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Centrifugal Granulating Process for Preparing Drug-Layered Pellets Based on Microcrystalline Cellulose Beads

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Academic Dissertation

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To the soul of my heavenly father,

my beloved mother, respected brother and sisters

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ABSTRACT

CENTRIFUGAL GRANULATING PROCESS FOR PREPARING DRUG-LAYERED PELLETS BASED ON MICROCRYSTALLINE CELLULOSE BEADS

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Centrifugal granulation is an advanced method of producing drug-layered pellets. It has numerous advantages such as, lower manufacturing costs, flexibility in operation and ease of automation over other pelletisation techniques. The main purpose of the present study was to investigate the feasibility of the centrifugal granulating technique for preparing microcrystalline cellulose (MCC) beads and, subsequently, drug-layered pellets using the MCC beads as substrates. Additionally, the effects of some independent material and process variables on the properties of MCC beads and layered pellets were also studied.

MCC beads were prepared using four formulations consisting of Emcocel 90M as initial processing materials and Emcocel SM15, 50M, 90M and HD90 as fillers. Povidone (Plasdone K-29/32) and maltodextrin (Maltrin M040 and M100) were used as binders for preparing drug-layered pellets. The material variables studied were concentration of the binder and size of the beads. The effect of the five independent process variables (rotor rotation speed, slit air flow rate, spray air rate, spray air pressure and the spray nozzle distance from the bottom plate) on the expected yield, mean size and shape characteristics (roundness, circularity, elongation, rectangularity, and modelx) of the MCC beads were studied using 2^{5-2} fractional factorial design. Furthermore, the effects of three independent process variables (rotor rotation speed, slit air flow rate and spray air volume) on the amount of drug loss, amount of agglomerates, bulk density, flowability, friability, shape and surface roughness of the pellets were investigated using 3^3 full factorial design.

The results suggested that different microcrystalline cellulose grades can be chosen as a starting material for preparing MCC beads by the centrifugal granulating process. All formulations studied yielded relatively spherical, smooth, free flowing and mechanically strong final beads. Based on the advantages and limitations of the bead formulation tested, the formulation with Emcocel 50M as a filler seems to be more acceptable than the others. Out of the process variables studied, the effects of rotor rotation speed, slit air flow rate and spray air rate were found to be the most potent on the bead responses studied.

The mechanism of the MCC bead formation and growth comprises a wetting phase (nucleation region) followed by a combination of coalescence between the previously formed nuclei and the layering of the smaller fine powder over the nuclei. Finally, layering and abrasion transfer the predominant mechanisms.

Povidone (Plasdone K-29/32) and maltodextrin (Maltrin M040 and M100) as binders were found to be suitable for preparing drug-layered pellets especially at higher concentrations and larger bead sizes in the centrifugal granulating technique. Plasdone K-29/32 showed better performance with a smaller loss of drug during the process and smaller amounts of undersized and friable pellets than the maltodextrin grades studied. Although the pellets obtained with Maltrin M040 were stronger and the amount of undersized pellets was smaller than with Maltrin M100, the latter was preferable because of the lower agglomeration tendency and the pellets obtained were better flowing, denser, more spherical and smoother. The binder concentration had significant influence on the drug loss during the process and on the proportion of undersized pellets whereas both binder concentration and bead size had a significant effect on the flowability and friability of the pellets.

As regards the drug-layering process, rotor rotation speed, slit air flow rate and spray air volume were found to have a significant influence on the responses studied. Drug-layered pellets with a spherical shape, higher density and flowability were obtained by increasing the rotor rotation speed and spray air rate. As the rotor rotation speed and the slit air flow rate were increased, both the amount of drug loss and the agglomerates increased. In addition to the main effects, there were some significant paired interaction between slit air flow rate and spray air as well as rotor rotation speed and slit air flow rate.

In conclusion, centrifugal granulation is a convenient and flexible technique for producing MCC beads and respective drug-layered pellets. The significance of both material and process parameters, however, should be taken into account in the preparation of pellets by this method.

List of original publications

This thesis is based on the following original papers, which are referred to in the text by their bolded Roman numerals I-IV.

I Harun Ar. Rashid, J. Heinämäki and J. Yliruusi, 1998. Evaluation of four microcrystalline cellulose grades for preparing spherical beads in a centrifugal granulating process. S. T. P. Pharma Sci, 8 (3) 163-168.

II Harun Ar Rashid, J. Heinämäki, O. Antikainen and J. Yliruusi, 1999. Effects of process variables on the size, shape, and surface characteristics of microcrystalline cellulose beads prepared in a centrifugal granulator. Drug Dev. Ind. Pharm., 25 (5), 605-611.

III Harun Ar Rashid, J. Heinämäki, O. Antikainen and J. Yliruusi, 2000. Povidone and maltodextrin as binders for preparing drug-layered pellets based on microcrystalline cellulose beads by centrifugal granulating process. S.T.P. Pharma Sci. 10 (5) 355-362.

IV Harun Ar Rashid, J. Heinämäki, O. Antikainen and J. Yliruusi, 2001. Influence of the centrifugal granulating process on the properties of layered pellets. In press, Eur. J. Pharm. Biopharm.

1. INTRODUCTION

1.1 Pellets

Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free-flowing, spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm, and are intended usually for oral administration (Gadjos 1983 and 1984, Kristensen and Schaefar 1987, Ghebre-Sellassie 1989). Implants of small, sterile cylinders formed by compression from medicated masses are also defined as pellets in pharmacy (Cox and Spanjers 1970, Rudnic and Schwartz 1990, Niskanen 1992). Pellets can be prepared by many methods, the compaction and drug-layering techniques being the most widely used today.

Regardless of which manufacturing process is used, pellets have to meet the following requirements (Vuppala et al. 1997):

(1) They should be near spherical and have a smooth surface, both considered optimum characteristics for subsequent film coating.

(2) The particle size range should be as narrow as possible. The optimum size of pellets for pharmaceutical use is considered to be between 600 and 1000 μm.

(3) The pellets should contain as much as possible of the active ingredient to keep the size of the final dosage form within reasonable limits.

