 1895, an editorial in the Pharmaceutical Journal predicted, "tablets have had their day and will pass away to make room for something else." After a century, tablets are still the most popular dosage form because they have significant advantages (Table 1.1).

**Table 1.1: Advantages of the tablet as a dosage form.**

| |
|---|
| **Simple administration** |
| **Accurate dosage** |
| **Easy to transport in bulk** |
| **Easy for the patient to carry** |
| **Inexpensive to manufacture** |
| **Uniform product** |
| **More stable than liquid preparations.** |

An alternative to the traditional swallow tablet is a special formulation, which will quickly disintegrate in water to form a suspension that can be drunk. It combines the

ease of swallowing and the potentially improved bioavailability of a liquid formulation (Kovacic et al, 1989; Milovac et al, 1990; Macia et al, 1995), with the accurate dosing, stability and ease of transportation of a tablet. Active ingredients unstable in aqueous solution may be stable as a dispersible tablet (Milovac et al, 1990).

The dispersible tablet provides a utility dosage form, reducing the need for multiple formulations of the same drug. In the current world health economy, this reduces development costs significantly. Today the pharmaceutical industry operates in an environment where cost containment and optimisation of drug delivery must be considered along with efficacy and safety before a new drug product will be licensed (Morton, 1996). It is for this reason that the German Registration Authorities (BGA) has advocated the formulation of dispersible tablets. Germany is not alone, however. The trend towards the formulation of dispersible tablets is evident across Europe (Martin, 1987). For example, all tablets marketed in the Netherlands must form an adequate dispersion when placed in water (Danish & Kottke, 1996).

## 1.2 Problems associated with conventional oral dosage forms.

### 1.2.1 Solid oral dosage forms.

The advantages offered by solid dosage forms mean that most drugs are initially marketed as a tablet or capsule. A liquid formulation is probably developed several years later. Marketing of a drug solely as a solid dosage form, results in the unavailability of a liquid for paediatric and geriatric use and others who have difficulty in swallowing tablets, are unconscious or those fed via a nasogastric tube (Mistry et al, 1995). Furthermore, there are certain drugs where different dosage forms are used to overcome local irritation of the gastro-intestinal tract after solid oral administration. Oesophageal ulceration can occur with potassium chloride (Evans & Roberts, 1976; Collins et al, 1979), doxycycline (Bokey & Hugh, 1975; Crowson et al, 1976), theophylline (Stoller, 1985), and non-steroidal anti-inflammatory drugs (Wilkins et al, 1984; Shallcross et al, 1990).

The absence of a liquid formulation is a particular problem when large doses must be administered orally, resulting in a very large tablet or capsule, especially when doses are taken frequently and chronically. This may result in considerable physical and psychological discomfort for the patient.

Problems in swallowing may only be detected in the oropharyngeal phase; the distal oesophagus has no somatic sensation. Consequently, patients are not aware of tablets or capsules lodged within the oesophagus and below the pharynx (Channer & Virgee, 1986). Hard gelatin, when moistened, becomes sticky and firmly adheres to the oesophageal mucosa. It has been suggested that capsule formulations are thus more

prone to delayed oesophageal transit (Channer, 1990). Lodged solid dosage forms can cause obstruction, oesophageal ulceration, stricture, haematoma, and in some cases haemorrhage (Cumins, 1966; Pemberton, 1970; Runyon, 1986; Piccione et al, 1987). The incidence of tablet retention in the oesophagus is increased considerably in patients with an enlarged left atrium in mitral stenosis (Howie & Strachan, 1975), hiatus hernia (Shallcross et al, 1990) or when the patient is lying down (Howie & Strachan, 1975). Theoretically, tumours and motility disorders might also be expected to predispose to this problem. Patients with variceal sclerotherapy also have an increased risk of tablet-induced oesophageal injury. These patients together with those with portal hypertension (Runyon, 1986) should avoid the use of solid dosage forms. The incidence of lodged tablets is a particular problem in the elderly, where oesophageal lesions are common (Danish & Kottke, 1996) and peristaltic activity may be impaired, delaying oesophageal transit (Robertson & Hardy, 1988). Dry mouth is also prevalent among older people and this may cause tablets to adhere to the oesophageal mucosa.

Solid dosage forms also pose problems for children. In addition to swallowing difficulties, clinical studies and case reports suggest highly variable absorption patterns in neonates and infants (Heimann, 1980) and there have been reports of incomplete absorption (Gilman et al, 1988). Therefore it is desirable to select a more readily bioavailable dosage form, such as a chewable tablet or liquid. It is standard practice in British hospitals for paediatric formulations, when not available commercially, to be extemporaneously prepared in the pharmacy (Mistry et al, 1995). In addition to the extra work this creates, the lack of data available regarding the stability of products in suspension or solution may mean that storage conditions or shelf life may not provide optimal activity at the time of administration (Martin, 1987). Adult patients may receive

treatment with an extemporaneously prepared liquid formulation or by nurses crushing tablets (Mistry et al, 1995). The practice of nurses crushing tablets is undesirable and in contravention of the Control of Substances Hazardous to Health (C.O.S.H.H.) Regulations. The medication and persons carrying out the procedure may be contaminated, and loss of medication will result in under dosing. When a controlled release preparation is crushed, the rate at which the drug is released and absorbed into the bloodstream may be too high and cause overdosing.

### 1.2.2 Liquid formulations.

Where a liquid formulation is available, it is usually in the form of a solution or suspension. Suspensions and solutions are often less stable than tablets and have shorter shelf lives. Furthermore, many liquid formulations have high sugar content, rendering them unsuitable for diabetic patients.

If a drug is poorly soluble in a pharmaceutically acceptable solvent, then formulation as a solution may not be possible and formulation as a suspension is usually required. In comparison to aqueous solutions, hydrolysis and oxidation is generally less and if the drug has an unpleasant taste, this will be less noticeable. However, suspensions are thermodynamically unstable systems and are usually much harder to formulate than a tablet or capsule. Aggregation of suspended particles, and sedimentation and impaction are a problem. The particle size of the drug is critical, and this may increase on storage because of Ostwald ripening (Higuchi, 1958). Temperature rises may cause the solubility of the drug to increase and on cooling crystallisation will occur (Ziller & Rupprecht, 1988). Ostwald ripening is a particular problem with slightly soluble drugs such as paracetamol. To reduce possible degradation of the drug, the prolonged contact

between the solid drug particles and the dispersion medium can be reduced by preparation of the suspension immediately prior to issue to the patient (Ball et al, 1978). For example, ampicillin is provided as either the base or the trihydrate, reconstituted on demand.

Preservatives must be added to solutions and suspensions to prevent the growth of microorganisms that may be present in the raw material and / or introduced into the product during use. This is expensive and creates problems. Where a tablet is dispersed immediately prior to use, a preservative is not required.

Accurate measurement and administration of the prescribed dose of a liquid formulation is a problem, since most are not packaged in unit-doses. Patients suffering from poor eyesight, arthritis, or tremors from neurological disorders are particularly likely to experience difficulty measuring doses accurately (Danish & Kottke, 1996). The inconvenience of carrying liquid is associated with a risk that patient compliance will be reduced (Mendizabal & Alcobendas, 1996).

Further difficulties are encountered if the medication is a suspension. Problems occur because a patient cannot see or disregards the words "Shake Well" on the label or is not able to exert the amount of agitation necessary to provide a uniform suspension. Uneven distribution, will result in under and overdosing.

## 1.3 Administration of solid oral dosage forms.

### 1.3.1 To aid swallowing.

Channer & Virgee (1986) showed that the shape and surface dimensions of tablets have a significant impact on transit time through the oesophagus. For psychological reasons, patients tend to find long, thin formulations such as oval tablets easier to swallow. Significantly reduced oesophageal transit times compared with round tablets of equal weight were demonstrated. Tablet surfaces with a high water adsorption capacity can also increase adherence to the oesophageal mucosa and increase transit times, especially if ingested with too little water.

**Table 1.2: Reducing the incidence of solid dosage form injury to the oesophagus.**

| |
|---|
| **Tablets should be taken standing or sitting upright, followed by a drink >75 ml.** |
| **Tablets should be taken with a meal, not afterwards, as is often advised.** |
| **Patients should not take medicines one hour before going to bed.** |
| **Use liquid preparations where possible.** |

In some instances, assisting with swallowing can relieve problems of taking oral solid dosage forms. Several authors (Runyon, 1986; Fink & Rohrmann, 1988; Robertson & Hardy, 1988) reporting the incidence of solid dosage form induced injury to the oesophagus have suggested methods to reduce the problem (Table 1.2). Frequently, patients have difficulty with the tablet not leaving the mouth, or lodging in the oesophagus and not reaching the stomach. Putting the tablet or capsule on the tongue, then taking two successive gulps of water, swallowing the dose with the second swallow, often overcomes the physical barrier to swallowing created by the epiglottis, hyoid and larynx.

### 1.3.2 The dispersion of conventional solid oral dose tablets.

Where a commercial liquid preparation is unavailable, the dispersion of conventional tablets in water immediately prior to administration has been proposed as a suitable alternative to the extemporaneous formulation of oral suspensions (Martin et al, 1993; Mistry et al, 1995). However, this is not suitable for many tablet preparations. Martin et al (1993) carried out a study to determine the proportion of 509 conventional tablets held in a hospital pharmacy stock that could be dispersed in water. Although testing was crude and judgements arbitrary, they attempted to mimic domestic conditions. They placed 20ml of tap water at (25 ± 2°C) in a cup. A tablet was added and swirled for four revolutions at twenty second intervals. Timing ceased when the tablet completely dispersed, or after five minutes (a time period they felt was acceptable for patients to wait before taking the drug). Of 509 named products tested, only 258 (51%) dispersed within five minutes and were considered dispersible.

## 1.4 Approaches to formulating a solid dosage form which rapidly disintegrates.

### 1.4.1 Effervescent tablets.

Effervescent tablets depend on the reaction of bicarbonate or carbonate with an acid or other excipient with the capacity to evolve a gas after contact with water. The tablet rapidly disintegrates to produce a solution or suspension. However, production is expensive and demanding and requires manufacturing at low relative humidity (Sendall et al, 1983). Many drugs are incompatible with bicarbonate and acids, which render them unsuitable.

**Table 1.3: Patented dispersible tablet formulations.**

| Active | Dose in tablet [mg] | Method of manufacture | Patent N° | Applicant | Inventor(s) |
|---|---|---|---|---|---|
| Aluminium hydroxide : Magnesium hydroxide | 200 : 250 | Wet granulation | EP 0 003 589 (1979) | The Wellcome Foundation Limited, London | Harden & Gayest |
| Trimethoprim : Sulphamethoxazole | 80 : 400 | Wet granulation | GB 2 067 900 (1981) | DDSA Pharmaceuticals, London. | Solomon |
| Oxazepam<br>Lorazepam<br>Temazepam<br>Lormetazepam<br>Frusemide<br>Bendrofluazide<br>Cyclopenthiazide<br>Isosorbide dinitrate<br>Indomethacin<br>Prochlorperazine maleate | 15 and 50<br>1, 2, 2.5, 4<br>10, 20<br>1<br>40<br>5<br>0.5<br>2.5, 5, 10<br>25, 50<br>50 | Freeze drying | GB 2 111 423 (1983) | John Wyeth and Brother Limited, Berkshire. | Gregory & Peach |
| Cyclandelate | 800 | Wet granulation | EP 0 181 650 (1986) | Gist-Brocades N.V. | Groenendaal & Sijbrands |
| Naproxen | 500, 750 | Wet granulation | EP 0 255 002 (1988) | Alfa Farmaceutici S.p.A, Bologna | Rotini & Marchi |

**Table 1.3 Continued.**

| Active | Dose in tablet [mg] | Method of manufacture | Patent N° | Applicant | Inventor(s) |
|---|---|---|---|---|---|
| Cimetidine | 800-1200 | Wet granulation | EP 0 347 767 (1989) | LEK, Ljubljana | Kovacic & others |
| Dihydroergotoxin | 4.5 | Wet granulation | EP 361 354 (1990) | LEK, Ljubljana | Milovac & others |
| Diclofenac | 46.5 | Wet granulation | EP 0 365 480 (1990) | Ciba-Geigy, Basel | Murphy & Mathews |
| Chlorpheniramine Maleate | 40 | Freeze drying | US 4 946 684 (1990) | American Home Products, New York | Blank & others |
| Lamotrigine | 100 | Wet granulation | WO 92 / 13527 (1992) | The Wellcome Foundation Limited, London | Fielden |
| Acyclovir | 800 | | | | |
| Amoxycillin : Clavulanic acid | 250 : 125 | Dry granulation | WO 92 / 19227 (1992) | Laboratorios Beecham Madrid | Martin & Romero |
| 2' 3'-dideoxyinosine | 150 | Dry granulation | EP 0 542 579 (1993) | Bristol-Meyers Squibb Company, New York | Ullah & Agharkar |
| Paracetamol | 325 | Vacuum drying | US 5 298 261 (1994) | Oregon, Albany | Pebley & others |
| Fluoxetine | 20 | Direct compression | EP 0 693 281 (1996) | Lilly S.A, Madrid | Mendizabal & Alcobendas |

### 1.4.2 Lyophilisation.

Lyophilisation (freeze drying) has been used to produce tablets with an open matrix which rapidly disintegrate in water or saliva. Examples of freeze-dried dispersible tablets are given in Table 1.3. This type of dosage form is a matrix of a water soluble / dispersible material impregnated with a unit dose of drug. A suspension of drug and excipients is dosed by weight into pre-formed blisters before freeze-drying. Although this type of product has good stability and can be easily dispersed in aqueous solution, the porous "open matrix network" produced by the sublimation process renders the tablet very fragile (Kearney & Yarwood, 1993) and handling is severely compromised. Peelable blister packaging has been developed to allow removal of dosage units from the pack without damage, as it is not possible to push them through aluminium sealing foil typically used in blister packs without rupturing the product.

The fragile nature of freeze dried products, along with expensive production costs and the specialised equipment required, has limited their widespread use (Pebley et al, 1994). Additionally, the formulation of very high dose actives is difficult. Referring to Zydis™ (R. P. Scherer), Yarwood & Virley (1990) reported that doses up to 125mg can be accommodated, but with higher doses it is more difficult to achieve dispersion.

### 1.4.3 Vacuum drying.

Vacuum drying has been used as an alternative method of removing liquid to produce a rapidly dispersing tablet (Pebley et al, 1994). It is claimed to have a lower porosity, greater density and greater mechanical strength, while still disintegrating in normal amounts of saliva / aqueous solution. However, there is a possible explosive release of

liquid from the material being dried, which may disrupt the structure of the material. For this reason, the process has previously been considered unsuitable for commercial production of well-formed shapes such as dispersible tablets. However, in the process described by Pebley et al (1994), it is claimed that maintaining the temperature of the matrix during primary drying between the collapse temperature and the equilibrium freezing point, gave a satisfactory product.

### 1.4.4 Wet compression.

Rapidly disintegrating tablets have been developed using wet powders containing drugs. Drug and excipients are blended and the powder mixture is moistened with a solvent containing a binding agent. The wet mass is either moulded or compressed under low force and dried in ambient air or an oven. Bi et al (1999) describe the mechanism and optimisation of a wet compression method to produce rapidly disintegrating lactose tablets. Low compression force gives high porosity, and solid bridge formation, which occurs due to drug recrystallisation, confers tensile strength.

### 1.4.5 Conventional tableting.

Conventional tableting is the most widely used method of producing dispersible tablets. It is simple and the least dependent on the use of specialised equipment. A review of the literature has revealed little work relating to the research and development of dispersible tablets using conventional tableting technology. Patents describing processes for the manufacture of specific products are the main source of published material (Table 1.3). The aim of the present research is to develop generic technology for the formulation of dispersible tablets using conventional tableting.

## 1.5 Dispersible tablets using conventional technology.

### 1.5.1 Standards.

Dispersible tablets BP are "uncoated tablets that produce a uniform dispersion in water." They are characterised by:

(i) High speed of disintegration in water (<3 minutes when examined by the BP disintegration test for tablets and capsules, using water at 19-20°C).

(ii) Dispersion of the particles below 710μm.

### 1.5.2 Method of manufacture.

The manufacturing process is critical to the design of a dispersible tablet formulation. The excipients used will depend to a large extent upon the process selected (Figure 1.1). This is influenced by the physicochemical properties of the drug and the dose (Table 1.3). Dispersible tablets are very sensitive to moisture and their stability is compromised by granulation. Direct compression (DC) is therefore the preferred technique. The most significant advantage is that tablets normally disintegrate more rapidly than those made by wet granulation which reduces the effective surface and requires the addition of binding agents which slow the disintegration rate (Mendizabel & Alcobendas, 1996). Using lithium carbonate tablets, Healy (1976) showed that in the absence of binder, tablets deaggregated to essentially the original powder.

Unfortunately, many drugs do not possess the necessary physical properties to be directly compressed. The maximum carrying capacity of a direct compression vehicle is limited to approximately 25% of a non-compressible drug (Wells & Langridge, 1981).

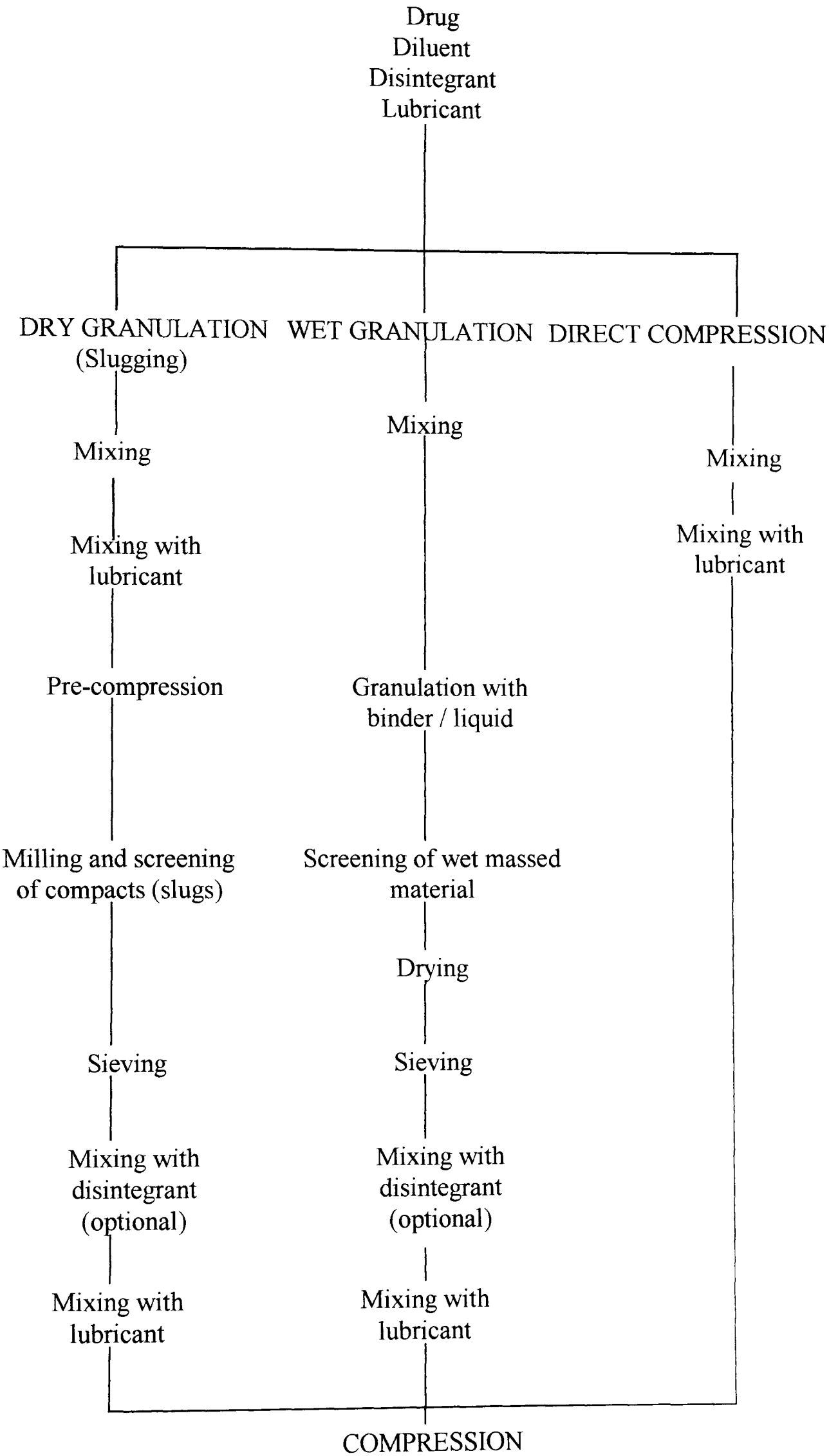



**Figure 1.1: Tablet production by granulation and direct compression.**

Doses greater than 100mg cannot be directly compressed because the weight of the tablet is too large (Armstrong, 1986). Therefore, for high dose drugs with poor flow and compressibility, a granulation process is used. Wet granulation is the traditional and the most popular method of granulation. In wet granulation, the liquid plays a key role in the process. Granule growth is initiated by the formation of liquid bridges between primary particles (Rumpf, 1962). The moist mass is then wet screened to further consolidate granules, increase particle contact points and the surface area to facilitate drying (Banker & Anderson, 1986). A drying process removes the solvent and reduces granule moisture content to an optimum (Shotton & Rees, 1966). During drying interparticulate bonds result from the recrystallisation of the binding agent. Powdered materials which are soluble in the granulating fluid will also form solid bridges due to solute migration (Wells & Walker, 1983). The size of solute crystals, and therefore the strength of the solid bridges, will be influenced by the rate of drying of the granules; the slower the drying time, the larger the particle size.

Dry granulation, or compression granulation, is useful where the dose is too high for direct compression and the drug is unstable when exposed to moisture or heat. For example, it has been employed in the manufacture of dispersible amoxycillin tablets (Martin & Romero, 1992).

A review of the patent literature reveals that wet granulation is the most commonly used method for the manufacture of dispersible tablets (Table 1.3). This is logical since most drugs formulated into a dispersible tablet are high dose drugs where patients commonly experience difficulties swallowing large tablets.

### 1.5.3 The theory of wet granulation.

Wet granulation produces size enlargement when small primary particles are aggregated to form larger, physically strong agglomerates where the original particles are identifiable. Bonds are formed between powder particles which adhere to form granules. The use of soluble adhesives, called binders, causes particle agglomeration and granules are influenced by binder type and its distribution within the aggregates (Seager et al, 1979). Granulation may be divided into binding mechanisms (Rumpf, 1958) and granule growth and formation (Newitt & Conway-Jones, 1958).

#### 1.5.3.1 Bonding mechanisms for agglomeration in wet massing.

Rumpf (1958) identified five mechanisms responsible for agglomeration, and stated that more than one applied to any particular system.

*[a] Adhesion and cohesion caused by immobile liquid films.*

Sufficient moisture must produce a thin, immobile adsorption layer to contribute to the bonding of fine particles, by decreasing the distance between particles and increasing the interparticulate contact area. Thin, immobile films of highly viscous solutions of adhesives can form exceptionally strong bonds.

*[b] Interfacial forces and capillary pressure at mobile liquid surfaces.*

When the liquid level on the surface increases beyond a thin film, mobile liquid forms bridges where capillary pressure and interfacial forces create strong bonds. This is reversible after drying. However, mobile liquid films are required to form solid bridges from binders dissolved in the granulating fluid.

*[c] Solid bridges.*

Solid bridges form by the crystallisation of dissolved substances. A hardening binder is a common bonding mechanism in pharmaceutical wet granulations. Liquid will form bridges and the adhesive will harden or crystallise on drying to form solid bridges.

Equally, the solvent may dissolve one of the powdered ingredients. When the granules are dried, crystallisation will take place and the dissolved substance then acts as a hardening binder. The size of the crystals produced in the bridge will be influenced by the rate of drying of the granules. Slower drying yields larger crystals (Wells & Walker, 1983).

*[d] Attractive forces between solid particles.*

Electrostatic forces are of importance in causing powder cohesion and the formation of agglomerates during mixing. However, they do not contribute significantly to the final strength of the granule.

*[e] Form-closed bonds or interlocking bonds.*

Fibres or particles can interlock or fold about each other resulting in "form-closed" bonds. Although mechanical interlocking of particles influences agglomerate strength, its contribution is generally considered small in comparison with other mechanisms.

With increasing liquid addition, granulation moves from an immobile liquid to a mobile liquid film state. Newitt & Conway-Jones (1958) defined the theory of granulation in terms of three states, and Barlow (1968) added a fourth. These four states are termed: pendular, funicular, capillary and droplet (or suspension).

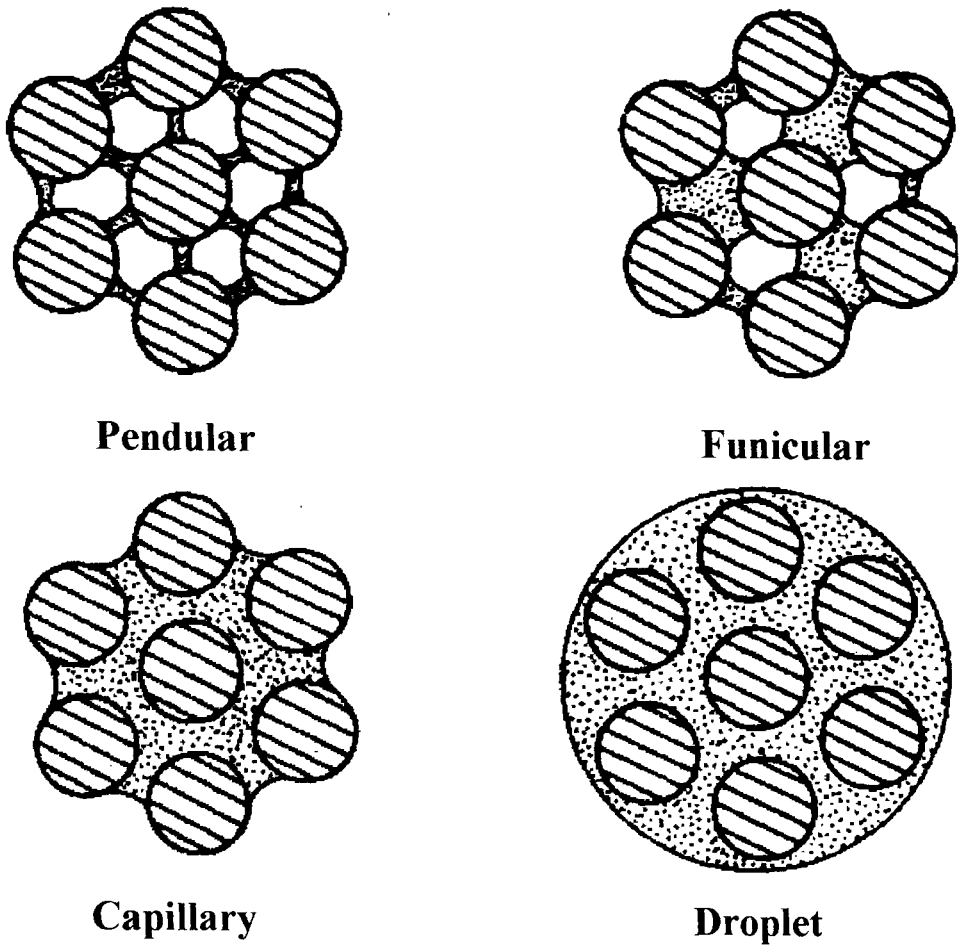



**Figure 1.2: Binding mechanisms by liquid bridges.**

Each state represents a progressive increase in moisture content. At low moisture contents water forms lens shaped rings at the points of contact of the particles. This is known as the pendular state. The particles are held together by surface tension at the solid-liquid-air interface and the hydrostatic pressure of the liquid bridge. As the moisture content increases, the rings coalesce to form a continuous network of liquid interspersed with air; the funicular state. A further increase in water content gives the capillary state when all granule pore spaces are completely filled with liquid and concave menisci develop. The droplet state occurs when liquid completely surrounds the granule, resulting in an external phase consisting of liquid with an internal solid phase.

### 1.5.3.2 Mechanisms of granule formation.

The proposed granulation mechanism can be divided into three stages (Barlow, 1968):

*[a] Nucleation.*

In nucleation, granule formation occurs when loose agglomerates or single particles are wetted by the binder solution and form small granules by pendular bridging.

*[b] Transition.*

Nuclei grow by two mechanisms:

I. Single particles can be added to the nuclei by pendular bridges.

II. Two or more nuclei may combine.

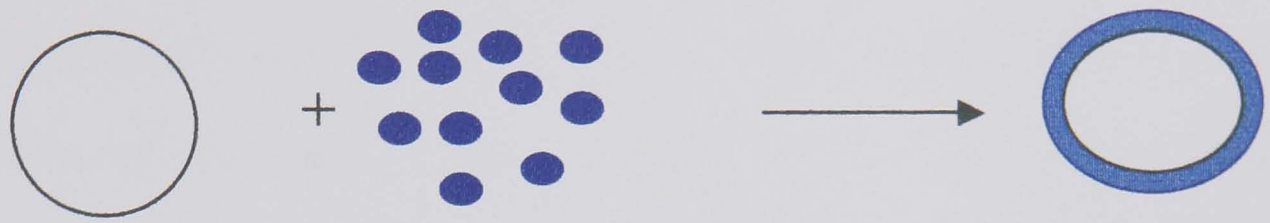
The transition stage is characterised by the presence of a large number of small granules with a fairly wide size distribution. If the size distribution is not excessively large, this point represents a suitable end point for granules used in tablet and capsule manufacture, as relatively small granules will produce a uniform die fill.

*[c] Ball growth.*

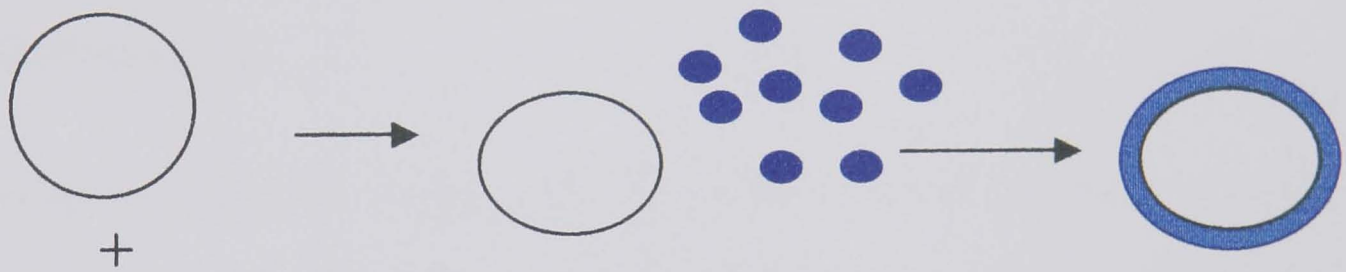
Further granule growth results in large, spherical granules, and the mean particle size of the granulating system increases with time. If agitation is continued, granule coalescence will continue and produce an unusable over-massed system. This is ultimately dependent on the amount of liquid added and the material properties. Sastry & Fuerstenau (1973) studied particle growth during agglomeration and summarized four principal mechanisms of ball growth, shown in Figure 1.3.

**Figure 1.3: Representation of granulation mechanisms.** (after Augsburger & Vuppala, 1997).

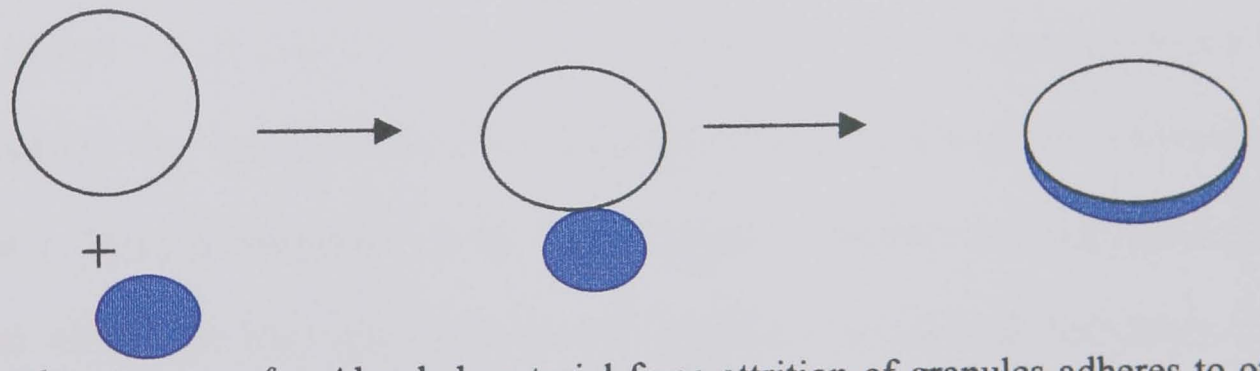
I. *Layering:* The powder mix added to the granulation, adheres to existing granules to form a surface layer and increase granule size.



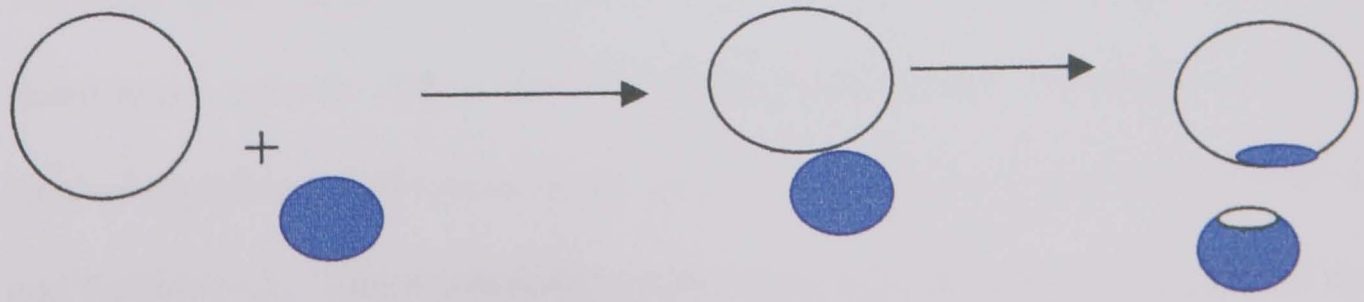
II. *Crushing and layering:* Some granules break into fragments which adhere to other granules forming a layer of material over their surface.



III. *Coalescence:* Two or more granules join to form a larger granule.



IV. *Abrasion transfer*: Abraded material from attrition of granules adheres to other granules, thereby increasing their size.



### 1.5.4 Dispersible tablet formulation.

#### 1.5.4.1 Drug.

High dose drugs which are highly water soluble, poorly compressible and hygroscopic pose the greatest difficulty in a dispersible tablet formulation. Excipients must be carefully selected to produce a tablet matrix with high compressibility and low aqueous solubility and hygroscopicity. However, there is a limiting tablet size (≅ 750mg) and where the dose of drug is high, the mass of excipients which can be used to modify the physical properties of the tablet is severely restricted.

#### 1.5.4.2 Disintegrants.

A disintegrant accelerates the rate at which a tablet breaks up in water. The current research will use so-called super disintegrants (Table 1.4), so-called because of high disintegrant efficiency attributed to their remarkable ability to absorb water and swell (Mitrevej & Hollenbeck, 1982). Many of these combine wicking and swelling action which allows a high and fast movement of water into the tablet structure at a low concentration. The mechanism of action of individual super disintegrants is discussed in Chapter 2. Super disintegrants can be used in smaller concentrations and therefore the negative effects on flow and compression, exhibited by most of the starches, are minimised.

Different grade specifications for a super disintegrant will cause differences in disintegrant activity. Using calcium diphosphate tablets, Caramella et al (1990a), showed significant differences in the disintegrant force generated by Polyplasdone-XL and Kollidon-CL. They attributed the difference to the different particle size of the two

commercial brands, since similar results were obtained when samples having the same particle size range were compared.

**Table 1.4: Super disintegrants.**

| Super disintegrant | Commercial variants |
|---|---|
| Sodium Starch Glycollate | Primojel™, Explotab™ |
| Cross-linked polyvinylpyrrolidone, (Crospovidone) | Polyplasdone- XL™, Kollidon-CL™ |
| Cross-linked sodium carboxymethyl cellulose (Croscarmellose) | Ac-Di-Sol™, CLD™ |
| Low substituted carboxymethyl cellulose | Nymcel-ZD10™, Nymcel-ZD16™ |
| Polacrin Potassium | Amberlite IRP88™ |

It has been postulated that larger particle size grades of sodium starch glycollate may be more efficient disintegrants than finer grades (Rudnic et al, 1980; Rudnic et al, 1982). Smallenbroek et al (1981) theorised that increased swelling pressure occurred in larger starch grains. Rudnic et al (1985) showed that relatively small changes in the cross-linkage and degree of substitution of commercially available sodium starch glycollate, can cause substantial modification of disintegrant properties. Swelling of particles was shown to be inversely proportional to the degree of substitution. The more soluble super disintegrants should be avoided in dispersible tablet formulation because the formation of a viscous layer retards water penetration (Van Kamp et al., 1983).

The choice of disintegrant depends on the physicochemical properties of the base formulation. In hydrophobic and water-insoluble base formulations, the disintegrant is capable of developing maximum swelling force and capillarity. Highly hydrophilic and strongly swelling disintegrants are preferable (Graf et al, 1981; Paronen et al, 1985). In

hydrophilic and water soluble formulae, the disintegrant assists in drawing water inside the compact but is not always able to develop maximum swelling force. This suggests that limited swelling disintegrants should work as well, or even better than, strongly swelling materials (Graf et al., 1981; Paronen et al., 1985).

Many workers support the idea that for a formulation there is a critical disintegrant concentration and below this concentration, disintegration is slow. At this critical concentration, disintegration time decreases, often dramatically. A critical amount of disintegrant corresponds to the setting up of a continuous hydrophilic network, which allows for fast movement of water throughout the tablet (Patel & Hopponen, 1966; Yuasa & Kanaya, 1986) and may therefore, correspond to a great increase in water uptake by the tablet (Ringard et al, 1977). Above this concentration, the disintegration time may continue to decrease slowly, remain constant at its lowest value or increase (Rudnic et al, 1981). The critical disintegrant concentration for a tablet formulation may be determined empirically. Alternatively, in idealised systems, a calculation method can be used (Ringard & Guyot-Hermann, 1988).

In a wet granulation, disintegrants may be added either intragranularly (+), extragranularly (-) or both (±). There are many conflicting reports about the best mode of incorporation (Lowenthal, 1972). Shotton & Leonard (1976) studied the effect of intragranular and extragranular disintegrants on disintegration time and the particle size of disintegrated tablets. They showed that the extragranular formulations disintegrated much more rapidly than the intragranular ones, but the latter gave a much finer dispersion of particles. A combination offered the best compromise. Similarly, Rubinstein & Bodey (1974) showed that 2% intragranular and 12.5% extragranular

disintegrant produced the best overall performance in tablets of calcium orthophosphate. The effect of super disintegrant location on tablet dispersion is discussed in Chapter 4.

### 1.5.4.3 Binder.

The binder and solvent in wet granulation have a profound effect on the disintegration properties of the tablet. The aqueous solubility of the binder will affect tablet disintegration properties, and this is well documented. Holstius & Dekay (1952) evaluated the disintegration of tablets containing different binders and disintegrants, and found that binders were more important.

**Table 1.5: Water soluble binders.**

| Binder |
|---|
| **Hydroxyethylcellulose** |
| **Hydroxypropylmethylcellulose** |
| **Methylcellulose** |
| **Polyvinylpyrrolidone** |
| **Sucrose** |

Kwan et al (1957) found that the rate of solution of the binder in water could determine disintegration behaviour since the dissolution rates of the dry binder films were in the same order as tablet disintegration times. Healy (1976) studied the effect of binders on the deaggregation of lithium carbonate tablets. He concluded that deaggregation was governed by the solubility of the binder and was unrelated to tablet disintegration rates. This is supported by Wells (1980), who reported that water soluble binders yielded faster tablet deaggregation and disintegration than insoluble binders.

However, there are examples of water insoluble binders used successfully in water dispersible tablets found in patented literature. However, in a generic approach, it is logical to initially evaluate water soluble binders (Table 1.5) as these are less likely to cause long disintegration times.

Binder solvent should be carefully selected, since this has a major influence on granule properties (Wells & Walker, 1983) and consequently tablet disintegration times. Using acetylsalicylic acid and PVP as a binder, Wells & Walker (1983) studied the influence of binder vehicle upon tablet properties. A range of ethanol : water mixtures provided binder vehicles in which the solubility of the drug widely differed. They demonstrated that high drug solubility produced tablets with poor disintegrating properties. This was attributed to solute migration and the formation of drug crystals in the solid bridges (secondary binding). To minimize secondary binding, a granulating fluid in which the drug and other excipients have low / no solubility should be chosen.

### 1.5.4.4 Diluents.

A diluent or filler facilitates the compression of a formulation and gives tablet strength and acceptable appearance. Diluents can be broadly categorised by their aqueous solubility and choice is dependent on the physico-chemistry of the drug; solubility, hygroscopicity, compression properties, instability and the method of manufacture. Diluents used in dispersible tablet formulations are listed in Table 1.6.

Chowhan et al (1991) investigated the effect of tablet matrix solubility on the efficacy of sodium starch glycollate, crospovidone and croscarmellose sodium in wet granulated tablets. As aqueous solubility increased, super disintegrant efficacy was reduced

(Paronen et al, 1985). When the tablet matrix is highly water soluble, porosity rapidly increases due to drug and excipient dissolution and there is space where super disintegrant particles swell without exerting pressure and disintegrating force is reduced (Ferrari et al, 1995). Decreased water penetration into the tablet may result from disintegrant particles partially filling the voids inside the tablet and increased viscosity due to rapid dissolution of the tablet matrix (Graf et al, 1982). These factors increase disintegration times.

Super disintegrant efficacy is related to the overall solubility of the tablet matrix. The importance of diluent aqueous solubility depends upon overall concentration and the solubility of other components, namely the active. Sugars are often incorporated into dispersible tablet formulations to improve taste and compression properties. However, tablets containing large quantities of sugars do not disintegrate conventionally, but decrease in size by solution from the tablet surface and disintegration times may be long (Guyot-Hermann & Leblanc, 1985).

**Table 1.6: Diluents and fillers.**

| Water insoluble | Partially soluble | Water soluble |
|---|---|---|
| **Calcium carbonate** | **Pre-gelatinised starch** | **Dextrose** |
| **Calcium phosphates** | **Low-substituted hydroxy-** | **Lactose** |
| **Magnesium carbonate** | **propyl cellulose -** | **Mannitol** |
| **Microcrystalline cellulose** | | **Sorbitol** |
| **Starch** | | **Sucrose** |

Hygroscopicity should also be considered. The effectiveness of super disintegrants in wet granulated tablet formulations containing highly hygroscopic materials is

decreased, probably due to a reduction in disintegrant activity by the hygroscopic component(s) competing for locally available water (Johnson et al, 1991).

Microcrystalline cellulose (MCC) is a particularly useful diluent in dispersible tablet formulations. It has high compressibility (Mendell, 1972; Lamberson & Raynor, 1976), produces strong tablets of low friability (Khan & Rhodes, 1975a), and is synergistic with disintegrants because of capillary properties.

Low-substituted hydroxypropyl cellulose (L-HPC) is also a useful diluent for rapidly disintegrating formulations. It is differentiated from classical HPCs by its low substitution and low aqueous solubility. In addition to facilitating compression, it also accelerates tablet disintegration due to high swelling capacity. Gissinger and Stamm (1980a) showed that the maximum swelling of L-HPC was about 10 times that of MCC.

In addition to modifying compression properties, the diluent may also function to protect the drug. In a dispersible lamotrigine formulation (Fielden, 1992), calcium carbonate protects the drug from acid hydrolysis when dispersed in water. Similarly, calcium carbonate and magnesium hydroxide have been used to buffer acid-labile dideoxy purine nucleoside derivatives (Ullah & Agharkar, 1993).

**1.5.4.5 Lubricants.**

Stearic acid salts, such as magnesium stearate, are potentially unsuitable in dispersible tablet formulations because they are hydrophobic, and may form a scum giving an unpleasant appearance (Mendizabel & Alcobendas, 1996). Paradoxically, however, most commercial dispersible tablets are lubricated using magnesium stearate. A "halo"

of magnesium stearate will be visible when a dispersible tablet is soluble but tablet formulations usually disperse to yield a suspension rather than a solution. The magnesium stearate will be adsorbed onto other undissolved constituents and does not form a layer at the surface.

Miller & York (1988) reviewed water soluble lubricants including sodium / magnesium lauryl sulphates and polyethylene glycols, which were much poorer lubricants than magnesium stearate with poor anti-adherent properties. Magnesium stearate is a relatively cheap, non-toxic material and therefore a logical first choice. However, it reduces the rate of water penetration into a tablet (Ganderton, 1969). Bolhuis et al (1982) studied the effect of magnesium stearate on insoluble tablet systems containing slightly and strongly swelling disintegrants. Although tablet swelling properties were hardly affected by magnesium stearate, in some cases disintegrant efficiency was. For a

**Table 1.7: Mechanism of action of strongly swelling disintegrants (after Bolhuis et al, 1982).**

| |
|---|
| **Water absorption of disintegrant particles at tablet surface.** |
| ⇓ |
| **Swelling of disintegrant particles** |
| ⇓ |
| **Breakup of tablet surface structure.** |
| ⇓ |
| **Water penetration into the opened tablet structure.** |
| ⇓ |
| **Chain reaction of absorption and disruption.** |
| ⇓ |
| **Disintegration** |

slightly swelling but hydrophilic disintegrant such as crospovidone, the penetration of water into the tablet is the controlling step in the process of disintegration, which consequently is strongly affected by the presence of hydrophobic lubricant. Conversely,with a strongly swelling disintegrant such as Ac-Di-Sol or Explotab, a chain reaction of disruption of the tablet structure (Table 1.7) is the dominant factor in the process of disintegration and is hardly affected by the presence of a hydrophobic lubricant.

When disintegrant poisoning does preclude a hydrophobic lubricant, a water soluble one should be used. Sodium stearyl fumarate will provide a clear solution (Saleh et al, 1984) and has been recommended as a good alternative to magnesium stearate (Suren, 1971). Magnesium stearate forms a water insoluble hydrophobic film around particles. This film interferes with tablet binding, causing a reduction in crushing strength (particularly with increased mixing intensity) and decreases the wettability of particles, which can cause increased disintegration and dissolution times. Sodium stearyl fumarate does not form a water insoluble hydrophobic film around particles, and is claimed not to have the disadvantages of magnesium stearate in respect of tablet strength, disintegration and dissolution (Lindberg, 1972).

### 1.5.4.6 Tablet coating.

The BP (2000) defines a dispersible tablet as an "uncoated tablet that produces a uniform dispersion in water." By definition, film coating has been considered by some to be inconsistent with the principle of a dispersible tablet (Groenendaal & Sijbrands, 1986). It has been claimed, without supporting evidence, that a dispersible tablet designed to be dispersed in water or directly swallowed, should preferably be film-

coated to aid swallowing (Fielden, 1992). Film coats may become tacky when moist and cause tablets to adhere to moist surfaces, whereas uncoated tablets have little adhesivity (Al-Dujaili et al, 1986). Disintegration generally reduces the risk of adhesion, but the possible "explosive" swelling of a rapidly disintegrating drug core from a film-coating of slowly dissolving material may increase the risk of retention in the oesophagus (Florence & Salole, 1990). Indeed, this problem was encountered with the early formulations of Cetiprin® (Al-Dujaili, 1985).

Compression coating of dispersible tablets may function to protect drugs that are prone to sublimation and recrystallisation on exposure to the atmosphere. Groenendaal & Sijbrands (1986) outlined an invention for the formulation of compression-coated cyclandelate tablets dispersing within three minutes. The dispersible core is covered by a compression coating rendered quickly dispersible by the addition of suitable disintegrants (e.g. Explotab).

### 1.5.4.7 Surfactants.

Fraser & Ganderton (1971) and Caramella et al (1990b) showed that in rapidly disintegrating tablets, water penetration determined the rate of disintegration. If a liquid is penetrating into a capillary in a solid, this is determined by the adhesion tension (AT).

$$\mathbf{AT} = \gamma_{L/V}\ \mathbf{Cos.}\ \theta \qquad \textbf{Equation (1.1)}$$

Where $\gamma_{L/V}$ is the surface tension between the penetrating liquid and its vapour, and $\theta$ is the contact angle. As $\gamma_{L/V}$ is always positive, the spontaneity of the process will be

controlled by **Cos.** θ. For penetration into capillaries under no applied pressure, AT must be positive. Reducing the value of θ will increase the magnitude of AT, to a maximum when θ = 0. Since surfactants increase the rate of wetting of the solid by reducing the critical angle, water soluble surfactants such as sodium lauryl sulphate could be added to a dispersible tablet, especially if it contains a hydrophobic drug.

### 1.5.4.8 Organoleptic properties.

Many drug substances are unpalatable and unattractive in their natural state (York, 1988). It is widely recognised that if a dosage form is unpalatable, patient compliance may be reduced, especially for long term treatment. Therefore, in dispersible tablet development, organoleptic properties are important and flavours and sweeteners may be added to modify and mask taste. A water insoluble derivative of the drug will have little or no taste and can be used as long as bioavailability remains unchanged. For example, it is better to disperse diclofenac as the free acid rather than the sodium salt because it has low solubility and is virtually tasteless (Murphy & Matthews, 1990). The dispersion produced by a tablet must have an acceptable mouth feel and this is related to the particle size and viscosity. Even where the microparticles are of a small size (0.3 to 0.6mm), when swallowed they may be perceived as individual grains in the mouth and can be caught on the spaces between the teeth (Ventouras, 1988). Ventouras (1988) describes a novel water dispersible tablet which rapidly disintegrates in water to form a homogenous high viscosity suspension that can be swallowed. This is claimed to overcome the unpleasant mouth feel of individual particles.

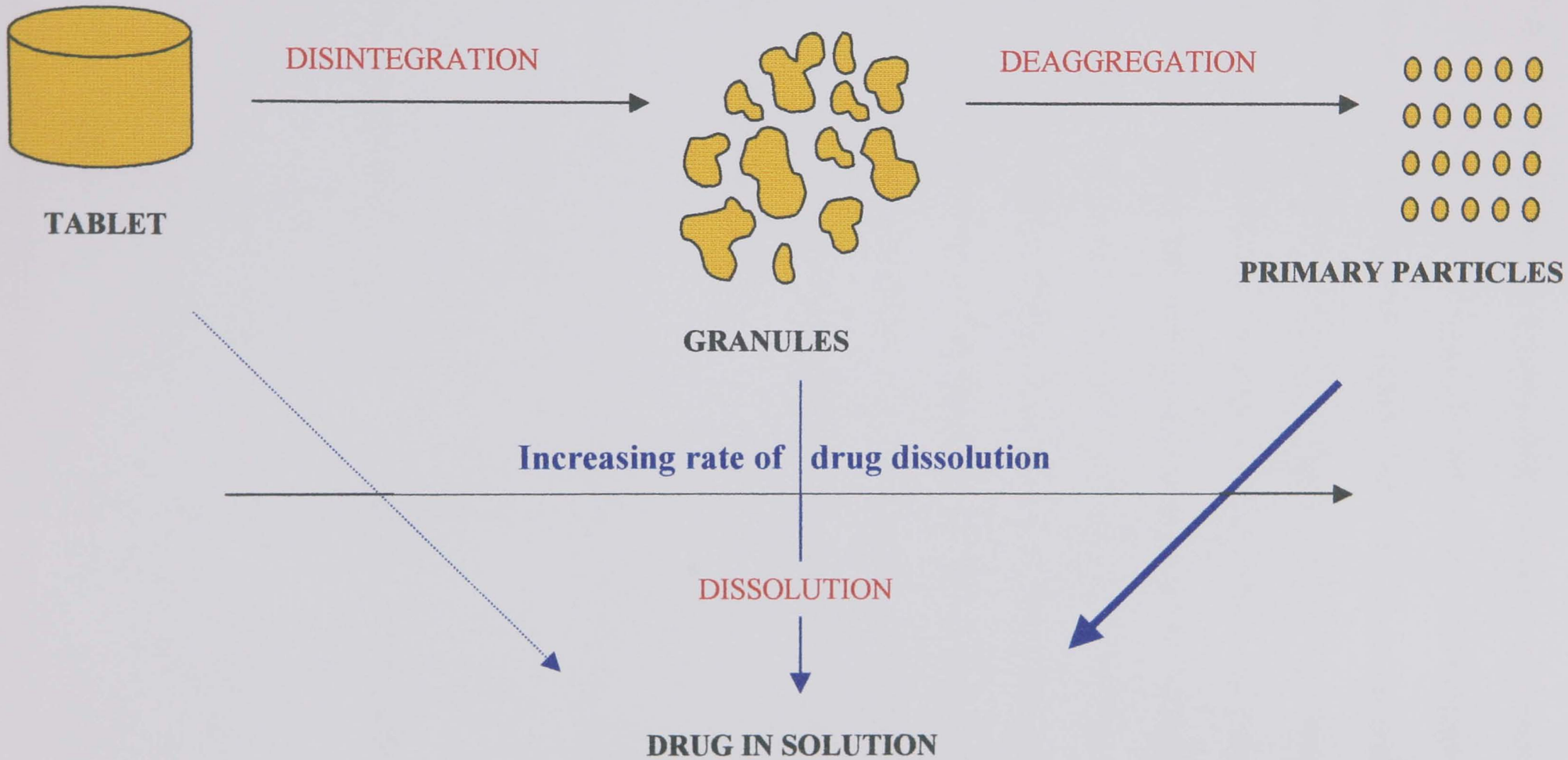



**Figure 1.4: Disintegration, deaggregation and dissolution in the breakdown of solid oral dosage forms (after Wagner 1969, Wells, 1980).**

## 1.6 The process of tablet disintegration and deaggregation.

Disintegration occurs when a tablet disrupts into fragments when brought into contact with fluid. This is followed by deaggregation, disintegration beyond the original granule size into the primary particles. Figure 1.4 relates tablet disintegration processes to drug dissolution (after Wagner, 1969; Wells, 1980) and shows the mutual dependence of disintegration and drug dissolution for a poorly soluble drug. Dissolution occurs most rapidly from primary particles since the available surface area is large, but to a limited extent from the intact tablet, and the aggregates generated during tablet disintegration (Wells, 1980). The degree to which each process contributes depends on the formulation. In an optimised dispersible tablet, size reduction to primary particles will proceed rapidly and mainly by deaggregation. In less efficient systems, granule size reduction may be more dependent on drug dissolution to yield a dispersion of particles below 710μm. The latter process is generally slower and is more likely to result in unacceptable dispersion times.

Smoluchowski (1918) showed that deaggregation followed a first-order process and Aguiar et al (1967) developed the equation:

$$\ln N_s / N_s - N = Kt \qquad \textbf{Equation (1.2)}$$

where $N_s$ is the number of particles when deaggregation is complete and N, the number at time t.

Berry & Ridout (1950) using alginic acid and potato starch as disintegrants observed two distinct patterns of disintegration. Alginic acid gave particles smaller than the original granules, while starch produced tablets which broke down into several large

fragments which then disintegrated into small aggregates.

Roland (1967) recognised three distinct processes:

| | |
|---|---|
| *i) Macrogranules:* | granules or plates which sediment rapidly and are non-dispersible. |
| *ii) Microgranules:* | (a) agglomerates which break down to microgranules. |
| | (b) immediate breakdown to microgranules. |
| *iii) Colloidal suspension:* | breakdown to particles of the original powder blend. |

In a dispersible tablet, type (iii) is ideal, however iia) and iib) may also be satisfactory since they both yield microgranules, which are freely dispersible.

Using a Coulter Counter™ to measure surface area, Rubinstein & Bodey (1976) demonstrated with dibasic calcium phosphate tablets containing maize starch, that tablets with identical disintegration times through a 10 mesh screen may undergo different types of breakdown and yield different surface areas. They theorised two types of disintegration in tablets:

Type A: Large fragments break down to produce smaller fragments; these fragments in

turn break down into finer fragments until, at the disintegration time, the largest aggregates just pass through the 10 mesh screen.

Type B: Large fragments erode away so that their size gradually diminishes. The disintegration time is the time taken for the largest particles to erode and pass through the screen.

Type A yielded a relatively large number of fragments, whereas type B produced a lot of fine material with relatively few large fragments.

## 1.7 Disintegration mechanisms.

### 1.7.1 Capillary action.

Although many different theories have been proposed relating to the mechanism of disintegration, the requirement for water uptake and penetration is a common factor. Some disintegrants act principally by capillary action. To draw water into the porous network of a tablet (called wicking) is essential (Khan & Rhodes, 1975b; Mitrevej & Hollenbeck, 1982). Some disintegrants, act principally by capillary action. Kornblum & Stoopak (1973) observed that cross-linked PVP rapidly takes up water even though there is little swelling. Rudnic et al (1983) showed that as the structure of sodium starch glycollate was modified to increase water uptake, disintegrant efficiency improved.

Water moving forward into a capillary network may cause tablet disintegration either by air pressure, or by breaking bonds in contact with water (Guyot-Hermann, 1992). Cartilier et al (1987) rejected swelling as the principle mechanism of action of native starches and proposed that disintegration occurs due to the elimination of interparticular cohesion forces when the tablet is placed in water. Hydrophilic, insoluble, granular

disintegrant particles create high capillary pressure within the tablet because of the formation of pores with hydrophilic walls and voids between particles. With conventional starches, porosity is not necessary if there is a continuous network of particles conducting water through the tablet by suction (Hess, 1978). This led to the theory of a critical disintegrant concentration to give a continuous hydrophilic network (Ringard & Guyot-Hermann, 1988).

Many workers have studied the influence of tablet porosity on disintegration time and results are conflicting. Porosity cannot generally be correlated with disintegration time (Nogami et al, 1967; Francois et al, 1972) and depends upon compression pressure, the base material and disintegrant type.

The interfacial characteristics of capillary walls is important. If hydrophilic, water can penetrate. The force with which this occurs may be theoretically quantified by the Jurin equation (Guyot-Hermann, 1992):

$$\textbf{Force of water penetration} = 2\gamma \cos\theta / r \qquad \textbf{Equation (1.3)}$$

where $\gamma$ is the surface tension of the penetrating liquid, $\theta$ is the contact angle of the liquid on the pore walls and r is the radius of the pore which depends on the particle size and compression force. To increase capillary action, the value of $\theta$ can be reduced by modifying the formulation. With a hydrophobic drug, the pore walls should be lined with a hydrophilic substance such as a disintegrant. Theoretically, a smaller pore will increase the force. However, this depends on the hydrophilicity of the system, and must be continuous, otherwise water cannot penetrate into the whole tablet structure and disintegration will be slow (Nakai et al, 1977).

Caramella et al (1990b) used multiple linear regression analysis to relate water penetration and force development to disintegration at different solubility and hydrophilicity. Water penetration was shown to correlate with disintegration time for a given formula, and was shown to be independent of the type of disintegrant and base material.

Ringard & Guyot-Hermann (1981) proposed a particle-particle repulsion theory of tablet disintegration based upon the observation that particles that do not swell may still disintegrate tablets. By altering the dielectric constants of the disintegrating media, they attempted to identify electrical repulsive forces and concluded that water is required for tablet disintegration. In the presence of water, there is a destruction of the cohesive forces between tablet particles followed by a particle-particle repulsion. Kanig & Rudnic (1984) criticised the reasoning of Ringard & Guyot-Hermann (1981) because they did not address the deformation phenomenon of starches, cited Avicel as a non-swellable excipient and did not take into consideration its wicking action.

### 1.7.2 Disintegrant swelling.

It has often been assumed that tablet disintegration is based upon the swelling of disintegrant particles (Berry & Ridout, 1950). The idea is logical since for many years disintegrants were essentially starches and their derivatives. Logically, when disintegrant particles swell, they push away the surrounding particles which enclose them and cause disintegration of the tablet. Many workers agree with this idea (Patel & Hopponen, 1966; List & Muazzam, 1979a; Caramella et al, 1984). When compression force is increased, disintegration time may decrease to a minimum (Colombo et al, 1980), which corresponds to a reduction in porosity, optimum for swelling force

development.

However, tablet porosity may be greater than the expansion of starch granules (Ingram & Lowenthal, 1966) and when tablets containing carboxymethyl starches with different swelling capacities are compared, those which do not swell may function as efficiently as those that do (Guyot-Hermann & Ringard, 1981).

In some materials there is a lack of correlation between the percentage swelling and maximum disintegrating force (Guyot-Hermann, 1992). A large volume expansion may not be required for effective disintegration if the disintegrant possesses enough swelling force. Using computer aided apparatus for the simultaneous measurements of water uptake and swelling force (Caramella et al, 1988), Ferrari et al (1995) investigated the influence of porosity and solubility on the "force equivalent" (the force developed per milligram of water taken up) of sodium starch glycollate. The ability of the disintegrant to develop disintegrating force depended on the type of base material. Higher swelling efficiency was observed in water-insoluble materials. In a highly soluble matrix, porosity rapidly increases due to drug dissolution and disintegrating force is reduced because there is more space for disintegrant particles to swell without disrupting the matrix. In all formulations, an increase in the "force equivalent" was observed by increasing the compression force. The influence of compression force, however, was more pronounced in insoluble base materials because disintegrant swelling plays a major role in the disintegration process and becomes more effective as porosity decreases (Colombo et al, 1984; Caramella et al, 1986). In water soluble bases, other mechanisms (dissolving, disruption of hydrogen bonding etc.) make disintegrant swelling and the influence of tablet porosity less important (Ferrari et al, 1995). For a

given formulation, the force equivalent tends to increase as mean pore diameter decreases. Some supporters of the swelling theory claim that there is a critical pore diameter. Using conventional starch Berry & Ridout (1950) claimed that if pore diameters are greater than the diameter of swollen disintegrant particles, no disintegration will take place, i.e. no pressure. However, in tablet disintegration, more than one mechanism occurs, and optimising conditions for one may compromise another. Porosity and mean pore diameter will affect both swelling and capillary action. The rate of swelling will affect disintegration. Nogami et al (1969) developed a method to measure swelling and water uptake simultaneously. Using a refined apparatus, Gissinger and Stamm (1980a) found a positive correlation between the rate of swelling and disintegrant action.

As the disintegrant particles swell there should be minimal accommodation by the tablet matrix. With slow swelling and force generation, the matrix may be able to adjust to the stress without loss of structural integrity. Rapid force development is less likely to result in matrix accommodation, but this will depend upon the elasticity and solubility. The rate of swelling of a disintegrant is related to the rate at which disintegrant force develops (Rudnic et al, 1982):

$$dF / dt = Sw\, dV / dt \qquad \textbf{Equation (1.4)}$$

where dV / dt is the rate of swelling and Sw is a constant for any given matrix at a constant porosity. If the porosity is high, then dV / dt will be governed by the properties of the disintegrant, such as surface area or number of functional groups which can be hydrated. However, if the porosity is low, then the value of dV / dt may be more dependent on the rate at which water can reach the disintegrant (Rudnic et al, 1982).

### 1.7.3 Deformation.

Return to the original shape of compressed particles on exposure to moisture may contribute to the disintegration process. Although starch, cellulose powder and cellulose derivatives primarily exhibit elastic behaviour at higher pressures, some deformation of particles can be observed (Erdos & Bezegh, 1977; Fuchs, 1970; Hess, 1978). Lowenthal (1972) reported that deformed starch particles do not regain their original shape when wetted, although Erdos & Bezegh (1977) reported the opposite. Hess (1978), with the aid of photomicrographs, demonstrated that disintegrant particles which deformed during tablet compression were shown to return to their original shape when exposed to moisture. Fuhrer (1964) showed that the swelling ability of potato starch granules may be improved by deformation during compression.

However, starch or cellulose particles may undergo permanent deformation on compression. Starch grains in carboxymethylstarches may be damaged at high pressure (Guyot-Hermann, 1992) with a consequential partial gelatinisation that may reduce water penetration and increase tablet disintegration times. Guyot-Hermann (1992) concluded that, if regeneration of the original shape of compressed particles on wetting contributed to the disintegration process, its effect is only likely to be secondary. Most studies have used starches and therefore the occurrence of this phenomenon in other disintegrants is uncertain.

### 1.7.4 Heat of wetting.

Matsumaru (1959) was the first to propose that the heat of wetting of disintegrant particles could be a mechanism of action. He observed that starch granules exhibit

slight exothermic properties when wetted, and theorised that the heat of absorption released would cause the expansion of air contained in the porous void spaces inside the tablets and cause disintegration due to over-pressure. However, List & Muazzam (1979b) found that exothermic reactions upon wetting did not occur for all disintegrants and when significant heat of wetting is generated there is not always a corresponding decrease in disintegration time. This does not describe the action of most modern disintegrating agents (Kanig & Rudnic, 1984).

## 1.8 The measurement of tablet disintegration and deaggregation.

The BP (1996) disintegration test determines the time taken for breakdown into particles that pass through an 8 mesh (2000μm) screen. This is less discriminating than earlier tests using a 10 mesh (1700μm) screen, which have been criticised for non-characterisation of the undermesh material (Nair & Bhatia, 1957). Consequently tablets with similar disintegration times may have different deaggregation profiles (Sandell & Helmstein, 1971). It only measures the time to reach the endpoint of disintegration, and little or no information can be gathered about the kinetics of the process. Visual observation of the samples during the test is the only way to approximate the onset of various mechanistic events that occur before the endpoint of disintegration.

Many workers have attempted to measure tablet deaggregation. The first attempt to measure particle size distribution was by Nogami et al (1959 a & b). They measured the size distribution of powders from their heats of solution. The thermal change $\Delta T$ is a measure of the drug dissolved, $d\Delta T / dt$ being proportional to the surface area of the tablet at time t. The disintegration time was taken as the time to produce maximum

surface area and $d\Delta T / dt$ reaches a maximum. By plotting $d^2 \Delta T / dt^2$ against t, the particle size distribution was derived from the slope of the curve.

Sanders (1969) attached three sieves of aperture 0.81, 0.54, 0.27mm in series within a tube to the USP disintegration apparatus. The percentage by weight of particles retained on each mesh was determined by loss on drying. Sandell (1970) simplified this by resting the tablet on the top screen (0.1, 0.5, and 2.0mm) standing in a beaker of water. However, these early techniques were poorly sensitive and did not discriminate between narrow size distributions or take into account the dissolution process which is significant in the disintegration process (Wells, 1980).

Van Ootegham et al (1969) quantified the size distribution produced by the disintegration of aspirin-starch tablets more accurately using a Coulter Counter™. They attempted to suppress the dissolution process by using drug-saturated water. Longer disintegration times were observed in tablets compressed at higher pressure. The recovered particles were smaller due to fragmentation but deaggregation to the original particles did not occur because the small particles agglomerated and the large fragmented. However, higher starch concentrations increased deaggregation. Khan & Rhodes (1975d) used a Coulter Counter™ to study the effect of compression force on the disintegration of dicalcium phosphate dihydrate tablets. The particle size generated was smaller at low pressure where fragmentation predominated, whereas at higher forces recombination occurred.

To investigate the effects of mode of disintegrant incorporation on the extent of tablet deaggregation, Shotton & Leonard (1972) combined wet sieving with Coulter™ analysis.

Fine particles less than 90μm were measured by Coulter Counter™ and wet sieving was used to characterise the larger aggregates. Extragranular resulted in more rapid disintegration, whereas intragranular yielded a finer dispersion. An optimum was obtained by using intra- and extragranular together, so that the extragranular agent breaks up the tablet rapidly to the original granules and the intragranular agent reduces the original particles. Wells (1980) criticised the way they combined the two incompatible size distributions and did not take account of drug dissolution and the solubility of the PVP binder.

Healey (1976) used a Coulter Counter™ to study the influence of binders on the deaggregation of lithium carbonate tablets. A tablet was placed in a USP basket containing a saturated solution of the drug and rotated at 100 rpm. The basket was removed periodically and a 13-point analysis was performed on the suspension using a 280μm orifice tube in drug saturated electrolyte. The mass of aggregates retained in the basket was determined by loss on drying. Tablets without a binder, deaggregated to the size of the original powder blend. Increasing concentration of soluble binders such as PVP slowed the rate of deaggregation. Insoluble binders e.g. starch resulted in disintegration to coarse aggregates that did not deaggregate further. The rate of deaggregation was dependent on the solubility of the binder and not the disintegration time.

These techniques were not capable of monitoring changes in particle size during disintegration and subsequent dissolution. Wells & Rubinstein (1976) used a Model $T_A$ Coulter Counter™, capable of handling and processing data instantaneously and followed the simultaneous processes of tablet disintegration, deaggregation and

dissolution using generated surface area. Using digoxin 250mcg tablets they found a good correlation between the time to achieve maximum generated surface ($T_{max}$) and the dissolution rate of the tablets. They concluded the rate of deaggregation was a primary variable in determining the dissolution rate of the tablets. No correlation was found between maximum surface area generated ($S_{max}$) and the dissolution rate of the digoxin tablets. The drug to excipient ratio was very low (0.0025) and therefore $S_{max}$ was almost totally determined by excipients. Conversely, using phenylbutazone tablets 100mg BP with a high drug to excipient ratio, Rubinstein & Wells (1977) showed a correlation between tablet dissolution and $S_{max,}$ which was largely determined by the drug. However, there was no correlation between $T_{max}$ and the dissolution rate, which they attributed to the sugar coating present on the tablets.

Using paracetamol as a model drug, Nelson & Wang (1977) described a method of determining the time course of disintegration by numerical analysis of the experimental dissolution profile of a tablet and the dissolution characteristics of the primary drug particles in the tablet. However, the principles were demonstrated in an idealised system. Tablets were directly compressed from drug particles of uniform size to permit disintegration directly to primary particles. The method assumes that powder dissolution follows the Hixson-Crowell equation (Hixson & Crowell, 1931). The system may not be applicable to a granulated system where the primary particles are modified and have a more complex disintegration pattern. Also the system assumes that compression force does not alter primary particles, and therefore may only be applicable at low force.

More recently, Timmermans et al (1995) monitored the disintegration kinetics of tablets

using a resultant-weight apparatus. Tablet disintegration is a process involving weight and / or volume variations with time, such as water penetration (weight increase), particle swelling (volume increase) and loss of tablet integrity (weight and volume increase). The apparatus used a force transmitter device to measure changes in force acting on the immersed tablet with time, shown to reflect changes in tablet weight and / or volume (Timmermans & Moes, 1990a & b; 1991). Resultant-weight – time curves showed disintegration kinetics. The total disintegration time was defined as the duration of time from immersion to that corresponding to the intersection between the resultant-weight curve and the zero baseline (where no solid is present). The method is potentially useful for tablets that do not have a homogeneous structure. For example, monitoring disintegration lag time in film-coated tablets and profiles of multi-layered tablets comprised of rate differing drug delivery formulations (e.g. instant and slow release). However, the authors suggested that for conventional fast disintegrating tablets, where the slope is steep and linear, the method offers no advantage to a conventional disintegration test. The resultant-weight apparatus does not permit agitation during the test and therefore the results are not directly comparable to those using a vertically moving basket.

The process of tablet disintegration and deaggregation has been largely ignored over the last two decades. Nowadays, tablet dissolution is more frequently used to assess conventional swallow tablet formulations. For a poorly soluble drug, dissolution indirectly measures the deaggregation rate and therefore deaggregation studies are not routinely carried out. However, the trend towards the formulation of dispersible tablets is evident across Europe (Martin, 1987). During development, there is a minimum requirement that deaggregation down to 710μm is measured. The technique should be

simple to allow rapid routine testing without requiring complex equipment.

**Table 1.8: Mesh sizes used in disintegration testing.**

| Mesh number (BS.410, 1986) | Aperture size (μm) | Application |
|---|---|---|
| **8** | **2000** | **BP (1990) Disintegration test** |
| **10** | **1700** | **BP (1973) Disintegration test** |
| **12** | **1400** | |
| **14** | **1180** | |
| **22** | **710** | **Dispersible tablet BP (1990)** |
| **40** | **425** | **Solution rate BP (1973)** |

Wells (1996) proposed that the current BP disintegration apparatus could be modified and made more discriminating for development purposes by using six different mesh sizes instead of one (Table 1.8). Testing of dispersible tablets in the current research will use this method. By adjusting the pH of the immersion fluid to change aqueous solubility, tablets of high dispersion will be quickly identified. Wells (1996) proposed that this apparatus might be useful during the development of conventional swallow tablets. Dealing with the cause is always better than the effect. Slow tablet deaggregation may cause long dissolution times. A method which can quickly identify poor deaggregation, may save many hours of labour intensive dissolution measurements. By carrying out disintegration and dissolution tests in the same media, good correlation is likely (Wells, 1996). Lu et al (1965) found a good correlation between disintegration and dissolution times in simulated intestinal fluid (pH 6.5) where the pH is similar for both tests.

## 1.9 Aims and objectives.

The main aim of this study was to develop generic technology for the formulation of dispersible tablets using wet granulation and conventional tableting. The project studied the formulation of two classes of drugs that are potentially difficult to formulate as dispersible tablets: high dose, poorly compressible drugs and high dose, highly soluble drugs. Paracetamol and Na-p-aminosalicylate were used as models of each class respectively. It was hoped that the work would generate general formulation guidelines that could be applied to formulating novel, high dose, poorly compressible or highly water soluble drugs in the future. Evaluation of the use of the super disintegrants sodium starch glycollate (Explotab), croscarmellose sodium (Ac-Di-Sol), crospovidone (Kollidon-CL) and polacrin potassium (Amberlite IRP88) in dispersible tablet formulations was considered important.

A wet granulation process should allow the highest possible proportion of drug to be compressed. Using paracetamol, a drug with low aqueous solubility, work in Chapter 3 aimed to determine the influence of granule size and intragranular disintegrant type on tablet properties, particularly dispersion characteristics.

In patents relating to dispersible tablets, it is often claimed that dispersion can be optimised using disintegrants in combination, with a different type employed intra- and extragranularly. Usually, however, the reasoning behind specific choices is not given. The work in Chapter 4 systematically studied disintegrant combinations in a general paracetamol formulation, with regard to rationalising disintegrant choice intra- and extragranularly and in combination.

Chapter 5 investigated the idea of "disintegrant poisoning" during the wet granulation process. The aim was to determine whether uptake of drug by disintegrant during wet granulation and recrystallisation at surfaces on drying, reduced subsequent disintegrant performance.

In a highly soluble matrix, rapid drug dissolution creates a viscous barrier at the tablet surface, which retards water penetration (Graf et al, 1992) and reduces disintegrant swelling force (Ferrari et al, 1995), causing tablets to dissolve away slowly (Khan & Rhodes, 1973) rather than deaggregate. The objective of Chapter 6 was to make a tablet matrix containing a highly soluble drug disperse.

# CHAPTER 2

# 2. MATERIALS AND METHODS.

## 2.1 Materials.

### 2.1.1 Choice of drug: Paracetamol.

Paracetamol is a widely used analgesic and antipyretic, typically at a dose of 500mg. Paracetamol (Figure 2.1) generally occurs as large monoclinic crystals, a form which is not easily deformed and resists compaction (Shangraw, 1989). Its poor compressibility results in weak and unacceptable tablets with a high tendency to cap (Krycer et al, 1982). This has been attributed to a low degree of plastic flow, high elasticity (Duberg & Nystrom, 1986), weak bonding between particles (Obiorah & Shotton, 1976) and a high brittle fracture propensity (Alderborn et al, 1985) during compaction.

It is soluble 1:70 in water and 1:7 in ethanol at 25°C. Its melting point is 169-172°C. Paracetamol is very stable in aqueous solution and its maximum stability is in the pH range 5 to 7 (Koshy & Lach, 1961; Connors et al, 1979). Instability of paracetamol is due to its hydrolysis which yields p-aminophenol and acetic acid.

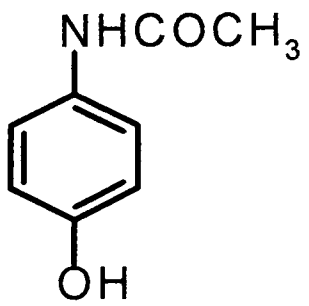



**Figure 2.1: Paracetamol.**

Its poor compaction properties, high dose and low aqueous solubility make paracetamol a suitable drug for this study. The paracetamol was obtained from Rhône- Poulenc, Roussillison, France.

### 2.1.2 Excipients.

#### 2.1.2.1 Disintegrants.

**(a) Ac-Di-Sol.**

Ac-Di-Sol, Type SD-711 (croscarmellose sodium, USPNF), FMC Corporation, Philadelphia.

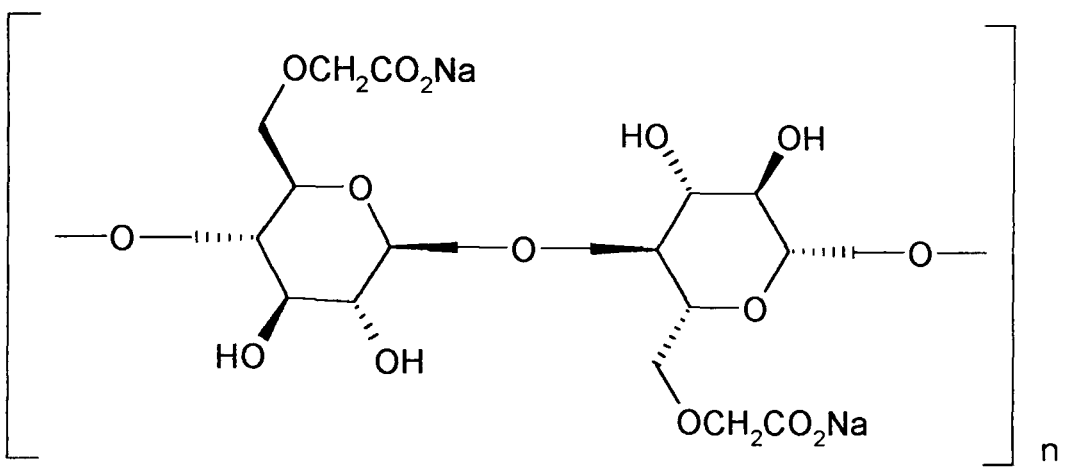



**Figure 2.2: Carboxymethylcellulose sodium (structure shown with a degree of substitution of 1.0).**

Ac-Di-Sol is a polymer of carboxymethylcellulose sodium. It has a low degree of substitution, 0.63-0.85 (Caramella et al, 1995), and a high degree of internal cross-linking which make it practically insoluble in water. The sodium substitution confers hydrophilicity upon the material.

Ac-Di-Sol is a white, hygroscopic powder which has a size distribution such that, not more than 2% is > 73.7μm and not more than 10% > 44.5μm.

The cross-linking of the polymer allows the disintegrant to swell and absorb many times its weight in water without loosing individual fibre integrity. It combines

rapid swelling (to 4-8 times its original volume) with wicking activity. Bhatia et al (1978) suggested that strong elastic relaxation of the cellulose fibres may leave large pores in a tablet matrix, facilitating rapid water penetration and the rupture of hydrogen bonds.

**(b) Explotab.**

Explotab (sodium starch glycollate BP, USPNF), Edward Mendell Co. Inc., Reigate, Surrey.

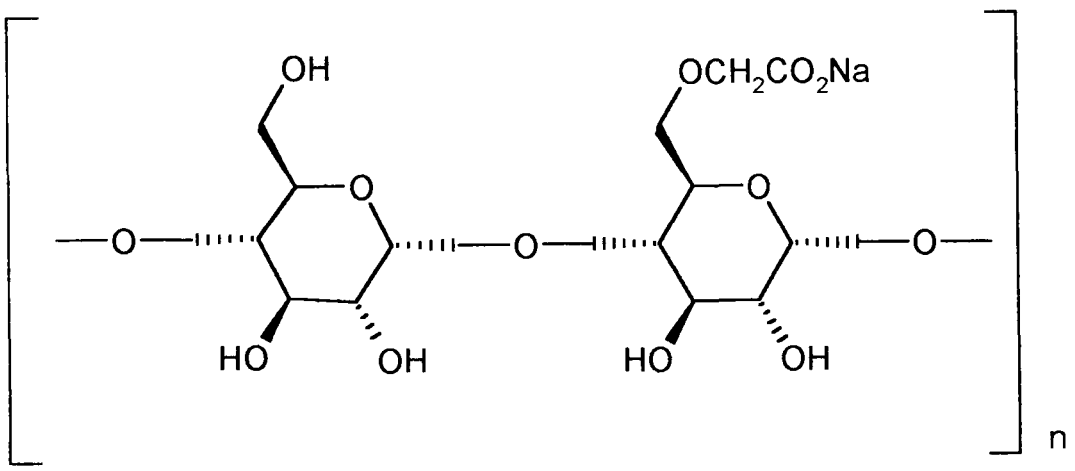



**Figure 2.3: Sodium starch glycollate.**

Sodium starch glycollate is the sodium salt of a poly-α-glucopyranose in which some of the hydroxyl groups are in the form of the carboxymethyl ether. The molecular weight is typically $5 \times 10^5 - 10^6$ daltons.

It may be characterised by the degree of substitution and cross-linking. Sodium starch glycollate is a white, free-flowing powder, consisting of oval or spherical granules. The average particle size of the brand Explotab is 42μm and all are less than 104μm.

Sodium starch glycollate is practically insoluble in water and sparingly soluble in ethanol (95%). At a concentration of 2% w/w it disperses in cold water and settles in the form of a highly hydrated layer. In water it swells up to 300 times its volume and disintegration occurs by rapid uptake of water followed by rapid and enormous swelling (Khan & Rhodes, 1975 b & c; Wan & Prasad, 1989).

**(c) Kollidon-CL.**

Kollidon-CL (cross-linked polyvivylpyrrolidone, USPNF), BASF plc., Cheadle, Cheshire.

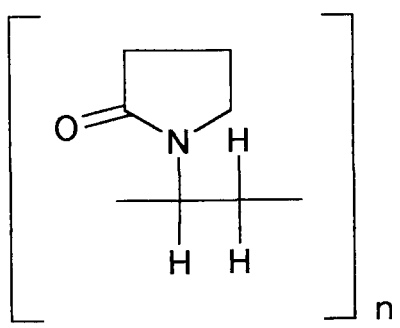



**Figure 2.4: Polyvinylpyrrolidone.**

Crospovidone is a synthetic cross-linked homopolymer of N-vinyl-2-pyrrolidone. It has a molecular weight > $10^6$ daltons. It is insoluble in water and most common organic solvents, but is highly hydrophilic.

The polymer is a white, odourless, free-flowing hygroscopic powder. It is commercially available in different particle sizes. Kollidon-CL has a particle size distribution such that approximately 50% of particles are greater than 50μm and a maximum of 1% greater than 250μm.

Shangraw et al (1980) reported that because of its low bulk density ($0.26 gml^{-1}$), crospovidone tends to distribute itself evenly in the tablet matrix, increasing

surface area and the number of sites for capillary action. Disintegrant activity is mainly due to its rapid capillary action and pronounced hydration capacity with secondary swelling activity (Korblum & Stoopak, 1973). Crospovidone swells only slightly in water (Bolhuis et al, 1982).

**(d) Amberlite IRP88.**

Amberlite IRP88 (polacrin potassium, USPNF), Sigma, St. Louis, USA.

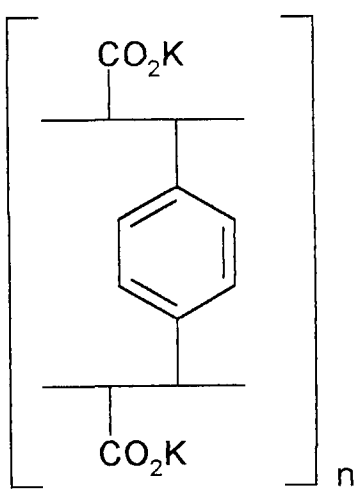



**Figure 2.5: Polacrin potassium.**

Amberlite IRP88, a weakly acidic cation-exchange resin, is a cross-linked polymer of methacrylic acid divinylbenzene, as the potassium salt. It is hydrophilic but insoluble in water and non-adhesive.