In the last two decades, pellets have established their position for many reasons (Ghebre-Sellassie 1989, Hellén 1992). Pellets offer a great flexibility in pharmaceutical solid dosage form design and development. They flow freely and pack easily without significant difficulties, resulting in uniform and reproducible fill weight of capsules and tablets (Conine and Hadley 1970, Lyne and Johnston 1981, Ghebre-Sellassie et al. 1985, Reynolds 1990, Niskanen 1992, Vuppala et al. 1997). Successful film coating can be applied onto pellets due to their ideal spherical shape and a low surface area-to-volume ratio (Rowe 1985, Vertommen et al. 1997). Pellets composed of different drugs can be

blended and formulated in a single dosage form. This approach facilitates the delivery of two or more drugs, chemically compatible or incompatible, at the same sites or different sites in the gastrointestinal tract. Even pellets with different release rates of the same drug can be supplied in a single dosage form (Ghebre-Sellassie et al. 1989, Wan et al. 1991).

The pelletised products can improve the safety and efficacy of the active agent. These multiple-unit doses are usually formulated in the form of suspensions, capsules or disintegrating tablets, showing a number of advantages over the single-unit dosage system (Bechgaard and Nielsin 1978, Bechgaard 1982, Ganderton 1985, Ghebre-Sellassie 1989). The pelletised product can freely disperse in the gastrointestinal tract as a subunit, thus maximising drug absorption and reducing peak plasma fluctuation. Consequently, potential side effects can be minimized without impairing drug bioavailability. Local irritation derived from high local concentrations of a drug from a single-unit dose, can be avoided.

The most important reason for the wide acceptance of multiple-unit products is the rapid increase in popularity of oral controlled-release dosage forms. Controlled-release oral solid dosage forms are usually intended either for delivery of the drug at a specific site within the gastrointestinal tract or to sustain the action of drugs over an extended period of time. With pellets, the abovementioned goals can be obtained through the application of coating materials (mainly different polymers), providing the desired function (Mehta et al. 1986, Ghebre-Sellassie et al. 1987, Ragnarsson et al. 1987, Ragnarsson and Johansson 1988, Bianchini and Vecchio 1989, Wesdyk et al.1990, Holm et al. 1991, IIey 1991, Zhang et al. 1991a, 1991b, Ragnarsson et al. 1992, Jørgensen et al. 1997, Marvola et al. 1999, Umprayn et al. 1999), or through the formulation of matrix pellets to provide the desired effect (O'Conner and Schwartz 1985, Zhang et al. 1990, Peh and Yuen 1995, Zhou et al. 1996, Montoussé et al. 1999).

The advantage of multiple-unit products as a controlled-release dosage form is believed to be their behaviour in vivo because of their advantageous dispersion pattern in the gastrointestinal tract and their special size characteristics. The transit time of a gastro-intestinal drug delivery system along the gastrointestinal tract is the most limiting

physiological factor in the development of a controlled-release gastrointestinal drug delivery system targeted to once-a-day medication (Chien 1992). Gastro-intestinal transit time, greatly affects the bioavailability of a drug from an orally administered controlled-release preparation (Davis et al. 1984, Sugito et al 1990). Gastric transit of both single- and multiple-unit solid dosage forms is prolonged in a fed stomach compared to a fasting one (Davis et al. 1987, Wilding et al. 1992, Yuen et al. 1993). Plastic spheres of 7 mm remained in the food-filled stomach even as food itself expelled steadily (Hinder and Kelly, 1977). Once the stomach had emptied, the spheres began to transit in clusters. It has been reported that pellets smaller than about 2.4 mm in diameter, are free from the digestive function of the stomach and the closing system of the pyloric sphincter to be emptied from the stomach (Freely et al. 1987, Davis et al. 1987). A maximum pellet diameter of 1.5 mm has been recommended for an optimal multiple-unit formulation (Bechgaard 1978, Bechgaard et al. 1982). Kelly 1981 and Devereux 1987 clearly showed that the threshold size must be below 1 mm. According to Khosla et al. (1989), there is no actual cut-off size for gastric emptying, but as the size of the pellets increase, predictable emptying from the fed stomach becomes uncertain and highly variable. However, it has been demonstrated that gastric emptying is not only dependent on the size but also on some other important factors, such as density of pellets (Devereux et al. 1990, Clarke et al. 1993, Tuleu et al. 1999), nature of food (Feely et al. 1987, Khosla et al. 1989) and inter-subject variation (Davis 1989). Clarke et al. 1993 and Tuleu et al. 1999 showed that both density and size of the pellets affect the gastrointestinal transit time. The higher density of the pellets prolonged the gastric transit time, while the larger size slightly prolonged the small gut transit time but not the gastric transit time. Controversial results have also been reported to the effect of pellets densities on the transit times through the gastrointestinal tract (Bechgaard et al. 1985).

1.2 Theory of pellet formation and growth

In order to judiciously select and optimise any pelletisation/granulation process, it is important to understand the fundamental mechanisms of granule formation and growth. Different theories have been postulated related to the mechanism of formation and growth of pellets. Some of these theories are derived from experimental results while

others are confined to visual observations (Sastry and Fuerstenau 1973 and 1977, Leuenberger and Imanidis 1986, Mehrotra and Sastry 1986). Results obtained from the experiments with some form of tracer technique are regarded as acceptable and convincing (Sastry and Fuerstenau 1973, Linkson et al. 1973). As the conventional granulation (Kapur et al. 1964 and 1966), the most throughly studied, most classified pelletisation process, which involves a rotating drum, a pan or a disc, has been divided into three consequtive regions: nucleation, transition and ball growth. However, based on the experiments on the mechanism of pellet formation and growth, the following steps were proposed: nucleation, coalescence, layering and abrasion transfer (Sastry and Fuerstenau 1973).

Nucleation (Figure 1A) is a common stage in all pelletisation/granulation processes and occurs whenever a powder is wetted with liquid (Juslin 1997). The primary particles are drawn together to form three-phase air-water-liquid nuclei and are attached together by liquid bridges which are pendular in nature (Ghebre-Sellassie 1989). The bonding strength is improved by reduction of particle size (Cape 1980). The sizes of the primary particles, the moisture content, the viscosity of the binding particles, the wettability of the substrate and the processing conditions, such as tumbling and drying rates, influence the size, the rate and the extent of nuclear formation (Ghebre-Sellassie 1989). Both the mass and the number of nuclei in the system change as a function of time, which is an important feature of nucleation (Sastry and Fuerstenau 1973).