Disintegrant properties are due to its swelling capacity in aqueous solutions. Gissinger & Stamm (1980a) showed that the rate at which pure samples of Amberlite IRP88 sucked in water was considerably less than Ac-Di-Sol, Explotab, or Polyplasdone XL. Amberlite IRP88 is able to develop a high swelling force despite a low swelling volume, and therefore, disintegrant activity is less

influenced by the availability of water than some other super disintegrants (Caramella et al, 1989).

### 2.1.2.2 Binder.

PVP Kollidon 90 (polyvinylpyrrolidone, BP, USP), BASF plc., Cheadle, Cheshire.

PVP K90 is a soluble grade of PVP, obtained by free radical polymerisation of vinylpyrrolidone in water or isopropanol, yielding a chain structure of polyvinylpyrrolidone (Figure 2.4). PVP K90 is soluble in a wide range of solvents; this extends from extremely hydrophilic solvents, such as water, to hydrophobic liquids (Kollidon, technical information, 1992). PVP K90 has an approximate molecular weight of $10^6$ daltons.

### 2.1.2.3 Diluent.

Avicel PH101 (microcrystalline cellulose, BP, USPNF), FMC Corporation, Philadelphia.

Microcrystalline cellulose is a purified, partially depolymerised form of α-cellulose. It has a molecular weight of 36000 daltons. It occurs as a white, tasteless, crystalline, hygroscopic powder.

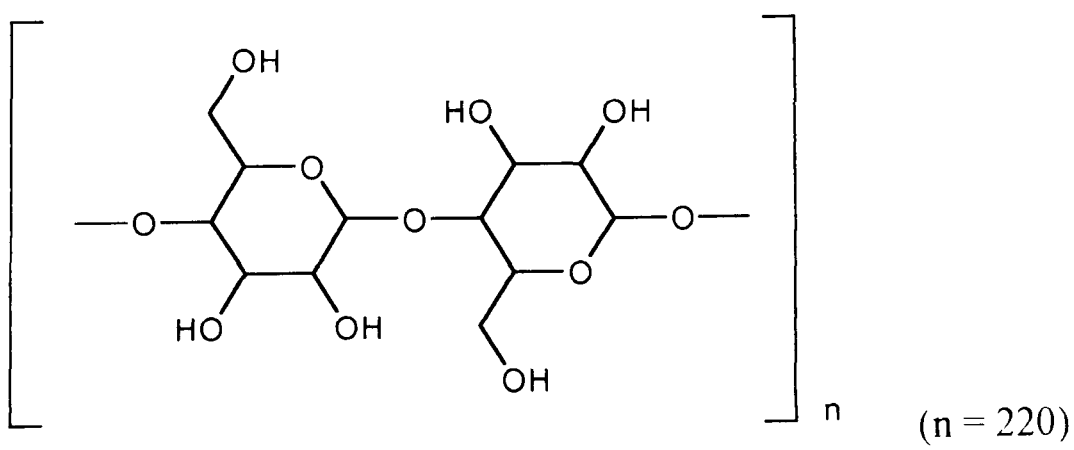



**Figure 2.6: Microcrystalline cellulose.**

Microcrystalline cellulose is highly compressible (Lamberson & Raynor, 1976; Mendell, 1972) and is often added to systems containing paracetamol to improve compaction properties (Malamataris et al, 1984; Bangudu & Pilpel, 1985). It is commercially available in different particle size grades. Avicel PH101 has a nominal mean particle size of 50μm and is commonly used in wet granulation processes.

Avicel PH101 is practically insoluble in water. It swells very slightly in water. Bolhuis et al (1982) showed a volume increase of $0.4cm^3cm^{-3}$ in water at 20 ± 0.5 °C. It only acts as a disintegrant at high concentrations, but may be synergistic with disintegrants because of its excellent wicking activity (Mendes & Roy, 1979).

**2.1.2.4 Lubricant.**

Magnesium stearate BP, BDH Laboratory supplies, Poole, England.

Magnesium stearate is a fine white powder of low bulk density, and is greasy to the touch. Its empirical formula is $(C_{17}H_{35}CO_2)_2Mg$. It possesses good anti-adherent and poor glidant properties in addition to lubricant action (York & Miller, 1988). Magnesium stearate is hydrophobic (Lerk et al, 1976) and is practically insoluble in water.

**2.1.3 Solvents.**

Absolute ethanol, BDH Laboratory supplies, Poole, England.

Methanol (Spectrosol®), BDH Laboratory supplies, Poole, England.

## 2.2 Methods.

### 2.2.1 Tablet manufacture.

#### 2.2.1.1 General method of granulation.

Paracetamol and Avicel PH101 were weighed out on a top pan balance (Sartorius type B4100, Sartorius, Germany). Super disintegrants, PVP K90 and magnesium stearate were weighed on an analytical balance (Oertling, UK).

Paracetamol, Avicel PH101 and intragranular disintegrant (if included in the formulation) were dry mixed in a planetary mixer (Kenwood chef model KM 200, Kenwood Limited, Hampshire) on speed setting one for fifteen minutes. PVP K90 was dissolved in distilled water to give a binder concentration of 6.0 % w/v. To granulate, the binder was added slowly over five minutes through a glass funnel to control the flow rate. The resultant material was wet massed through the required sieve. Granules were tray dried in an oven (Philip Harris model DZS, Philip Harris Ltd, Shenstone) at 55°C for 16 hours. In addition to the temperature and the duration of the drying process, the moisture content and flow rate of the circulating air can affect granule strength (Sherwood, 1929) and therefore to standardise, the amount of granules tray-dried was kept within an approximate range of 600-900g. The residual granule moisture content was determined by loss on drying as described in section 2.2.1.3. Granules were stored in double polythene bags until use to prevent moisture loss / gain.

If included, the appropriate quantity of 2% w/w extragranular disintegrant was mixed with the dried granules at 21 rpm for twenty minutes in a cube mixer (Erweka type UG, N° 21276, Erweka Apparatus, G.m.b.H. Heusenstamm, Germany). To lubricate, 1%

w/w of magnesium stearate was added to the granules and mixed in the cube mixer at 21 rpm for five minutes. Granulations were stored in amber glass airtight jars until use.

### 2.2.1.2 Granulation size analysis.

Granule size analysis was carried out using wire sieves (Endecott Ltd., London) and a sieve shaker (Endecott model E.V.I.1, Endecott Ltd., London). The sizes were: 1400, 1000, 850, 710, 500, 355, 250, 150, 75, 45 μm and a 100g sample was placed on the top sieve. The sieve shaker was operated for 10 minutes at a moderate speed, a period of time which had been found adequate for complete separation of the granules. The mass of granules retained on each sieve was weighed (Precisa model 3510D, Oerlikon, Zurich). Cumulative % oversize (by mass) was plotted against granule size on Logarithm × probability graph paper. Mean granule size was taken as that at 50% cumulative weight oversize. The mean and standard deviation of each size distribution are the result of two determinations.

### 2.2.1.3 Granulation loss on drying.

Granule moisture content was determined by loss on drying. Approximately 500mg samples were accurately weighed in glass weighing bottles and placed in an oven heated to 55°C (Memmert, Germany). At regular intervals these were removed, their lids replaced and allowed to cool in a desicator containing silica before re-weighing. At constant weight the percentage loss on drying was calculated. Mean and standard deviations were calculated from the results of three determinations. The loss on drying of tablets was not determined since this could not be accurately measured without crushing the tablets, a process which could result in moisture changes.

### 2.2.1.4 Tablet compression.

Granulations were compressed on a Manesty F3 single punch tablet machine (Manesty Machines Ltd, Liverpool). This was set to produce flat, bevelled-edged 12.5mm diameter tablets at the required weight and compression forces. A strain gauge and voltmeter (Apt Electronic Industries Ltd.) were connected to the tablet machine. This was calibrated to allow compaction force to be recorded on a chart recorder (Scientific & Medical products Ltd. model SE 120, Manchester). For all tablet batches compression speed was kept constant at 21 cycles per minute. The first 10 and last 10 tablets of each batch were rejected to prevent weight variation due to initial flow resistance and insufficient weight of granulation to the hopper respectively.

In preliminary work, problems with uncontrolled moisture sorption occurred in granules during tableting. Highly variable moisture contents made direct comparison of different dispersible tablet formulations impossible. The relative humidity of the tableting area monitored morning, midday and afternoon over a 3 week period, ranged from 38-65% RH. Fisher & Shepky (1995) studied the effect of hygroscopic components on the sorption characteristics of tablets and reported that hygroscopic additives did not begin to have any marked effects on the sorption isotherms until the relative humidity reached 62%. However this cannot be applied to all systems as the critical relative humidity, the relative humidity above which significant moisture sorption occurs, will differ according to the components. Therefore, in the present work a limit of 50% RH was set as the maximum relative humidity at which tableting was carried out.

### 2.2.2 Tablet evaluation.

#### 2.2.2.1 Tablet storage.

After ejection tablets were stored in amber glass air tight containers. Testing was carried out 24 hours after ejection to allow for equilibration hardening and elastic recovery before measurement.

#### 2.2.2.2 Disintegration testing.

All formulations were tested using the same disintegration test apparatus. Disintegration / dispersion properties were measured using a Manesty Mk.4 disintegration tester (Manesty Machines Ltd, Liverpool). A 2.8cm diameter tube which is vertically raised and lowered 30 times a minute, 7.5cm through water. The apparatus was modified by attaching a different screen size to the base of each tube (2000, 1700, 1400, 1180 and 710 μm) to allow better characterisation of the particle size distribution produced on tablet disintegration.

600ml of disintegration media was used, a quantity such that the basket of the disintegration apparatus just broke the surface of the water on its upward motion. As in the BP test for dispersible tablets, distilled water at 19- 21°C was used. Plastic discs were not used; tablets did not float and in preliminary work plastic discs were observed to sometimes stick to tablets resulting in less consistent disintegration times. Their removal also improved the visibility of the end points. Moreover, the effect of magnesium stearate on tablet disintegration can be masked by the use of discs in the disintegration apparatus (Bolhuis et al, 1981), therefore not giving a true indication of dispersion characteristics. The use of discs also reduces discrimination between good and bad formulations since the palpable residue on the mesh would not pass through

without applying pressure and thus violating the principle of fluid penetration and particle separation (Wells, 1996). The mean disintegration times and the relative standard deviations are the result of six individual tablets.

Statistics were not performed on the disintegration test results. The current British Pharmacopoeia (2000) does not use statistical analysis to compare disintegration data. The interpretation of the meaning of differences requires consideration of the magnitude of disintegration times and their relative standard deviations and a degree of common sense needs to be applied. For example, in formulations containing intragranular Ac-Di-Sol which tended to disperse well within a minute and the results of six tablets were within 2 or 3 seconds of each other, then differences of approximately 20 seconds between tablets can be considered meaningfully different. Conversely, in tablets where the magnitude of disintegration times and standard deviations of the six tablets tested is much greater, then obviously different limits apply. Na-p-aminosalicylate tablets tended to take 8-10 minutes to disintegrate and the results of six tablets were within approximately 0.5 to 1 minute of each other. Clearly differences in disintegration times needed to be greater than a minute to be meaningful.

#### 2.2.2.3 Crushing strength.

The diametrical crushing strength of tablets was measured using a Schleuniger Model 6D tablet tester. The mean and relative standard deviation were calculated from 20 determinations.

### 2.2.2.4 Friability.

20 tablets were dusted and weighed ($W_0$) before rotation (25 rpm) for 4 minutes in a Roche friabilator (J.Engelsmann A.G., Germany). Tablets were then dusted and re-weighed (W) and the friability calculated as the % loss in weight. The friability (F) is given by equation 2.1.

$$\mathbf{F\ \% = (W_0 - W) / W0 \times 100} \qquad \textbf{Equation (2.1)}$$

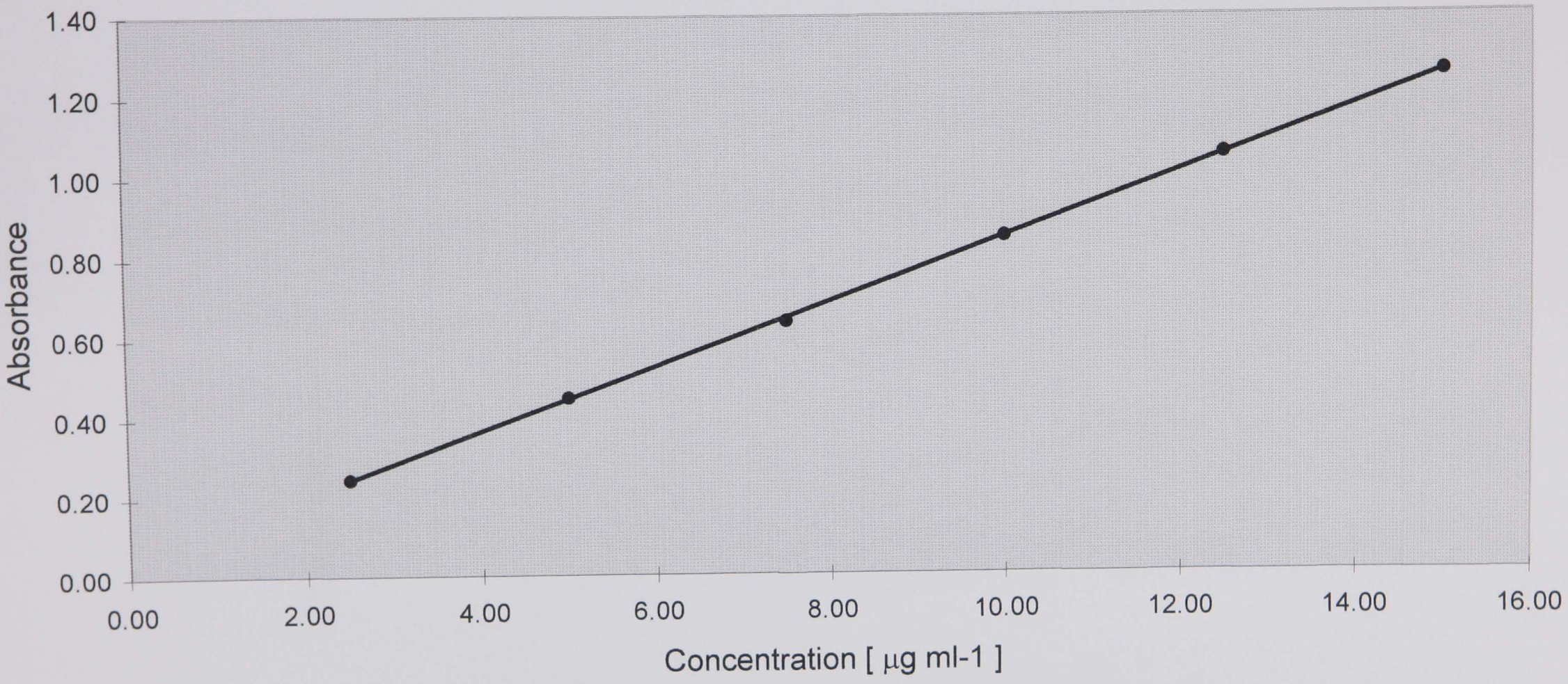
### 2.2.2.5 Weight variation.

20 tablets were weighed using an analytical balance (Oertling, model WA205-1AAZM13A-A, Oertling, UK). The mean and relative standard deviation was calculated.

## 2.2.3 UV assay of paracetamol.

The assay of paracetamol content was carried out in methanolic HCl (0.01N HCl) to ensure complete extraction of the drug. UV absorbances were measured on a diode array spectrophotometer (Hewlett Packard HP 8452A, Waldbrom, Germany). A wavelength scan was carried out on a 10μg $ml^{-1}$ Paracetamol solution. An absorbance maximum was observed at 250nm. The UV absorbances for solutions containing different concentrations of paracetamol (2.5 to 15μg $ml^{-1}$) in methanolic HCl at 250nm were determined (Figure 2.7). The best fit for the Beer's law plot of UV absorbance versus paracetamol concentration is given in Equation 2.2. Methanolic HCl was used as a blank.

**Figure 2.7: Calibration curve of paracetamol In methanolic HCl at 250nm.**




**Absorbance = 0.0809C + 0.0472 (r = 0.9999) Equation 2.2**

where C is the concentration of paracetamol in $\mu g\ ml^{-1}$

# CHAPTER 3

# 3. INFLUENCE OF GRANULE SIZE ON THE PROPERTIES OF WET GRANULATED PARACETAMOL TABLETS.

## 3.1 Introduction.

A wet granulation process should use the minimum quantity of super disintegrant and allow the highest possible proportion of drug to be compressed. In preliminary work, with some intragranular disintegrants, a few large granules failed to disperse through a 710μm mesh which resulted in a gross distortion of the disintegration profile and therefore unacceptable dispersion. Although mean dispersion times for a dispersible tablet may be within accepted limits, high variability is unsatisfactory.

Granule size has an important role in compression and physical properties, particularly disintegration and many workers have investigated the effect of granule size. Kassem et al (1972) using a lactose / starch / sodium alginate granulation found that as granule size decreased, the disintegration time increased and the coefficient of variation for disintegration time decreased. Decreasing granule size causes tablet weight to increase and weight variation to decrease because of better die fill and a decrease in the proportion of void spaces. The increase in die fill leads to an increase in compression and better bonding between the granules, which may cause an increase in hardness. Increased inteparticulate bonding makes particle separation in the disintegration process more difficult. A reduction in weight variation with decreasing granule size gives more uniform compression and a reduction in tablet to tablet variation in disintegration time.

Femi-Oyewo & Adefesco (1993) studied the influence of granule size on paracetamol granule and tablet properties. Wet granulated paracetamol, lactose and maize starch using PVP in five granule size fractions (75-250μm, 250-355μm, 355-500μm, 500-

710μm and 710-1000μm), gave disintegration times that decreased with increasing granule size up to the 355-500μm size fraction. This correlated with tablet hardness, which increased with decreasing granule size due to the increase in points of contact for bonding during compression. This reversed on increasing granule size beyond 500μm, but the results were not explained. The disintegration times of tablets of the different granule size fractions were generally lower than that of the unfractionated granules, which also corresponded to their hardness results.

Femi-Oyewo & Adefesco (1993) also studied the variation in drug content uniformity of tablets with granule size. The paracetamol content increased as the granule size decreased to the 710-500μm size fraction, attributed to increased granule flow-rate and tablet weight. Further reductions in size produced lower drug contents, but with fluctuations. This was explained by several factors: reduced flow-rate as granule size was reduced below certain values, heterogeneous distribution of the drug, which may result at the compression stage, and the solubility of the drug (1.428% w/v). With such a solubility, more of the drug could be bound within larger granules by the binder solution, since these contain more of the binder. This was confirmed by the fact that the tablets of the larger granules (above 500μm) contained higher drug content than those of smaller granules.

Marks & Sciarra (1968) studied the effect of granule size on the physical properties of tablets using starch as a disintegrant in a lactose / dicalcium phosphate dihydrate granulation. As granule size decreased, tablet weight increased and weight variation decreased. With decreasing granule size there is better die fill because of the decrease in the proportion of voids resulting in closer packing of the granules. However, they did

not find a relationship between granule size, tablet hardness and disintegration time, attributed to the limitations of the disintegration apparatus.

Leonard (1971) studied the influence of granule size on the disintegration time of wet granulated sulphadiazine : maize starch formulations. Three size fractions (1200-1000μm, 850-710μm, 500-355 μm) were compared and individual tablets were externally lubricated to reduce the effect of magnesium stearate. The effect of granule size depends upon the disintegrant position. When the disintegrant was incorporated intragranularly, disintegration time decreased as granule size increased. The results agree with Forlano & Chavkin (1960) for tablets of lactose and sodium bicarbonate using intragranular cornstarch. Leonard (1971) attributed this to larger granule size increasing the pore and void spaces, thus increasing the rate of penetration by disintegrating medium. Results were not clear when the disintegrant was located extragranularly. Smaller granulations tended to produce more rapid disintegration i.e., a reversal of the effect found with intragranular starch. The size of the voids and pores determined disintegration time. Tablets compressed from smaller granules will have less void space than those from larger sizes and swelling of extragranular disintegrant will more quickly disrupt the matrix. Swelling force generation will be less at higher extragranular porosity. Leonard (1971) observed that the effect of granule size on the particle size distribution recovered after disintegration was influenced by disintegrant location. When extragranular, the particle size distribution decreased with granule size and a high proportion of the granules recovered did not deaggregate beyond the original granule size. Microscopic examination showed that the extragranular starch rapidly fractured intergranule bonds, but did not significantly disrupt individual granules. However, in formulations containing intragranular disintegrant, granule size had little effect on the particle size recovered.

The effect of granule size is dependent on the particular system and there is little work using super disintegrants. The present work studies the relationship in a wet granulated paracetamol formulation (Table 3.1) to determine the influence of disintegrant type. Tablet deaggregation has been measured down to 710μm, and the use of Explotab, Ac-Di-Sol, Kollidon-CL and Amberlite IRP88 compared.

## 3.2 Materials and Methods.

### 3.2.1 Materials.

See Section 2.1.

### 3.2.2 Methods.

#### 3.2.2.1 Granulation method.

Paracetamol, a relatively water insoluble drug was chosen to highlight differences in disintegrant efficiency. With a very water soluble drug it is likely that any differences in the amount of completely or partially undisintegrated granules resulting from differences in disintegrant efficiency would be more difficult to detect due to their faster dissolution (Gordon & Chowhan, 1987).

Granulations were made using Explotab, Ac-Di-Sol, Kollidon-CL and Amberlite IRP88 as intragranular disintegrants in the general formula given in Table 3.1. When used at high concentration, differences in disintegrant efficiency can be masked (Rudnic et al, 1981). Therefore for comparison, a low level of 2% w/w disintegrant was used. The method of granulation is given in Section 2.2.1.1. Granules were wet massed through 2000μm and dry sieved through 1400μm aperture sizes. Lubrication was carried out after separation of the granule fractions.

**Table 3.1: Standard formulation.**

| Component | Mg / tablet | % w/w |
|---|---|---|
| Paracetamol | 500.00 | 75.76 |
| Avicel PH101 | 127.00 | 19.24 |
| Intragranular disintegrant | 13.20 | 2.00 |
| PVP K90 | 13.20 | 2.00 |
| Magnesium stearate | 6.60 | 1.00 |
| Compression weight | 660.00 | 100.00 |

### 3.2.2.2 Granule size of the bulk granulation.

See Section 2.2.1.2.

### 3.2.2.3 Separation of the granules into different size fractions.

Different granule size fractions were obtained by sieving using mesh wire sieves (Endecott Ltd., London) and a sieve shaker (Endecott Ltd., London). The following sieves were arranged in decreasing aperture size (μm): 1400, 1000, 710, 500, 250. The shaker was operated for 20 minutes and the resultant size fractions (1400-1000μm, 1000-710μm, 710-500μm, 500-250μm) stored in airtight amber glass bottles. Before fractionation, a quantity of each bulk granulation was removed as a control.

### 3.2.2.4 Determination of granule fraction drug uniformity.

The paracetamol content of the bulk granulation and granule size fractions were determined by UV assay as described in section 2.2.3. Dilutions were made to give a paracetamol concentration of approximately $10\mu gml^{-1}$. 50mg of each sample was dissolved in 50ml of methanolic HCl and ultrasonicated (Sonicor instrument corporation, New York) for 30 seconds to ensure complete dispersion. 1.5ml of this

solution was pipetted into a 100ml volumetric flask and made up to volume with methanolic HCl. The resultant solution was filtered through a 0.2μm cellulose acetate filter (Nalgene™, BDH Laboratory supplies, Poole England), the first few ml discarded and the absorbance measured three times to give a mean value. Results were duplicated for each sample. The paracetamol content of the bulk granulation and each granule size fraction was determined and the content as a percentage of the unfractionated granulation calculated. To check for possible interference by the PVP K90 present in the granules, which is soluble in methanol, a 10μg $ml^{-1}$ solution of PVP K90 was scanned at 250nm. No interference occurred.

### 3.2.2.5 Loss on drying of the granule size fractions.

See Section 2.2.1.3.

### 3.2.2.6 Compression.

The method in Section 2.2.1.4 was used. Tablets containing intragranular Ac-Di-Sol were compressed first and forces of 7, 10, 15 and 20 ± 0.5kN were used. However, since 5kN was found to give tablets of acceptable integrity in subsequent formulations, 5 rather than 7kN was used to widen the pressure range studied.

### 3.2.2.7 Evaluation of tablets.

See Section 2.2.2

## 3.3 Results and Discussion.

### 3.3.1 Mean granule size of the unfractionated granulations.

Sieve analysis showed that the size distribution and mean granule size of the bulk granulations was similar with each intragranular disintegrant (Table 3.2).

**Table 3.2: Mean granule size of the bulk granulations.**

| Granulation | Mean granule size [μm] ± rsd |
|---|---|
| Explotab | 550 ± 0.41 |
| Ac-Di-Sol | 560 ± 0.41 |
| Kollidon-CL | 560 ± 0.35 |
| Amberlite IRP88 | 550 ± 0.38 |

* where rsd ≡ relative standard deviation.

### 3.3.2 Effect of granule size on drug content.

**Table 3.3: The effect of granule size on drug content uniformity.**

| Granule size fraction [μm] | Paracetamol content % ± rsd [Bulk granule = 100%] | |
|---|---|---|
| | Explotab | Ac-Di-Sol |
| 1400-1000 | 98.22 ± 0.57 | 98.79 ± 0.14 |
| 1000-710 | 99.89 ± 0.97 | 97.53 ± 1.19 |
| 710-500 | 98.99 ± 1.26 | 102.55 ± 1.52 |
| 500-250 | 101.38 ± 1.10 | 100.76 ± 0.86 |

Absorbance readings for the assays of granulations containing Amberlite IRP88 and Kollidon-CL were erroneous and therefore values are omitted from Table 3.3. A slurry of each disintegrant in methanolic HCl was filtered and the absorbance at 250nm measured. Interference was shown to occur with both disintegrants. This would indicate

they contain components that are soluble in methanolic HCl which cause interference. Kollidon-CL forms reversible chemical complexes with a large number of drugs, particularly those with a phenol group including paracetamol in acidic media (Kollidon, technical information, 1992) and will also cause assay interference.

For granulations containing Ac-Di-Sol and Explotab, the paracetamol content of the different granule fractions were similar (Table 3.3). Smaller size fractions had slightly higher paracetamol content, but practically the differences were small. Thus differences in tablet properties compressed from different granule size fractions cannot be attributed to drug content. The present results show that the material was well mixed and granulated and is supported by no capping in any of the formulations. Intragranular disintegrants were used at low concentration (2% w/w) and it is very unlikely they affected drug distribution and therefore the drug content of the granule fractions containing Amberlite IRP88 and Kollidon-CL were assumed to be similar to those of Ac-Di-Sol and Explotab.

### 3.3.3 Granule loss on drying.

After drying, the four bulk granulations had very similar residual moisture contents (Table 3.4). After fractionating, loss on drying of the smaller granule size fractions tended to be higher than for the larger fractions, due to the greater surface area for moisture loss occurring during fractionation. This highlights a potential problem in fractionating granulations. Although loss was not major in this case, the effect may be more pronounced in formulations of greater hygroscopicity.

**Table 3.4: Granule loss on drying.**

| Granule size [μm] | Mean loss on drying ± rsd [% w/w] Granules before compression | | | |
|---|---|---|---|---|
| | Explotab | Ac-Di-Sol | Kollidon-CL | Amberlite IRP88 |
| Bulk granulation | 1.49 ± 5.37 | 1.44 ± 8.33 | 1.13 ± 5.31 | 1.10 ± 6.36 |
| 1400-1000 | 1.40 ± 8.57 | 1.47 ± 6.12 | 1.07 ± 7.48 | 1.00 ± 11.00 |
| 1000-710 | 1.32 ± 4.55 | 1.31 ± 12.21 | 1.06 ± 10.38 | 0.93 ± 8.60 |
| 710-500 | 1.29 + 6.20 | 1.37 ± 13.87 | 0.90 ± 7.78 | 0.80 ± 15.00 |
| 500-250 | 1.19 + 8.40 | 1.30 ± 3.85 | 0.92 ± 5.43 | 0.53 ± 16.98 |

### 3.3.4 Tablet weight uniformity.

**Table 3.5 Effect of granule size on tablet weight uniformity.**

| Granule size fraction [μm] | **Explotab** | | **Ac-Di-Sol** | | **Kollidon-CL** | | **Amberlite IRP88** | |
|---|---|---|---|---|---|---|---|---|
| | $\bar{x}$ **[mg]** | rsd | $\bar{x}$ **[mg]** | rsd | $\bar{x}$ **[mg]** | rsd | $\bar{x}$ **[mg]** | rsd |
| Bulk granulation | **667** | 1.17 | **664** | 1.34 | **663** | 0.90 | **662** | 0.45 |
| 1400-1000 | **655** | 0.93 | **658** | 0.59 | **655** | 1.22 | **665** | 0.45 |
| 1000-710 | **656** | 0.91 | **664** | 0.45 | **668** | 0.90 | **672** | 0.59 |
| 710-500 | **660** | 0.76 | **663** | 0.45 | **659** | 0.76 | **667** | 0.45 |
| 500-250 | **657** | 0.30 | **661** | 0.30 | **669** | 0.75 | **662** | 0.61 |

All weights fell within the range 660mg ± 5% (Table 3.5). In agreement with others (Kassem et al, 1972; Femi-Oyewo & Adefeso, 1993), weight variation decreased as the granule size decreased due to better die fill and closer, more uniform packing.

Tablet weight did not increase with granule size because die fill was adjusted for each granule fraction to give the correct mean tablet weight. This was necessary to avoid

increases in tablet crushing strength resulting from greater tablet weights (Kassem et al, 1972) which would complicate the interpretation of results.

### 3.3.5 Tablet crushing strength.

For all formulations and granule size fractions, tablet crushing strength increased with compaction force due to greater interparticulate bonding (Figures 3.1 - 3.4). Disintegration time and tablet crushing strength may be directly related (Femi-Oyewo & Adefeso, 1993). The increased interparticulate bonding makes particle separation in the deaggregation process more difficult.

At the same compression force, granule size fractions containing intragranular Explotab and Ac-Di-Sol tend to produce tablets of slightly higher crushing strengths than those containing Kollidon-CL and Amberlite IRP88. These differences may be attributed to slightly higher residual granule moisture content on compaction (Table 3.4). Garr & Rubinstein (1992) studied the influence of moisture content on the consolidation and compaction properties of paracetamol. They found that increasing moisture content up to 6% w/w progressively increased compact strength. They attributed this to the hydrodynamic lubrication effect of moisture, which increases force transmission from the upper to lower punch, facilitating greater powder consolidation. In addition, it is thought that the improved plastic deformation resulting from increased moisture content promotes interparticle contact and plasticisation of the binder (Wells et al, 1982) and this is more likely. Crushing strength was generally unaffected by granule size, although occasionally it decreased with granule size. Magnesium stearate has a negative influence on tablet crushing strength by weakening bonds between particles (Lewis & Shotton, 1964). Larger granule sizes have greater coverage. However, the negative

**Figure 3.1: Effect of granule size fraction on the crushing strength of tablets containing 2% intragranular Explotab.**

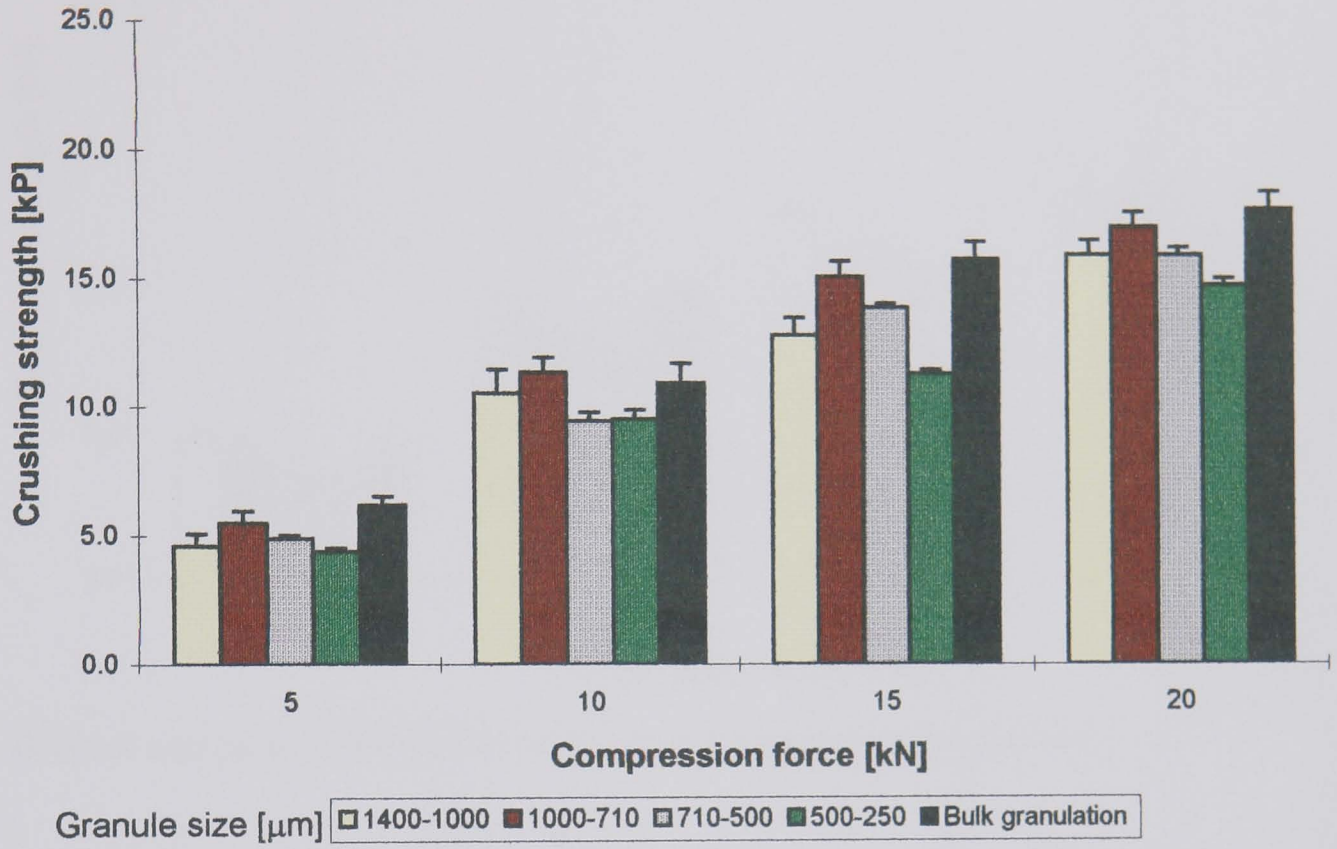



**Figure 3.2: Effect of granule size fraction on the crushing strength of tablets containing 2% intragranular Ac-Di-Sol.**

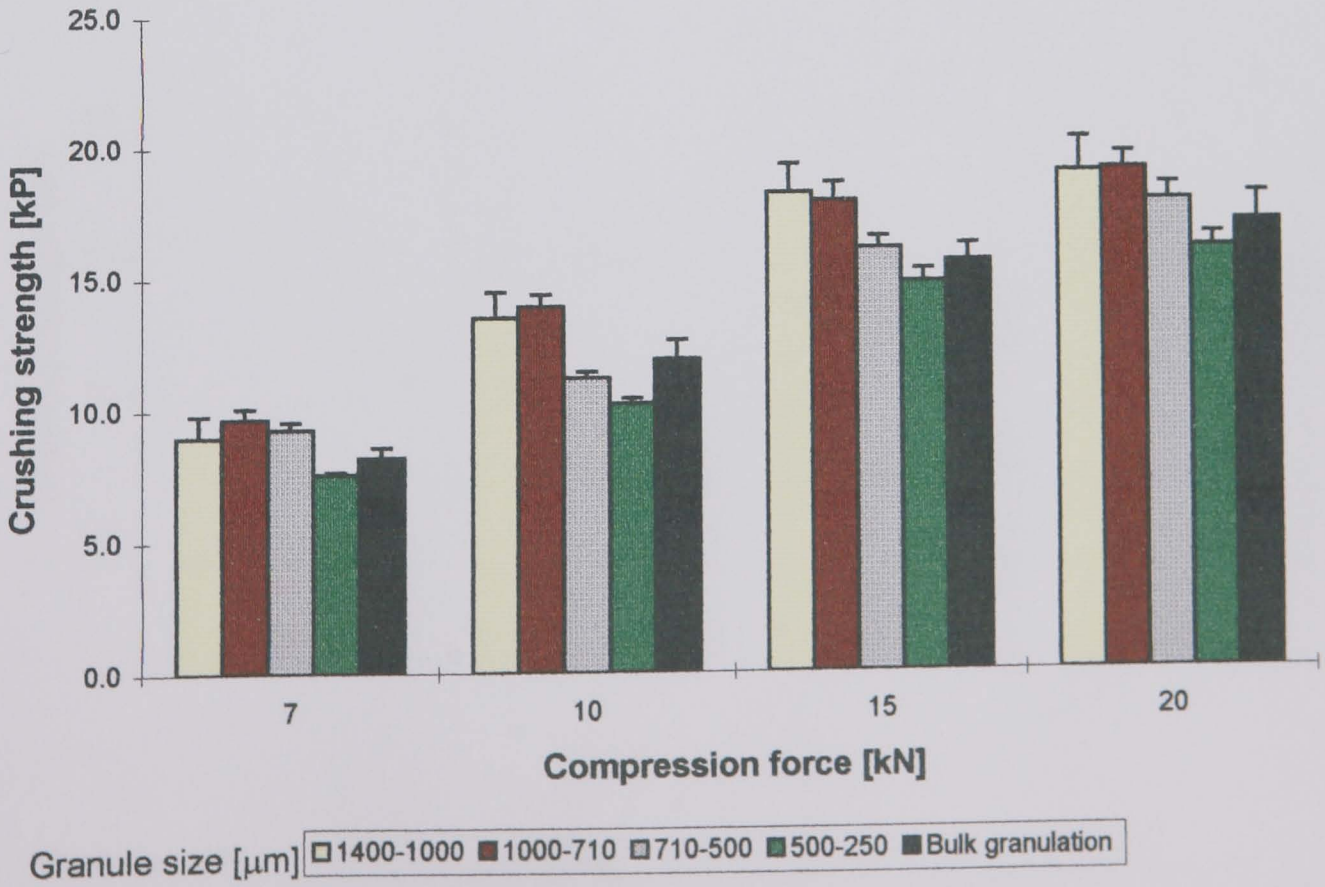


**Figure 3.3: Effect of granule size on the crushing strength of tablets containing 2% intragranular Kollidon CL.**

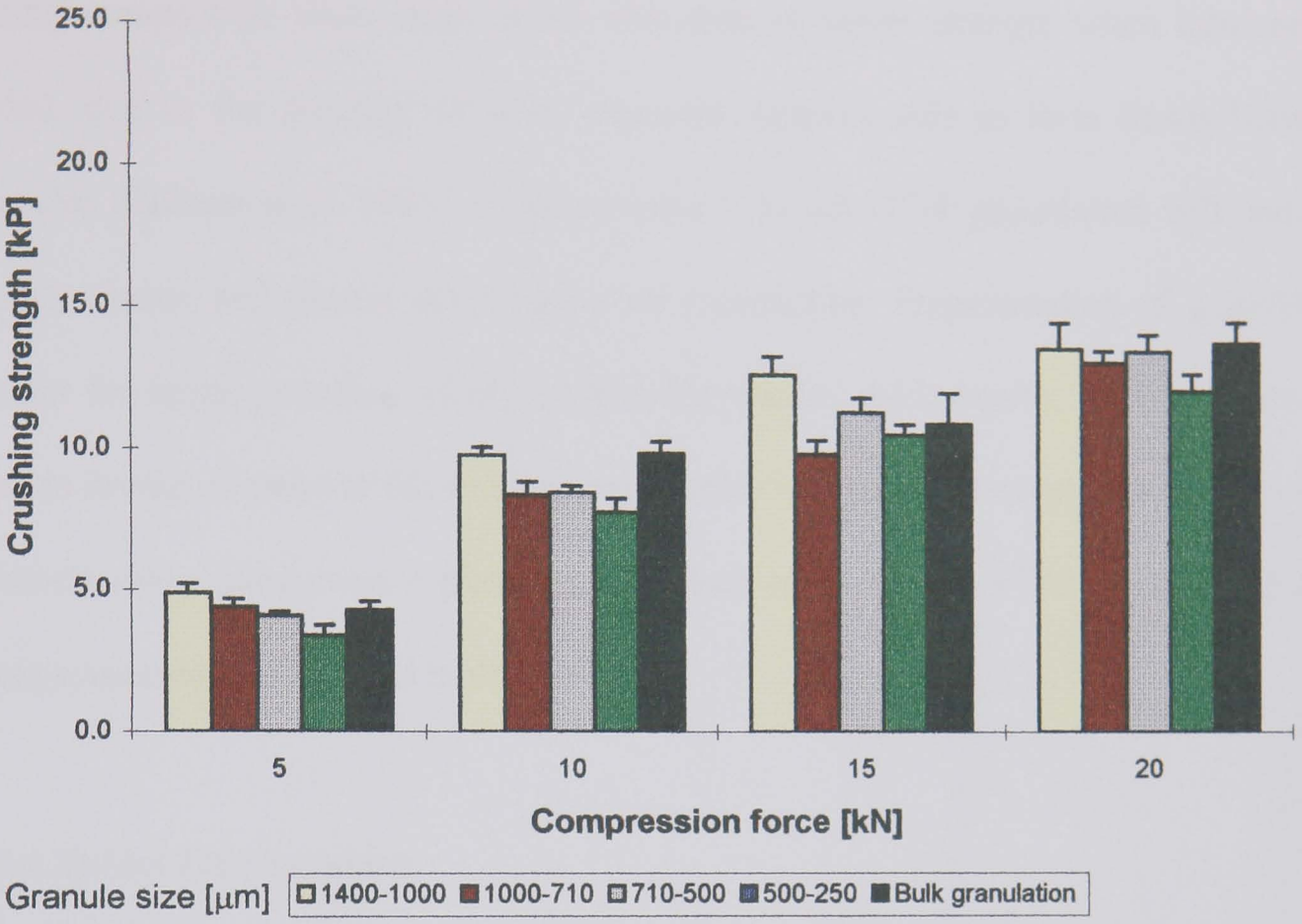
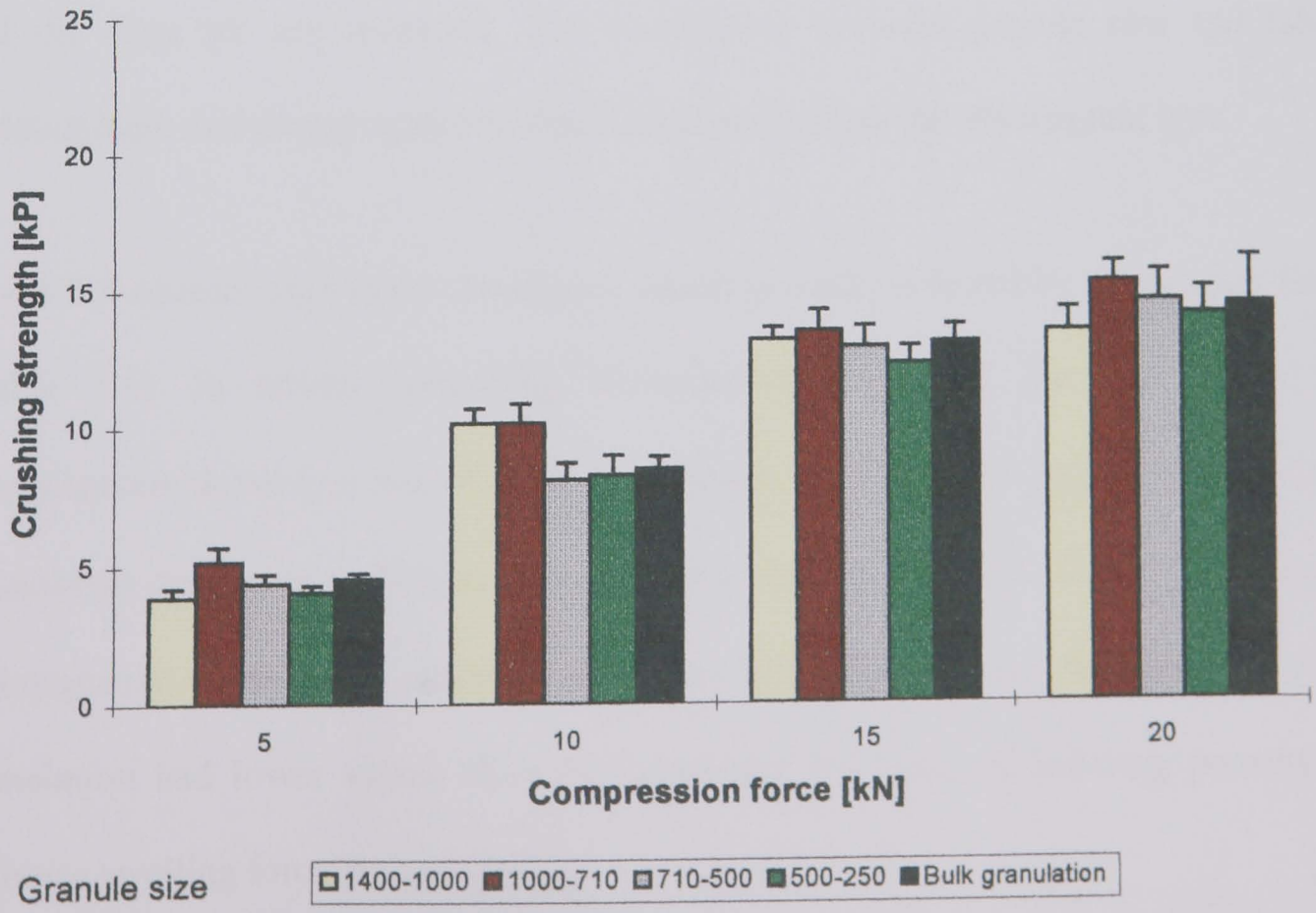



**Figure 3.4: Effect of granule size fraction on the crushing strength of tablets containing 2% intragranular Amberlite IRP88.**



effect of lubricant on tablet strength is strongly dependent on the degree of fragmentation during compaction (de Boer et al, 1978). Materials which fragment during compaction show little or no reduction in tablet strength when lubricant is added, due to the creation of new, uncoated surfaces able to form bonds between particles (Bolhuis et al, 1975). A paracetamol / Avicel / PVP granulation will undergo mainly elastic and plastic deformation on compaction. Fragmentation of granules is greater for larger granules, which explains the results. Additionally, the lower residual loss on drying of some of the smaller granule size fractions will cause a reduction in the hydrodynamic lubrication / plasticising effects of moisture, which leads to greater interparticulate bonding and tablet strength.

### 3.3.6 Tablet disintegration.

Disintegration times for tablets containing intragranular Ac-Di-Sol, Explotab, and Amberlite IRP88 are given in Tables 3.6, 3.7 and 3.8 respectively. Tablets containing intragranular Kollidon-CL took longer than 30 minutes to disintegrate at each mesh size and the data are not tabulated. The relationship between granule size and tablet disintegration and deaggregation is dependent on intragranular disintegrant type.

Ac-Di-Sol caused rapid tablet dispersion, which is hardly affected by compaction force (Table 3.6). In tablets containing intragranular Ac-Di-Sol, the time taken for deaggregation down to a size of 1180μm is largely unaffected by granule size fraction. Monitoring dispersion to 710μm is more discriminating (Table 3.6, Figure 3.6). Longer disintegration times were observed with increasing granule size fraction. The bulk granulation had lower values than the larger size fractions, by reducing porosity to optimise swelling force generation.

**Table 3.6: Effect of granule size / compression force on the disintegration of tablets containing 2% intragranular Ac-Di-Sol.**

| Mesh aperture size [μm] | Granule size [μm] | Disintegration time [Min] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 7kN | | 10kN | | 15kN | | 20kN | |
| | | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd |
| 2000 | Bulk granulation | **0.29** | 3.45 | **0.33** | 6.06 | **0.50** | 2.00 | **0.81** | 2.47 |
| 1700 | | **0.33** | 6.06 | **0.38** | 5.26 | **0.52** | 5.77 | **0.87** | 2.30 |
| 1400 | | **0.36** | 8.33 | **0.38** | 2.63 | **0.58** | 1.72 | **0.88** | 9.09 |
| 1180 | | **0.42** | 9.52 | **0.47** | 2.13 | **0.60** | 3.33 | **0.77** | 2.50 |
| 710 | | **0.69** | 5.80 | **0.48** | 4.17 | **0.67** | 13.43 | **0.81** | 4.94 |
| 2000 | 1400-1000 | **0.30** | 3.33 | **0.38** | 7.89 | **0.59** | 5.08 | **0.74** | 5.41 |
| 1700 | | **0.45** | 8.89 | **0.44** | 6.82 | **0.62** | 4.84 | **0.74** | 4.05 |
| 1400 | | **0.49** | 4.08 | **0.48** | 6.25 | **0.65** | 6.15 | **0.78** | 5.13 |
| 1180 | | **0.52** | 3.85 | **0.52** | 5.77 | **0.67** | 10.45 | **0.79** | 3.80 |
| 710 | | **1.44** | 3.47 | **1.50** | 11.33 | **1.54** | 46.10 | **1.63** | 36.20 |
| 2000 | 1000-710 | **0.40** | 5.00 | **0.38** | 2.63 | **0.55** | 7.27 | **0.70** | 5.71 |
| 1700 | | **0.40** | 10.00 | **0.43** | 4.65 | **0.60** | 10.00 | **0.72** | 2.78 |
| 1400 | | **0.45** | 8.89 | **0.46** | 4.35 | **0.64** | 7.81 | **0.74** | 2.70 |
| 1180 | | **0.45** | 6.67 | **0.45** | 6.67 | **0.58** | 1.72 | **0.71** | 1.41 |
| 710 | | **0.94** | 4.26 | **0.99** | 28.28 | **0.94** | 9.57 | **1.20** | 5.00 |
| 2000 | 710-500 | **0.31** | 12.90 | **0.33** | 6.06 | **0.51** | 7.84 | **0.60** | 3.33 |
| 1700 | | **0.39** | 7.69 | **0.43** | 4.65 | **0.51** | 3.92 | **0.62** | 4.84 |
| 1400 | | **0.47** | 4.26 | **0.51** | 7.84 | **0.56** | 3.57 | **0.64** | 6.25 |
| 1180 | | **0.42** | 4.76 | **0.55** | 5.45 | **0.57** | 3.51 | **0.66** | 3.03 |
| 710 | | **0.86** | 4.65 | **0.96** | 4.17 | **0.84** | 8.33 | **1.01** | 2.97 |
| 2000 | 500-250 | **0.28** | 3.57 | **0.27** | 3.70 | **0.42** | 2.38 | **0.57** | 3.51 |
| 1700 | | **0.29** | 3.45 | **0.28** | 7.14 | **0.49** | 2.04 | **0.57** | 7.12 |
| 1400 | | **0.31** | 3.23 | **0.32** | 6.25 | **0.53** | 1.89 | **0.57** | 1.75 |
| 1180 | | **0.32** | 3.13 | **0.33** | 6.06 | **0.50** | 4.00 | **0.60** | 5.00 |
| 710 | | **0.40** | 5.00 | **0.36** | 8.33 | **0.57** | 1.75 | **0.64** | 3.13 |

Disintegrant efficiency of Ac-Di-Sol is higher than Explotab and Amberlite IRP88 because whereas the latter two mainly cause disintegration by swelling (Caramella et al, 1989), Ac-Di-Sol combines high swelling activity with wicking properties. Wicking activity causes rapid penetration of water into the tablet (Gissinger & Stamm, 1980a)

and allows intragranular Ac-Di-Sol to function effectively in a tablet without extragranular disintegrant (Gordon et al, 1990).

Explotab functioned less efficiently than Ac-Di-Sol. Increasing granule size and compression force adversely affected the dispersion of tablets containing intragranular Explotab. Disintegration time increased with granule size when deaggregation was monitored through 2000μm (Figure 3.8), 1700μm (Figure 3.9), 1400μm (Figure 3.10), 1180μm (Figure 3.11) and 710μm (Figure 3.5) and the increase was greater as mesh aperture size decreased. Poorer disintegrant efficiency means that size reduction of granules is more dependent on dissolution and therefore larger granules tend to exhibit longer disintegration times. Greater covering of larger granules by magnesium stearate will reduce water penetration and will contribute to slower deaggregation. Porosity may be higher in tablets compressed from larger granule sizes. Ferrari et al, (1995) observed an inverse relationship between tablet porosity and the disintegrating force generated by sodium starch glycollate. At higher intragranular porosity, the disintegrant particles have sufficient space to swell without disrupting granules and the disintegrating force is reduced. At very high intergranular porosity, the force generated intragranularly is less efficiently transmitted to cause disruption of the tablet.

Generally, tablets made from the larger granules (1400-1000μm) had a marbled surface, probably indicating higher intergranular porosity due to the lack of fine particles to fill intergranular spaces. When tested through the larger mesh sizes, tablets compressed from the bulk granulation exhibited quicker deaggregation than in some of those compressed from smaller size fractions (Figures 3.8, 3.9). This is due to overall reduction in tablet porosity because of fine material contained in the bulk granulation.

**Table 3.7: Effect of granule size / compression force on the disintegration of tablets containing 2% intragranular Explotab.**

| Mesh aperture size [μm] | Granule size [μm] | Disintegration time [Min] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 5kN | | 10kN | | 15kN | | 20kN | |
| | | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd |
| 2000 | Bulk granulation | **1.21** | 3.31 | **1.31** | 12.21 | **1.83** | 3.83 | **2.40** | 1.25 |
| 1700 | | **1.23** | 4.07 | **1.42** | 16.20 | **2.03** | 2.96 | **2.96** | 0.34 |
| 1400 | | **1.62** | 20.99 | **1.73** | 4.62 | **2.89** | 2.77 | **3.92** | 0.51 |
| 1180 | | **3.27** | 17.13 | **2.19** | 4.11 | **3.02** | 7.95 | **4.00** | 49.5 |
| 710 | | **6.65** | 30.98 | **4.18** | 5.98 | **5.20** | 10.38 | **5.60** | 18.75 |
| 2000 | 1400-1000 | **1.04** | 4.81 | **1.54** | 7.14 | **2.21** | 13.57 | **2.90** | 7.93 |
| 1700 | | **1.37** | 3.65 | **1.71** | 6.43 | **2.45** | 2.86 | **3.58** | 10.06 |
| 1400 | | **1.54** | 3.25 | **1.95** | 3.59 | **3.18** | 6.92 | **4.42** | 6.79 |
| 1180 | | **5.01** | 4.59 | **3.43** | 4.96 | **3.67** | 25.61 | **5.68** | 15.14 |
| 710 | | **6.79** | 24.45 | **5.03** | 17.30 | **6.25** | 5.60 | **6.89** | 12.19 |
| 2000 | 1000-710 | **0.94** | 5.32 | **1.38** | 4.35 | **2.05** | 4.88 | **2.89** | 6.57 |
| 1700 | | **1.07** | 4.67 | **1.39** | 13.67 | **2.44** | 0.82 | **3.16** | 2.53 |
| 1400 | | **1.44** | 45.83 | **1.56** | 5.13 | **2.59** | 8.88 | **3.50** | 2.29 |
| 1180 | | **2.30** | 53.48 | **2.39** | 0.84 | **2.46** | 12.20 | **4.15** | 11.33 |
| 710 | | **5.98** | 17.39 | **4.06** | 8.62 | **4.58** | 12.01 | **5.68** | 10.56 |
| 2000 | 710-500 | **0.88** | 5.68 | **1.28** | 5.47 | **2.04** | 2.94 | **2.62** | 3.82 |
| 1700 | | **0.93** | 6.45 | **1.30** | 5.38 | **2.08** | 1.92 | **2.80** | 7.50 |
| 1400 | | **0.93** | 7.53 | **1.54** | 7.79 | **2.23** | 3.59 | **3.09** | 9.06 |
| 1180 | | **1.05** | 11.43 | **1.49** | 4.03 | **2.35** | 16.17 | **3.41** | 4.11 |
| 710 | | **1.69** | 18.34 | **2.44** | 5.33 | **3.00** | 7.33 | **3.80** | 5.53 |
| 2000 | 500-250 | **0.78** | 14.10 | **1.17** | 8.55 | **1.49** | 3.36 | **1.85** | 6.49 |
| 1700 | | **0.68** | 19.12 | **1.22** | 4.10 | **1.54** | 3.90 | **1.98** | 7.58 |
| 1400 | | **0.92** | 30.43 | **1.34** | 6.72 | **1.66** | 0.60 | **2.16** | 6.02 |
| 1180 | | **1.19** | 32.77 | **1.31** | 7.63 | **1.74** | 19.54 | **2.49** | 7.23 |
| 710 | | **1.21** | 20.66 | **1.51** | 7.95 | **1.96** | 9.18 | **2.94** | 4.42 |

This trend diminishes as the mesh aperture size decreases and deaggregation of individual granules is increasingly the rate-limiting step (Figures 3.6, 3.10, 3.11). In tablets compressed from all granule size fractions, the disintegration times remained the same or more usually increased with compaction force. It is probable that in tablets compressed at higher forces, greater disintegrating forces generated at lower porosity

are counterbalanced by increased intergranular bonding, giving increased crushing strength. Additionally, reduced water penetration at lower tablet porosity also reduces disintegrant efficiency (Lerk et al, 1979). Notable exceptions occur when disintegration down to sizes below 1180 and 710μm was measured in tablets compressed from the larger size fractions (1400-1000μm, 1000-710μm and the bulk granulation, Figures 3.6, 3.11). The relationship between compression force and disintegration time exhibited a minimum. Increased disintegrating force generated at reduced porosity is greater than the effect of increased tablet crushing strength.

The poor disintegrant efficiency of Amberlite IRP88, leads to longer disintegration times with increasing granule size fraction (Figures 3.7, 3.12 - 3.15). Dispersion times of tablets containing Amberlite IRP88 were longer than those containing Explotab. Gissinger & Stamm (1980a) evaluated these two disintegrants and reported greater wetability and swelling rate and volume for Explotab. This may account for the observed differences in dispersion rates.

Monitoring deggregation down to 1180μm (Figures 3.12-3.15) shows that the tablets compressed from the bulk granulation disintegrate as rapidly as the 250-500μm size fraction. This indicates that Amberlite IRP88 is highly dependent on an optimum porosity for efficient swelling force generation.

For the smaller granule sizes (250-500μm, 500-710μm, 710-1000μm), dispersion time did not increase with compression force and in some cases decreased. In the 1000-1400μm fraction and bulk granulation, a minimum was observed. Disintegrant action is mainly dependent on swelling force generation, which is higher at lower porosity.

**Figure 3.5: Effect of granule size / compression force on the disintegration of tablets containing 2% intragranular Explotab through 710μm.**

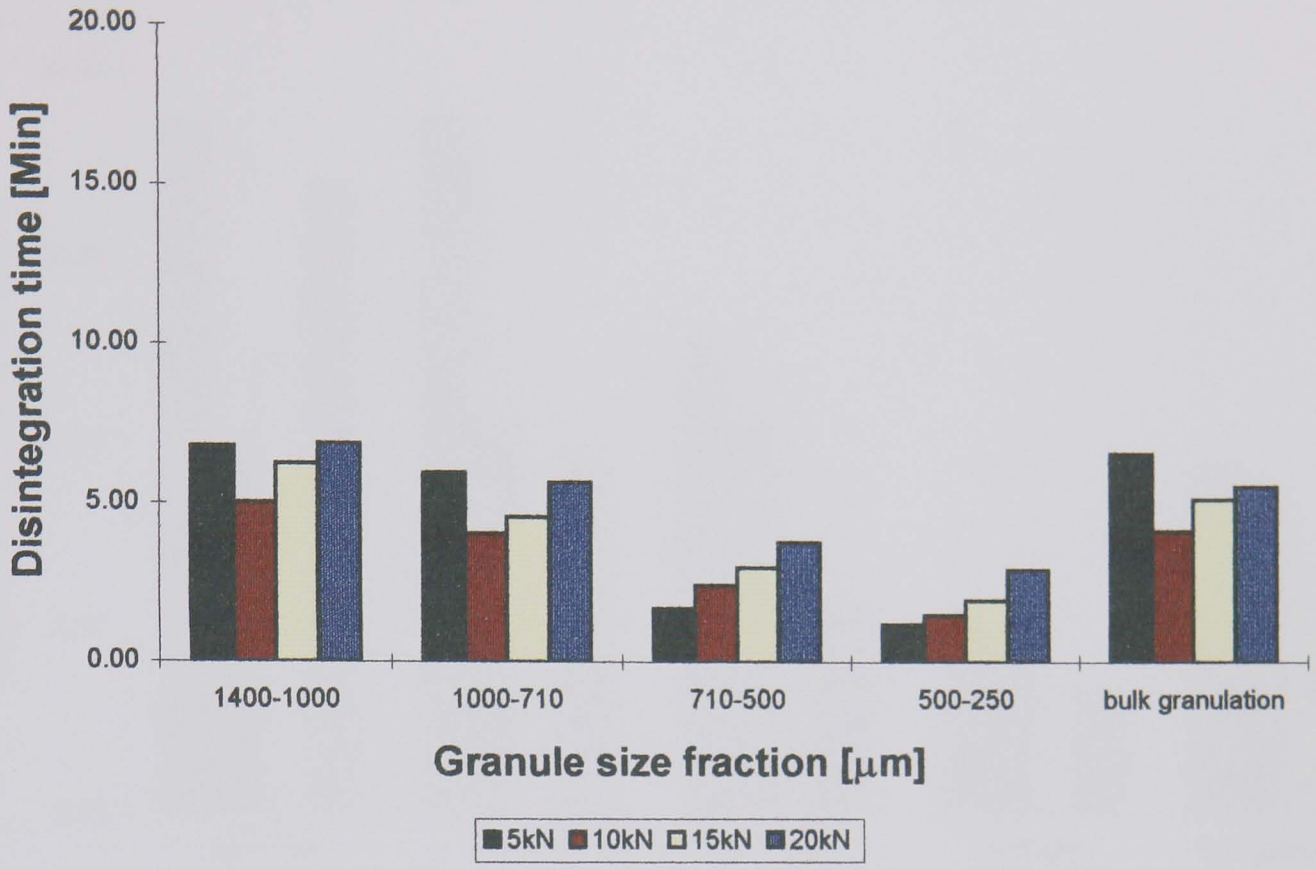



**Figure 3.6: Effect of granule size / compression force on the disintegration of tablets containing 2% intragranular Ac-Di-Sol through 710μm.**

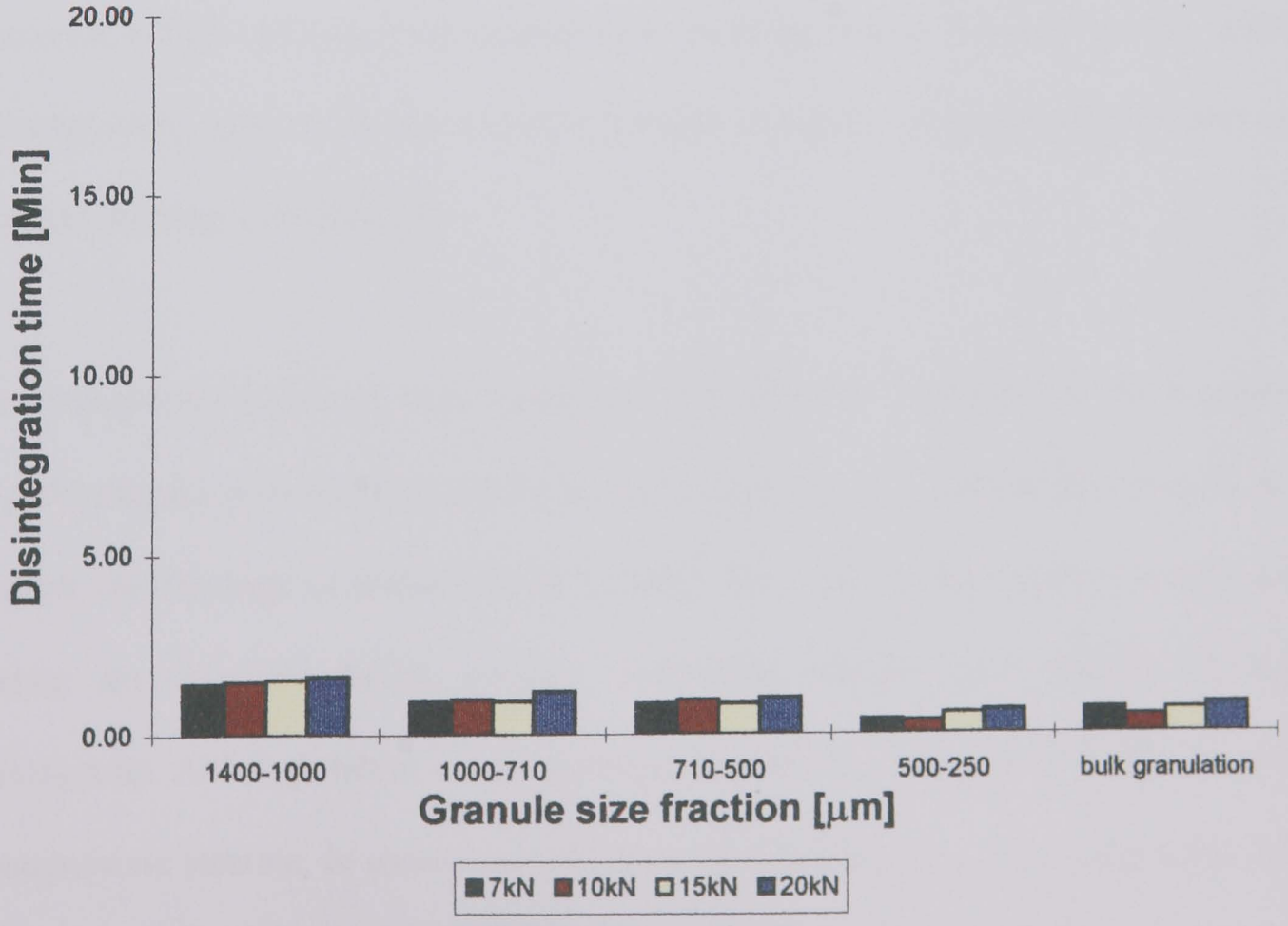
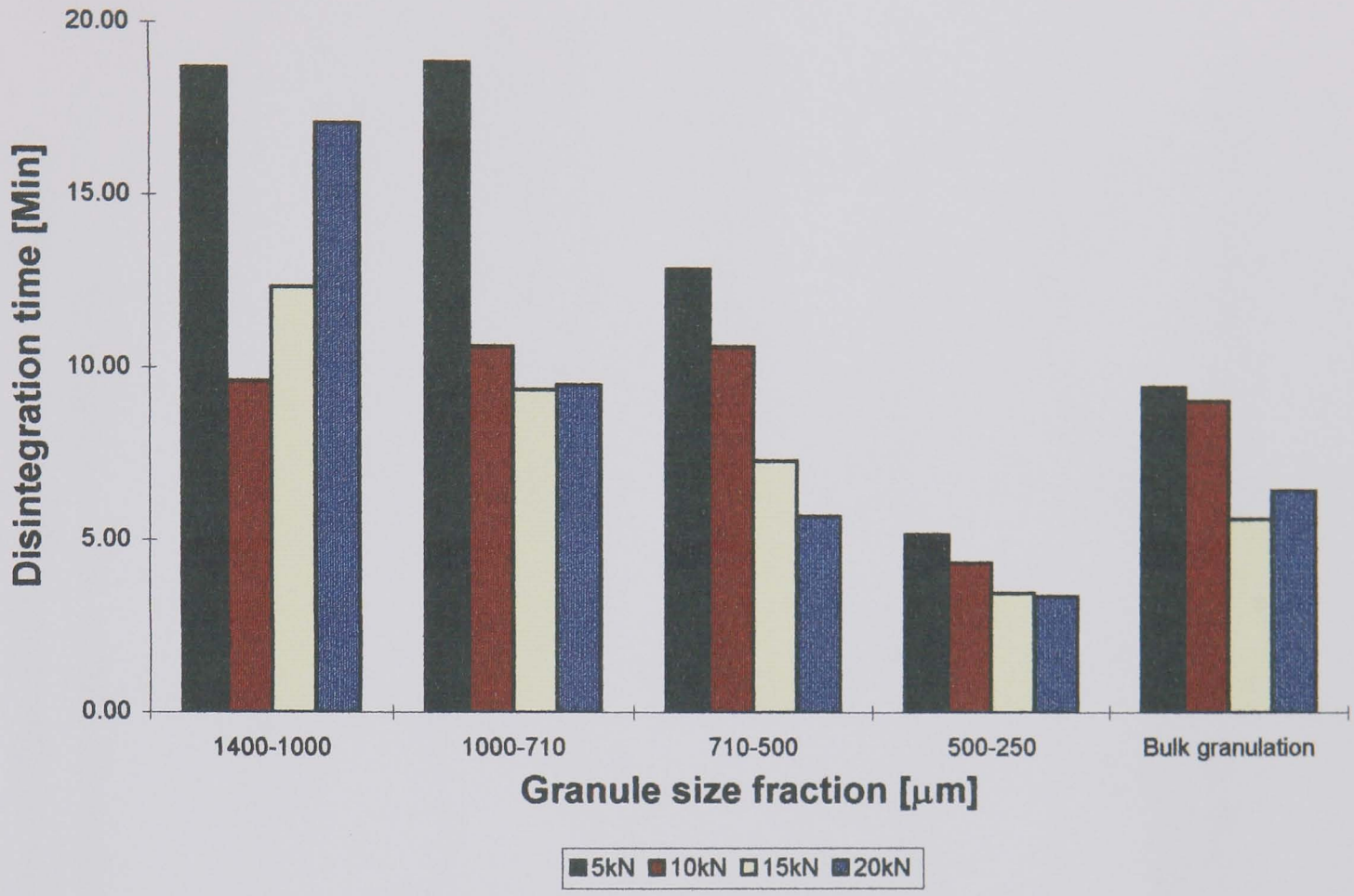


**Figure 3.7: Effect of granule size / compression force on the disintegration of tablets containing 2% intragranular Amberlite IRP88 through 710μm.**




Amberlite IRP88 is less influenced by water availability than Explotab because it is able to develop a high swelling force despite a low swelling volume (Caramella et al, 1989). Reduced water penetration due to lower porosity at higher compaction forces does not decrease disintegrant efficiency.

The hydrophobic lubricant, magnesium stearate, probably accounts for the unusually long disintegration times observed for tablets containing intragranular Kollidon-CL and supports the findings of Bolhuis et al, (1982). They studied the effect of magnesium stearate on insoluble tablet systems containing slightly and strongly swelling disintegrants. Although tablet swelling properties were hardly affected by the presence of magnesium stearate, in some cases disintegrant efficiency was. They concluded, for a slightly swelling but hydrophilic disintegrant such as crospovidone, the penetration of

**Figure 3.8: Effect of granule size / compression force on the disintegration of tablets containing 2% intragranular Explotab through a screen aperture size of 2000μm.**

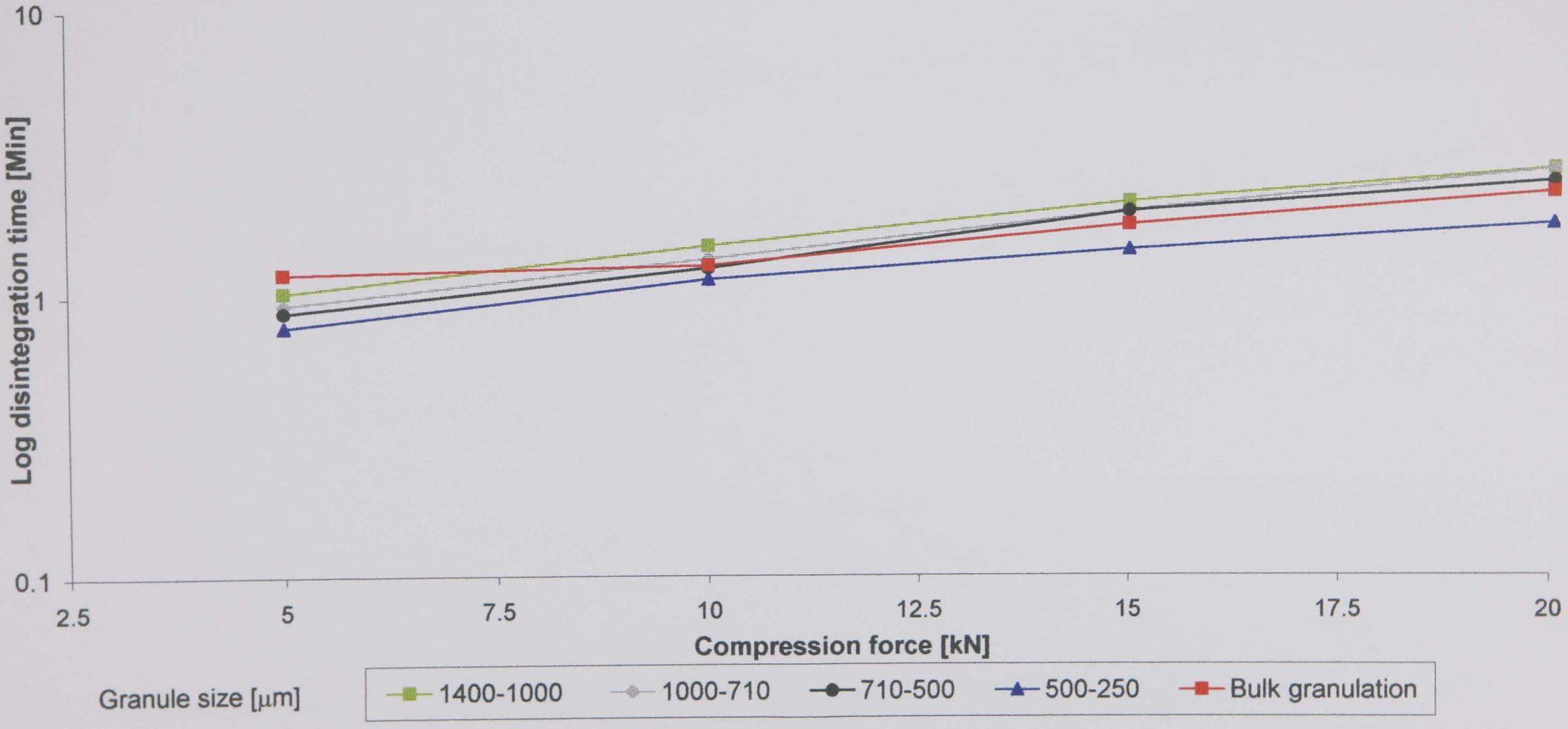


**Figure 3.9: Effect of granule size / compression force on the disitegration of tablets containing 2% intragranular Explotab through a screen aperture size of 1700μm.**

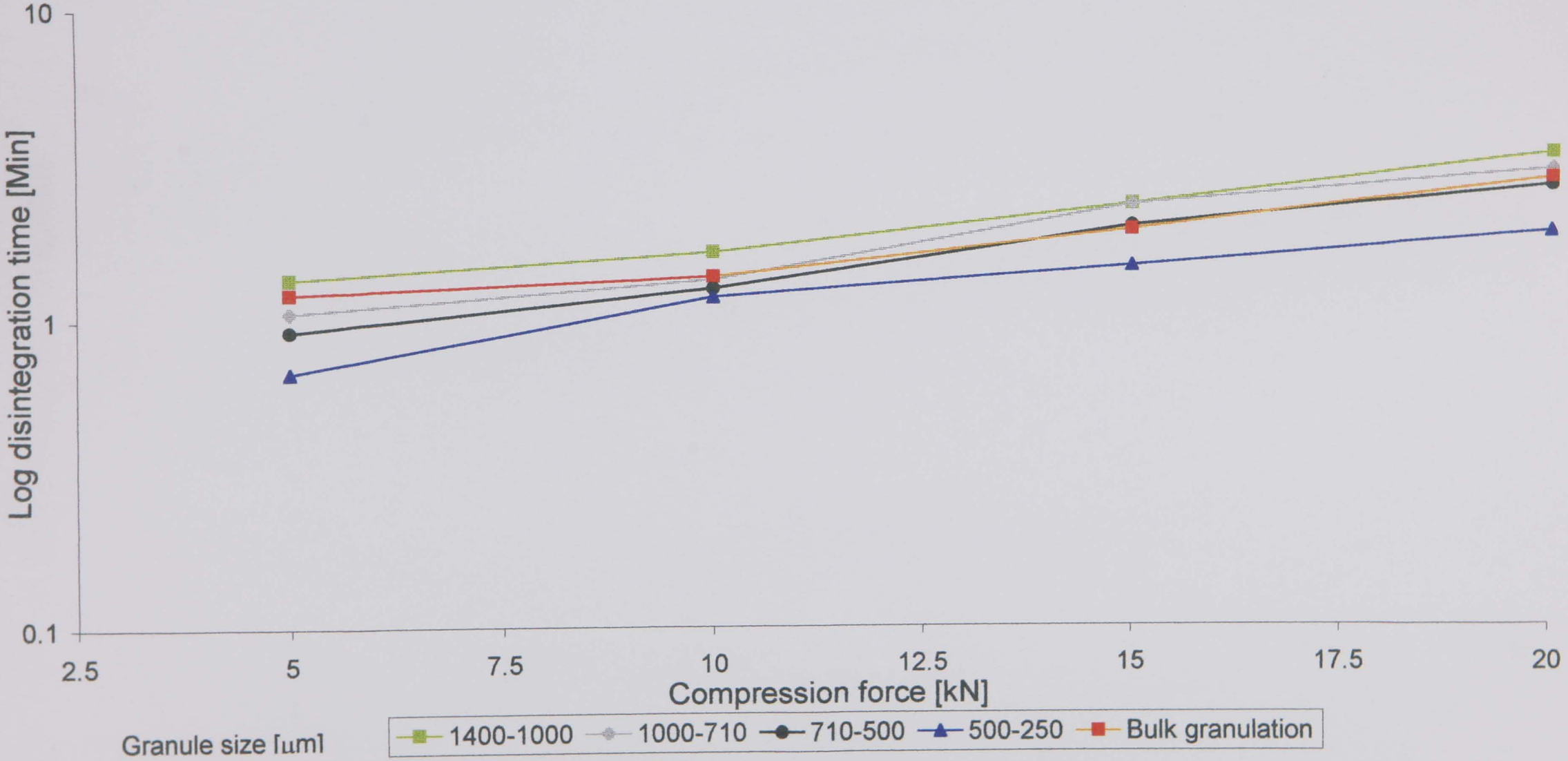


**Figure 3.10: Effect of granule size / compression force on the disintegration of tablets containing 2% intragranular Explotab through a screen aperture size of 1400μm.**

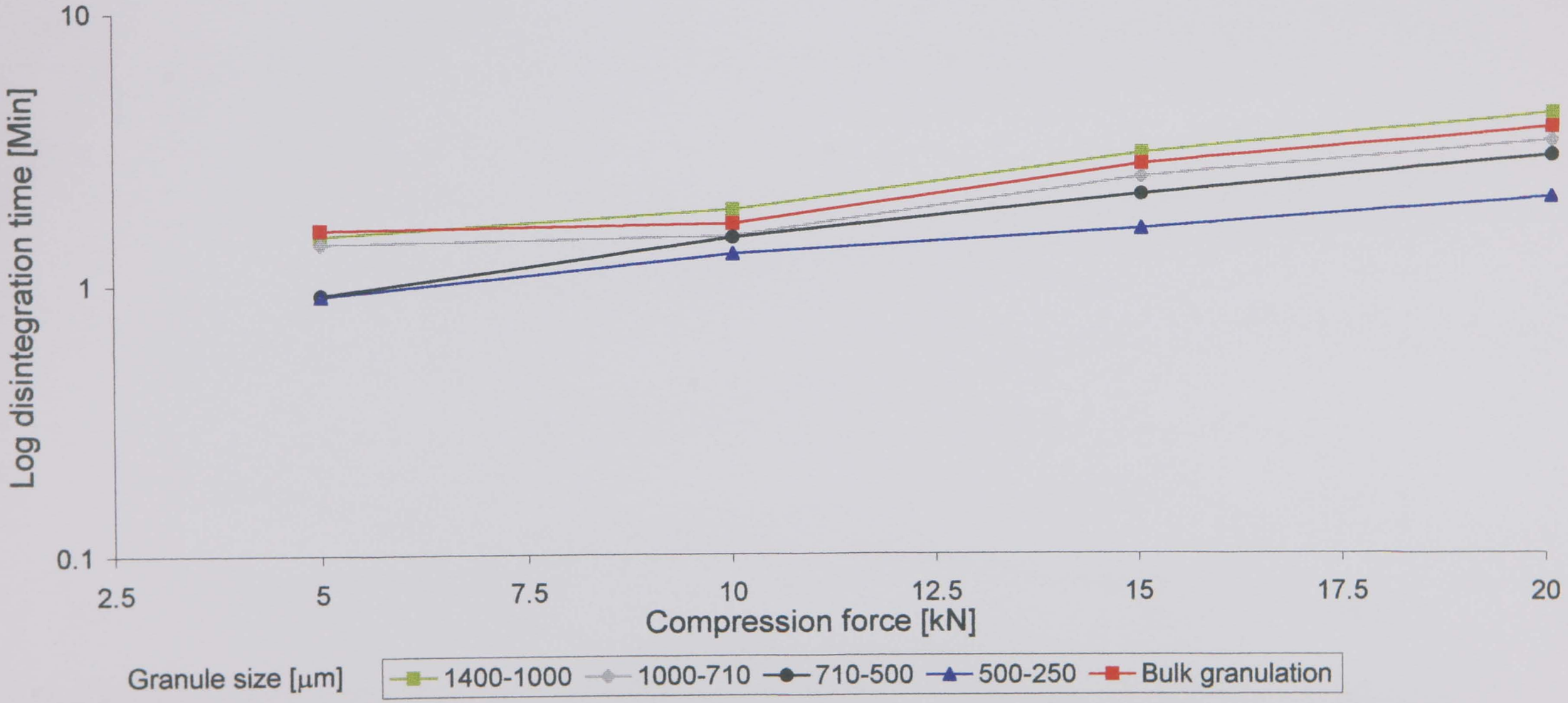
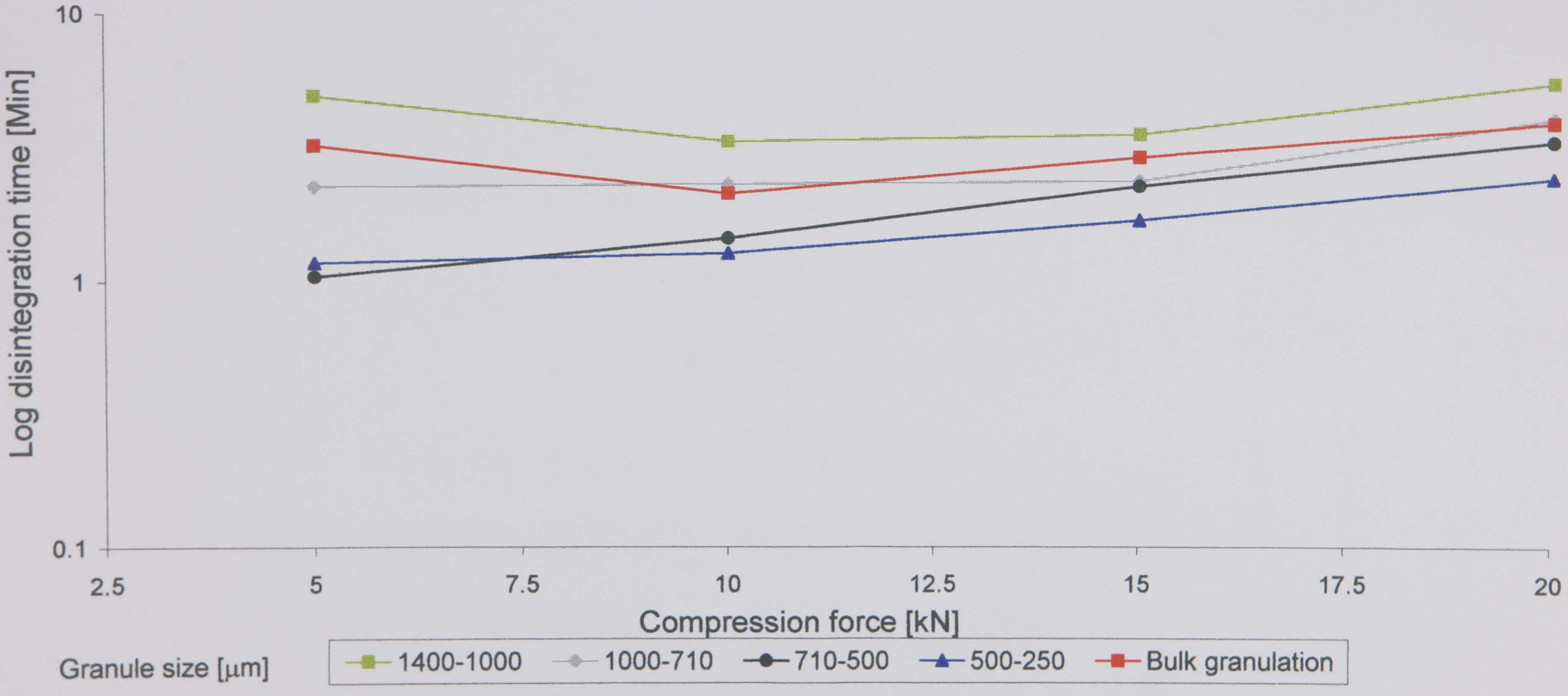


**Figure 3.11: Effect of granule size / compression force on the disintegration of tablets containing 2% intragranular Explotab through a screen aperture size of 1180μm.**



water into the tablet is the controlling step in the process of disintegration and is consequently strongly affected by the presence of hydrophobic lubricant. The dispersion of tablets containing Kollidon-CL would be more rapid using a hydrophilic lubricant.