Nucleation is followed by a transition phase, and the growth mechanisms affecting the transition region are coalescence and layering (Sherrington and Oliver 1981, Juslin 1997, Parikh 1997). Coalescence (Figure 1B) is defined as the formation of large-sized particles by random collision of well-formed nuclei, and the mechanism requires slight excess moisture on the nuclear surface (Kristensen and Schaefar 1987, Juslin 1997). Although the number of nuclei is progressively reduced, the total mass of the system remains unchanged during this step. Layering (Figure 1C) is a slow growth mechanism and involves the successive addition of fragments and fines on an already formed nucleus (Ghebre-Sellassie 1989). In the layering step, the number of particles remains the same, but the total mass in the system increases due to increasing particle size as a function of time. The fragments or fine particles can be formed by particle size reduction

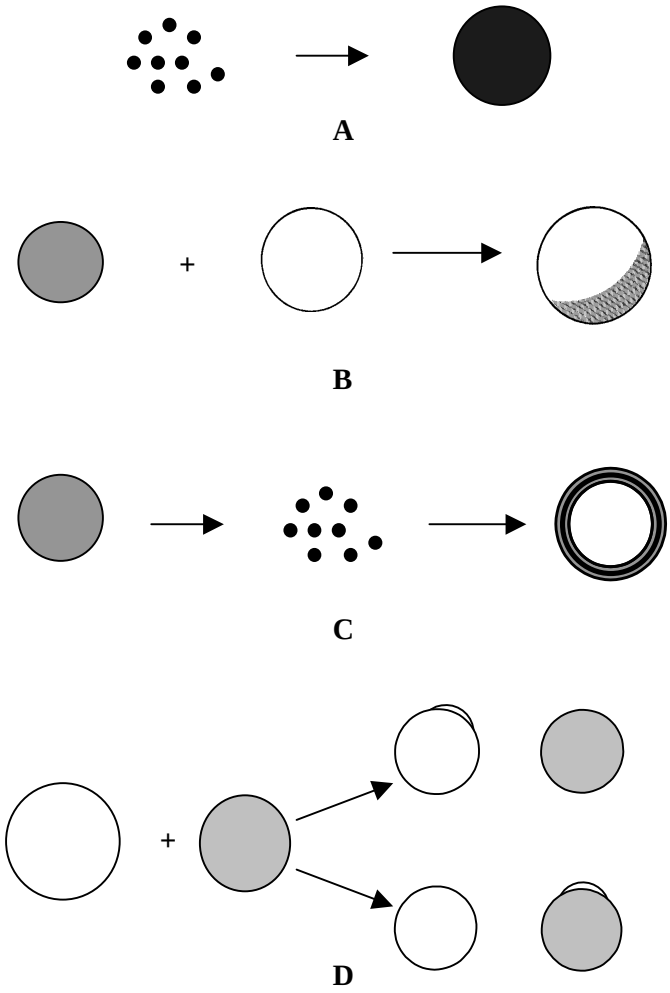


Figure 1. Pellet growth mechanisms. (A) Nucleation, (B) coalescence, (C) layering and (D) abrasion transfer (modified from Ghebre-Sellassie 1989).

that occurs due to attrition, breakage and shatter (Ghebre-Sellassie 1989). The fines and the fragments that are produced through size reduction are picked up by large pellets. Production of fines and subsequent coalescence and layering continues until the number of favourable collisions declines rapidly, thereby leading to a reduction in the rate of

growth of the pellets. At this point the third phase, the ball growth region, is reached (Ghebre-Sellassie 1989).

In the ball growth phase the main mechanism affecting the slow growth of agglomeration is the abrasion transfer (Figure 1D) which involves the transfer of materials from one granule formed to another without any preference in either direction. This situation does not result in a change in the total number or mass of the particles. The particles, however, undergo a continuous change in size as long as the conditions that lead to the transfer of material exist (Ghebre-Sellassie 1989).

1.3 Methods of preparing pellets

Compaction and drug layering are the most widely used pelletisation techniques in pharmaceutical industry. Of the compaction techniques, extrusion and spheronization is the most popular method. Recently, however, melt pelletisation has been used frequently in making compaction pellets using a different type of equipment, e.g. a high-shear mixer (Ghali et al. 1990, Schaefer and Mathiesen 1996, Zhou et al. 1996). Other pelletisation methods, such as globulation, balling and compression are also used in the development of pharmaceutical pellets although in a limited scale (Ghebre-Sellassie 1989).

1.3.1 Extrusion-spheronisation

Extrusion-spheronisation is a multiple-step compaction process comprising dry mixing of the ingredients with excipients, wet granulation of the mass, extrusion of the wetted mass, charging the extrudates into the spheroniser to produce a spherical shape, drying the wet pellets in a dryer and, finally, screening to achieve the required size distribution (Conine and Hadley 1970, Reynolds 1970, O'Conor et al. 1984, Hellén 1992, Erkoboni 1997, Gazzaniga et al. 1998, Thoma and Ziegler 1998, Schmidt and Kleinebudde 1999). The granulation step can be performed both in batch-type processors, including a conventional planetary mixer, and in vertical or horizontal high-shear and sigma-blade mixers (Schaefer 1988, Titley 1988, Ghali et al. 1990, Erkoboni 1997), and in

continuous mixers, such as Nica M6 instant (Hellén 1992), and high-shear twin-screw mixer-extruders (Kleinebudde and Linder 1993).

Extruders for the extrusion process (step) have been classified generally as screw, sieve and basket, roll and ram extruders (Sherrington and Oliver 1981, Hicks and Freese 1989). Based on the type of feed mechanism used to transport the mass towards the die, they have been broadly classified as screw, gravity or piston-type extruders (Rowe 1985). Most spheronisers have been designed based on a revolving grooved plate driven by a variable-speed drive unit at the base of a smooth-walled drum. The drum capacity, plate diameter and plate design may vary (Chapman 1985). In order to increase the capacity of the spheronisation stage, a continuously working spheroniser has been introduced (Appelgren 1987)

The process produces products ranging from barely-shaped, irregular particles like the conventional granulation, to very spherical particles with drastically different properties (Woodruff et al. 1972, Erkoboni 1997). Tabletting characteristics can be altered by modifying the composition, the granulating fluid or the process conditions (Malinowski and Smith 1974, Schwartz et al. 1994, Millili and Schwartz 1990, Erkoboni 1997). The main advantage over other methods of producing drug-loaded spheres or pellets is the capacity to produce spherical pellets of a uniform size and a high drug content up to 90% (Ghali et al. 1990, Hellén 1992, Erkoboni 1997).

Recently, different types of fluidised bed rotary processors have been developed more successfully for preparing compaction-type pellets such as the extrusion-spheronisation process in a one-step process. This technique has solved many problems related to the multi-step extrusion and spheronisation process; it consumes less time, requires lower labour costs and less space (Jäger and Bauer 1982, Hodges et al. 1990, Robinson and Hollenbeck 1991, Sienkiewicz et al. 1997, Vecchio et al. 1994, Heng et al. 1996, Sienkiewicz et al. 1997, Vertommen and Kinget 1997, Vertommen et al. 1998, Kristensen et al. 2000).

1.3.2 Drug layering

The layering process comprises the deposition of successive layers of drug entities from solution, suspension or dry powder on nuclei which may be crystals or granules of the same material or inert starter seeds. In solution/suspension layering, drug particles are dissolved or suspended in the binding liquid (Gamlen 1985, Jackson et al. 1989). In powder layering, complete dissolution does not occur, due to low liquid saturation, irrespective of the solubility of the active agent in the binding liquid. In powder drug layering, a binder solution is first sprayed onto the previously prepared inert seeds, followed by the addition of powder (Sherrington 1969, Ghebre-Sellassie 1985 and 1989, Gajdos 1983 and 1984, Niskanen 1990abc, Mohammed et al.1991, Nastruzzi et al.2000).

Conventional pan coaters have been used from the very beginning of the history of drug layering pelletisation. From the economic point of view, however, use of conventional pan coaters is not very reasonable due to the higher labour costs and time consumption, and lower yield. An important disadvantage of pan coaters is the shortage of process control (Ghebre-Sellassie 1989, Niskanen 1992). More recently modified forms of pan coaters have been developed, which resolves many of the drawbacks related to the old system (Nastruzzi et al. 2000).

The problems of drug layering pelletisation by conventional pan coaters had led to the development of two types of rotary granulators (fluidised-bed and centrifugal granulators) presented by Bauer (1979) and Funakoshi et al. (1971, 1977 and 1980), respectively. These devices offer many advantages including lower manufacturing costs, flexibility of operation and ease of automation (Ghebre-Sellassie 1989). The main features and differences of the four types of rotor granulators are presented in Table 1.

Centrifugal granulators can be used for manufacturing multiple-unit, immediate or controlled-release drug products for oral use. Through the use of these systems, initial beads can be prepared and subsequently drug-layered and coated in the same equipment, resulting in highly spherical multi-layered granules with adequate controlled-release characteristics (Gajdos 1984, Ghebre-Sellassie et al. 1985, Niskanen 1992). The

schematic diagram of the centrifugal granulating process is shown in Figure 1 (Section 3.2).

Table 1. Summary of the main features of four types of rotor granulators (Ghebre-Sellassie 1989).

Feature	**Rotor granulator (Glatt)**	**Rotor-processor (Aeromatic)**	**Spir-a-Flow (Freund)**	**CF-granulator (Freund)**
Control of drying air	Disc height; pan speed	Chamber wall height, pan speed	Plenum dampers and disc height: pan speed	Pan speed
Spray location	Tangential	Tangential and top (angled)	Tangential and top (vertical)	Tangential
Powder application	Tangential into bed	Top-angled	-	Top vertical
Die speed	Variable	Variable	Variable	Variable
Charging	Port in expansion chamber	Port in expansion chamber	Port in chamber	Top loaded
Discharging	Port in product chamber	Port in product chamber	Port in product chamber	Port in product chamber

1.3.2.1 Material considerations and variables

The major material variables related to the preparation of spherical particles with centrifugal granulators include type and concentration of binder, binder solvent system, size and shape of non-pareil seeds**,** type and amount of filler and particle size of (powdered) filler (Aulton and Banks 1981, Hodges et al. 1990, Niskanen 1992).

The initial materials required for the preparation of pellets by the layering process are the inert starter seeds over which the powdered drug(s) is (are) layered and the possible coating applied. The quality of the coated pellets has been found to be closely related to the physical and mechanical properties of the initial seeds. Important properties of the coated pellets like uniform coating thickness, non-segregation during capsule filling, rate of drug release, film disposition and formation during coating, packing properties, etc.,

are greatly influenced by the particle size distribution, smoothness, roundness and bulk density of the initial seeds used as substrates (Ghebre-Sellassie 1989).

Non-pareils have been widely used as initial substrates in the preparation of pellets by the layering process. However, sucrose, the main component of non-pareils, has some well-known drawbacks like harmful effects on diabetics and potential cariogenicity (Reynolds 1993, Wade and Weller 1994). Most recently, microcrystalline cellulose (MCC) has been tested as a substrate for drug layering (Agyilirah 1995). So far, however, there are no extensive studies on MCC for the preparation of initial cores/beads in a centrifugal granulating process.

Binders play an important role in wet-granulating and drug-layering processes, affecting the physical, mechanical and release properties of the final product. Ghebre-Sellassie et al. (1985) evaluated the centrifugal granulation with commonly used binders (i.e. gelatin, povidone, carboxymethyl cellulose, hydroxypropyl methylcellulose) and different sizes of non-pareils. All binders studied were acceptable for preparing pellets, but gelatin and carboxymethyl cellulose were the most suitable ones with respect to the friability of the pellets. Niskanen et al. (1992) observed that the concentration of the binder and the particle size of the drugs affect the physical and mechanical properties of the pellets, the latter being more critical. Virtually no studies on the effects of binders on drug layering using MCC beads have been reported.

Maltodextrins are hydrolysed starches that are used as water-soluble, non-viscous binders in pharmaceutical and food industry (Wade and Weler 1994). There are different commercially available grades of maltodextrins with respect to dextrose equivalent (DE) value and manufacturing process. The reports on the effectiveness of maltodextrins as a binder in preparing granules and tablets are promising but somewhat contradictory (Symecko 1993, Becker 1997). So far, no studies on the use of maltodextrins in a centrifugal drug layering process have been published.

1.3.2.2 Process variables

Centrifugal granulation is a typical multivariate process and, consequently, it is important to identify and control all critical process variables and conditions. The most important process variables related to this technique include fluidised air flow rate, air temperature, humidity, atomising liquid flow rate, atomising air flow rate and pressure, spraying regime, droplet size, spray angle, powder dropping rate, batch size, rotor rotation speed and distance of the nozzle from the product bed (Aulton and Banks 1981, Hodges et al. 1990, Niskanen 1992).

The centrifugal granulation technique for drug-layered pellets was commercially developed about three decades ago. Only a limited number of studies on the effect of process variables on the characteristics of pellets have been published during this long period of time. In the 1980's, the most significant studies were performed by Gajdos (1983, 1984), following the exact processing system of the original centrifugal technique. He studied the effect of three process variables (powder dropping rate, binder spray rate and rotor rotation speed) on the properties of layered pellets. The powder addition rate was found to be the most critical parameter and the main reason was attributed to its influence on the particle moisture. The binder spray rate was the next significant parameter tested. The spray rate had a negative effect on the yield and was assumed to be due to the shortage of friction of the twin pellets and agglomerates at the wall of the processing chamber.