**Table 3.8: Effect of granule size / compression force on the disintegration of tablets containing 2% intragranular Amberlite IRP88.**

| Mesh aperture [μm] | Granule size [μm] | Disintegration time [Min] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 5kN | | 10kN | | 15kN | | 20kN | |
| | | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd |
| 2000 | Bulk granulation | **2.12** | 22.64 | **1.76** | 12.50 | **1.56** | 7.05 | **1.82** | 10.44 |
| 1700 | | **3.01** | 4.98 | **2.63** | 17.11 | **2.10** | 26.67 | **1.92** | 25.00 |
| 1400 | | **3.61** | 21.88 | **3.60** | 21.67 | **2.77** | 12.27 | **3.15** | 13.65 |
| 1180 | | **5.81** | 36.83 | **3.80** | 34.47 | **2.78** | 14.75 | **3.04** | 14.80 |
| 710 | | **9.56** | 23.12 | **9.17** | 31.41 | **5.70** | 8.42 | **6.53** | 34.61 |
| 2000 | 1400-1000 | **4.61** | 3.47 | **4.52** | 17.04 | **4.77** | 16.14 | **4.55** | 12.75 |
| 1700 | | **5.98** | 27.76 | **6.35** | 18.74 | **5.88** | 20.58 | **4.95** | 16.77 |
| 1400 | | **6.90** | 19.28 | **7.60** | 10.26 | **6.74** | 9.94 | **7.37** | 12.48 |
| 1180 | | **8.67** | 33.45 | **7.79** | 39.41 | **8.63** | 26.54 | **10.37** | 20.93 |
| 710 | | **18.70** | 13.64 | **9.63** | 24.71 | **12.37** | 9.14 | **17.11** | 14.67 |
| 2000 | 1000-710 | **4.47** | 13.65 | **3.65** | 14.79 | **4.18** | 32.06 | **4.46** | 1.35 |
| 1700 | | **5.66** | 49.82 | **5.86** | 20.48 | **5.11** | 24.07 | **4.73** | 20.72 |
| 1400 | | **6.52** | 11.81 | **6.30** | 10.00 | **6.63** | 4.37 | **5.33** | 18.76 |
| 1180 | | **11.76** | 10.63 | **5.73** | 37.17 | **6.41** | 28.08 | **5.23** | 22.94 |
| 710 | | **18.90** | 10.63 | **10.67** | 28.12 | **9.42** | 10.08 | **9.56** | 13.91 |
| 2000 | 710-500 | **5.29** | 8.51 | **3.38** | 10.36 | **3.29** | 9.42 | **3.06** | 10.46 |
| 1700 | | **7.77** | 13.77 | **4.36** | 6.19 | **3.79** | 2.37 | **3.85** | 6.49 |
| 1400 | | **8.61** | 3.60 | **5.15** | 10.87 | **4.39** | 12.30 | **4.33** | 16.40 |
| 1180 | | **8.77** | 10.95 | **6.92** | 21.97 | **4.15** | 9.40 | **4.77** | 6.92 |
| 710 | | **12.94** | 8.73 | **10.69** | 26.94 | **7.37** | 23.47 | **5.75** | 5.57 |
| 2000 | 500-250 | **2.94** | 21.43 | **1.81** | 7.73 | **2.27** | 11.01 | **1.81** | 9.39 |
| 1700 | | **3.44** | 27.62 | **2.14** | 11.68 | **2.49** | 10.44 | **1.85** | 9.73 |
| 1400 | | **3.98** | 21.36 | **2.78** | 16.55 | **2.68** | 14.18 | **2.30** | 13.48 |
| 1180 | | **4.01** | 19.70 | **4.20** | 24.29 | **2.37** | 6.75 | **2.10** | 26.19 |
| 710 | | **5.21** | 14.78 | **4.40** | 22.73 | **3.51** | 7.41 | **3.42** | 6.43 |

**Figure 3.12: Effect of granule size / compression force on the disintegration of tablets containing 2% intragranular Amberlite IRP88 through a screen aperture size of 2000μm.**

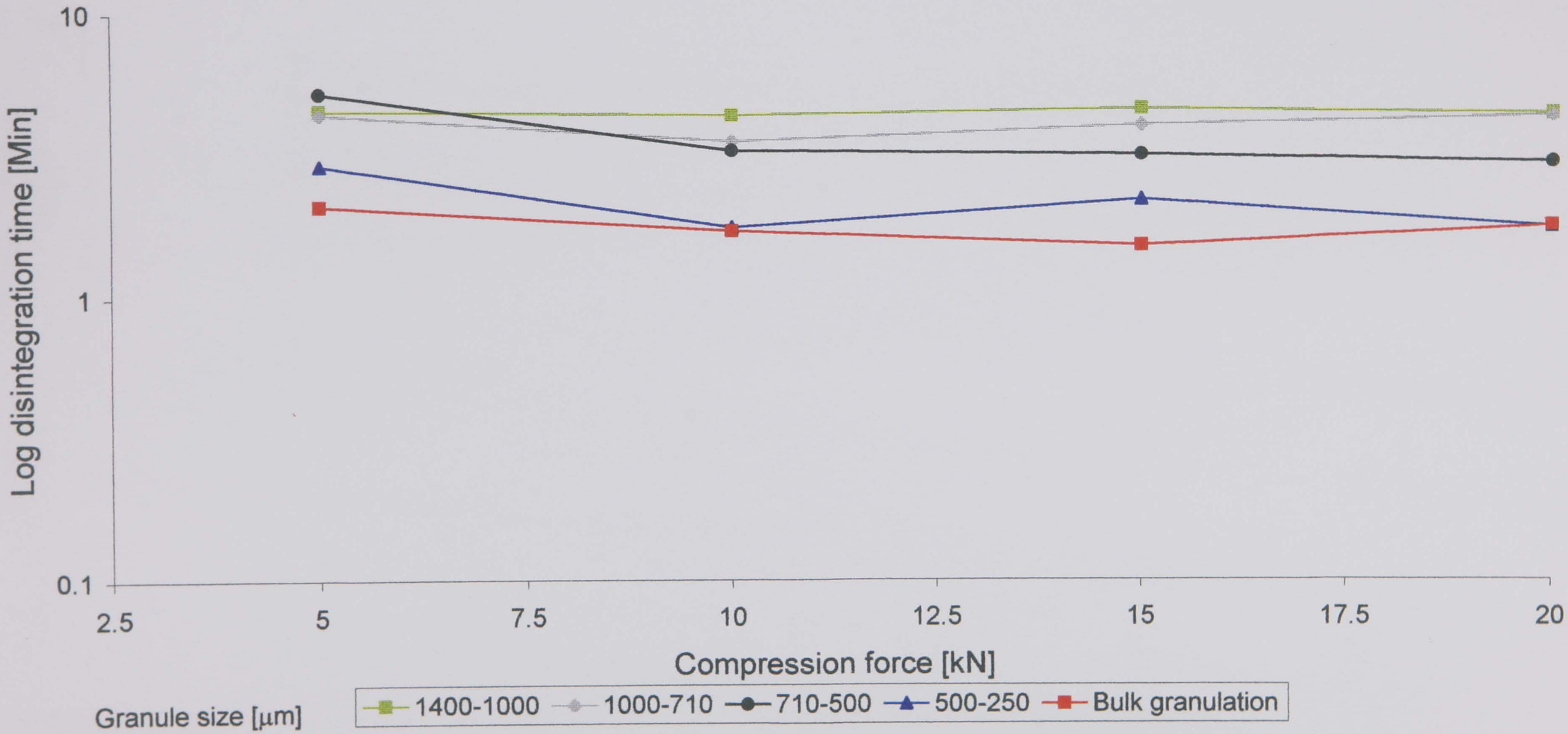


**Figure 3.13: Effect of granule size / compression force on the disintegration of tablets containing 2% intragranular Amberlite IRP88 through a screen aperture size of 1700μm.**

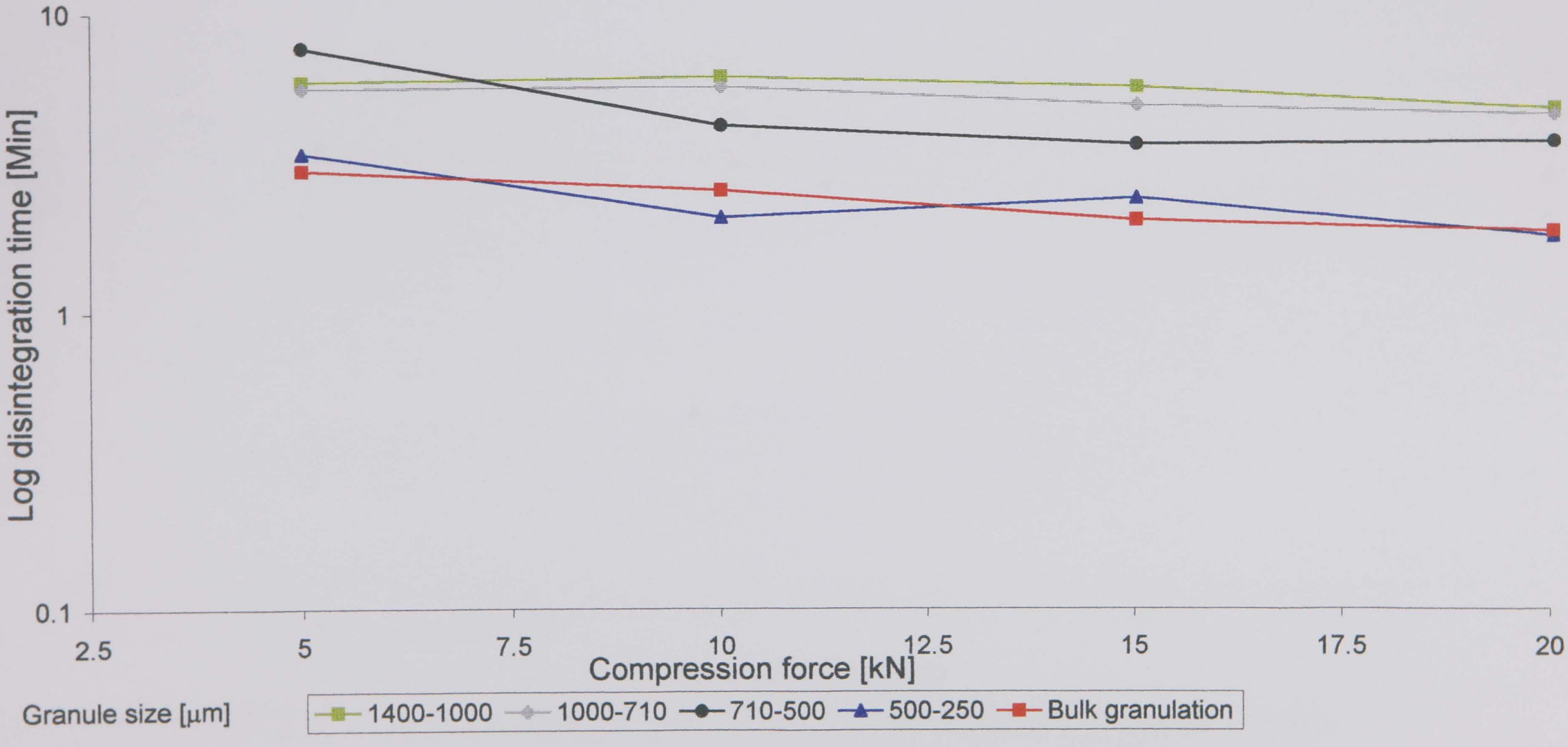


**Figure 3.14: Effect of granule size / compression force on the disintegration of tablets containing 2% intragranular Amberlite IRP88 through a screen aperture size of 1400μm.**

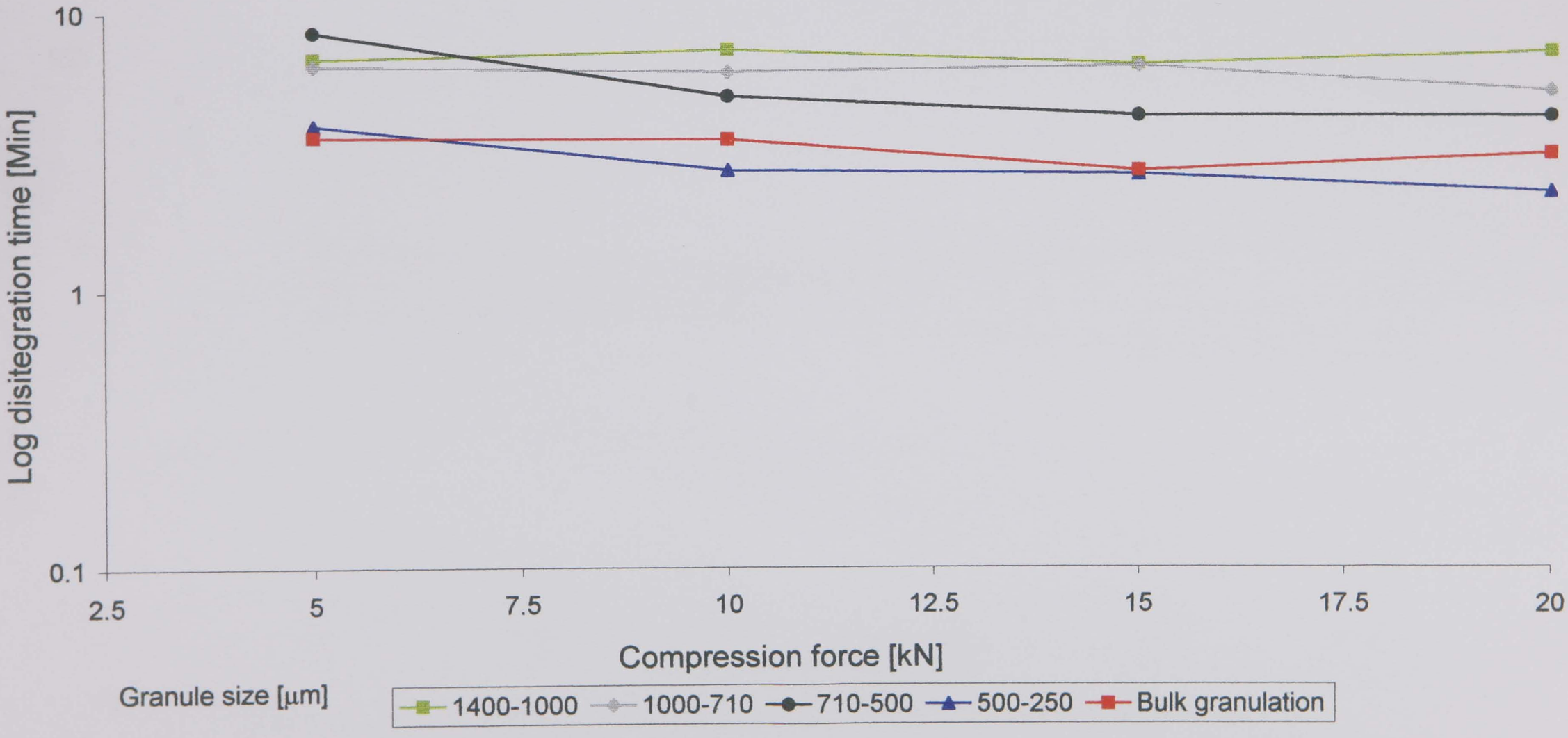
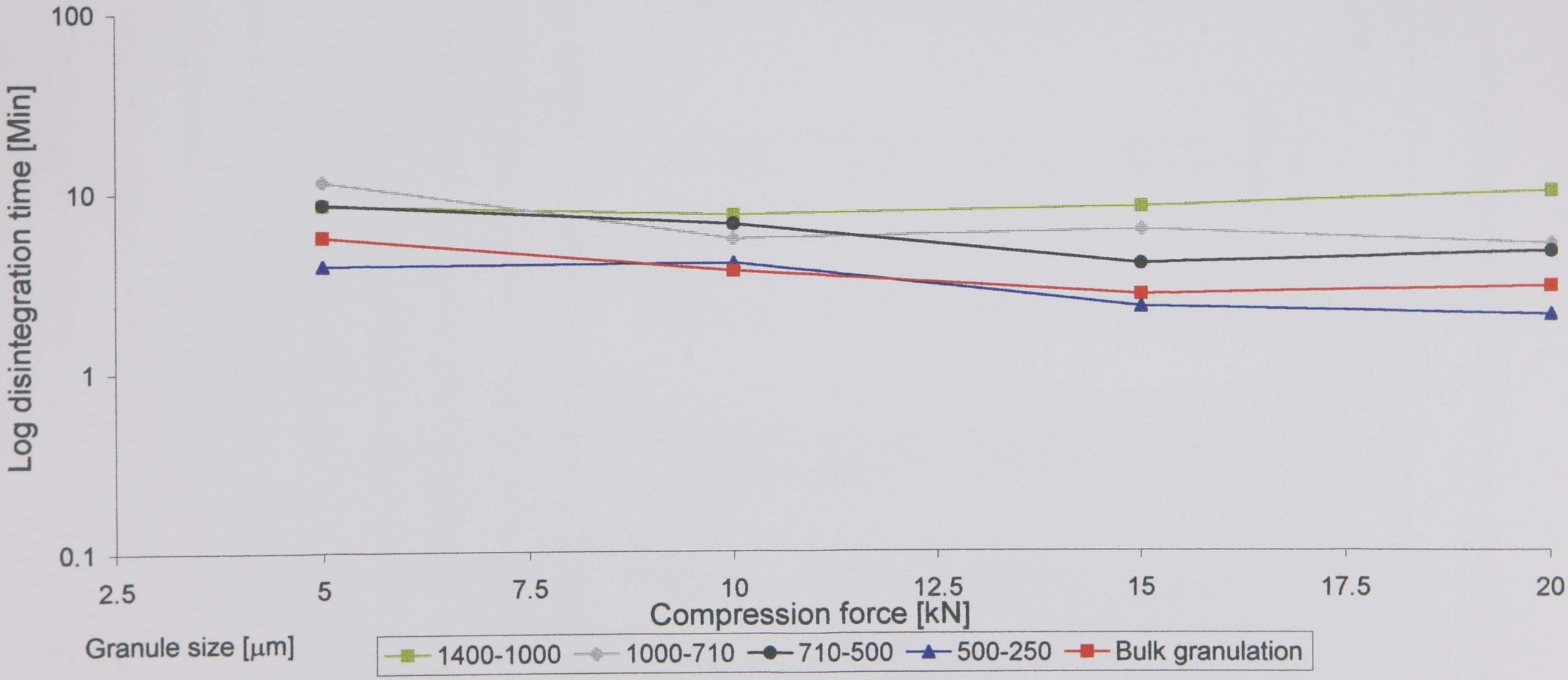


**Figure 3.15: Effect of granule size / compression force on the disintegration of tablets containing 2% intragranular Amberlite IRP88 through a screen aperture size of 1180μm.**



### 3.3.7 Tablet friability.

**Table 3.9: Effect of granule size, intragranular disintegrant type and compression force on tablet friability.**

| Intra-disintegrant | Comp. Force [kN] | Friability [% w/w] | | | | |
|---|---|---|---|---|---|---|
| | | Granule size fraction [μm] | | | | |
| | | Bulk granulation | 1400-1000 | 1000-710 | 710-500 | 500-250 |
| Ac-Di-Sol | 7 | 1.41 | 0.86 | 0.67 | 1.19 | 2.32 |
| | 10 | 0.79 | 0.69 | 0.30 | 0.59 | 0.82 |
| | 15 | 0.46 | 0.75 | 0.29 | 0.39 | 0.52 |
| | 20 | 0.44 | 0.47 | 0.15 | 0.30 | 0.37 |
| Explotab | 5 | 3.16 | 1.23 | 2.22 | 3.48 | 3.73 |
| | 10 | 1.40 | 0.73 | 0.87 | 1.43 | 1.45 |
| | 15 | 0.95 | 0.51 | 0.43 | 0.92 | 0.86 |
| | 20 | 0.54 | 0.38 | 0.95 | 0.92 | 0.67 |
| Amberlite IRP88 | 5 | 2.12 | 2.25 | 1.51 | 1.27 | 2.22 |
| | 10 | 1.14 | 0.72 | 0.27 | 0.46 | 0.62 |
| | 15 | 0.58 | 0.44 | 0.26 | 0.30 | 0.33 |
| | 20 | 0.57 | 0.45 | 0.12 | 0.25 | 0.30 |
| Kollidon-CL | 5 | 3.12 | 1.50 | 2.13 | 3.28 | 4.23 |
| | 10 | 1.37 | 1.00 | 0.72 | 1.45 | 1.73 |
| | 15 | 1.07 | 0.63 | 0.93 | 0.69 | 1.16 |
| | 20 | 0.90 | 0.24 | 0.32 | 0.67 | 0.99 |

Resistance to abrasion or friability is an important consumer attribute. It indicates how the tablet will withstand the tumbling effect encountered during manufacture, packaging, transport and handling. There is no clear relationship between granule size fraction and tablet friability (Table 3.9). In all formulations friability decreased with increasing compression force, due to increased tablet crushing strength. However, friability does not appear to be simply a function of crushing strength. For example, tablets containing intragranular Amberlite IRP88 tended to have lower crushing strength than those containing intragranular Explotab and friabilities also tended to be lower. Tablet crushing strength, however, does not necessarily reflect granule strength (Wells

& Walker, 1983) and this may explain the observed differences. It is possible that intragranular disintegrant type may influence granule structure, however, it is unlikely at very low concentrations, and no clear trends are apparent from the present results.

## 3.4 Conclusions.

Many of the differences in disintegrant efficiency were not evident when disintegration times were monitored at 2000μm (BP 1990). In a dispersible tablet formulation, where deaggregation to < 710μm must occur, a much more discriminating test is required.

The rate and variability of dispersion was greatly influenced by intragranular disintegrant type, which had a greater influence on dispersion than granule size, compression force or tablet crushing strength. Tablets containing Ac-Di-Sol disintegrated most rapidly with least variability. The dispersion characteristics of tablets containing intragranular Explotab / Amberlite IRP88 are less consistent. Used alone intragranularly, disintegrant efficiency can be summarised as:

Ac-Di-Sol > Explotab > Amberlite IRP88 > Kollidon-CL.

The influence of compression force on dispersion down to 710μm varied with intragranular disintegrant type, and was least with intragranular Ac-Di-Sol. In tablets containing intragranular Explotab, using the smaller granule sizes, disintegration times increased with compression force. However, with larger sizes, a minimum corresponded to a reduction in porosity and an optimum for swelling force was observed. In tablets containing intragranular Amberlite IRP88, a minimum was observed in the 1000 - 1400 fraction and the bulk granulation. However, in the smaller size fractions (250-500, 500-710, 710-1000 μm) the dispersion times were unaffected or decreased with increasing compression force.

The disintegrant efficiency of Kollidon-CL was probably affected by the use of magnesium stearate and comparison with a water soluble lubricant would be interesting.

Fractionating the bulk granulation containing Amberlite IRP88 had a negative effect on the dispersion, presumably due to a dependency on porosity for efficient swelling force generation.

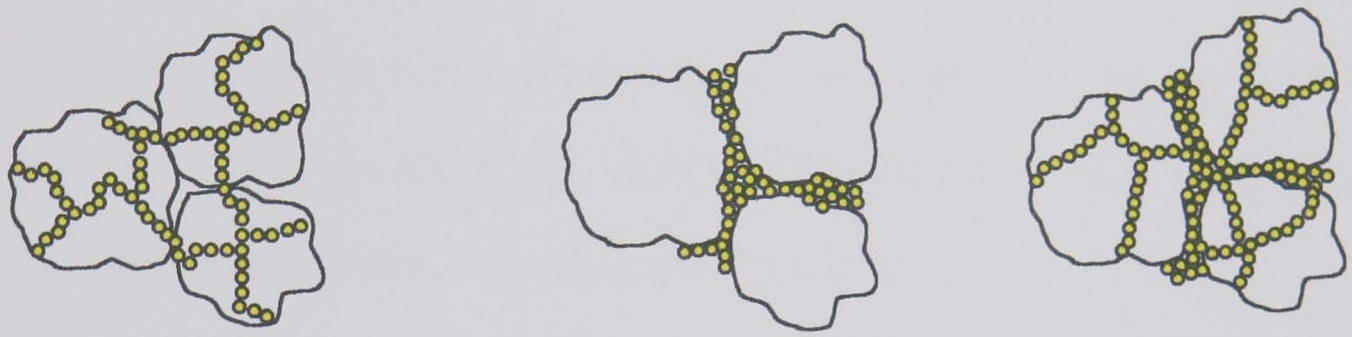
The choice of intragranular disintegrant has a more profound effect on tablet dispersion characteristics than granule size. Where disintegrant efficiency is high, dispersion characteristics may be practically unaffected by changes in granule size. However, as it decreases, granule size becomes more important and disintegration time tends to increase with granule size because size reduction is increasingly dependent on drug dissolution. With the correct disintegrant choice, Ac-Di-Sol in this particular system, the whole granulation may be used successfully.

# CHAPTER 4

# 4. EFFECT OF SUPER DISINTEGRANT LOCATION ON THE DISPERSION OF WET GRANULATED PARACETAMOL TABLETS.

## 4.1 Introduction.

Super disintegrants such as croscarmellose sodium, sodium starch glycollate and crospovidone are routinely employed to improve tablet disintegration and increase the rate of drug dissolution (Shangraw et al, 1980). Disintegrants in wet granulation processes are either added intragranularly, extragranularly or both (Figure 4.1).



(A) Intragranular (+) (B) Extragranular (-) (C) Intra + Extragranular (±)

**Figure 4.1: Distribution of disintegrant in wet granulated tablets.**

Shotton & Leonard (1976) compared the effectiveness of five conventional disintegrating agents in sulphadiazine tablets. Using a combination of wet sieving and the Coulter Counter™, they size analysed the suspension resulting from tablets subjected to the BP disintegration test. More rapid disintegration occurred for extragranular rather than intragranular, which, however, gave a much finer dispersion. The optimum was obtained by using both intra- and extragranular. The extragranular agent breaks up the tablet rapidly to the original granules and the intragranular produces the original particles. Khan & Rhodes (1972a) and Maly et al (1968) found alginates and celluloses were more effective, when used extragranularly. Asker et al (1981), found the inclusion

of intra- and extragranular starch substantially decreased the disintegration time of prednisolone tablets.

Many reports have compared the effects of super disintegrant location in wet granulated tablets, which can be incorporated either intragranularly (Kornblum & Stoopak, 1973; Gissinger & Stamm, 1980b) or extragranularly (Sakr et al, 1975) or both (Bhatia et al, 1978). Bhatia et al (1978) used croscarmellose sodium (CLD) both intra- and extragranularly in a calcium sulphate granulation. However they incorporated disintegrant in different concentrations, so that no conclusions can be drawn. Where the effect of location has been evaluated, reports are conflicting. Most of the observed differences seem to be attributed to the physicochemical properties of the tablet matrix, the super disintegrant and the method of manufacture.

Boymond et al (1982) compared the effect of sodium starch glycollate (Primojel) distributed either 5% intra- or extragranularly in phenacetin tablets. Tablets with extragranular disintegrant did not disintegrate at all in 30 minutes and showed slow drug dissolution. With a poorly soluble drug, disintegrant incorporation extragranularly results in a greater quantity of completely or partially dispersed granules, which reduce in size slowly, mainly by dissolution. Disintegration time depended largely on the size of the granules formed on tablet disintegration. With increasing granule size and decreasing solubility, granule deaggregation is increasingly the rate-limiting step to passage through a mesh. Faster disintegration is observed when the disintegrant is located intragranularly. Gordon et al (1990) demonstrated with a poorly soluble tablet base, that including croscarmellose intragranularly resulted in faster tablet dissolution than when the disintegrant was incorporated partially or completely extragranularly.

This can be explained by the increased surface area generated by rapid granule deaggregation with intragranular disintegrant.

For a poorly soluble drug, although intragranular incorporation results in faster disintegration times, a combination mode is often more efficient by producing a continuous hydrophilic network throughout the tablet matrix (Figure 4.1). The extragranular disintegrant facilitates rapid disintegration of the tablet and intragranular speeds deaggregation of the granules and drug dissolution. Intragranular disintegrants confined within the granules present a less wettable matrix. Miller et al (1980) reported that the disintegration of paracetamol tablets containing extragranular Ac-Di-Sol, was enhanced when part of the added disintegrant was incorporated intragranularly. More recently Khattab et al (1993a) studied the effect of super disintegrant distribution in paracetamol tablets produced using fluid-bed granulation rather than traditional wet granulation. The shortest disintegration times were achieved when croscarmellose, sodium starch glycollate and crospovidone were incorporated in the combined mode (±).

Khattab et al (1993b) investigated the effect of distributing (±) croscarmellose in wet granulated paracetamol tablets. 25 : 75, intra: extra granular disintegrant was optimum for disintegration time, but they did not measure the differences in the particle size of the resultant dispersions. The optimum ratio of intra : extra granular disintegrant will depend on the system and the dispersion required. As the extent of tablet deaggregation required increases, the ratio of intra : extra granular disintegrant will increase.

However, some workers have shown that the mode of incorporation has little effect on the disintegration time in a soluble tablet matrix, whereas others, that extragranularly is

more efficient. Khan & Rhodes (1973) and Sakr & Farrag (1975) observed only a small effect with Primojel on the disintegration and dissolution properties of tablets, prepared from a lactose granulation. Khan & Rooke (1976a) showed that sodium carboxymethylcellulose (Nymcel) and calcium carboxymethycellulose were more effective in lactose tablets when used extragranularly. For sulphaguanidine tablets, Sakr & Farrag (1975) reported that sodium starch glycollate (Primojel) was most effective when incorporated extragranularly, rather than intragranularly or both. In a freely soluble tablet matrix, water penetration throughout the tablet and disintegration into constituent granules is the rate-limiting step to tablet deaggregation. Undispersed granules, which are highly soluble, will dissolve very rapidly. Size reduction is therefore less dependent on the presence of intragranular disintegrant.

In a highly soluble matrix, a hydrophilic network between the granules is needed to ensure that the tablet rapidly disintegrates. If disintegration does not occur rapidly, the soluble component will rapidly dissolve on the outer layer of the tablet matrix. The rate of fluid diffusion into successive layers will be retarded, particularly if highly concentrated or viscous solutions are formed (Graf et al, 1982). The tablet may decrease in size by solution from the tablet surface (Guyot-Hermann & Leblanc, 1985) and because generated surface area is low, disintegration times will be long.

The disintegrant employed in either mode should not agglutinate when wetted. Jaminet et al (1969) compared disintegration and dissolution properties of phenobarbitone tablets containing 5% disintegrant and lactose as filler. The freely water soluble, highly substituted sodium carboxymethylcellulose, Copagel™, was found to lose its disintegration properties during granulation, being more effective when incorporated

extragranularly. It becomes viscous and hydrated and acts as a binder rather than a disintegrant during wet granulation, and therefore slows granule deaggregation.

In patents relating to dispersible tablets, it is often stated advantageous to combine the use of disintegrants and use a different type intra- and extragranularly (Murphy & Mathews, 1990; Fielden, 1992; Martin & Romero, 1992). Although many workers have studied the effect of the mode of incorporation of super disintegrants, this has been largely restricted to the use of a single type. There is a lack of work reporting the effect when different super disintegrants are combined. The work will systematically study the effect of extragranular disintegrant type on dispersible paracetamol tablets containing different intragranular disintegrants, using Explotab, Ac-Di-Sol, Kollidon-CL and Amberlite IRP88.

## 4.2 Materials and Methods.

### 4.2.1 Materials.

See Section 2.1.

### 4.2.2: Methods.

#### 4.2.2.1 Granulation method.

The different intra- and extragranular formulations used are given in Table 4.1. The general formulation used is given in Table 4.2. A control without any intra- / extragranular disintegrant was also included.

Four batches of granules were made, each containing a different intragranular disintegrant, and split into five equal amounts. Four lots were mixed with extragranular disintegrant (according to Table 4.1) and one without, to act as a control. Granulations were made and lubricated according to the general method given in section 2.2.1.1. Granulated material was wet massed through a 1700μm sieve and dry sieved through 1000μm.

#### 4.2.2.2: Granulation loss on drying.

Before mixing with extragranular disintegrant, granulation loss on drying was determined according to the method in section 2.2.1.3.

#### 4.2.2.3: Compression.

Granules were compressed at 5, 10, 15 and 20 ± 0.5kN (Section 2.2.1.4). Tablets were compressed to a weight of 660mg ± 5%.

### 4.2.2.4 Evaluation of tablets.

See section 2.2.2.

**Table 4.1: Formulation plan.**

| Formulation N° | Intragranular | Extragranular |
|---|---|---|
| 1 | Explotab | Ac-Di-Sol |
| 2 | | Explotab |
| 3 | | Kollidon-CL |
| 4 | | Amberlite IRP88 |
| 5 Control | | *(without extragranular)* |
| 6 | Ac-Di-Sol | Explotab |
| 7 | | Ac-Di-Sol |
| 8 | | Kollidon-CL |
| 9 | | Amberlite IRP88 |
| 10 Control | | *(without extragranular)* |
| 11 | Amberlite IRP88 | Explotab |
| 12 | | Ac-Di-Sol |
| 13 | | Kollidon-CL |
| 14 | | Amberlite IRP88 |
| 15 Control | | *(without extragranular)* |
| 16 | Kollidon-CL | Explotab |
| 17 | | Ac-Di-Sol |
| 18 | | Kollidon-CL |
| 19 | | Amberlite IRP88 |
| 20 Control | | *(without extragranular)* |
| 21 | Control without intra- / extragranular disintegrant | |

**Table 4.2: Standard formulation.**

| Component | Mg / tablet | % w/w |
|---|---|---|
| Paracetamol | 500.00 | 75.76 |
| Avicel PH101 | 113.80 | 17.24* |
| Intragranular disintegrant | 13.20 | 2.00 |
| Extragranular | 13.20 | 2.00 |
| PVP K90 | 13.20 | 2.00 |
| Magnesium stearate | 6.60 | 1.00 |
| **Compression weight** | **660.00** | **100.00** |

* Control without intra- / extragranular disintegrant, containing 21.24% w/w Avicel; control formulations without extragranular disintegrant containing 19.24% w/w Avicel.

## 4.3: Results and Discussion.

### 4.3.1: Mean granule size of the bulk granulations.

**Table 4.3: Mean granule size of the bulk granulations.**

| Granulation | Mean granule size ± rsd [μm] |
|---|---|
| Explotab | 220 ± 1.02 |
| Ac-Di-Sol | 210 ± 0.89 |
| Kollidon-CL | 200 ± 1.19 |
| Amberlite IRP88 | 230 ± 0.94 |

The size distribution and mean granule size of the four bulk granulations was similar.

### 4.3.2: Granulation loss on drying.

To reduce effects on compaction due to moisture levels, residual loss on drying for all granulations was maintained within the range of 1.2 - 1.4 % w/w.

### 4.3.3: Tablet crushing strength.

Addition of 2% w/w extragranular disintegrant did not notably affect tablet crushing strength (Table 4.4). Control formulations had crushing strengths similar to those with extragranular disintegrant, regardless of type. Tablet crushing strength may decrease with increasing concentration of externally incorporated super disintegrant, especially starch derivatives (Sakr et al, 1975) due to their poor compression properties. Starch exhibits elastic properties (Hess, 1978) and the grains when incorporated extragranularly do not fuse together. It is probable that the concentration of extragranular disintegrant used was low enough for compression properties not to be adversely affected.

For tablets compressed at the same compaction force, those containing intragranular Kollidon-CL tended to be stronger. CL-PVP has been shown to be directly compressible in pure form (Kornblum & Stoopack, 1973). This indicates good compression properties in a wet granulated system.

**Table 4.4: Effect of extragranular disintegrant type on tablet crushing strength.**

| Compression Force [kN] | Extra granular | Intragranular disintegrant | | | |
|---|---|---|---|---|---|
| | | Explotab | Ac-Di-Sol | Kollidon-CL | Amberlite |
| | | Crushing strength [KP] | | | |
| | | $\bar{x}$ | $\bar{x}$ | $\bar{x}$ | $\bar{x}$ |
| 5 | Explotab | 3.99 | 4.13 | 4.32 | 4.33 |
| | Ac-Di-Sol | 4.08 | 4.25 | 4.81 | 3.57 |
| | Kollidon-CL | 4.18 | 4.17 | 4.13 | 3.88 |
| | Amberlite | 3.38 | 4.00 | 4.55 | 3.92 |
| | Control | 4.12 | 3.98 | 4.91 | 3.83 |
| 10 | Explotab | 8.83 | 8.87 | 8.81 | 8.52 |
| | Ac-Di-Sol | 8.53 | 8.99 | 10.18 | 9.37 |
| | Kollidon-CL | 8.82 | 9.00 | 8.67 | 9.26 |
| | Amberlite | 8.10 | 9.03 | 9.66 | 8.48 |
| | Control | 8.35 | 9.21 | 10.87 | 9.15 |
| 15 | Explotab | 12.20 | 12.52 | 14.63 | 12.71 |
| | Ac-Di-Sol | 12.82 | 12.63 | 14.65 | 12.00 |
| | Kollidon-CL | 12.09 | 12.14 | 13.53 | 12.01 |
| | Amberlite | 12.50 | 12.35 | 13.64 | 13.14 |
| | Control | 12.15 | 12.59 | 14.38 | 13.40 |
| 20 | Explotab | 14.66 | 15.11 | 15.91 | 14.14 |
| | Ac-Di-Sol | 14.53 | 15.00 | 16.12 | 15.07 |
| | Kollidon-CL | 14.47 | 15.24 | 15.31 | 14.91 |
| | Amberlite | 14.40 | 15.23 | 15.84 | 15.29 |
| | Control | 14.47 | 14.98 | 16.04 | 15.12 |

### 4.3.4: Tablet disintegration.

The control formulation without any intra- or extragranular disintegrant not surprisingly had very poor intrinsic disintegrant activity and did not disperse. Tablets disintegrated into large aggregates that dissolved away very slowly. Tablets compressed at 5kN took longer than 10 minutes to disintegrate through all mesh sizes (10kN > 30 minutes and at 15 and 20kN > 60 minutes).

Extragranular disintegrant increases the rate of dispersion with intragranular Explotab (Table 4.5) to constituent granules through mesh sizes of 1180μm and below. Explotab does not have significant wicking activity and water penetration throughout the tablet matrix limits the rate of disintegration. Large reductions in disintegration time with extragranular disintegrant are observed at higher pressures, when water penetration into the tablet is limited. Quick breakdown into granules results in more rapid granule deaggregation to 710μm (Figure 4.2).

The effect on disintegration of extragranular addition to tablets containing intragranular Explotab was consistent regardless of the type of extragranular disintegrant used. Notable exceptions were observed when Explotab and Amberlite IRP88 were used at high compression force. Under these conditions, extragranular Explotab caused noticeably less improvement of tablet dispersion. This disintegrant is dependent on swelling, which is limited when water penetration is reduced at high pressures. Starch grains in carboxymethylstarches may be damaged at high pressure (Guyot-Hermann, 1992) with a consequent partial gelatinisation that may reduce water penetration. Conversely, the disintegrating force generated by Amberlite IRP88 is less dependent on water availability than the other disintegrants (Caramella et al, 1989) and it therefore performed slightly better at high compression force.