In the 1990's, pellet preparation by the centrifugal granulating process was performed using a modified technique. The centrifugal granulating technique was developed to substitute the single-step method for more time consuming multiple-step extrusion and spheronisation process (Vecchio et al. 1994, Heng et al. 1996, Holm et al. 1996, Vertommen and Kinget 1997). In these studies, some process variables were evaluated together with the material variables in order to develop this technique for preparing matrix pellets, although the main part of the studies was confined to the development of material variables. When indobufen pellets were made by the centrifugal rotary fluidised-bed technique without starting seeds from a mixure of indobufen and microcrystalline cellulose, the water spray rate was found to be an important parameter

for the pellet growth (Vecchio et al. 1994). The average pellet growth was proportional to the spray rates of the water added. With increasing spray rate the average particle sizes increased accordingly.

Vertommen and Kinget (1997) studied the influence of two formulation variables (microcrystalline cellulose content and water to microcrystalline cellulose ratio) and three process variables (rotor rotation speed, spheronisation time after water addition and water addition rate) on pellet size and friability. Both formulation variables and the three process variables had a major influence on the pellet size and the friability. With increasing independent process variables the size increased and the friability decreased. Process variables, except for spheronisation time after water addition, rotor rotation speed and water addition rate, had a positive effect on the size distribution. With increasing spheronisation time the size distribution became narrower, although this effect was not significant ($p = 0.148$).

The reproducibility of the preparation of pellets from powder mixture by centrifugal rotary processing was investigated by Heng et al. 1996. Two process variables, the amount of moistening liquid (300 to 450 ml) and spray rate (28 to 59 ml/min), were varied to optimize the process conditions. The quality of the spheroids produced was evaluated using three criteria, i.e., percent yield between 0.85 and 1.18 mm, geometric mean diameter and geometric standard deviation of the spheroids. It showed that a minimum water level must be achieved, regardless of the spray rate, in order to obtain spheroids of a suitable size range and yield. On the contrary, if the amount of moistening liquid was increased indiscriminately, a stage will be reached whereby the size distribution of the spheroids will remain skewed. The geometric standard deviation at any fixed amount of moistening liquid studied decreased with increasing spray rate, whereas at any fixed spray rate the geometric standard also decreased with increasing amount of moistening liquid.

Holm et al. (1996a,b) investigated the effect of two process variables (disc speed and spray rate) using formulations containing lactose and microcrystalline cellulose, and dibasic calcium phosphate and microcrystalline cellulose in different proportions, on the pellet growth, shape and porosity in a roto-processor. Pellets of the narrowest size

distribution were produced with the highest disc speed, and spray rate had no effect on the standard deviation of the size distribution (a minor effect on the quality). As regards the effects on the porosity, both disc speed and spray rate had a significant effect, and the effect of disc speed ($p < 0.001$) was dominant compared to spray rate ($p < 0.02$). However, the effect of the process variables tested on the porosity of the pellets was dependent on the formulations. Pellets containing lactose were free from this effect, whereas formulations containing dibasic calcium phosphate were more affected.

The present literature review clearly indicates that most of the studies on the centrifugal granulating technique were confined to the utilisation of traditional non-pareils as substrates and to the characterisation of modified centrifugal granulating techniques. There are virtually no studies on the effects of process variables on the properties of the recently introduced beads or pellets prepared with the basic centrifugal technique. Consequently, and for the reasons mentioned above, it is important to thoroughly evaluate also this special technique of preparing drug-layered pellets.

1.3.3 Other pelletisation methods

Other pelletisation methods such as globulation, agitation and compaction (compression) are also used, although in a limited scale, in the preparation of pharmaceutical pellets (Ghebre-Sellassie 1989).

Globulation, or droplet information, consists of two related processes, spray drying and spray congealing. Spray drying is the process in which drugs in the suspension or solution without excipient are sprayed into a hot stream to produce dry and more spherical particles. This process is commonly used for improving the dissolution rates, hence bioavailability of poorly soluble drugs (Turkan et al. 1991, Ghebre-Sellassie 1989).

Spray congealing is the process in which a drug is allowed to melt, disperse or dissolve in hot melts of gums, waxes or fatty acids, and is sprayed into an air chamber where the temperature is kept below the melting point of the formulation components, to produce spherical congealed pellets. Both immediate- and controlled-release pellets can be

prepared in this process depending on the physicochemical properties of the ingredients and other formulation variables (Ghebre-Sellassie 1989).

Compresssion is one type of compaction technique for preparing pellets. Pellets of definite sizes and shapes are prepared by compacting mixtures or blends of active ingredients and excipients under pressure. The formulation and process variables controlling the quality of pellets prepared are similar to those used in tablet manufacturing (Kader et al. 1998).

Balling is the pelletisation process in which pellets are formed by a continuous rolling and tumbling motion in pans, discs, drums or mixers. The process consists of conversion of finely divided particles into spherical particles upon the addition of appropriate amounts of liquid (Ghebre-Sellassie 1989).

1.4 Characterisation of pellets

Pellets with rapid drug release are seldom delivered (supplied) as a finished product without using an extra coating (Niskanen et al. 1992). The pellets are mainly coated for aesthetic, taste masking, stability, enteric-release or controlled-release purposes. The coating thickness of the pellets must be uniform in order to achieve any of these end product performances. For uniform coating thickness, the formulation, equipment and process variables are usually selected based on the reproducibility of the size distribution, surface area, shape, surface roughness, density and friability, including the reproducibility of morphologic properties of the pellets (Mehta 1989).

1.4.1 Size distribution

The size distribution of the pellets should be as narrow as possible due to the following reasons:

1. For acceptable film coating, a narrow size distribution of pellets is a prerequisite (in addition to spherical shape and smooth surface). The size distribution affects both

the performance of the coating (Wesdyk et al. 1990, IIey 1991) and the release rate of the drug (Ragnarsson and Johansson 1988, Husson et al. 1991). A narrow size distribution will ensure minimum variation in coating thickness throughout the batch of pellets and therefore result in a uniform performance of pellets within the batch (Mehta 1989)

2. Segregation is a common occurence in capsule-filling and tablet compression due to the wide size distribution of pellets and thus results in variations in content uniformity and/or dosage form performance.