**Figure 4.2: Effect of extragranular disintegrant type / compression force on the disintegration of tablets containing intragranular Explotab through a screen aperture size of 710 μm.**

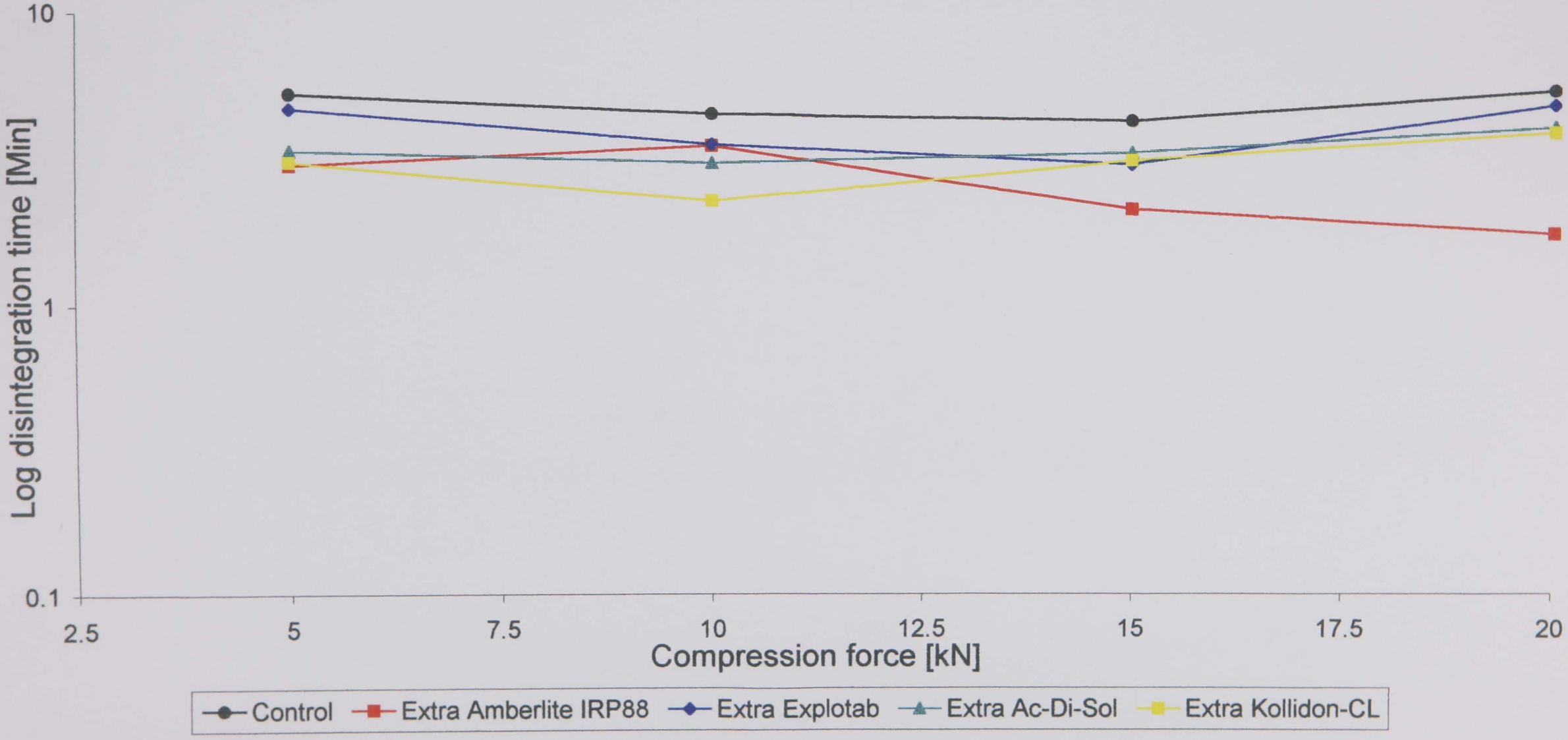


**Figure 4.3: Effect of extragranular disintegrant type / compression force on the disintegration of tablets containing intragranular Ac-Di-Sol through a screen aperture size of 710μm.**

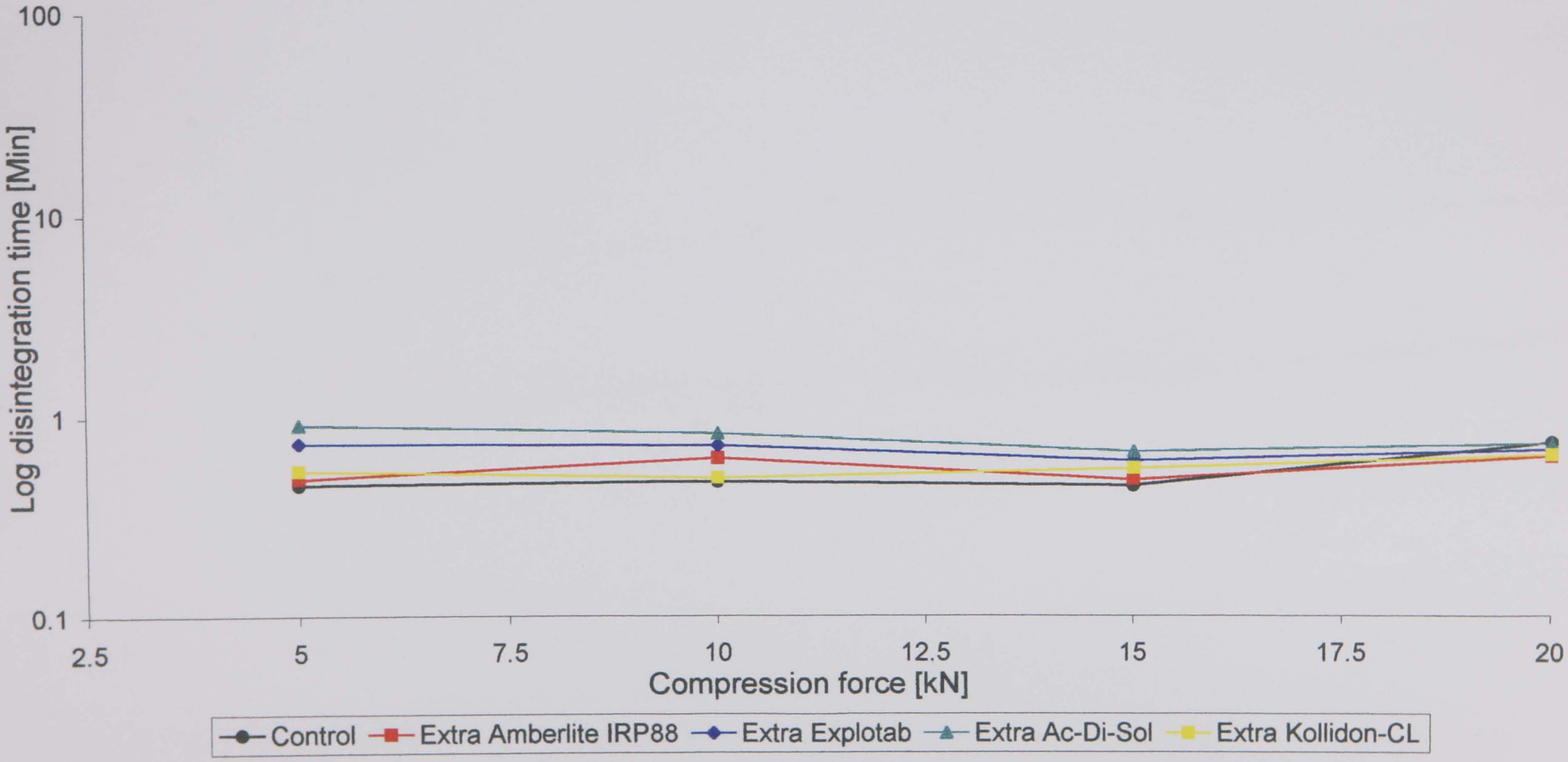


**Figure 4.4: Effect of extragranular disintegrant type / compression force on the disintegration of tablets containing intragranular Kollidon-CL through a screen aperture size of 710μm.**

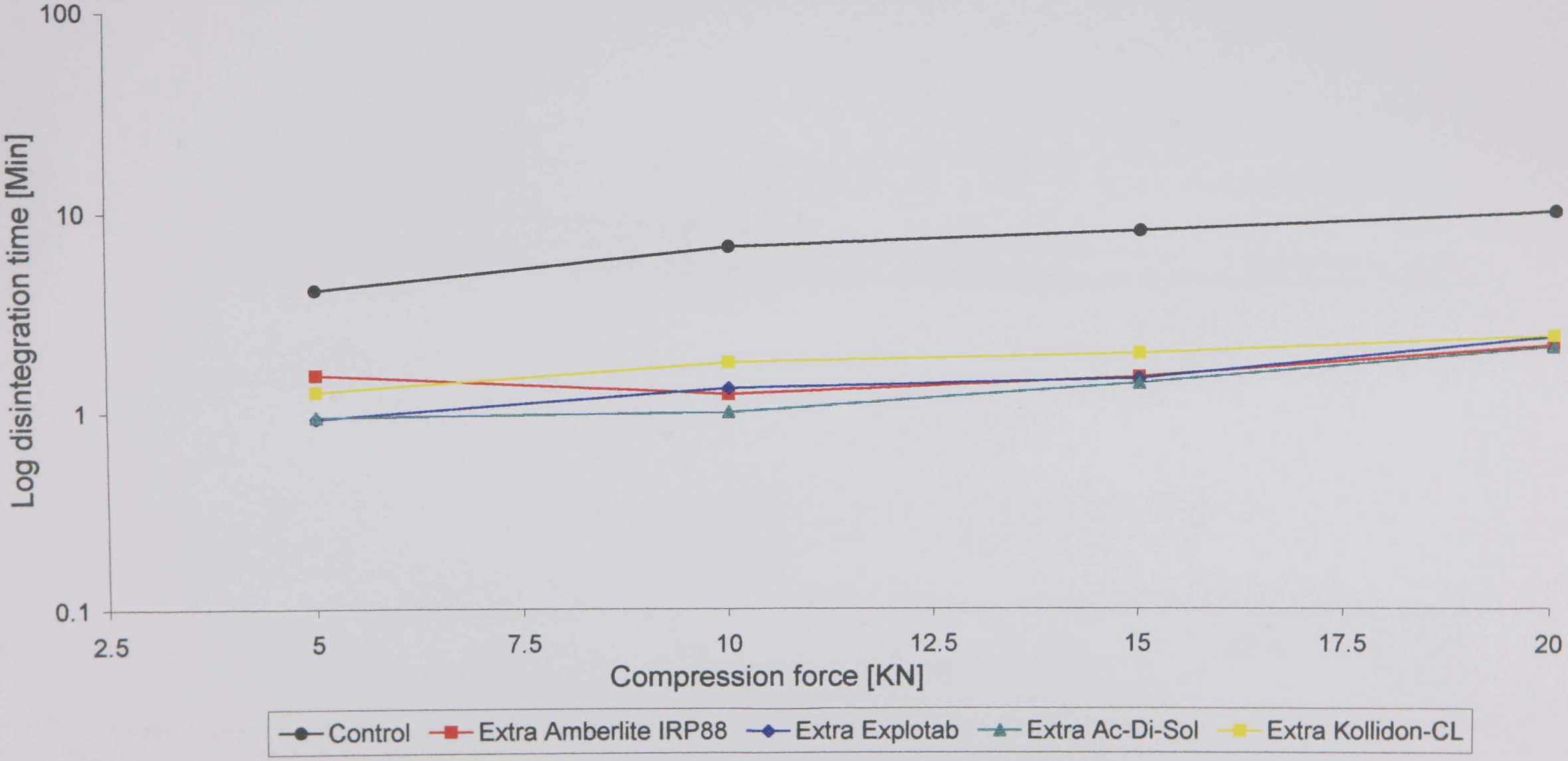


**Figure 4.5: Effect of extragranular disintegrant type / compression force on the disintegration of tablets containing intragranular Amberlite IRP88 through a screen aperture size of 710μm.**

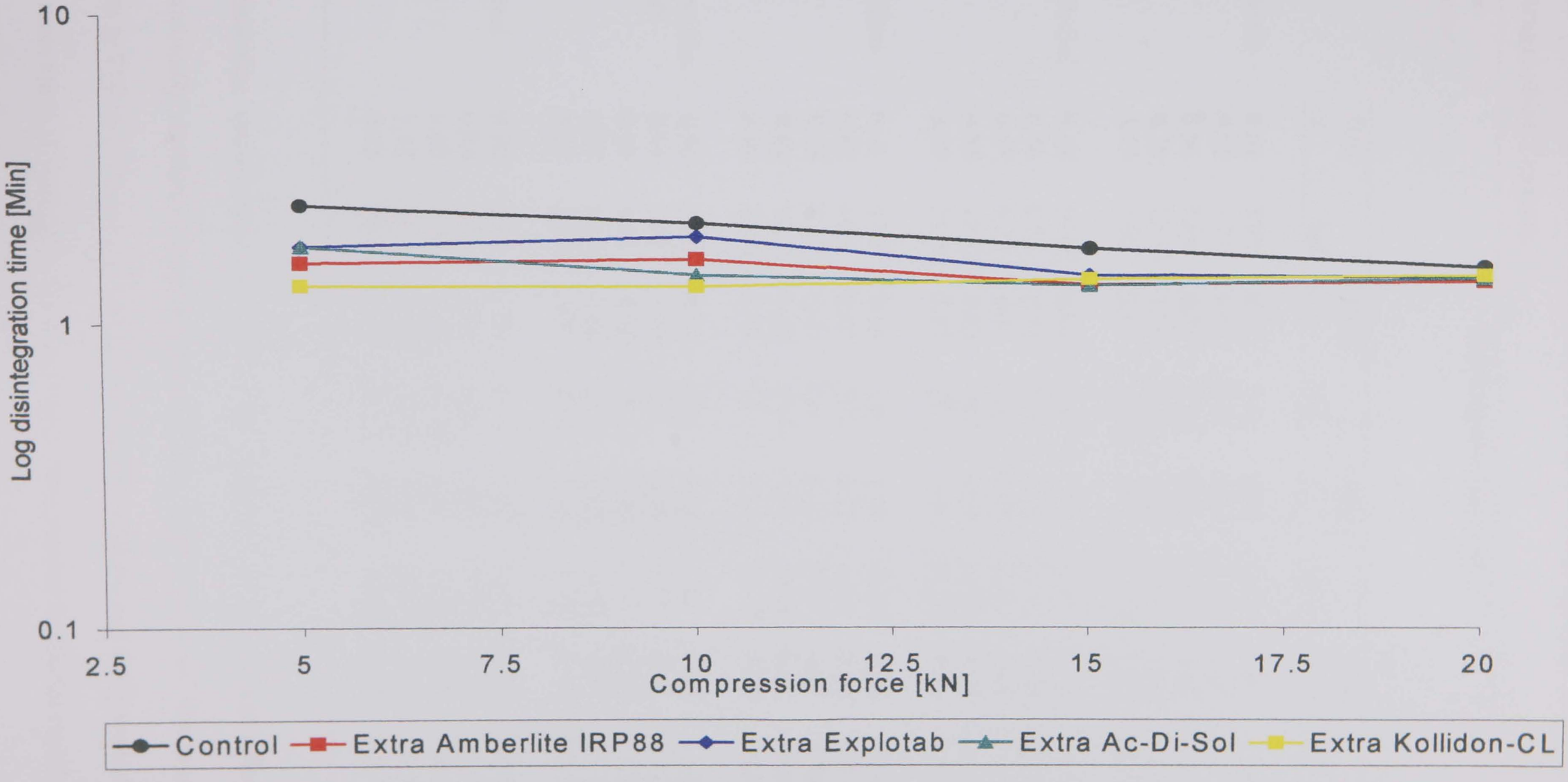


**Table 4.5: Effect of extragranular disintegrant type on the disintegration of tablets containing intragranular Explotab.**

| Mesh aperture size [μm] | Extra-granular | Disintegration time [Min] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 5kN | | 10kN | | 15kN | | 20kN | |
| | | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd |
| 2000 | Explotab | **0.51** | 3.92 | **0.77** | 5.19 | **0.85** | 2.35 | **1.08** | 5.56 |
| 1700 | | **0.53** | 3.77 | **0.84** | 9.52 | **0.91** | 1.10 | **1.11** | 6.31 |
| 1400 | | **0.56** | 7.14 | **0.85** | 5.88 | **0.96** | 2.08 | **1.21** | 5.79 |
| 1180 | | **0.75** | 17.33 | **1.06** | 14.15 | **1.05** | 8.57 | **1.60** | 27.5 |
| 710 | | **4.73** | 2.96 | **3.61** | 12.30 | **3.07** | 27.69 | **4.83** | 19.58 |
| 2000 | Ac-Di-Sol | **0.42** | 19.05 | **0.44** | 6.82 | **0.70** | 8.57 | **0.76** | 7.89 |
| 1700 | | **0.46** | 6.52 | **0.46** | 5.34 | **0.74** | 5.41 | **0.80** | 6.25 |
| 1400 | | **0.47** | 6.38 | **0.47** | 4.26 | **0.75** | 5.33 | **0.88** | 7.95 |
| 1180 | | **0.55** | 12.73 | **0.55** | 18.18 | **0.83** | 10.84 | **0.95** | 19.05 |
| 710 | | **3.38** | 24.26 | **3.12** | 15.06 | **3.36** | 46.13 | **4.05** | 15.31 |
| 2000 | Kollidon- | **0.41** | 4.88 | **0.40** | 5.00 | **0.50** | 6.00 | **0.55** | 3.64 |
| 1700 | CL | **0.43** | 4.65 | **0.42** | 9.52 | **0.51** | 5.88 | **0.60** | 8.33 |
| 1400 | | **0.48** | 8.33 | **0.45** | 11.11 | **0.52** | 5.77 | **0.69** | 8.70 |
| 1180 | | **0.48** | 12.50 | **0.48** | 22.92 | **0.77** | 19.48 | **0.95** | 16.84 |
| 710 | | **3.10** | 24.52 | **2.31** | 30.30 | **3.16** | 16.14 | **3.90** | 20.51 |
| 2000 | Amberlite- | **0.50** | 2.00 | **0.47** | 6.38 | **0.45** | 4.44 | **0.46** | 6.52 |
| 1700 | IRP88 | **0.52** | 1.92 | **0.53** | 7.55 | **0.48** | 4.17 | **0.49** | 6.12 |
| 1400 | | **0.52** | 3.85 | **0.58** | 17.24 | **0.49** | 2.04 | **0.58** | 7.69 |
| 1180 | | **0.57** | 10.53 | **0.66** | 18.18 | **0.63** | 15.87 | **0.67** | 25.37 |
| 710 | | **3.03** | 27.73 | **3.57** | 41.46 | **2.15** | 33.62 | **1.76** | 27.55 |
| 2000 | Control | **0.98** | 4.42 | **1.00** | 5.56 | **1.23** | 9.87 | **1.74** | 6.08 |
| 1700 | | **0.93** | 3.95 | **1.01** | 6.58 | **1.29** | 5.68 | **1.51** | 24.56 |
| 1400 | | **1.00** | 3.79 | **1.23** | 12.36 | **1.33** | 12.54 | **1.62** | 40.69 |
| 1180 | | **1.12** | 24.36 | **1.50** | 28.95 | **1.61** | 20.15 | **1.72** | 39.52 |
| 710 | | **5.32** | 29.66 | **4.59** | 36.58 | **4.32** | 24.60 | **5.42** | 40.26 |

In tablets containing intragranular Ac-Di-Sol, the presence of an extragranular disintegrant practically unaltered dispersion times (Table 4.6), even when this was measured down to 710μm (Figure 4.3). Ac-Di-Sol is very hydrophilic and easily wetted, with a zero contact angle (Gissinger & Stamm, 1980a). Intragranular Ac-Di-Sol rapidly

draws water into the granules. This rapidly penetrates the matrix via the hydrophilic capillary network produced by Avicel and Ac-Di-Sol. The addition of extragranular disintegrant does not increase the rate of tablet deaggregation. The initial swelling of extragranular disintegrant particles may actually block pores and reduce the rate of water penetration into the tablet. This explains the slight decreases in the rates of dispersion with the use of some extragranular disintegrants.

The greatest increase in the rate of dispersion with the addition of extragranular disintegrant is seen with intragranular Kollidon-CL (Table 4.7, Figure 4.4). Kollidon-CL functions most poorly in this system when used alone intragranularly. Its disintegrant action is reduced by hydrophobic lubricant (Bolhuis et al, 1982). In the absence of extragranular disintegrant, a hydrophobic film may almost completely coat the granules during the mixing process. When extragranular disintegrant is incorporated, its adherence to the granules probably reduces this, and allows water to more easily penetrate the granules. The percentage coverage of the granules with magnesium stearate will also be less.

Other factors may also contribute to the very poor disintegrant activity of Kollidon-CL when used alone intragranularly. The interaction between the lubricant and the disintegrant will be strongest when the disintegrant is incorporated extragranularly because there is direct contact. However, Kollidon-CL still performs efficiently when incorporated extragranularly. Disintegrant properties may be reduced by wet granulation. Recrystallisation of the drug inside the disintegrant fibers during the drying phase could reduce capillarity and swelling on rehydration. Extragranular Amberlite IRP88, Ac-Di-Sol and Kollidon-CL in tablets containing intragranular Kollidon-CL were equally effective. Explotab was less effective at high compression forces.

**Table 4.6: Effect of extragranular disintegrant type on the disintegration of tablets containing intragranular Ac-Di-Sol.**

| Mesh aperture size [μm] | Extra-granular | Disintegration time [Min] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 5kN | | 10kN | | 15kN | | 20kN | |
| | | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd |
| 2000 | Explotab | **0.57** | 4.01 | **0.51** | 6.54 | **0.51** | 1.97 | **0.57** | 3.35 |
| 1700 | | **0.58** | 3.09 | **0.53** | 5.25 | **0.54** | 5.21 | **0.57** | 2.12 |
| 1400 | | **0.59** | 2.05 | **0.55** | 3.65 | **0.53** | 3.57 | **0.58** | 3.29 |
| 1180 | | **0.58** | 8.25 | **0.54** | 7.06 | **0.56** | 4.49 | **0.56** | 4.44 |
| 710 | | **0.74** | 1.63 | **0.73** | 18.22 | **0.61** | 5.44 | **0.69** | 11.50 |
| 2000 | Ac-Di-Sol | **0.78** | 13.21 | **0.60** | 5.04 | **0.59** | 3.72 | **0.54** | 6.63 |
| 1700 | | **0.79** | 17.30 | **0.64** | 10.05 | **0.59** | 2.56 | **0.59** | 6.27 |
| 1400 | | **0.85** | 9.77 | **0.72** | 13.81 | **0.61** | 7.34 | **0.59** | 6.07 |
| 1180 | | **0.86** | 18.07 | **0.71** | 12.01 | **0.66** | 3.05 | **0.70** | 15.19 |
| 710 | | **0.92** | 13.52 | **0.84** | 13.48 | **0.68** | 1.77 | **0.74** | 15.20 |
| 2000 | Kollidon-CL | **0.41** | 9.09 | **0.40** | 6.30 | **0.45** | 3.01 | **0.56** | 6.18 |
| 1700 | | **0.44** | 5.19 | **0.41** | 7.02 | **0.47** | 7.05 | **0.57** | 4.01 |
| 1400 | | **0.47** | 7.10 | **0.46** | 2.63 | **0.46** | 6.64 | **0.57** | 9.02 |
| 1180 | | **0.50** | 8.40 | **0.42** | 11.27 | **0.50** | 5.32 | **0.60** | 12.17 |
| 710 | | **0.54** | 9.95 | **0.50** | 18.71 | **0.56** | 10.12 | **0.65** | 27.22 |
| 2000 | Amberlite-IRP88 | **0.42** | 3.36 | **0.40** | 7.69 | **0.42** | 5.54 | **0.38** | 7.20 |
| 1700 | | **0.45** | 4.46 | **0.42** | 6.64 | **0.44** | 2.97 | **0.40** | 3.78 |
| 1400 | | **0.48** | 9.05 | **0.46** | 3.93 | **0.46** | 3.90 | **0.42** | 1.18 |
| 1180 | | **0.46** | 2.39 | **0.45** | 8.61 | **0.46** | 5.83 | **0.46** | 2.39 |
| 710 | | **0.49** | 4.08 | **0.63** | 30.06 | **0.49** | 4.90 | **0.64** | 22.57 |
| 2000 | Control | **0.34** | 3.24 | **0.38** | 3.18 | **0.39** | 2.82 | **0.44** | 4.97 |
| 1700 | | **0.37** | 6.17 | **0.39** | 2.82 | **0.41** | 2.46 | **0.45** | 4.94 |
| 1400 | | **0.39** | 8.01 | **0.39** | 3.35 | **0.41** | 5.65 | **0.45** | 5.08 |
| 1180 | | **0.39** | 9.61 | **0.40** | 5.03 | **0.43** | 7.44 | **0.51** | 3.95 |
| 710 | | **0.46** | 9.09 | **0.48** | 3.37 | **0.46** | 5.93 | **0.75** | 11.38 |

**Table 4.7: Effect of extragranular disintegrant type on the disintegration of tablets containing intragranular Kollidon-CL.**

| Mesh aperture size [μm] | Extra-granular | Disintegration time [Min] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 5kN | | 10kN | | 15kN | | 20kN | |
| | | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd |
| 2000 | Explotab | **0.33** | 3.33 | **0.49** | 3.69 | **0.93** | 5.19 | **1.10** | 5.44 |
| 1700 | | **0.34** | 3.24 | **0.48** | 10.97 | **0.96** | 4.15 | **1.15** | 4.77 |
| 1400 | | **0.36** | 5.07 | **0.51** | 2.92 | **1.00** | 4.60 | **1.18** | 4.68 |
| 1180 | | **0.39** | 3.12 | **0.54** | 12.17 | **1.01** | 3.36 | **1.38** | 22.22 |
| 710 | | **0.93** | 7.73 | **1.34** | 27.42 | **1.51** | 6.63 | **2.43** | 9.37 |
| 2000 | Ac-Di-Sol | **0.28** | 1.82 | **0.31** | 5.77 | **0.50** | 2.98 | **0.67** | 3.87 |
| 1700 | | **0.29** | 4.21 | **0.29** | 7.53 | **0.51** | 2.16 | **0.68** | 3.41 |
| 1400 | | **0.30** | 7.46 | **0.30** | 4.95 | **0.51** | 4.90 | **0.68** | 1.47 |
| 1180 | | **0.30** | 8.05 | **0.32** | 1.55 | **0.49** | 6.69 | **0.70** | 2.56 |
| 710 | | **0.95** | 13.16 | **1.01** | 14.29 | **1.43** | 17.60 | **2.17** | 18.71 |
| 2000 | Kollidon-CL | **0.44** | 5.29 | **0.43** | 1.17 | **0.61** | 13.60 | **0.71** | 8.29 |
| 1700 | | **0.44** | 6.87 | **0.52** | 11.46 | **0.68** | 14.56 | **0.79** | 13.76 |
| 1400 | | **0.48** | 10.97 | **0.56** | 10.39 | **0.71** | 7.16 | **0.85** | 15.24 |
| 1180 | | **0.65** | 14.20 | **0.73** | 19.92 | **0.90** | 7.65 | **0.99** | 4.53 |
| 710 | | **1.27** | 27.35 | **1.82** | 20.52 | **2.03** | 17.17 | **2.46** | 16.08 |
| 2000 | Amberlite-IRP88 | **0.49** | 15.37 | **0.36** | 6.30 | **0.37** | 4.93 | **0.46** | 16.92 |
| 1700 | | **0.50** | 12.60 | **0.39** | 3.85 | **0.41** | 3.16 | **0.52** | 8.43 |
| 1400 | | **0.54** | 8.01 | **0.43** | 2.81 | **0.44** | 2.50 | **0.57** | 8.45 |
| 1180 | | **0.56** | 5.21 | **0.49** | 2.03 | **0.51** | 3.65 | **0.63** | 6.54 |
| 710 | | **1.55** | 0.57 | **1.25** | 6.56 | **1.54** | 1.88 | **2.21** | 11.92 |
| 2000 | Control | **2.19** | 21.83 | **2.88** | 11.62 | **3.24** | 6.38 | **5.21** | 3.25 |
| 1700 | | **2.22** | 9.05 | **3.18** | 13.98 | **3.99** | 4.58 | **5.81** | 14.59 |
| 1400 | | **2.51** | 8.10 | **3.67** | 8.65 | **4.13** | 4.26 | **6.39** | 9.41 |
| 1180 | | **3.03** | 7.91 | **4.54** | 3.97 | **4.28** | 6.33 | **8.52** | 13.75 |
| 710 | | **4.17** | 10.68 | **6.96** | 8.83 | **8.40** | 9.44 | **10.28** | 2.91 |

Dispersion of tablets containing intragranular Amberlite IRP88 was only slightly improved by the addition of extragranular disintegrant (Table 4.8, Figure 4.5) and was more effective when used alone intragranularly than Explotab or Kollidon-CL. Gissinger and Stamm (1980a) showed the rate at which pure samples of Amberlite

**Table 4.8: Effect of extragranular disintegrant type on the disintegration of tablets containing intragranular Amberlite IRP88.**

| Mesh aperture size [μm] | Extra-granular | Disintegration time [Min] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 5kN | | 10kN | | 15kN | | 20kN | |
| | | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd |
| 2000 | Explotab | **0.34** | 6.41 | **0.31** | 5.84 | **0.35** | 6.29 | **0.39** | 5.60 |
| 1700 | | **0.36** | 6.63 | **0.34** | 3.24 | **0.38** | 8.20 | **0.40** | 6.04 |
| 1400 | | **0.38** | 6.09 | **0.38** | 7.11 | **0.39** | 8.40 | **0.51** | 3.52 |
| 1180 | | **0.38** | 5.03 | **0.59** | 14.19 | **0.58** | 15.35 | **0.66** | 16.86 |
| 710 | | **1.79** | 16.15 | **1.94** | 23.52 | **1.46** | 17.58 | **1.43** | 5.44 |
| 2000 | Ac-Di-Sol | **0.51** | 4.87 | **0.51** | 3.56 | **0.51** | 1.97 | **0.59** | 2.56 |
| 1700 | | **0.52** | 3.67 | **0.52** | 4.40 | **0.50** | 5.46 | **0.60** | 4.85 |
| 1400 | | **0.53** | 5.14 | **0.52** | 4.25 | **0.50** | 2.98 | **0.62** | 1.95 |
| 1180 | | **0.48** | 10.17 | **0.47** | 12.92 | **0.49** | 4.52 | **0.56** | 5.23 |
| 710 | | **1.79** | 16.79 | **1.46** | 27.84 | **1.35** | 17.92 | **1.42** | 16.80 |
| 2000 | Kollidon-CL | **0.37** | 9.26 | **0.35** | 7.37 | **0.34** | 10.68 | **0.41** | 3.63 |
| 1700 | | **0.39** | 4.64 | **0.36** | 9.58 | **0.38** | 3.18 | **0.44** | 4.07 |
| 1400 | | **0.38** | 4.96 | **0.36** | 6.67 | **0.39** | 11.45 | **0.51** | 3.16 |
| 1180 | | **0.44** | 5.29 | **0.42** | 6.67 | **0.48** | 6.32 | **0.56** | 3.20 |
| 710 | | **1.34** | 34.81 | **1.34** | 27.92 | **1.42** | 17.68 | **1.45** | 46.09 |
| 2000 | Amberlite-IRP88 | **0.33** | 10.54 | **0.34** | 3.58 | **0.33** | 9.64 | **0.34** | 11.40 |
| 1700 | | **0.36** | 9.39 | **0.36** | 6.20 | **0.38** | 8.80 | **0.37** | 2.97 |
| 1400 | | **0.37** | 6.18 | **0.40** | 7.60 | **0.38** | 7.07 | **0.38** | 3.66 |
| 1180 | | **0.41** | 4.44 | **0.48** | 6.88 | **0.39** | 3.32 | **0.39** | 8.67 |
| 710 | | **1.59** | 17.64 | **1.64** | 8.56 | **1.36** | 31.39 | **1.39** | 30.58 |
| 2000 | Control | **0.68** | 9.71 | **0.60** | 3.03 | **0.61** | 4.45 | **0.70** | 6.73 |
| 1700 | | **0.80** | 13.03 | **0.65** | 5.12 | **0.70** | 10.61 | **0.71** | 3.25 |
| 1400 | | **0.79** | 8.33 | **0.77** | 5.20 | **0.73** | 4.80 | **0.76** | 7.51 |
| 1180 | | **0.91** | 3.97 | **0.84** | 9.86 | **0.80** | 5.36 | **0.91** | 9.23 |
| 710 | | **2.44** | 15.43 | **2.14** | 22.59 | **1.78** | 23.67 | **1.54** | 17.56 |

IRP88 drew in water was considerably less than Explotab or Polyplasdone XL. Its superior performance in this system may be partially attributed to the hydrophobic lubricant. Since it generates a high disintegrating force despite a low swelling volume, for reduced water availability, performance is influenced less. Avicel PH101 may

enhance the performance of intragranular disintegrants that possess less wicking action. It exhibits swelling and wicking activity and may be synergistic with disintegrants. Ideally, the tablet matrix should not have any intrinsic disintegrant activity. However, the addition of Avicel was necessary to achieve satisfactory compressibility.

For intragranular Amberlite IRP88, extragranular Explotab performed as effectively as the other disintegrants. Increased disintegration times at high compression force, were not observed, compared with intragranular Kollidon-CL and Explotab. Differences are related to intragranular disintegrant. At the surface of the tablet this contributes to the action of the extragranular disintegrant. That disintegrant activity of Amberlite IRP88 is not reduced at high pressure may explain the observed differences.

### 4.3.5: Tablet friability.

Tables 4.4 and 4.9 show that tablet friability is related to compression force and crushing strength and not extragranular disintegrant type. Intragranular Kollidon-CL at high compression forces produced stronger tablets, resulting in lower friabilities than other intragranular disintegrants.

**Table 4.9: Effect of intra-/ extragranular disintegrant type on tablet friability.**

| | | Intragranular disintegrant | | | |
|---|---|---|---|---|---|
| | | **Explotab** | **Ac-Di-Sol** | **Kollidon-CL** | **Amberlite** |
| **compression force [kN]** | **Extra-granular** | | | | |
| 5 | Explotab | 4.17 | 4.38 | 4.23 | 5.11 |
| | Ac-Di-Sol | 4.33 | 4.26 | 3.98 | 4.90 |
| | Kollidon- CL | 4.18 | 4.08 | 4.25 | 4.71 |
| | Amberlite | 3.38 | 4.69 | 4.30 | 4.86 |
| | Control | 4.12 | 4.11 | 3.85 | 5.02 |
| 10 | Explotab | 1.80 | 2.00 | 1.93 | 2.38 |
| | Ac-Di-Sol | 2.26 | 1.68 | 1.38 | 2.10 |
| | Kollidon- CL | 2.26 | 1.94 | 1.67 | 1.91 |
| | Amberlite | 2.14 | 1.87 | 1.14 | 2.47 |
| | Control | 2.17 | 1.78 | 1.70 | 1.93 |
| 15 | Explotab | 1.70 | 1.36 | **1.05** | 1.48 |
| | Ac-Di-Sol | 1.53 | 1.56 | **1.27** | 1.66 |
| | Kollidon- CL | 1.77 | 1.64 | **1.16** | 1.45 |
| | Amberlite | 1.72 | 1.51 | **1.14** | 1.42 |
| | Control | 1.74 | 1.45 | **0.88** | 1.29 |
| 20 | Explotab | 1.20 | 1.05 | **0.82** | 1.52 |
| | Ac-Di-Sol | 1.21 | 1.15 | **0.79** | 1.14 |
| | Kollidon- CL | 1.26 | 0.87 | **0.94** | 1.39 |
| | Amberlite | 1.15 | 1.21 | **1.00** | 1.16 |
| | Control | 1.20 | 0.99 | **0.77** | 1.31 |

## 4.4: Conclusions.

The relative importance of the intragranular / extragranular disintegrant used in a dispersible tablet formulation depends upon the size of compressed granules. In the present system, deaggregation below 710μm is more dependent on the type of disintegrant used intragranularly than extragranularly. The addition of extragranular disintegrant at a level of 2%w/w does not adversely affect the mechanical properties of the tablets.

When used alone intragranularly, the relative efficiencies of the disintegrants can be summarised as: Ac-Di-Sol > Amberlite IRP88 > Explotab > Kollidon-CL.

Tablets containing intragranular Ac-Di-Sol disintegrated most rapidly to give a dispersion of 710μm or less. Dispersion rates were not improved by the addition of extragranular disintegrant, and in some cases were reduced. Similarly, the rate of dispersion of tablets containing intragranular Amberlite IRP88 was only slightly increased. The greatest improvement in tablet dispersion with the addition of extragranular disintegrant, occurred in tablets containing intragranular Kollidon-CL, followed by Explotab.

Amberlite IRP88, Ac-Di-Sol and Kollidon-CL were equally effective as extragranular disintegrants at low and intermediate compression forces. Amberlite IRP88 tended to be better at high compression forces, whereas, the use of extragranular Explotab should be avoided.

# CHAPTER 5

# 5. EFFECT OF DRUG SOLUBILITY IN THE BINDER ON DISINTEGRANT EFFICIENCY.

## 5.1 Introduction.

Super disintegrants are highly efficient and effective at low levels (Rudnic et al, 1981). Nevertheless, careful formulation and control of the manufacturing process are required to ensure that disintegration in the finished tablet is not adversely affected.

As the aqueous solubility of a tablet matrix increases, super disintegrants function less efficiently (Paronen et al, 1985; Chowhan et al, 1991; Ferrari et al, 1995). A similar effect has been shown to occur with increasing hygroscopicity attributed to competition for locally available water (Gordon & Chowhan, 1987).

Gould & Tan (1985) investigated the effect of recompression after comminution and regranulation on disintegrant efficiency in wet massed tablets containing Explotab, Ac-Di-Sol and Polyplasdone XL, intra- and extragranular. The formulation contained Avicel PH101 (59%) and a highly soluble experimental compound (33%), wet massed with an aqueous PVP K90 binder. All disintegrant efficiencies, both intra and extragranular were reduced by tablet rework. Extragranularly, Polyplasdone XL and Ac-Di-Sol showed greater decreases in disintegrant efficiency than Explotab. They postulated the sponge-like Polyplasdone XL and the fibrous Ac-Di-Sol were broken down by compression. This may have reduced subsequent capillary action. Additionally, the disintegrant activity of slightly swelling hydrophilic disintegrants, like crospovidone, is adversely affected by hydrophobic lubricants (Bolhuis et al, 1982).

which is made worse by relubrication on rework. However, strongly swelling disintegrants such as sodium starch glycollate are unaffected by magnesium stearate (Smallenbroek et al, 1981; Proost et al, 1983). The reduction in the efficiency of extragranular Explotab was attributed to grains splitting open on compression (Hess, 1978) and impaired wetting. The rework efficiencies of all three disintegrant systems intragranularly were substantially reduced. All had rework efficiencies essentially the same as with no disintegrant (the control). The substantial reduction in rework efficiency of Explotab when used intra- rather than extragranularly was attributed to the additional wetting and drying processes of rework. Explotab shows considerable structural changes on absorbing water, leading to pre-swelling and partial dissolution (Khan and Rhodes, 1975b), but is not reversible on drying, causing permanent modification to the disintegrant grains (Mitrevej & Hollenbeck, 1982).

Gould & Tan (1985) also prepared stressed disintegrants by simulating two other components of the rework process: comminution and slurrying with water. The "stressed" disintegrants were incorporated extragranularly. After the slurrying process, the moisture stress in wet granulation decreased the efficiency of Ac-Di-Sol and Explotab, probably due to incomplete reversal of the structural changes on wetting and drying. Paradoxically, the disintegrant efficiency of Polyplasdone XL was significantly increased. However, the results were not explained. Possibly prior hydration favourably alters the structural arrangement of the polymer, enabling more rapid rehydration.

Milling had a negligible effect on the disintegration efficiency of Explotab, slightly increased the disintegration efficiency of Ac-Di-Sol and significantly increased the

efficiency of Polyplasdone XL, but was not explained. Milling increases surface area and the number of sites for capillary action, which may explain the results for the wicking disintegrants. Explotab works largely by swelling, which is so great that a reduction in size will be expected to have little effect on swelling force generation. Gould & Tan (1985) concluded that other factors in the rework process such as lubrication or compaction must be responsible for reducing the disintegrant efficiency of Polyplasdone XL.

The present work concerns the effect of drug solubility in the binder solvent on super disintegrant efficiency and whether "disintegrant poisoning" occurs during the wet granulation process. During wet massing and drying, the drug and excipients that dissolve and then recrystallise, form solid interparticulate bridges as the binder vehicle is evaporated. Drug crystals may be deposited around disintegrant particles or inside if drug saturated binder is drawn in during wet massing. Wells & Walker (1983) studied the influence of drug solubility in the granulating fluid upon granule and tablet properties. They used a model system containing acetylsalicylic acid, polyvinylpyrrolidone as binder and Polyplasdone XL as a disintegrant. A range of ethanol : water mixtures was used as binder vehicles. Although disintegration was influenced by differences in granule properties, they showed that high drug solubility in the binder produced tablets with poor disintegration. Where the binder solvent volatility was low, so was drug solubility and this resulted in little solute deposition and the generation of relatively large crystals. Where volatility and drug solubility was high, they reported considerable solute deposition and the crystals produced were small. Secondary binding due to the recrystallisation of dissolved drug increases intragranule

bonding and increases disintegration times. They also attributed increased disintegration times to fine crystals of acetylsalicylic acid blocking the tablet capillary network and deposition around the PVP-XL preventing penetration of fluid and impairing the swelling potential of the disintegrant.

The present work will investigate the influence of drug solubility in the binder on the disintegrant efficiency of Ac-Di-Sol, using paracetamol as a model drug, PVP K90 as binder and ethanol : water mixtures as binder solvent.

## 5.2 Materials and Methods.

### 5.2.1 Materials.

See Section 2.1.

### 5.2.2 Methods.

#### 5.2.2.1 Solubility of paracetamol in ethanol : water mixtures.

The following ethanol : water mixtures were produced by appropriate dilution of 95% ethanol (GPR grade, BDH) with purified water: 85:15; 75:25; 50:50; 25:75. The saturated solubility of paracetamol in purified water and ethanol : water mixtures was determined at room temperature (22°C). A 200ml sample of each solution was placed in a stoppered glass flask. The solutions were saturated with paracetamol powder added in excess and shaken for 16 hours on a flask shaker (Grant Instruments Ltd, Cambridge) to reach equilibrium. Excess paracetamol was removed by centrifuging for 5 minutes at 6000RPM using a Baird & Tatlock Autobench centrifuge Mark IV. Supernatant samples were collected, diluted appropriately with methanolic HCl and UV assayed according to Section 2.2.3.

#### 5.2.2.2 "Poisoning" of Ac-Di-Sol.

To obtain samples of Ac-Di-Sol with different levels of paracetamol contamination. In theory, slurrying Ac-Di-Sol in paracetamol solutions with different saturated concentrations should result in varying levels of the drug being drawn into disintegrant

during the hydration process and deposited on drying.

As an initial approach to "poisoning" the disintegrant, paracetamol saturated ethanol : water PVP K90 solutions were used. This is preferable to saturated ethanol : water solutions, since binder solution more closely represents the system in the wet granulation process. However, this method was found to be inappropriate for two reasons. The concentration of paracetamol in saturated ethanol : water PVP K90 solutions could not be determined due to precipitation of the paracetamol after centrifugation or filtration and after slurrying the disintegrant it was not possible to separate it from the viscous PVP K90 solutions.

Consequently paracetamol saturated ethanol : water solutions (Section 5.2.2.1) were used to slurry the disintegrant. 100ml of each solution was stirred and 6g of Ac-Di-Sol was added to give a homogeneous suspension. Experiments were carried out in duplicate. Beakers were double sealed with Parafilm™, agitated for 15 minutes on a flask shaker, the suspension centrifuged and the supernatant discarded. The pellet of poisoned disintegrant was removed and filtered under vacuum using a Buchner filter and Whatman filter paper (N° 1) to remove excess saturated paracetamol solution. With increasing water concentration of the solvent, separation of the solvent from the disintegrant was more difficult, because the disintegrant gelled with water. The 95% and 85% ethanol solutions did not form a gel with Ac-Di-Sol and complete separation was possible. With solvents of higher water concentration complete separation was not possible. The recovered disintegrant was then spread out on a glass petri dish and dried in a vacuum oven, at 50°C for 72 hours.

### 5.2.2.3 The extent of poisoning of Ac-Di-Sol with paracetamol.

Dried samples of poisoned disintegrant were gently agitated in a pestle and mortar to deaggregate any aggregated particles to give a fine powder. Those suspended in 95% and 85% v/v ethanol solutions yielded fine powders resembling untreated Ac-Di-Sol. However, the recovered disintegrant slurried in solutions with a higher water content formed hard "glassy" clumps which were difficult to grind to a powder.

The residual solvent content was determined by loss on drying as described in Section 2.2.1.3. Samples of poisoned disintegrant equivalent to 1.00g (adjusted for residual solvent content) were suspended in stoppered glass flasks containing 50ml of 95% ethanol in duplicate (determinations a and b). Suspensions were agitated on a flask shaker (Grant Instruments Ltd, Cambridge) for 24 hours to extract the paracetamol. Samples of the supernatant were taken and filtered through a 0.2μm cellulose acetate filter (Nalgene™, BDH laboratory supplies, Poole, England). Resultant solutions were diluted appropriately with methanolic HCl and UV assayed according to the method described in section 2.2.3. Assuming full extraction of the paracetamol from the poisoned disintegrant, the percentage paracetamol content of the poisoned Ac-Di-Sol was calculated.

### 5.2.2.4 The effect of Ac-Di-Sol poisoning on disintegrant efficiency.

The aim of the study was to test the hypothesis that deposition of paracetamol onto surfaces of the Ac-Di-Sol particles on wet granulation reduces disintegrant efficiency. This was tested by incorporating the "poisoned" disintegrant into a tablet system and

testing disintegration properties. The sample from slurrying with paracetamol saturated 85 : 15 ethanol : water was used. Disintegrant efficiency was evaluated in a formulation without other excipients with intrinsic disintegrant action, which would mask any change in disintegrant action.

**[a] Preparation of formulations.**

paracetamol powder was wet granulated with a 6% w/v solution of PVP K90 to give a directly compressible form, consisting of 98% paracetamol and 2% PVP K90 (dry weight). The granulated material was passed through a 2000μm sieve, dried for 2 hours at 50°C and then passed through a 1000μm sieve. This was dried for a further 2 hours, passed through a 500μm sieve and dried for a further 12 hours. Loss on drying was carried out using the method in Section 2.2.1.3. The granulated material was dried to a loss on drying of 1.63 ± 0.05 % w/w.

The directly compressible material used had the following general formulas:

**Table 5.1: Formula 5.1. General formula for formulations containing disintegrant.**

| **Component** | **% w/w** | **mg/ tablet** | **g** |
|---|---|---|---|
| Granulated paracetamol/ PVPK90 | 97 | 500 | 200 |
| Disintegrant | 2 | 10.31 | 4.12 |
| Magnesium stearate | 1 | 5.15 | 2.06 |
| **Compression weight** | | **515.46** | 206.18 |

**Table 5.2: Formula 5.2. Control formulation.**

| Component | % w/w | mg/ tablet | g |
|---|---|---|---|
| Granulated paracetamol / PVPK90 | 99 | 500 | 200 |
| Magnesium stearate | 1 | 5.05 | 2.02 |
| **Compression weight** | | **505.05** | 202.02 |

The following four formulations were made:

**A**: Control formulation.

**B**: Formula 5.1 using untreated Ac-Di-Sol.

**C**: Formula 5.1 using Ac-Di-Sol solvent treated Ac-Di-Sol. Solvent treated Ac-Di-Sol was prepared by treating the disintegrant in the same process used to prepare the "poisoned" Ac-Di-Sol using an ethanol : water, 85 : 15 mixture.

**D**: Formula 5.1 using "poisoned" disintegrant, slurried with paracetamol saturated 85% ethanol, determination 1, was used. To achieve a level of 2% w/w Ac-Di-Sol, the weight added was adjusted to account for the paracetamol content.

The appropriate quantity of 2% w/w extragranular disintegrant was mixed with the paracetamol granulation at 21 rpm for twenty minutes in a cube mixer (Erweka type UG, N° 21276, G.m.b.H, Heusenstamm, Germany). To lubricate, 1% w/w magnesium stearate was added to the granules and mixed in the cube mixer at 21 rpm for five minutes. The compression mix was stored in amber glass airtight jars until use.

**[b] Compression of formulations.**

The method in section 2.2.1.4 was used. Each formulation was compressed at 5, 10, 15

and 20kN ± 0.5kN. Tablets were compressed to the target weight ± 5%.

**[c] Evaluation of tablets.**

Testing was carried out 24 hours after ejection. Tablet disintegration, crushing strength and weight variation were measured using the methods given in Section 2.2.2.

## 5.3 Results and Discussion.

Table 5.3 shows the relationship between Ac-Di-Sol poisoning and paracetamol solubility in ethanol : water mixtures used to slurry the disintegrant.

Maximum solubility occurred at 85% ethanol. Such maxima exist in many mixed solvent systems (Lordi et al, 1964; Paruta & Irani, 1965) and are related to a specific dielectric requirement of the solute in the solvent (Paruta et al, 1962).

The amount of paracetamol taken up by disintegrant particles on slurrying with a saturated solution is dependent not only on the saturated drug concentration but also on the ability of the disintegrant to take up the solvent. Caramella et al (1989) studied the effect of disintegration medium on disintegration properties of directly compressed tablets containing 4% disintegrant. Experiments were carried out in model tablet formulations of dibasic calcium phosphate dihydrate and acetylsalicylic acid, hydrophilic and hydrophobic water insoluble substances, respectively. The disintegration properties of tablets containing Ac-Di-Sol in various ethanol : water mixtures was studied. In dibasic calcium phosphate dihydrate and acetylsalicylic acid tablets, a decrease in the water content of ethanol / water mixtures resulted in a decrease in maximum disintegrating force and the time taken for force development. This caused a substantial increase in disintegration times, attributed to reduced swelling because of reduced water availability.

**Table 5.3: Relationship between Ac-Di-Sol poisoning and paracetamol concentration of the ethanol : water mixture used to slurry the disintegrant.**

| Ethanol : Water | paracetamol solubility [mgml$^{-1}$] | | Paracetamol content of the poisoned Ac-Di-Sol [% w/w] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Determination 1a | | Determination 1b | | Determination 2a | | Determination 2b | |
| | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd |
| 95 : 5 | **14.62** | 0.68 | **14.62** | 0.68 | **15.15** | 2.11 | **13.34** | 2.25 | **13.69** | 1.10 |
| 85 : 15 | **15.47** | 0.58 | **15.47** | 0.58 | **15.12** | 1.31 | **14.73** | 2.31 | **14.61** | 1.85 |
| 75 : 25 | **18.72** | 1.60 | **18.72** | 1.60 | **17.76** | 1.52 | **16.75** | 1.19 | **16.88** | 0.71 |
| 50: 50 | **31.00** | 0.98 | **31.00** | 0.98 | **32.34** | 1.86 | **30.33** | 1.51 | **31.15** | 0.83 |
| 25 : 75 | **70.16** | 1.23 | **70.16** | 1.23 | **71.23** | 1.11 | **71.54** | 2.10 | **72.01** | 1.31 |
| 0 : 100 | **5.14** | 0.92 | **5.14** | 0.92 | **4.48** | 0.78 | **6.32** | 1.15 | **5.97** | 1.02 |

Ac-Di-Sol has a greater capacity for water uptake than ethanol. If the amount of drug deposited inside / around the disintegrant particles during the wet granulation process does influence subsequent efficiency, then clearly the capacity of the disintegrant to absorb the binder solvent is an important formulation factor.

Gelling of the Ac-Di-Sol with solvent mixtures with water contents of 25% or more gave values (Table 5.3) which are not true values for the "poisoning" of the disintegrant i.e. that adsorbed in and around the disintegrant particles. The high values represent incomplete separation from the saturated paracetamol solutions used to slurry the disintegrants. The very low values for 100% water are due to incomplete extraction of paracetamol from the dried gelled material. The 85% and 95% ethanol solutions do not form a gel with Ac-Di-Sol and complete separation was possible.

The results of disintegration testing are shown in Table 5.4. All tablets without disintegrant (formulation A) took longer than one hour to disintegrate. Comparing disintegration times for formulations B and C shows that the process of treating Ac-Di-Sol with solvent mixture and then drying does slightly reduce its disintegration properties. Gould & Tan (1985) reported that slurrying the disintegrant with water and drying reduced its efficiency, due to incomplete reversal of the structural changes brought about by the adsorption of moisture. However, Mitrevej & Hollenbeck (1982) reported that after absorbing water and drying, Ac-Di-Sol showed a complete reversal of swelling and that the dried material closely resembled the initial material. However, they did not investigate the effect on disintegrant efficiency. Solvent stress increases the aggregation of Ac-Di-Sol particles and will affect disintegrant dispersion. If local

concentrations of the disintegrant are lowered, then the ability to form an efficient capillary network will be reduced.

Comparing the disintegration of formulations C and D shows that paracetamol in and around the Ac-Di-Sol does slightly decrease disintegrant efficiency. When the disintegrant efficiency is reduced by slurrying with solvent or contamination with paracetamol, increases in disintegration times tend to be greatest in tablets compressed at higher compaction forces and in deaggregation to smaller particle sizes. Reduction in disintegrant efficiency is more evident at high compaction forces, because tablet porosity and therefore water penetration into the tablet is reduced. Paracetamol adsorbed onto the surfaces of the disintegrant may limit the accessibility of water to the disintegrant surfaces and reduce its capillary and swelling properties.

However, comparing the disintegration times for tablets containing paracetamol "poisoned" disintegrant to those without disintegrant, shows that Ac-Di-Sol retains significant disintegrant efficiency even after solvent stress and contamination with drug. Results in this system indicate that in terms of the formulation of a traditional swallow tablet, the effect of disintegrant poisoning on disintegrant efficiency is probably insignificant. However, in terms of dispersible tablet formulation, where tablets must deaggregate to give a dispersion of particles less than 710μm in less than three minutes. the effect is more important.

The deposition of crystallised substances at disintegrant surfaces on disintegrant efficiency will be dependent on the system used. It is logical that the physicochemical nature of the drug or other substances which recrystallise at disintegrant surfaces must

**Table 5.4: Effect of poisoning Ac-Di-Sol with paracetamol on disintegration times.**

| | Disintegration time [Min] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Mesh μm** | **2000** | | **1700** | | **1180** | | **1400** | | **710** | |
| | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd |
| **Formulation A** | **All longer than 1 hour.** | | | | | | | | | |
| **Formulation B** | | | | | | | | | | |
| 5kN | **0.29** | 10.34 | **0.31** | 9.68 | **0.30** | 10.00 | **0.29** | 3.45 | **0.31** | 3.23 |
| 10kN | **0.32** | 3.13 | **0.34** | 5.88 | **0.33** | 9.09 | **0.31** | 9.68 | **0.33** | 9.09 |
| 15kN | **0.32** | 6.25 | **0.32** | 6.25 | **0.32** | 3.13 | **0.31** | 6.45 | **0.35** | 11.43 |
| 20kN | **0.56** | 3.57 | **0.57** | 1.75 | **0.58** | 1.72 | **0.56** | 3.57 | **0.58** | 1.72 |
| **Formulation C** | | | | | | | | | | |
| 5kN | **0.29** | 13.79 | **0.32** | 13.79 | **0.30** | 10.00 | **0.31** | 9.68 | **0.51** | 21.57 |
| 10kN | **0.51** | 1.96 | **0.50** | 8.00 | **0.48** | 16.67 | **0.52** | 1.92 | **0.90** | 12.22 |
| 15kN | **0.75** | 2.67 | **0.78** | 5.13 | **0.79** | 6.33 | **0.91** | 5.49 | **1.17** | 6.84 |
| 20kN | **1.03** | 4.85 | **1.04** | 4.81 | **1.05** | 4.76 | **1.04** | 7.69 | **1.36** | 5.88 |
| **Formulation D** | | | | | | | | | | |
| 5kN | **0.35** | 12.00 | **0.37** | 7.41 | **3.28** | 10.71 | **0.45** | 25.71 | **1.42** | 12.30 |
| 10kN | **0.57** | 3.51 | **0.61** | 8.20 | **0.58** | 8.62 | **0.71** | 29.58 | **1.88** | 19.15 |
| 15kN | **1.24** | 1.61 | **1.39** | 7.19 | **1.26** | 6.35 | **1.34** | 4.48 | **2.61** | 32.18 |
| 20kN | **1.64** | 1.27 | **1.77** | 10.73 | **1.72** | 10.73 | **1.72** | 5.81 | **2.21** | 18.10 |

influence the interaction with the disintegrant and any subsequent reduction in efficiency. Yen et al (1997) used differential scanning calorimetry to study the interaction between nifedipine and super disintegrants in a solvent deposition system. Disintegrant was mixed with a nifedipine / chloromethane solution and then dried, leaving small drug particles adsorbed on the surface of the disintegrant. Using differential scanning calorimetry they showed that Kollidon-CL had a much stronger interaction with nifedipine than Ac-Di-Sol or Explotab. Hydrophobic substances at disintegrant surfaces are likely to cause a greater reduction in the rate of hydration than hydrophilic ones. Capacity of the drug to adsorb onto surfaces of the disintegrant may also be an important factor. Solvent properties may also affect disintegrant poisoning. The solvent may affect the crystalline form, the strength of bonding between drug and excipient, and the orientation of the drug on the surface of the excipient (McGinity & Harris, 1980).

## 5.4 Conclusions.

Disintegrant poisoning does occur during the wet granulation process. Both solvent stress (possibly resulting in irreversible structure change) and the uptake of paracetamol by Ac-Di-Sol contribute to a reduction in disintegrant efficiency. However, the efficiency of Ac-Di-Sol remained high after poisoning, and the effect is not of practical importance unless rapid disintegration to give a very fine dispersion is required.

The extent of disintegrant poisoning which occurs during wet granulation will be controlled by the solubility of the drug in the granulating solvent and the ability of the disintegrant to take up the solvent. Higher water content results in greater uptake by Ac-Di-Sol and gelling, causing irreversible structural changes that reduce disintegrant efficiency. Similarly, using a solvent which is taken up by the disintegrant, higher drug solubility will cause greater drug deposition around / inside disintegrant particles.

To reduce the poisoning of Ac-Di-Sol during the wet granulation process, ideally the solvent should be one with a low aqueous content in which the drug is not soluble / very poorly soluble.

# CHAPTER SIX

# 6. THE FORMULATION OF A HIGHLY SOLUBLE DRUG IN A DISPERSIBLE TABLET.

## 6.1 Introduction.

It is extremely difficult to formulate a highly soluble drug in a tablet to disintegrate and disperse. The main problem is that tablets containing high concentrations of water soluble drugs erode or dissolve away like a lozenge rather than disintegrate (Botzolakis & Augsburger, 1984). For example, Khan & Rhodes (1973) investigated the disintegration of tablets containing various disintegrants in formulations containing Na-salicylate and lactose, which are both soluble. The disintegration of the tablets appeared to be independent of disintegrant included. They concluded that when a freely soluble drug is present in a soluble system, the disintegration time may approximate to the solution time instead. Prolonged disintegration times can cause gastrointestinal irritation e.g. potassium chloride tablets which dissolve away slowly (Sheth et al, 1980).

Deaggregation and disintegration are difficult to achieve due to decreased water penetration into a highly soluble tablet matrix. Initially, an increased penetration rate may be found because of pore widening by dissolution (Van Kamp et al, 1986). Penetration, however, will slow down as rapid dissolution of the tablet matrix increases the viscosity of the penetrating liquid. As the outer layer of the tablet dissolves, a viscous barrier will form, retarding further water penetration. Decreased water penetration may also result from disintegrant particles partially filling the voids inside the tablet (Graf et al, 1982).

Using Ca-p-aminosalicylate as a model drug, Nogami et al (1963) examined the influence of penetrating fluid viscosity. Increased viscosity using methylcellulose 400 decreased penetration rate, and disintegration times increased.

Unfortunately super disintegrants tend to function less efficiently in soluble tablet bases. The efficiency of disintegrant swelling has been defined as the capability to transform water taken up into disintegrating force, expressed as "force equivalent" of a given amount of water (Caramella et al, 1990b). Ferrari et al (1995) studied the effect of formula solubility and porosity on the "force equivalent" of sodium starch glycollate. Simultaneous water uptake and force measurements were performed with the apparatus described by Caramella et al (1988). They demonstrated that the "force equivalent" of the sodium starch glycollate was considerably lower in water soluble materials, e.g. lactose and mannitol, than in insoluble materials such as dicalcium phosphate dihydrate. A strongly swelling disintegrant cannot develop its greatest swelling force in a water-soluble formulation because of the rapid increase in tablet porosity due to rapid dissolution of the tablet matrix. Thus, limited swelling disintegrants should function as well (Graf et al, 1981; Paronen et al, 1985).

Disintegrant efficacy is influenced by the overall solubility of the tablet matrix. If the drug content is low, then insoluble excipients such as dicalcium phosphate and microcrystalline cellulose can be used to create a tablet with low water solubility and super disintegrants function efficiently. For example, Bi et al (1996) produced a low dose (50mg) rapidly disintegrating ascorbic acid (high aqueous solubility) tablet using a matrix of microcrystalline cellulose and low-substituted hydroxypropylcellulose (4 : 1) incorporating the drug at 25% w/w.

However, when the dose is high, tablet size will limit the quantity of insoluble excipients. If an insoluble excipient is added, but the overall tablet solubility remains high, then the tablet may still dissolve away rather than disintegrate. Furthermore because the tablet is larger, it will take longer to dissolve away and disintegration time will be increased. Dissolution rate is a function of solubility (Ozturk et al, 1988).

The aim of the current work is to formulate a water dispersible tablet of Na-p-aminosalicylate, a highly soluble drug (soluble 1 in 2 of water), typically used in dosage units of 500mg. The initial approach incorporates acidic buffers to manipulate pH and suppress drug solubility and dissolution and therefore the rate at which porosity and viscosity develop.

According to Nelson (1957, 1958), the pH of the diffusion layer surrounding a soluble acid or salt will be relatively independent of the bulk pH because of intrinsic buffering action. The solution rate of the acid or salt would be controlled by the pH of the diffusion layer rather than the bulk pH. According to Noyes & Whitney (1897) and Nelson (1957), the diffusion layer is saturated with dissolving solids, and therefore contains other substances besides the drug. The influence on the pH of the diffusion layer by other components such as diluents and buffers will depend upon their aqueous solubilities and their acidic or basic properties.

Pharmaceutical additives have been included in formulations in order to modify the microenvironmetal pH. Disodium hydrogen citrate and trisodium citrate have been claimed to provide a range of buffered pH environments in penicillin formulations (Dwight, 1972). The aim of buffered formulations is to provide a diffusion around the dissolving particles to promote dissolution (Levy & Hayes, 1960; Cotty et al, 1965).

Doherty & York (1989) used an internal buffer system of disodium hydrogen orthophosphate and citric acid in a frusemide-polyvinylpyrrolidone solid dispersion.

This study attempts to create the reverse situation and suppress the aqueous solubility of Na-p-aminosalicylate at the diffusion layer. Reduced drug dissolution will reduce viscosity and promote better penetration throughout the tablet matrix. In theory, decreasing the dissolution rate of the Na-p-aminosalicylate should reduce the rate at which porosity develops within the tablet, therefore allowing greater disintegrant swelling force generation.

The acidic buffer salt sodium dihydrogen orthophosphate and citric acid will be incorporated to lower the diffusion layer pH such that conversion to the free acid (pKa 3.25), which is poorly water soluble (1 in 500 of water), is favoured.

## 6.2 The effect of acidic buffers on the disintegration properties of Na-p-aminosalicylate tablets.

### 6.2.1 Materials.

#### 6.2.1.1 Choice of drug: Na-p-aminosalicylate.

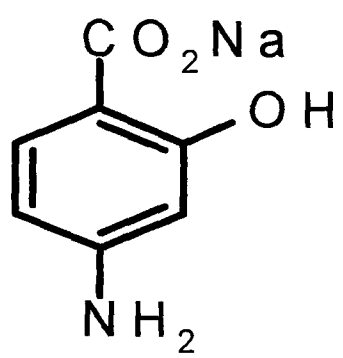



**Figure 6.1: The chemical structure of Na-p-aminosalicylate.**

4-aminosalicylic acid, sodium salt dihydrate (99%), Aldrich chemical company. Na-p-aminosalicylate is a white to cream coloured, practically odourless, crystalline powder, soluble 1 in 2 of water.

Na-aminosalicylate was previously used in the treatment of tuberculosis. It is a good model drug because of high aqueous solubility and the poor aqueous solubility (1 in 500) of the free acid, p-aminosalicylic acid.

#### 6.2.1.2 Buffers.

Citric acid anhydrous, BDH Laboratory Supplies, Poole, England. Crystals are monoclinic. The anhydrous form of citric acid has a melting point of 153°C. At 25°C, $pK_1$ 3.128, $pK_2$ 4.761, $pK_3$ 6.396 (Merck Index, 1996). It has a solubility in water at 20°C of 59.2% w/w.

Sodium dihydrogen orthophosphate dihydrate, BDH Laboratory Supplies. Poole, England. Orthophosphoric acid is a tribasic acid: $pKa_1$ 2.15; $pKa_2$ 7.09; $pKa_3$ 12.32. It has a solubility in water at 20°C of 1 in 1.

**6.2.1.3 Disintegrant.**

See section 2.1. Ac-Di-Sol was chosen because it combines rapid swelling with wicking activity and its disintegrant efficiency remains high after wet granulation.

**6.2.1.4 Binder.**

See Section 2.1.2.2.

**6.2.1.5 Lubricant.**

See Section 2.1.2.4.

## 6.2.2 Methods.

### 6.2.2.1 Granulation.

Tablets were prepared by wet granulation. A formula containing 2% intra- / 2% extragranular Ac-Di-Sol without buffer salts was used as a control. This was modified to contain 0.1M, 0.2M, 0.5M Na-dihydrogen orthophosphate dihydrate (MW 156.01) and 0.2M citric acid (MW 192.13) (Table 6.1).

Na-p-aminosalicylate, intragranular disintegrant and buffer (if included) were mixed in a planetary mixer (Kenwood chef model KM 200, Kenwood Limited, Hampshire) on speed setting one for fifteen minutes. Before addition, buffers were finely powdered in a pestle and mortar, to facilitate even distribution. PVP K90 was dissolved in distilled water to give a binder concentration of 12.0 % w/v (≡ 2% w/w in the tablet). The binder was added slowly over five minutes through a glass funnel to control the flow rate. The resultant material was wet massed through 2000μm. Granules were tray dried in an oven (Philip Harris model DZS, Philip Harris Ltd, Shenstone) for 16 hours at 50° C and dry sieved through 1700μm.

Extragranular disintegrant was mixed with the dried granules at 21 rpm for twenty minutes in a cube mixer (Erweka type UG, N° 21276, G.m.b.H, Heusenstamm, Germany). To lubricate, 1% w/w of magnesium stearate was then added to the granules and mixed in the cube mixer at 21 rpm for five minutes. The compression mix was stored in amber glass airtight jars.

**Table 6.1: Na-p-aminosalicylate 500mg tablet formulations containing 2% intra- / 2% extragranular Ac-Di-Sol and acidic buffers.**

| | **Buffer** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **no buffer (control)** | | **0.1M $NaH_2PO_4.2H_2O$** | | **0.2M $NaH_2PO_4.2H_2O$** | | **0.5M $NaH_2PO_4.2H_2O$** | | **0.2M Citric acid anhydrous** | |
| **Component** | mg / tablet | % w/w | mg / tablet | % w/w | mg / tablet | % w/w | mg / tablet | % w/w | mg /tablet | % w/w |
| Na-p-aminosalicylate | 500.00 | 93.00 | 500.00 | 91.44 | 500.00 | 89.88 | 500.00 | 85.20 | 500.00 | 89.16 |
| Ac-Di-Sol * PVP K90 | 10.75 | 2.00 | 10.94 | 2.00 | 11.13 | 2.00 | 11.74 | 2.00 | 11.22 | 2.00 |
| Magnesium stearate | 5.38 | 1.00 | 5.47 | 1.00 | 5.56 | 1.00 | 5.87 | 1.00 | 5.61 | 1.00 |
| $NaH_2PO_4.2H_2O$ | - | - | 8.53 | 1.56 | 17.36 | 3.12 | 45.77 | 7.80 | - | - |
| Citric acid anhydrous | - | - | - | - | - | - | - | - | 21.53 | 3.84 |
| **Compression weight** | 537.63 | | 546.82 | | 556.31 | | 586.86 | | 560.80 | |

* *each formulation contained 2% intra- / extragranular Ac-Di-Sol.*

### 6.2.2.2 Compression.

Granulations were compressed within 24 hours. Granules were compressed at 5, 10, 15 & 20kN ± 0.5kN (Section 2.2.1.4), using 12.5mm flat bevelled edge tooling. Tablets were compressed to the target weight ± 5%.

### 6.2.2.3 Disintegration testing.

All tablets were tested in distilled water according to Section 2.2.2.2. The disintegration of the control formulations without buffers (Table 6.1) was also tested in 0.1M sodium dihydrogen orthophosphate and 0.1M citric acid.

The pH of each disintegration fluid was measured using a pH meter (Phillips Model PW 9421, Phillips, England).

a) Distilled water (pH 5.73)

b) 0.1M sodium dihydrogen orthophosphate (pH 4.51)

c) 0.1M citric acid (pH 2.05)

### 6.2.2.4 Tablet crushing strength.

See Section 2.2.2.3.

### 6.2.2.5 Tablet weight variation.

See Section 2.2.2.5.

### 6.2.2.6 Measurement of the saturated pH of tablets ($pH_{SAT}$).

The saturated pH of tablets was determined by measuring the pH of 4 tablets crushed and mixed with 5ml of distilled water. A Phillips pH meter, Model PW 9421 was used, Philips, England. This was calibrated with 3 buffer solutions of pH; 4 ± 0.02, 7 ± 0.02 and 9 ± 0.02 (BDH Laboratory supplies, Poole, England) at 20°C.

### 6.2.3 Results and Discussion.

Buffers were added during the wet massing stage to create a continuous network at granule particle surfaces, to dissolve away and favour the formation of the free acid. Using paracetamol as a model drug and gelatin as a binder, Seager et al (1979) showed that granules prepared by wet massing and screening consisted of drug particles bound together by a sponge-like network of solid binder, elucidated by a solvent extraction technique.

Both citric acid and sodium dihydrogen orthophosphate are highly water soluble. During wet granulation the acid buffer salt crystals will dissolve at the surface and react with Na-p-aminosalicylate, which produces the insoluble free acid. This should protect the buffer from further reaction during wet granulation. Assuming this model, recrystallised buffer / binder will be distributed as a matrix throughout the granule structure.

Dissolving the buffers in the binder would have been a more ideal way to guarantee uniform distribution. However addition of the buffer salt to the binder solution at the required concentration caused precipitation of the PVP K90 binder solution. During granulation, acidic buffer dissolving in the binder solution may have caused some precipitation of the binder, but this was not visually apparent. The highly soluble Na-p-aminosalicylate gives a basic solution on dissolving, raising the pH.

The inclusion of citric acid and sodium dihydrogen orthophosphate in the tablet matrix failed to convert a dissolving matrix into a dispersing tablet (Table 6.2). Upon visual

observation, all tablet formulations dissolved away slowly without visible disintegration. Only after tablets had dissolved to a thin layer did they start to break up.

**Table 6.2: The effect of acid on the disintegration properties of Na-p-aminosalicylate tablets in distilled water.**

| Buffer Salt | Mesh aperture size [μm] | Disintegration time [Min] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 5kN | | 10kN | | 15kN | | 20kN | |
| | | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd |
| **No buffer** | 2000 | **8.94** | 8.39 | **10.36** | 2.99 | **11.42** | 2.63 | **10.90** | 5.69 |
| **(control)** | 1700 | **8.77** | 3.65 | **10.16** | 1.77 | **11.06** | 1.72 | **10.22** | 0.39 |
| | 1400 | **8.66** | 9.58 | **10.15** | 1.67 | **10.90** | 3.12 | **10.51** | 4.95 |
| | 1180 | **8.42** | 4.87 | **9.94** | 5.53 | **9.94** | 1.91 | **9.90** | 3.74 |
| | 710 | **7.72** | 2.72 | **8.98** | 5.12 | **9.66** | 2.59 | **9.71** | 3.19 |
| **0.1M** | 2000 | **10.14** | 1.68 | **10.47** | 3.72 | **10.31** | 2.81 | **10.78** | 1.95 |
| **$NaH_2PO_4.2H_2O$** | 1700 | **10.07** | 5.06 | **10.18** | 1.47 | **10.03** | 1.79 | **10.48** | 0.48 |
| | 1400 | **9.78** | 5.52 | **10.00** | 1.70 | **10.11** | 2.67 | **10.48** | 0.57 |
| | 1180 | **9.36** | 2.14 | **9.70** | 1.86 | **9.47** | 1.37 | **10.19** | 2.85 |
| | 710 | **8.53** | 5.39 | **9.39** | 7.45 | **9.35** | 2.14 | **9.47** | 1.37 |
| **0.2M** | 2000 | **8.94** | 3.80 | **9.78** | 2.15 | **9.86** | 8.52 | **10.48** | 1.62 |
| **$NaH_2PO_4.2H_2O$** | 1700 | **8.45** | 4.38 | **9.33** | 7.07 | **10.06** | 2.68 | **10.20** | 1.76 |
| | 1400 | **8.45** | 4.50 | **9.33** | 3.11 | **10.11** | 3.36 | **9.96** | 0.40 |
| | 1180 | **8.00** | 4.38 | **8.64** | 3.94 | **9.34** | 3.21 | **9.64** | 2.07 |
| | 710 | **7.86** | 3.44 | **8.48** | 2.83 | **9.25** | 6.59 | **9.50** | 0.84 |

**Table 6.2: Continued.**

| Buffer Salt | mesh aperture size [μm] | Disintegration time [Min] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 5kN | | 10kN | | 15kN | | 20kN | |
| | | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd |
| **0.5M** | 2000 | **9.89** | 2.30 | **10.25** | 6.93 | **10.73** | 1.30 | **11.65** | 1.29 |
| **$NaH_2PO_4.2H_2O$** | 1700 | **9.28** | 4.42 | **10.25** | 5.85 | **10.36** | 0.87 | **10.90** | 2.29 |
| | 1400 | **9.29** | 4.20 | **10.09** | 6.34 | **10.26** | 3.12 | **10.65** | 1.88 |
| | 1180 | **8.78** | 4.56 | **9.38** | 5.44 | **9.80** | 1.94 | **10.38** | 2.31 |
| | 710 | **8.09** | 5.56 | **9.33** | 4.72 | **9.62** | 2.08 | **10.13** | 2.27 |
| **0.2M** | 2000 | **8.40** | 1.07 | **9.40** | 4.04 | **9.70** | 4.12 | **10.79** | 1.30 |
| **Citric acid** | 1700 | **8.15** | 4.05 | **9.17** | 3.93 | **9.69** | 2.68 | **10.33** | 2.42 |
| | 1400 | **8.27** | 2.90 | **8.99** | 1.56 | **9.72** | 2.37 | **10.39** | 2.69 |
| | 1180 | **8.05** | 6.21 | **8.49** | 4.36 | **9.09** | 3.41 | **9.96** | 1.31 |
| | 710 | **7.50** | 5.07 | **8.17** | 3.79 | **8.60** | 2.56 | **9.54** | 2.20 |

Since tablets dissolved away rather than deaggregating, there was little difference in measured disintegration times on different mesh sizes. The slightly decreased times observed on smaller mesh sizes may be attributed to increased turbulence and agitation of the tablets, causing them to dissolve more quickly.

At lower compression forces, tablet disintegration times tended to be slightly less. This may be explained by greater porosity allowing easier water penetration and weaker intermolecular bonding in the tablet. However, disintegration times were high at all

compression forces used and at higher compression forces there was a general trend for disintegration time to be independent of compression force / tablet crushing strength.

For all tablet formulations, tablet crushing strength increased with compression force (Table 6.3). Comparing the tablet formulations containing buffer salts to the control shows that their inclusion increased tablet crushing strengths at each compression force used. Since high acidity causes precipitation of PVP K90, the buffer salts may alter the way it behaves in situ during granulation. This may affect the way in which the binder recrystallises and its compression properties.

**Table 6.3: The effect of buffers in Na-p-aminosalicylate tablets containing 2% intra- / 2% extragranular Ac-Di-Sol on tablet crushing strength.**

| **Buffer salt** | **Tablet crushing strength [kP]** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 5kN | | 10kN | | 15kN | | 20kN | |
| | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd |
| **No buffer (control)** | **3.28** | 28.35 | **9.98** | 5.57 | **15.68** | 7.46 | **16.76** | 8.71 |
| **0.1M $NaH_2PO_4.2H_2O$** | **7.04** | 6.39 | **11.62** | 5.77 | **16.14** | 3.97 | **18.26** | 5.42 |
| **0.2M $NaH_2PO_4.2H_2O$** | **4.82** | 7.88 | **11.02** | 5.54 | **18.36** | 4.68 | **18.96** | 7.23 |
| **0.5M $NaH_2PO_4.2H_2O$** | **5.72** | 5.24 | **11.76** | 3.06 | **17.48** | 4.06 | **19.97** | 3.56 |
| **0.2M Citric acid** | **5.02** | 8.61 | **12.60** | 5.08 | **17.74** | 6.02 | **20.54** | 2.29 |

On contact with water, the rapid solution of a highly soluble drug will increase water viscosity and cause a viscous film around the tablet. This is probably a more significant factor in limiting water penetration into the tablet, and therefore disintegration, than reduced porosity caused by higher compression forces. Ferrari et al (1995) reported that the influence of compression force on disintegrant efficiency and tablet disintegration was less in water-soluble tablet formulations than insoluble. In water insoluble formulations, disintegrant swelling plays the major role in the disintegration process

and becomes more effective as porosity decreases (Colombo et al, 1984; Caramella et al, 1986). They postulated that in water-soluble formulations, other mechanisms (dissolving, disruption of hydrogen bonding) that are responsible for disintegration are activated by water entry, thus making disintegrant swelling and the influence of tablet porosity less important.

**Table 6.4: The $pH_{SAT}$ of Na-p-aminosalicylate tablets containing 2% intra-/ 2% extragranular Ac-Di-Sol and acidic buffers.**

| Buffer inside the tablet | $pH_{SAT}$ |
|---|---|
| No buffer (control) | 7.61 |
| 0.1M $NaH_2PO_4.2H_2O$ | 6.70 |
| 0.2M $NaH_2PO_4.2H_2O$ | 6.48 |
| 0.5M $NaH_2PO_4.2H_2O$ | 6.14 |
| 0.2M Citric acid | 6.30 |

The saturated pH was used as a method of approximating the saturated microenvironmental pH of the tablets. Serajuddin & Jarowski (1985) compared pH-dissolution and pH- solubility data for salicylic acid and sodium salicylate using a pH stat apparatus to control bulk pH. When solubility at the pH of a saturated solution of the drug in the dissolution medium was used, the pH-dissolution and pH-solubility data correlated. This supports the concept that the pH of the diffusion layer resembles that of a saturated solution of the drug in the dissolution medium (Doherty & York, 1989)

$pH_{SAT}$ values for the tablets (Table 6.4) indicate the inclusion of buffers did not lower the microenvironmental pH within and around the tablet matrix enough. Increasing the amount of sodium dihydrogen orthophosphate or using citric acid, which has greater acidity, did not appreciably reduce the pH. The pKa of p-aminosalicylic acid is 3.25 and

because the $pH_{SAT}$ of all buffered tablets was > 6, it can be assumed that the microenvironmental pH would not favour conversion to the free acid.

During the wet granulation process some of the acidic buffer salt will have reacted with the Na-p-aminosalicylate. The reaction of the buffer at crystal surfaces may have formed an insoluble coating with p-aminosalicylic acid, which would prevent it from rapidly dissolving in the tablet to alter microenvironmental pH. Alternatively, it is possible that not enough unchanged buffer salt remained unreacted. Adding the buffer extragranularly as well as intragranularly may have improved pH manipulation.

Both the acidic buffer salts and the drug dissolved in the aqueous binder solution. A better choice of granulating agent may have been one in which the buffer but not the drug dissolved.

It would have been interesting to monitor the change in diffusion layer pH with time. When the tablet is in contact with water, it is logical that the depletion of a highly soluble acidic buffer will reduce the time in which a lowered microenvironmental pH can be maintained around the drug particles. Thus there will be an optimal proportion of a particular buffer with the drug. In practice the amount of buffer that can be added to a tablet formulation may be limited by toxicology factors.

The effect of the disintegration fluid on the disintegration of Na-p-aminosalicylate tablets is given in Table 6.5. Tablets tested in distilled water dissolved away slowly with no visible disintegration. On testing in 0.1M sodium dihydrogen orthophosphate, tablets compressed at 5kN showed slight disintegration for a few seconds and then dissolved away slowly. All tablets compressed at higher forces dissolved away slowly with no

visible disintegration. Disintegration times for tablets in distilled water and 0.1M sodium dihydrogen orthophosphate dihydrate are the times measured for the tablets to dissolve to a small enough size to pass through the appropriate mesh size.

All tablets tested in 0.1M citric acid failed to disintegrate after one hour. However, in 0.1M citric acid solution considerable deaggregation and disintegration of the tablets was seen to occur and this was greater at low compression. In the first few minutes of immersion macro deaggregation (Roland, 1967) took place. The extent of deaggregation was higher at lower compression forces, and these aggregates dissolved away very slowly. The pH of 0.1M citric acid = 2.05, below the pKa. Disintegration occurred at this pH because the sodium salt at the tablet surface on immersion would be rapidly converted to the free acid, which is very poorly soluble (1 in 500). This would prevent a viscous barrier forming around the tablet and allow fluid penetration into the tablet. Greatly reduced drug dissolution and rate of porosity development at this pH would also favour disintegrant force generation on disintegrant swelling. However once the tablets deaggregated, granules changed slightly in appearance, as if coated. Further disintegration was probably prevented as a coating of free acid quickly formed at granule surfaces. Covering of the granules with a material of high water insolubility may have greatly limited water penetration into the granules. The salt of an acidic or basic drug can lead to precipitation of an insoluble layer on the surface of a dissolving tablet and this can hinder dissolution (Higuchi et al, 1965). The disintegration behaviour in citric acid solution may be similar to that in-vivo in the acid conditions of the stomach, if the tablet is swallowed.

**Table 6.5: The effect of immersion fluid pH on the disintegration of Na-p-aminosalicylate tablets containing 2% intra-/ 2% extragranular Ac-Di-Sol.**

| Disintegration fluid | Mesh aperture size[μm] | Disintegration time [Min] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 5kN | | 10kN | | 15kN | | 20kN | |
| | | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd |
| **Distilled water (pH 5.73)** | 2000 | **8.94** | 8.39 | **10.36** | 2.99 | **11.42** | 2.63 | **10.90** | 5.69 |
| | 1700 | **8.77** | 3.65 | **10.16** | 1.77 | **11.06** | 1.72 | **10.22** | 0.39 |
| | 1400 | **8.66** | 9.58 | **10.15** | 1.67 | **10.90** | 3.12 | **10.51** | 4.95 |
| | 1180 | **8.42** | 4.87 | **9.94** | 5.53 | **9.94** | 1.91 | **9.90** | 3.74 |
| | 710 | **7.72** | 2.72 | **8.98** | 5.12 | **9.66** | 2.59 | **9.71** | 3.19 |
| **0.1M $NaH_2PO_4.2H_2O$ (pH 4.51)** | 2000 | **7.97** | 12.30 | **10.23** | 4.69 | **10.49** | 3.15 | **10.63** | 2.45 |
| | 1700 | **7.72** | 12.56 | **9.58** | 5.01 | **10.45** | 3.25 | **10.62** | 2.64 |
| | 1400 | **7.68** | 19.04 | **9.43** | 3.61 | **10.59** | 0.94 | **10.73** | 3.82 |
| | 1180 | **7.62** | 11.15 | **8.88** | 4.39 | **9.88** | 2.63 | **9.94** | 6.24 |
| | 710 | **6.71** | 18.48 | **8.73** | 3.32 | **9.73** | 3.70 | **9.54** | 3.98 |
| **0.1M Citric acid (pH 2.05)** | | **> 60** | | | | | | | |

### 6.2.4 Conclusions.

This method of buffer incorporation was not successful in achieving disintegration of Na-p-aminosalicylate tablets, attributed to an insufficient lowering of the pH. Testing tablets without buffer in 0.1M citric acid showed that some disintegration could be achieved where the disintegration medium was below the drug pKa. However, this stopped after the first few minutes of testing. If a low enough microenvironmental pH could be achieved at tablet diffusion layers by a dissolving component, tablet disintegration may occur. Disintegration fluid penetration retarded by free acid formation around tablet aggregates should not, in theory, be a great problem when water is the disintegration medium.