3. A narrow particle size-distribution improves (facilitates) the blending process in blending different types of pellets or different batches of pellets (Mehta 1989).

The size distributions of pellets are determined by different methods. The most common and widely used method is sieve analysis (Kristensen et al. 2000). The reasons for its extensive use are simplicity, lower costs, low time consumption and low turnover of operators. Sieve loading, type of motion (vibratory or tap), intensity and duration of intensity are recognized critical variables. In spite of the simple and easy technique, sieving has some disadvantages, such as the screen skewing particle size data due to the inability of the sieve to detect variation in the shapes of particles.

Another widely used method of measuring the size distribution of pellets is microscopy. The main advantage of this method over most other methods of size analysis is that the particle profile itself is measured rather than some property which is dependent on the particle size. Optical microscopy has been developed for particles size analysis from simple eyepiece graticules to fast device projectors and comparators, and the latest popular computerized method of image analysis (Hellén et al.1992b). Scanning electron microscopy can also be used for measuring the size of the pellets. Both types of microscopic techniques are tedious and time consuming, since a large number of particles need to be measured individually to make a size-frequency distribution plot. In addition, variation in the generated data is possible among operators.

Another method developed for the measurements of pellet size distribution is laser diffraction (Niskanen 1992, Hellén et al. 1992, Schaefer et al. 1996). This method is most suitable for spherical particles.

1.4.2 Shape and surface roughness

One of the important objects of pellet preparation (pelletisation) is to produce spherical and smooth particles, suitable for subsequent successful coating, i.e., optimal for controlled-release products. Moreover, spherical particles help the transfer of materials due to their good flow characteristics. And, last but not least, good spherical properties are useful in processes that require an exact metering of granules such as capsule filling (Vertommen et al. 1997). Different methods have been proposed for measuring the shape and surface roughness of the pellets. The commonly used method is the analysis of microscopic or non-microscopic pictures of objects of interest. However, the most widely accepted advanced technique is optical microscopy with image analysis (Lövgren and Lundberg 1989, Wan et al. 1993, Podczeck and Newton 1994). The direct measurement of surface roughness/smoothness by the image analysis method is not sensitive enough. Instead, fractal geometry of particle obtained by microscopy with image analysis, is used for the measurement of surface smoothness of pellets (Vertommen et al.1997). In the pharmaceutical field, fractal geometry has mainly been used in the study of surface roughness of powders, either excipient or drugs (Holgado et al. 1995a,b). Since it has been revealed that powder or granule characteristics (Thibert et al. 1988, Cartilier and Tawashi 1993) like flow and packing properties, are also related to the smoothness of the particle surface, knowledge about the smoothness of the pellet surface is important.

Electron microscopy (SEM) is the technique of choice for measuring the shape and surface smoothness of the pellets to support visually the other qualitative and quantitative results (Hellen 1992, Vuppala et al.1997, Vecchio et al. 1998, Umprayn et al.1999).

1.4.3 Surface area

The characteristics of pellets, those controlling the surface area, are mainly size, shape, porosity and surface roughness. Knowledge of the surface area of pellets is desirable especially if film coating is considered. Because the thickness of the film applied to pellets in a sustained-release -type dosage form dictates the rate at which drug is released, knowledge about the surface area is important even in case of uncoated pellets, since drug release is influenced by the surface area available (Vertommen et al. 1998).

There are three methods of measuring the surface area of pellets. It can be calculated from the particle-size distribution by measuring/using the mean diameter, since the surface area is equal to πd^2. However, this calculation does not account for the contributions of the surface area arising from other morphologic characteristics, such as porosity, surface roughness and shape of the pellets. Therefore, two techniques, i.e. gas adsorption (Lowell and Shields, 1991, Niskanen et al 1992) and air permeability (Lowell and Shields 1991, Eriksson et al. 1993), permit direct calculation of surface area.

Quick and simple, air permeability methods are widely used pharmaceutically for specific surface measurement, especially to control batch to batch variations. The principal resistance to the flow of a fluid - such as air – through a plug of compacted material is the surface area of the material. The applicability of air permeability methods for pellets is not highly acceptable since the flow rate through the plug or bed is also affected by the degree of compression of the material.

The gas adsorption method (commonly known as the BET method) was developed by Brunauer, Emmett and Teller (1937). In this method the volume of nitrogen that is adsorbed by the substrate contained in an evacuated glass bulb is measured at different pressures, and the results are plotted as $P/V\ (p_0-p)$ versus p/p_0 to generate a linear plot where V is the volume of gas in cm^3 adsorbed per gram of substare at pressure p and p_0 is the saturation vapour pressure of liquefied nitrogen at the temperature of the experiment. The slope and intercept of the plot yield the values b and V_m. The specific

surface (s_w) of the pellets is then obtained by using the following equation:

$$S_W = 4.35 * V_m$$

1.4.4 Porosity

The porosity of pellets influences the rate of release of drugs from the pellets by affecting the capillary action of the dissolved drug. It also affects film deposition and formation during coating. The porosity of the pellets can be measured qualitatively by scanning electron microscopy (SEM) and quantitatively by mercury porosimetry (Leitner 1981, Moscou and Lub 1981, Ghebre-Sellassie et al. 1987, Iley 1991, Thoma et al. 1992a, 1992b, Zhou et al. 1996,Vuppala et al. 1997, Vertommen et al. 1998). The porosity of pellets can be determined quantitatively also by using optical microscopy and scanning electron microscopy together with image analysis (Wang and Zaidi 1991).

1.4.5 Density

The density of pellets can be affected by changes in the formulation and/or process, which may affects other processs or factors, such as capsule filling, coating, and mixing. Variation of density from batch to batch affects the potency of the finished capsule, causes problems in batch size determination during coating and produces segregation during mixing.

The bulk density of the pellets can be measured by an automated tapper. It is indicative of the packing properties of particles and, therefore, is greatly influenced by the diameter and the size distribution of the pellets.

True density indicates the extent of densification or compactness of substances. The true density of pellets can be determined by an air-comparison pycnometer, a helium pycnometer or by the solvent displacement method (Sonaglio et al. 1995, Kleinebudde et al. 1999).

1.4.5 Friability

The essential requirement of pellets is to have an acceptable friability to withstand further processing, especially the subsequent coating. A high amount of attrition during the coating procedure could modify the release behaviour due to the incorporation of small particles in the film (Ghebre-Sellassie 1989, Schultz and Kleinebudde 1995). A friability of less than 0.08% is generally accepted for tablets, but for pellets this value could be higher due to the higher surface area/unit and subsequent involvement of frictional force (Ghebre-Sellassie 1985).

A number of different methods for the determination of pellet friability have been described in the literature and an overview of the present methods is shown in Table 2.

Table 2. Overview of friability testing methods for pellets (modified from Schultz and Kleinebudde 1995).

Method	Description	References
Erweka friabilator Roche friabilator Pharma Test friabilator ”Friabilator”	Rotating drum like friability testing apparatus for tablets	Baert et al. 1992, Funck et al.1991, Goskonda et al. 1993 and 1994, Knop et al. (1989, 1991and 1992), Millilli and Schwarz 1990, Zhang et al. 1990, Biachini et al. 1992, Nastruzzi et al. 2000, Gazzaniga et al. 1998, Eerikäinen 1991, Wan et al. 1985, Hellen et al.1993, Vecchio et al. 1994, Ghebre- Sellassie 1985, Kim et al. 1991, Mesiha and Valles 1993
Turbula	Turbula blender (closed test system)	Niskanen et al. 1990a, Ghebre-Sellassie 1985, De Doeuff et al. 1992, Noche et al. 1994.
Born Friabimat Retsch ball mill	Horizontal shaker (closed system)	Körber et al. 1990, Lindner et al. 1994
Laboratory coating apparatus	Fluid bed device (open system)	Thoma et al. 1986

2. AIMS OF THE STUDY

The main objective of the present study was to develop and characterise a centrifugal granulating process for preparing microcrystalline cellulose (MCC) beads and subsequent drug-layered pellets.

Special aims of the study were:

- to evaluate different grades of MCC for preparing highly spherical beads (i.e. substrates for drug-layering) by the centrifugal granulating process

- to investigate the mechanism of formation and growth of the MCC beads in a centrifugal granulating process

- to clarify the effects of aqueous binders and initial bead size on the properties of drug-layered pellets

- to study the effects of some process variables in a centrifugal granulator on the properties of MCC beads and drug-layered pellets

3. EXPERIMENTAL

3.1 Materials

For preparing spherical microcrystalline cellulose (MCC) beads, Emcocel 90M (NF, JP, Ph.Eur., E. Mendell, Finland) was used as initial seed material (**I, II**). As fillers, Emcocel 90M, 50M (NF, JP, Ph.Eur., E. Mendell, Finland) HD90 and SM15 (NF, JP, Ph.Eur., E. Mendell, United States) were used (**I, II**). Purified water (Ph.Eur.) was used as a wetting agent.

Drug-layered pellets (**III, IV**) were prepared by using MCC beads previously prepared in the centrifugal granulator as substrates. The bead size fraction used was 355-1000 μm. Povidone and maltodextrin were used as aqueous binding agents. Povidone is a widely used binder studied both for granule and pellet preparation (Ghebre-Sellassie et al. 1985, Knop and Lippold 1989, Robinson and Hollenbeck 1991, Niskanen et al.1992). Two grades of Povidone (Plasdone K-29/32 and K-25) at concentrations of 12%, 16%, 18% and 20%, (w/w) were studied. Maltodextrins are water-soluble hydrolysed starchs commercially available in different grades. They differ mainly due to their DE (dextrose eqivalent) values. The maltodextrin grades used were Maltrin M040 and M100 at concentrations of 12%, 16% and 20% (w/w).

As a model drug and solvent, previously milled sparingly water-soluble caffeine anhydride (Ph.Eur.) and purified water (Ph.Eur.) were used, respectively (**III, IV**).

3.2. Equipment

A laboratory-scale centrifugal granulator (Freund CF-360EX, Freund Industrial Co., Ltd., Tokyo, Japan) was used for preparing both MCC beads and subsequent drug-layered pellets **(I-IV)**. The schematic diagram of the equipment is presented in Figure 2. The principal units of the equipment are as follows:

a) *Product processing chamber* - The chamber (marked C in Figure 1) consists of a fixed cylindrical stator and a non-perforated rotating disc (D). The speed of the disc is controlled by a variable-speed rotor attached to the bottom. The fluidized air (A) enters the product area through the slit between the chamber and the rotating disc which is 0.2 mm. The dust accumulation during the operation is minimised by a cover and outlet air tube (B). The cover has openings to allow the position of clamp assembly, tubings of the spray guns and a powder delivery tube within the chamber. The product temperature and moisture are monitored by probes positioned just above the rotating disc (I).

b) *Powder feeding device* - This device (F) is situated over the processing chamber and consists of a vertical feed screw, a hopper and a hopper agitator. The rotation speed of the screw controls the powder dropping rate.

c) *Liquid spray assembly* – The assembly has two main units: 1) an exchangeable speed flow gear pump (G) situated near the processing chamber and 2) a spray gun (E), the position and angle of which can be altered as desired by means of a clamp unit. The binders and coating solutions of different viscosities are delivered suitably with the gear pump. The liquid is atomised by using air pressure through the spray gun which is usually of a binary type.

d) *Air supply system* - Air supply into the processing chamber is maintained by a blower (J). The blower air is supplied through a heat exchanger into the air chamber below the processing chamber and then entered in the process chamber via the slit (A). The function of the air is to facilitate the drying, to enhance the motion as well as to prevent the blocking of the slit during the processing of fine granules.

e) *Control panel* – It consists of (1) a basic control panel with on-off switches, pilot lamps, a thermometer and rotation speed meters, and is designed, on production units, for remote locating and (2) optional moisture feed back control panels that optimise agglomeration and granulating times by controlling the moisture content of the bed during agglomeration.