## 6.3 The use of Amberlite IRP88 as a disintegrant in Na-p-aminosalicylate tablets with and without PVP K90 binder.

### 6.3.1 Aims.

To evaluate the use of Amberlite IRP88 as a disintegrant in Na-p-aminosalicylate tablets. The work will also study the effect of omitting the binder in the wet granulation process.

### 6.3.2 Materials.

See Section 6.2.1.

### 6.3.3 Methods.

#### 6.3.3.1 Granulation.

Tablets were prepared by wet granulation according to the formulations given in Table 6.6 and the method of granulation described in Section 6.2.2.1. In formulations without PVP K90 binder, the granulation was carried out in a similar way but using the appropriate quantity of distilled water.

#### 6.3.3.2 Compression.

See Section 6.2.2.2.

#### 6.3.3.3 Evaluation of tablets.

See Section 2.2.2.

**Table 6.6: Na-p-aminosalicylate 500mg tablet formulations containing Amberlite IRP88.**

| | With binder | | | | Without binder | | | |
|---|---|---|---|---|---|---|---|---|
| | 2% intra- / 2% extra Amberlite IRP88 | | 4% intra- / 4% extra Amberlite IRP88 | | 2% intra- / 2% extra Amberlite IRP88 | | 4% intra- / 4% extra Amberlite IRP88 | |
| **Component** | **mg / tablet** | **% w/w** | **mg / tablet** | **% w/w** | **mg / tablet** | **% w/w** | **mg / tablet** | **% w/w** |
| Na-p-aminosalicylate | 500.00 | 93.00 | 500.00 | 89.00 | 500.00 | 95.00 | 500.00 | 91.00 |
| Amberlite IRP88 * | | | | | | | | |
| PVP K90 | 10.75 | 2.00 | 11.24 | 2.00 | - | - | - | - |
| Magnesium stearate | 5.38 | 1.00 | 5.62 | 1.00 | 5.26 | 1.00 | 5.49 | 1.00 |
| **Compression weight** | **537.63** | | **561.80** | | **526.32** | | **549.45** | |

**tablets contained either 2% or 4% intra / extragranular Amberlite IRP88.*

### 6.3.4 Results and Discussion.

Comparing the disintegration times of tablets containing 2% intra- / 2% extragranular Amberlite IRP88 with PVP K90 (Table 6.7) to those in Table 6.2 for 2% intra- / 2% extragranular Ac-Di-Sol, shows that Amberlite IRP88 is a more effective disintegrant. It is able to develop a high swelling force despite a low swelling volume (Caramella et al, 1989). It functions more efficiently than Ac-Di-Sol in this soluble tablet formulation where water availability is limited, due to increased viscosity and reduced penetration.

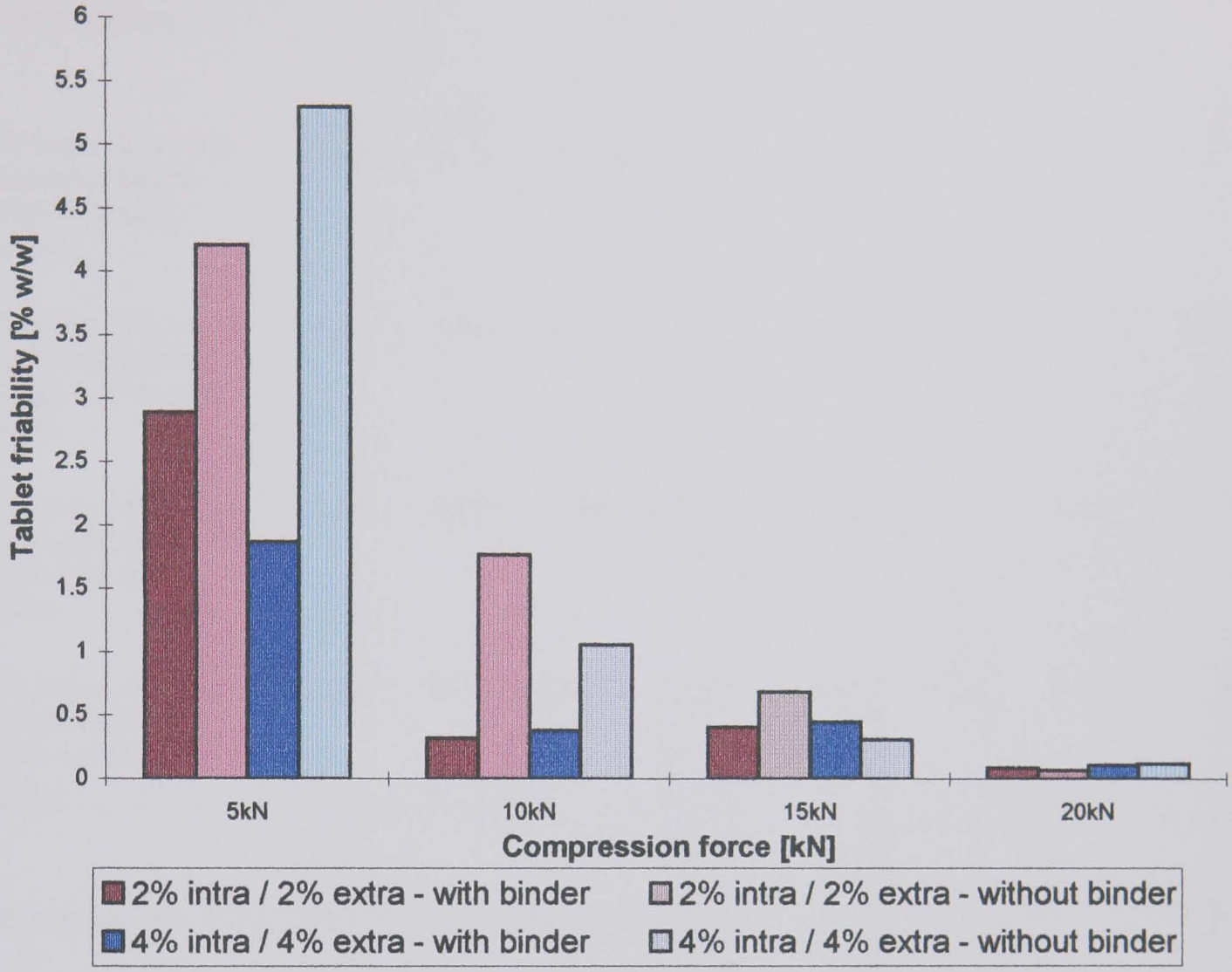
Removing the PVP K90 binder improved disintegration properties. Disintegration times were decreased (Table 6.7) and visual observations showed that greater deaggregation and disintegration occurred, rather than tablets simply dissolving away. In the formulations with binder, tablets compressed at 5kN disintegrated into large aggregates that dissolved away. At higher forces, they dissolved away without any noticeable tablet deaggregation. However, in the formulations without binder, visible tablet disintegration and deaggregation was seen in all tablets, except those compressed at 20kN, but this was greater at lower compression forces. Tablets compressed at 5kN disintegrated into small aggregates that dissolved. At 10 and 15kN, tablets disintegrated into large aggregates that dissolved away slowly.

When water penetrates the tablet, dissolution of the drug / excipients at the pore walls will take place and results in the dissolution of binding agents during the penetration process, which increases penetrating fluid viscosity. In practice, a binder is usually needed to achieve acceptable mechanical properties. In a water dispersible tablet, care should be taken to select one with low aqueous viscosity.

**Table 6.7: The effect of Amberlite IRP88 concentration and PVP K90 on the disintegration of Na-p-aminosalicylate tablets.**

| Formulation | Mesh aperture size [μm] | Disintegration time [Min] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 5kN | | 10kN | | 15kN | | 20kN | |
| | | $\bar{x}$ | RSD | $\bar{x}$ | RSD | $\bar{x}$ | RSD | $\bar{x}$ | RSD |
| **2% intra / 2% extra** | 2000 | **3.16** | 27.53 | **7.81** | 3.46 | **7.20** | 7.08 | **7.81** | 2.43 |
| **Amberlite IRP88** | 1700 | **3.01** | 22.92 | **7.50** | 6.27 | **7.04** | 1.14 | **7.60** | 2.24 |
| **With PVP K90** | 1400 | **3.45** | 6.67 | **6.78** | 7.23 | **7.22** | 4.02 | **7.60** | 1.71 |
| **binder** | 1180 | **3.38** | 12.72 | **6.82** | 3.67 | **6.78** | 2.80 | **7.06** | 1.13 |
| | 710 | **3.52** | 21.88 | **6.69** | 4.04 | **6.65** | 1.95 | **6.99** | 0.29 |
| **2% intra / 2% extra** | 2000 | **0.39** | 7.69 | **4.50** | 1.78 | **5.78** | 10.03 | **5.70** | 0.88 |
| **Amberlite IRP88** | 1700 | **0.50** | 6.00 | **4.55** | 5.49 | **5.55** | 10.99 | **5.56** | 3.06 |
| **Without PVP K90** | 1400 | **0.52** | 3.85 | **4.61** | 5.64 | **5.54** | 10.83 | **5.58** | 2.51 |
| **binder** | 1180 | **0.68** | 19.12 | **4.38** | 9.82 | **5.06** | 12.45 | **5.06** | 5.34 |
| | 710 | **1.17** | 7.69 | **4.67** | 3.64 | **5.04** | 7.34 | **4.89** | 2.66 |
| **4% intra / 4% extra** | 2000 | **1.97** | 28.43 | **6.12** | 6.54 | **6.94** | 4.90 | **7.11** | 4.78 |
| **Amberlite IRP88** | 1700 | **1.71** | 32.16 | **5.98** | 5.18 | **6.61** | 2.87 | **6.86** | 2.19 |
| **With PVP K90** | 1400 | **2.12** | 26.42 | **6.00** | 7.00 | **6.70** | 0.75 | **6.86** | 1.46 |
| **binder** | 1180 | **1.42** | 72.53 | **5.62** | 3.91 | **6.28** | 0.80 | **6.74** | 2.97 |
| | 710 | **1.92** | 44.27 | **5.73** | 3.84 | **6.42** | 3.43 | **6.64** | 0.75 |
| **4% intra / 4% extra** | 2000 | **0.20** | 15.00 | **2.77** | **17.69** | **5.27** | 4.55 | **5.63** | **3.37** |
| **Amberlite IRP88** | 1700 | **0.33** | 3.03 | **2.59** | **15.44** | **5.38** | 8.18 | **5.56** | **2.34** |
| **Without PVP K90** | 1400 | **0.40** | 7.50 | **3.06** | **9.80** | **5.07** | 11.83 | **5.77** | **4.51** |
| **binder** | 1180 | **0.51** | 21.57 | **2.92** | **26.37** | **5.13** | 6.04 | **5.04** | **7.74** |
| | 710 | **0.55** | 12.73 | **3.08** | **14.94** | **4.92** | 13.01 | **5.06** | **1.58** |

**Figure 6.2: The effect of PVP K90 binder / Amberlite IRP88 concentration on the friability of Na-p-aminosalicylate tablets.**




The crushing strengths of tablets are given in Table 6.8. No binder reduces their strength. However, those without binder are mechanically strong. Highly soluble drugs are adhesive, and therefore tablets wet granulated with water may have acceptable mechanical properties.

Figure 6.2 gives tablet friabilities. When tablets are compressed at low compression force, the friability of tablets without PVP K90 binder is much higher than those with. However, when compressed at 15kN and 20kN differences are negligible.

**Table 6.8: The effect of PVP K90 and Amberlite IRP88 concentration on the crushing strength of Na-p-aminosalicylate tablets.**

| Formulation | Tablet crushing strength [kP] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 5kN | | 10kN | | 15kN | | 20kN | |
| | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd | $\bar{x}$ | rsd |
| **2% intra / 2% extra Amberlite IRP88 With PVP K90 binder** | **4.64** | 12.72 | **9.18** | 6.86 | **14.08** | 2.49 | **14.86** | 3.77 |
| **2% intra / 2% extra Amberlite IRP88 Without PVP K90 binder** | **4.86** | 9.88 | **8.18** | 7.58 | **10.56** | 7.01 | **11.74** | 8.09 |
| **4% intra / 4% extra Amberlite IRP88 With PVP K90 binder** | **4.66** | 6.01 | **8.90** | 4.83 | **12.06** | 2.90 | **12.80** | 4.77 |
| **4% intra / 4% extra Amberlite IRP88 With out PVP K90 binder** | **4.42** | 12.90 | **6.64** | 7.98 | **10.12** | 6.42 | **10.98** | 7.38 |

Increasing the concentration of disintegrant from 4 to 8%, with or without PVP K90, tended to decrease disintegration times slightly. The greatest decrease was seen in tablets compressed at lower compression forces. For disintegrant force generation, absorption of water is necessary and water penetration into a highly soluble tablet is limited. Therefore, increasing disintegrant concentration beyond a certain level may have little if any effect because of lack of water for the disintegrant to function. For tablets at lower compression, water will initially penetrate more easily and therefore increased concentrations of disintegrant will be more effective.

In Table 6.8 tablets both with and without PVP K90 binder, and at each compression force studied, increasing the concentration of Amberlite IRP88 from 4 to 8% reduces

the mechanical crushing strengths, attributed to the poor compression characteristics of the disintegrant (Khan & Rhodes, 1973).

### 6.3.5 Conclusions.

In conclusion, Amberlite IRP88 may be a good choice of disintegrant in soluble tablet formulation where water penetration is limited. Increasing disintegrant concentration may improve disintegration, however above a certain level may have little or no effect, and can produce mechanically poorer tablets.

In a highly soluble tablet formulation where the drug dissolves to form a highly viscous solution, as with Na-p-aminosalicylate, it may be possible to omit the use of binder in the wet granulation process and still achieve mechanically acceptable tablets by using adequate compression. Potentially this will increase the extent and rate of tablet disintegration and deaggregation.

# CHAPTER 7

# 7. GENERAL DISCUSSION.

The aim of this study has been to develop generic technology for the formulation of dispersible tablets using wet granulation and conventional tableting technology. The project used two model drugs that are potentially difficult to formulate as a dispersible tablet:

I. **A high dose, poorly compressible drug** (Paracetamol).

II. **A high dose, freely aqueous soluble drug** (Na-p-aminosalicylate).

## 7.1 Formulation of a high dose, poorly compressible drug.

### 7.1.1 Drug compaction properties.

Before attempting the formulation of a high dose, poorly compressible drug, it is necessary to understand the compression characteristics to allow rational excipient choice. A compression profile can be obtained from compaction simulator studies (Akande, 1996).

Tablet strength depends on the inherent ability of a powder to reduce in volume during compression and the amount of interparticulate attraction in the final compact (Milosovich, 1963). Pharmaceutical materials consolidate by one or more of the following mechanisms: particle rearrangement, elastic deformation, plastic deformation and particle fragmentation (De Boer et al, 1978; Duberg & Nystrom, 1986). Elastic deformation is detrimental to strong tablet formation since the individual crystals return to their original shape when the pressure is released. Consequently a high elastic

component causes a high incidence of capping and lamination (Malamataris et al, 1984). Plastic deformation produces greater compact densification and enormously increases the number of contact points and the area of contact between crystals (Milosovich, 1963) resulting in enhanced bond formation and strong tablets (Duberg & Nysrom, 1982).

Paracetamol is a good model since its poor compression properties are well documented (Leigh et al, 1967; Obiorah & Shotton, 1976; Krycer et al, 1982; Alderborn et al, 1985; Duberg & Nystrom, 1986). Fragmentation is the dominant mechanism during compaction of pure paracetamol powder (Garekani, 1996; Roberts & Rowe, 1985), with a high elastic deformation (Duberg & Nystrom, 1986) resulting in weak and capped tablets (Krycer et al, 1982). However, conflicting evidence has been reported (Doelker & Shotton, 1977) that paracetamol shows a degree of plastic flow and brittle behaviour (Humbert-Droz, 1983).

Wet granulation, used in the present studies, improves the compressibility by increasing the plasticity of the material, which is usually attributed to the binder used (Milosovich, 1963). Knowledge of the compression properties of potential binders alone and in combination with the drug will help to develop better formulations (Morton, 1996). Leigh et al (1967) showed that granulating paracetamol with 3% w/w PVP, gave a compression profile of a body with a constant yield stress, rather than behaviour of a Mohr's body with water alone, and tablets did not cap or laminate. Good compression was achieved in this study using 2% w/w PVP K90. Leigh et al (1967) did not specify the grade and in this study microcrystalline cellulose will have contributed to improved plasticity.

In addition to the ability to increase plastic flow and produce strong tablets with low friability, binder disintegration properties need to be considered. Unfortunately, binders that confer superior mechanical properties often cause longer disintegration times and vice versa (Becker et al, 1997) and the best compromise should be found. Becker et al (1997) demonstrated lower disintegration times in paracetamol tablets with Lycatab PGS™ (a pre-gelatinised maize starch, with reduced soluble components) than with PVP or Cellulose HP-M 603™ (hydroxypropylmethylcellulose). However mechanically acceptable tablets could not be produced.

In this study microcrystalline cellulose (Avicel PH101™) at ≅20% w/w produced strong paracetamol tablets without capping. It consolidates predominantly by plastic flow (David & Augsburger, 1977; Roberts & Rowe, 1986) and permits rapid passage of water into tablets (Lamberson & Raynor, 1976) making it very useful for dispersible tablet formulations. Rosovsky (1995) prepared a dispersible paracetamol tablet by wet granulation containing 50% w/w paracetamol and 28% w/w microcrystalline cellulose. Watanabe et al (1995) used 9:1 microcrystalline cellulose:low-substituted hydroxypropylcellulose in a directly compressed low dose dispersible tablet.

The present work used a single punch tablet machine at a speed of 21 cycles per minute. However, for a commercial preparation, the influence of speed on formulation compression properties should be studied, as plastic flow may decrease with increased tableting speeds (Roberts & Rowe, 1985).

### 7.1.2 Effect of granule size and intragranular disintegrant type on the dispersion of a tablet matrix with low aqueous solubility.

When designing a granulation process for a dispersible tablet formulation, the effect of granule size should be considered. Using paracetamol / Avicel / PVP as a model granulation with low aqueous solubility, the relationship between intragranular disintegrant type and tablet dispersion was investigated in Chapter 3.

A variety of mesh sizes was more discriminating in comparing disintegrant efficiencies than the BP disintegration test, which uses a 2000μm screen. Whilst intragranular performance of some disintegrants tested at 2000μm was comparable, it widely differed at 710μm. Data using a 2000μm screen will not be representative of behaviour, when dispersion is required below 710μm.

Intragranular disintegrant had a greater influence on dispersion to 710μm than granule size or compression force, though the relationship depended on disintegrant type. Where intragranular disintegrant function was poorer, tablet disintegration time increased with granule size because granule dispersion was less and size reduction by drug dissolution was more pronounced.

Ac-Di-Sol was the best intragranular disintegrant, producing most rapid dispersion with least variability. Dispersion down to 710μm was achieved in less than two minutes with all granule sizes (including unfractionated granules) and compression forces. Gordon et al (1990) reported that the use of Ac-Di-Sol intragranularly in an insoluble matrix was capable of promoting tablet disintegration directly into primary particles. Disintegration times increased slightly with increasing compression force and increasing granule size

fraction, however, the increases were unimportant in terms of compliance with BP standards. With large granule sizes, high tablet porosity may decrease Ac-Di-Sol functioning due to poorer swelling force generation. This is supported by lower disintegration times with the bulk granulation than 1400-1000, 1000-710 and 710-500μm size fractions.

During the wet granulation process solvent stress (presumably causing detrimental irreversible structural change) and deposition of paracetamol on the Aci-Di-Sol, decrease its disintegrant efficiency (Chapter 5). Recrystallised paracetamol at disintegrant surfaces will restrict water penetration into the Ac-Di-Sol and crystals within the capillary network may impair wicking action. However, the disintegrant efficiency of Ac-Di-Sol remains high after wet granulation and this explains its high performance as an intragranular disintegrant.

Using Ac-Di-Sol intragranularly, granule size can be adjusted to give optimum compressibility and flow characteristics without detrimentally affecting tablet dispersion. Adequate dispersion, independent of compression force, allows the production of mechanically strong tablets with low friability. On scaling up a formulation, the granule size distribution will alter on a production scale and batch-to-batch variation may occur. Ac-Di-Sol is less likely to produce unacceptable batch-to-batch differences in dispersion to 710μm, than intragranular disintegrants more affected by granule size.

The performance of Explotab was poorer than Ac-Di-Sol. With intragranular Explotab, adequate dispersion to < 710μm was only achieved within three minutes using the 710-500μm and 250-500μm granule size fractions, and with these sieve cuts dispersion

times increased with compression force. Adequate times could only be achieved with the 710-500μm fraction at low compression force, where tablet strength was low and friability high.

Granule size could be decreased to accommodate poorer disintegrant efficiency, and here reduced granule size increased weight uniformity in all formulations due to closer, more uniform die fill. This supports the findings of Kassem et al (1972) and Femi-Oyewo & Adefesco (1993). However reduction below a certain size may be impractical because bridging reduces the flow rate (Marks & Sciarra, 1968).

With larger granules containing intragranular Explotab (1400-1000, 1000-710μm) and the bulk granulation, a minimum was observed in the disintegration time with increasing compression force. This supports the findings of Ferrari et al (1995) that sodium starch glycollate requires an optimum porosity for good swelling force generation. Granule porosity was not measured, but may have been too high for good swelling force generation. If Explotab is used as an intragranular disintegrant, the granulation process should be designed to give optimum porosity.

Ferrari et al (1995) demonstrated the high disintegrating efficiency of sodium starch glycollate in an insoluble directly compressed matrix. However, this study suggests it may not be the best choice of intragranular disintegrant for a wet granulated dispersible tablet formulation, possibly because the process can irreversibly and detrimentally alter its structure (Mitrevej & Hollenbeck, 1982; Gould & Tan, 1985) and its adhesive behaviour when wetted (Guyot-Herman et al, 1983) will oppose disintegrating forces.

The present study compared disintegrant efficiency at low concentration. In a formulation of low aqueous solubility, increasing the concentration of Explotab and using an extragranular disintegrant may improve the rate and extent of tablet deaggregation to meet BP dispersible tablet standards. Harden & Gayst (1979) describe a wet granulated, aluminium hydroxide (an insoluble base) dispersible antacid tablet. A successful formulation was achieved using intragranular Explotab at a concentration of 6.8% w/w with extragranular Avicel.

Tablet dispersion with intragranular Amberlite IRP88 was poorer than with intragranular Explotab; none of the tablets dispersed to 710μm within 3 minutes. The effect of granule size on its performance as an intragranular disintegrant was more pronounced than with the other disintegrants, with larger increases in disintegration times with granule size. The results suggest Amberlite IRP88 has the greatest dependence on an optimum low tablet porosity to function efficiently. This is supported by the shortest disintegration times in the 250-500μm size fraction and bulk granulation. A decrease in disintegration time with increasing compression force occurred at 200-500μm, whereas in other tablets it tended to increase. In all granule size fractions and the whole granulation, the increase in tablet crushing strength with compression force was comparable, again supporting increased swelling force generation in the smallest size fraction.

The mean granule size of the whole granulation was 550μm (rsd ± 0.39μm). However, in the experiments looking at the effect of extragranular disintegrant (Chapter 4), a granulation of the same formulation with a mean size of 230μm (rsd ± 0.94) was used. In the latter, the performance of Amberlite IRP88 used alone intragranularly was greatly enhanced (and superior to Explotab), and all tablets showed acceptable dispersion to

710μm. This demonstrates that, with a suitably small granule size, it may be used successfully in a dispersible tablet formulation. Where high compression forces are required and the use of Ac-Di-Sol is precluded, Amberlite IRP88 may be useful as an intragranular disintegrant.

Explotab and Amberlite IRP88 cause disintegration predominantly by swelling and do not have high wicking ability to promote rapid penetration of water into the tablet. The capillary properties of microcrystalline cellulose (≅20%) in the matrix may have encouraged water penetration into the tablet and in theory, used alone in a matrix without intrinsic wicking ability (eg dicalcium phosphate) disintegration times may be longer.

Kollidon-CL was the worst intragranular disintegrant, with all tablets taking longer than 30 minutes to disintegrate. This result was surprising. The disintegrant combines swelling and wicking activity (Kornblum & Stoopak, 1973) and like Ac-Di-Sol, might be expected to perform better in a tablet without extragranular disintegrant than disintegrants without capillary action. With crospovidone, a slightly swelling hydrophilic disintegrant, water penetration is the rate determining step in disintegration (Bolhuis et al, 1982), and the use of a hydrophobic lubricant such as magnesium stearate will significantly reduce this (Bolhius et al, 1981). However, Kollidon-CL performed efficiently as an extragranular disintegrant (Chapter 4) in a formulation lubricated with magnesium stearate, and this suggests that reduction of disintegrant efficiency by the wet granulation process may be more important. Ullah & Agharkar, (1993) successfully used crospovidone (Polyplasdone-XL) as an intragranular disintegrant in a dry granulated dispersible tablet formulation lubricated with magnesium stearate.

Wells & Walker (1983) demonstrated increased disintegration times with crospovidone on increasing drug solubility in the binder solvent and suggested that the deposition of fine drug crystals inside and around the disintegrant particles may impair its capillary and swelling properties. Gould & Tan (1985) showed that slurrying the crospovidone with water did not decrease its disintegrant properties. This indicates it is "poisoning" with deposited drug rather than the solvent stress of the wet granulation process that is detrimental, although the effect of individual solvents may differ. Paracetamol is relatively insoluble in the granulation solvent (water, 1 in 70). However, the complex formed with PVP increases solubility (BASF Technical Information, 1992). It is possible that paracetamol solution drawn into the disintegrant and deposited in and around during drying, impairs disintegrant efficiency. Paracetamol undergoes a sorption reaction with crospovidone due to their moderate binding tendency (Fromming et al, 1981) and this may have increased the amount adsorbed on and in the disintegrant.

In general terms, the compression properties of a drug and the excipients used will influence the effect of granule size on tablet dispersion. The type of deformation and degree of granule fragmentation on compaction will be influential. Compaction has a significant influence on the particle size of the granules, either increasing their size by consolidation (Khan & Rhodes, 1975d) or decreasing by fragmentation (Nelson, 1955). This will influence tablet strength and deaggregation.

Compression properties will determine the effect of hydrophobic lubricant (De Boer et al, 1978). In this study granule size did not have a large effect on crushing strength, although larger granule size fractions tended to produce slightly stronger tablets. This is because granule fragmentation, which will have increased with granule size, allowed bonding between unlubricated surfaces.

There was no clear relationship between granule size and tablet friability. The influence of magnesium stearate on tablet crushing strength and the tendency for lower moisture content (reducing the plasticising effect [Garr, 1992]) in smaller size fractions complicated results. At the very low concentrations used, intragranular disintegrant type is unlikely to have had a major influence.

The use of the whole granulation is desirable economically and the present study shows that it is advantageous in terms of optimising porosity to improve disintegrant performance and tablet dispersion and avoiding potential granule moisture loss by fractionation. When formulating a novel drug in a matrix of low aqueous solubility, Ac-Di-Sol is probably the best first line choice of intragranular disintegrant. Its ability to function efficiently without an extragranular disintegrant is advantageous because it allows a shorter and more efficient manufacturing process.

### 7.1.3 Effect of intra- and extragranular disintegrant on the dispersion of a tablet matrix with low aqueous solubility.

Using paracetamol / Avicel / PVP as a model formulation with low aqueous solubility the performance of different intra- / extragranular disintegrant combinations was compared in Chapter 4.

No super disintegrant in the matrix containing ≅ 20% microcrystalline cellulose produced very poor deaggregation, with tablets compressed at higher forces (15, 20kN) having disintegration times >60 minutes. Mendell (1974) stated that in large quantities (> 20%) microcrystalline cellulose functions as a disintegrant. However, disintegration properties have been shown to be greatly reduced by magnesium strearate (Bolhuis et al, 1982) and high pressure (Vadas et al, 1984) and the current study supports this. The

intrinsic disintegration properties of the matrix will affect intra- and extragranular disintegrant performance. It is reasonable to assume that microcrystalline cellulose will enhance disintegrant performance, especially those lacking capillary action, but this may only be important if a water soluble lubricant is used.

Tablet disintegration time is directly related to water penetration, and the relationship is independent of the base material solubility or type of disintegrant (Caramella et al, 1990b). The function of an extragranular disintegrant is to increase water penetration and speed up deaggregation. Added at a level of 2% w/w, this was demonstrated in all tablets except those containing intragranular Ac-Di-Sol.

Tablets containing intragranular Ac-Di-Sol without extragranular disintegrant had virtually identical disintegration times through 2000, 1700, 1400 and 1180μm meshes. This can be attributed to high disintegrant efficiency at tablet / granule surfaces producing rapid water penetration and tablet deaggregation. Consequently, extragranular disintegrant did not reduce disintegration times. In fact, its addition caused slight increases, but differences of only tens of seconds are not practically important. If intragranular disintegrant can very rapidly draw in water at granule surfaces, then adding extragranular may reduce total penetration by narrowing or blocking intergranule pore space. Increases in disintegration times may potentially be greater with extragranular disintegrant concentrations.

Intragranular Amberlite IRP88 alone caused rapid tablet deaggregation and the addition of extragranular disintegrant only resulted in very slight decreases in disintegration times. Although Amberlite IRP88 does not have a wicking action, it is able to generate a high swelling force with limited water availability (Caramella et al, 1989). Water

absorption and swelling by disintegrant particles at the outside of the tablet will cause disintegration of the tablet surface structure, opening it for further water penetration causing a chain reaction (Bolhuis et al, 1982).

The performance of intragranular Kollidon-CL and Explotab was considerably poorer and increasing disintegration times with decreasing mesh size on testing through 2000, 1700, 1400 and 1180μm shows tablet deaggregation to constituent granules is a rate-limiting step to dispersion down to 710μm. The addition of extragranular disintegrant speeded up tablet deaggregation, shown by reduced disintegration times at each mesh size and lower differences between them. The greatest reductions were seen in tablets containing intragranular Kollidon-CL, which is logical since this had the poorest performance intragranularly.

The performance of Kollidon-CL, Ac-Di-Sol and Amberlite IRP88 as extragranular disintegrants was similar, except the latter was superior in tablets compressed at high compression force. The disintegrant efficiency of Amberlite IRP88 increases with compressional pressure (Khan & Rooke, 1976b).

Explotab was the poorest extragranular disintegrant, especially when used at high compression force. Explotab forms an adhesive jelly with high viscosity (Guyot-Herman et al, 1983), which will reduce water penetration and increase the forces maintaining tablet integrity. In theory this will be more problematic at higher extragranular concentrations and should be avoided. Ac-Di-Sol also gels in water. Used at a concentration of 2% w/w, its performance as an extragranular disintegrant was comparable to Kollidon-CL and Amberlite IRP88. However in theory its use may be

more problematic at higher concentrations. Non-adhesive extragranular disintegrants are preferable.

In tablets without extragranular disintegrant, dispersion down to 710μm was considerably longer with intragranular Kollidon-CL than Explotab. However, after the addition of extragranular disintegrant, the situation reversed. This suggests that extragranular disintegrant not only contributes to tablet deaggregation but may aid granule dispersion. During the mixing process it is likely that some extragranular disintegrant will enter granule pores and function intragranularly. The extent to which this occurs will depend on granule structure. Increases in dispersion rate may depend on the intragranular disintegrant. The adhesive nature of intragranular Explotab may give limited dispersion, possibly explaining greater enhancement for intragranular Kollidon-CL.

The choice of intragranular disintegrant is the most important factor determining dispersion to 710μm, and with the correct choice, an extragranular disintegrant may not be needed. Where an extragranular disintegrant is used, the ratio to intragranular should be optimised and this will depend on the matrix and the dispersion required.

## 7.2 The formulation of a high dose, freely aqueous soluble drug as a dispersible tablet.

### 7.2.1 Use of acidic buffers to aid tablet dispersion.

The effect of acidic buffer on the disintegration of a tablet of a freely water-soluble, high dose drug was investigated in Chapter 6. Na-p-aminosalicylate / PVP / Ac-Di-Sol was used as a model. In a highly soluble matrix, rapid drug dissolution creates a viscous barrier at the tablet surface, which retards water penetration (Graf et al, 1992) and reduces disintegrant swelling force (Ferrari et al, 1995), causing tablets to dissolve away slowly (Khan & Rhodes, 1973). Lowering the microenvironmental pH at tablet surfaces below the drug pKa favours conversion to the poorly soluble free acid and therefore suppresses drug dissolution. Unfortunately, incorporating the acidic buffers sodium dihydrogen orthophosphate dihydrate (0.1, 0.2, 0.5M) and citric acid (0.2M) during wet granulation did not achieve this, with measured $pH_{SAT}$ values (the approximate diffusion layer pH) above 6.00 in all tablets. This explains why it did not convert a matrix taking $\cong$ 9-10 minutes to dissolve into a dispersing tablet with short disintegration times. With and without buffer, disintegration times at the lowest compression force (5kN) were slightly less ($\cong$ 8-9 minutes), which may be attributed to increased porosity for water penetration and weaker interparticulate forces. However above this, the rate at which tablets dissolved was independent of compression force. The formation of a viscous barrier has greater influence retarding water penetration than reduction of pore size and porosity with increasing compression force. However, the relationship between compression force and dissolution of a highly soluble matrix is dependent on the type of disintegrant used (Khan & Rooke, 1976b) and therefore full compression studies will be required for each disintegrant evaluated in a new formulation.

Tablets without buffer exposed to disintegration fluid of 0.1M citric acid (pH =2.04) gave macro deaggregation (Roland, 1967) for the first few minutes of immersion and then aggregates dissolved away slowly. Visible precipitation of an insoluble coating of free acid reduced water penetration, and this may have prevented further disintegration. This suggests that for a highly water soluble drug whose solubility is pH dependent, buffer incorporation may potentially cause a dissolving matrix to disperse if optimum pH conditions can be created. The pH of 0.1M citric acid was considerably lower than the drug pKa. Creating a tablet diffusion layer pH nearer or slightly above the pKa may be better, because theoretically while still suppressing dissolution and viscosity formation, it will reduce the rate at which free acid is deposited on aggregates. If water penetration is not quickly reduced in this way, the extent of deaggregation may be increased. Repeating disintegration testing of unbuffered tablets over a narrow range of pH above and below the pKa would have been useful to confirm this.

Assuming an optimum microenvironmental pH (balancing suppression of dissolution and rate of free acid formation) could be determined, the method of buffer incorporation into the tablet will be important. The use of an aqueous binder solution in this study will have caused reaction of the drug and buffer during the wet granulation process. A non-aqueous granulation fluid in which drug and buffer are insoluble may be preferable, avoiding this reaction and resulting in more unchanged buffer in the finished tablet. Also insoluble free acid formation around buffer particles should not occur, allowing faster buffer dissolution in the tablet. Ideally, buffer aqueous solubility should be greater than the drug, so that when the tablet is immersed in water a favourable microenvironment pH is achieved before appreciable drug dissolution has occurred. For a drug with high aqueous solubility, the use of a non-aqueous granulation fluid is also

advantageous in terms of reducing secondary binding, which can increase disintegration times (Wells & Walker, 1983).

### 7.2.2 Use of Amberlite IRP88 as a disintegrant in a highly soluble tablet matrix with and without PVP K90 binder.

Comparing 2% intra- / extragranular Ac-Di-Sol and Amberlite IRP88 in a Na-p-aminosalicylate matrix, the latter had superior disintegrant efficiency. With Ac-Di-Sol all tablets with binder dissolved away slowly. However, similar tablets containing Amberlite IRP88 compressed at low compaction force (5kN) deaggregated and although those compressed at higher forces dissolved away slowly, disintegration times were ≅ 3 minutes lower than with Ac-Di-Sol. Amberlite IRP88 is able to develop high swelling force under conditions of limited water availability (Caramella et al, 1989), and therefore may be more efficient in a water soluble matrix where water penetration is limited than disintegrants with greater water requirements. Also, Amberlite IRP88 is non-adhesive (Khan & Rhodes, 1973), whereas Ac-Di-Sol forms an adhesive gel in water (Chapter 5). Adhesive disintegrants in soluble wet granulation systems will increase disintegration times, especially at high concentration, (Fakouhi et al, 1963; Billups & Cooper, 1964; Feinstein & Bartilucci, 1966) because the increased viscosity and adhesion opposes the positive forces of water penetration and particle swelling. This phenomenon may be more pronounced in a hydrophilic system (Fakouhi et al, 1963; Billups & Cooper, 1964; Feinstein & Bartilucci, 1966) where interparticulate adhesion is stronger than in a hydrophobic system (Khan & Rhodes, 1972b). Conversely, poor adhesion between disintegrants and other tablet components has been shown to increase their disintegration efficiency in a soluble system because wicking is enhanced (Khan & Rhodes, 1973).

In a tablet of low aqueous solubility, Ac-Di-Sol is a better intragranular disintegrant (Chapters 3 & 4) and its efficiency is high at relatively low concentration (2% w/w). In a highly soluble drug matrix, current findings support the use of a non-adhesive disintegrant such as Amberlite IRP88. Kollidon-CL is non-adhesive and in theory may also be a suitable choice. However, the process of wet granulation may reduce its efficiency (Chapters 3 & 4).

Increasing the concentration of Amberlite IRP88 from 2 % intra- / 2% extragranular to 4% in each phase only caused a noteworthy reduction in disintegration times in tablets compressed at low compression force (5kN). At intermediate and high forces differences were negligible. Possibly limited water availability due to increased viscosity restricts the functioning of increased quantities of disintegrant. Initial water penetration will be greater in tablets compressed at low force due to higher porosity and this may account for greater enhancement of matrix deaggregation with increased disintegrant concentration. Unfortunately, tablets compressed at low compaction force may have unacceptably high friabilities. Additionally, increases in friability with increased disintegrant concentration, due to poor disintegrant compression properties, were greatest at low compression forces where enhanced disintegration occurs. Therefore, increasing the disintegrant concentration may not be the best way to increase the deaggregation and dispersion of a highly soluble matrix because to achieve this would result in mechanically unacceptable tablets. However, Amberlite IRP88 has poor compression characteristics (Khan & Rhodes, 1973) and in theory, a non-adhesive disintegrant with superior compression properties may produce better tablets at low compression force. Gissinger & Stamm (1980a) reported that high extragranular concentrations of crospovidone do not bring about negative effects on tablet mechanical properties.

Omitting the PVP K90 binder from the formulation and granulating with water gave greater enhancement of tablet deaggregation than increasing disintegrant concentration. It caused a dissolving matrix to disintegrate in all tablets except those compressed at very high compression force (20kN) and the size of the aggregates decreased with compression force. This may be attributed to weaker bonding within the tablet and reduced adhesion and viscosity. Although no binder resulted in lower crushing strengths, those tablets compressed at intermediate and high compression force (15 and 20kN) had similar friability values to those with binder.

Therefore when formulating a new highly soluble tablet it may be possible to omit the use of an adhesive binder. However, this will largely depend on the compression properties of the drug. Although a drug of high aqueous solubility may be self-adhesive in water and form an acceptable granulation, if this is poorly compressible, a binder may be necessary to improve compaction. Then the binder selected should have the lowest possible aqueous viscosity.

# FUTURE WORK.

1) The effect of intragranular disintegrant type on the dispersion of a sparingly soluble drug matrix using magnesium stearate as a lubricant has been studied. It is likely that the disintegrant efficiency of Kollidon-CL was reduced by the use of a water insoluble hydrophobic lubricant, and it would be worthwhile to compare a water soluble, hydrophilic lubricant e.g. Na-stearyl fumarate. Performance rankings of the various disintegrants may change.

2) The idea of reduced disintegrant performance by drug deposition in and around Ac-Di-Sol during the wet granulation process was studied and "poisoning" did not considerably affect disintegration times. The very poor performance of intragranular Kollidon-CL suggests that "disintegrant poisoning" may be greater for Kollidon-CL and it would be interesting to investigate this.

3) Investigating the effect of acidic buffer incorporation on the disintegration of Na-p-aminosalicylate tablets using a non-aqueous granulating solvent could provide more positive results. Dispersion may be more successful because buffer and drug will not react during the wet granulation process, which may increase the reduction of $pH_{SAT}$ by the buffer in the tablet on immersion in water.

4) As an alternative approach to increasing the dispersion of a highly soluble drug matrix, coating of the granulation may be effective. Micro-granules may be produced and coated with a non-adhesive material of intermediate water solubility before compression. If initial dissolution at granule and tablet surfaces can be reduced, then water may penetrate efficiently during this lag time and

allow extragranular disintegrant to function efficiently to disperse the matrix. Coating with a material of intermediate solubility should allow dispersed micro-granules to dissolve away quite quickly.

5) To investigate the effect of tablet shape on disintegration time, as this will alter the surface area in contact with the dispersion medium.

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# ATTENDANCE AT CONFERENCES

1) UK Controlled Release Society Conference, London, UK, January 1998.

2) Attendance at Postgraduate Research Seminars at the School of Pharmacy and Chemistry, Liverpool John Moores University.