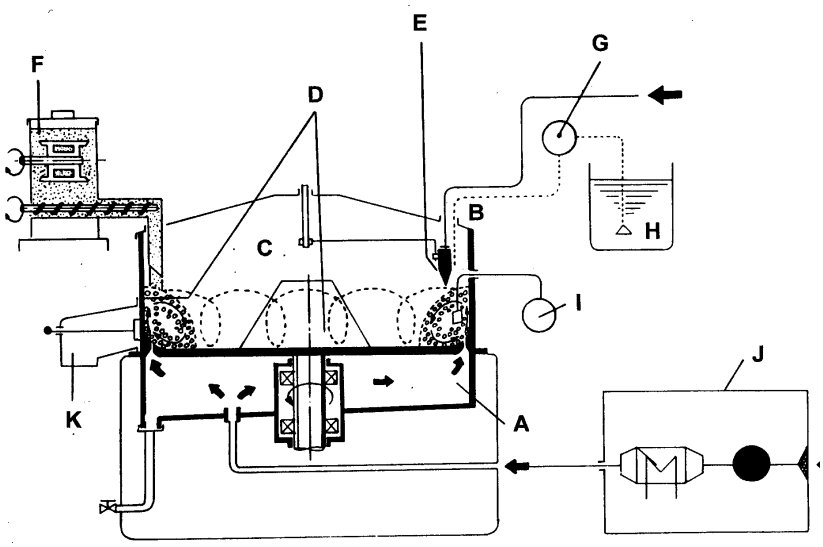


Figure 2. Schematic diagram of the centrifugal granulator. Key: Inlet air (A), Outlet air (B), Granulation chamber (C), Rotor (D), Solution spray system (E), Powder feeder (F), Liquid pump (G), Liquid vessel on a balance (H), Moisture sensor (I), Blow air generator system (J) and Product outlet (K) (modified from Goodhart 1989).

3.3. Methods

3.3.1 Characterisation of materials

*Moisture content **(I, III)***

Moisture content was determined as the loss of weight using an infrared dryer (Sartorious Thermocontrol YTC0IL, Sarturius GmbH, Germany). A 2-g sample was heated up to 120 °C until the loss of weight was less than 0.1 mg in 50 s. Three parallel determinations were performed in each case.

*Bulk and tapped densities (**I, III**)*

The bulk density was determined by pouring 50 g of materials into a 250-ml graduated glass cylinder which was kept at an angle of 45^0 to horizontal while pouring. The cylinder was straightened up and the volume occupied by the materials read to the nearest 1 ml. The bulk density was calculated by dividing the weight by the occupied volume. The tapped density was determined by a tapped density tester (Erweka SVMI, Erweka GmbH, Germany) in which the glass cylinder was tapped 750 times. The tapped density was calculated in the same way as the bulk density. The Hausner ratio, i.e. the ratio between the tapped and the bulk density, was calculated on the basis of bulk and tapped density data. All measurements were made in triplicate.

*Flow rate and angle of repose (**I**)*

The flowability was determined by an automatic, non-commercial flow rate recorder made by Orion Pharmaceutica, Finland, as the time required for 50 g of materials to flow through a standard orifice (10mm). The angle of repose was determined in the same equipment. All measurements were made in triplicate.

*Particle size and size distribution (**I, III**)*

The particle size and size distribution were determined by sieve analysis. Twenty grams of beads and pellets were shaken for 10 min in an automatic shaker (Fritsch Laborgerätebau, Germany) using a series of 1400-µm, 1250-µm, 1000-µm, 800-µm, 710-µm, 630-µm, 500-µm, 450-µm, 355-µm and 250-µm sieves. The amplitude was 6. The determinations were performed in triplicate.

*Shape and surface characteristics (**I, III**)*

The shape and surface structure were studied by scanning electron microscopy (Jeol JSM-840A, Jeol, Japan). Before taking the photograph, the sample of the material was coated with gold in an argon atmosphere by an ion sputter coater (SDOO4, Baltzers Union, Liechtenstein).

3.3.2 Preparation of MCC initial beads (I, II)

The composition of the spherical bead formulations tested are shown in Table 3. Tables 4 and 5 represent the constant operating process parameter settings (**I, II**) and the levels of the process parameters tested (**II**), respectively.

Table 3. Composition of MCC bead formulations tested (**I**).

Material	**Formulation**			
	I	**II**	**III**	**IV**
As initial seed material:				
Emcocel 90M	500g	500g	500g	500g
As filler:				
Emcocel SM15	500g	-	-	-
Emcocel 50M	-	500g	-	-
Emcocel 90M	-	-	500g	-
EmcocelHD90	-	-	-	500g

In each experiment, 500 g of MCC (Emcocel 90M) was placed in the processing chamber and allowed to moisten for 21.2 min. During the first 10.0 min the rotor rotation speed was kept at 100 rpm/min and was then set at 200 rpm/min. After 21.2 min of wetting the filler was added to the wetted mass, keeping all the process parameters constant. The final product was taken out at 36.0 min after finishing the addition of the filler, and dried at 60 °C in a fluidised-bed dryer for 40 min.

Table 4. Operating parameter settings during initial bead preparation (**I**).

Parameter	**Setting**
Rotor rotation speed (rpm)	100-200
Slit air (l/min)	200
Spray air (l/min)	12.0
Spray air pressure (kg/cm^2)	0.8
Spray rate (ml/min.)	25
Filler dropping rate (g/min)	33.8
Spray nozzle distance from bottom plate (cm)	6.0

Table 5. Levels of process variables studied (Fractional Factorial Design, FFD 2^{5-2}) (**II**)

Process parameter	**Level (-)**	**Level (+)**
X1, rotor rotation speed (rpm)	180	280
X2, slit air flow rate (l/min)	140	240
X3, spray air pressure (kg/cm^2)	0.6	1.4
X4, spray air rate (l/min)	10	16
X5, spray nozzle distance from bottom plate (cm)	5.0	7.0

3.3.3 Preparation of drug-layered pellets (III, IV)

2^2 and 3^3 full factorial designs were used for preparing drug-layered pellets. The levels of the material and process variables studied as well as the constant process parameter settings are presented in the original papers **III** and **IV** (Tables 6 and 7 enclosed).

Table 6. Matrix of the 3 x 2^2 design with three replicate experiments in the middle point.

Exp.	X1	X2
PVP		
1	20	905
2	20	555
3	12	905
4	12	555
5	16	710
6	16	710
7	16	710
M040		
1	20	905
2	20	555
3	12	905
4	12	555
5	16	710
6	16	710
7	16	710
M100		
1	20	905
2	20	555
3	12	905
4	12	555
5	16	710
6	16	710
7	16	710

X1 = binder concentration (% w/w)
X2 = initial beadsize (µm)

Table 7. Matrix of full factorial design (3^3).

Exp.	X1	X2	X3
1	-1	-1	-1
2	-1	0	0
3	0	0	-1
4	0	1	0
5	0	-1	1
6	1	0	1
7	1	1	-1
8	-1	1	1
9	1	-1	0
10	0	-1	-1
11	0	0	0
12	1	0	-1
13	1	1	0
14	1	-1	1
15	-1	0	1
16	-1	1	-1
17	0	1	1
18	-1	-1	0
19	1	-1	-1
20	1	0	0
21	-1	0	-1
22	-1	1	0
23	-1	-1	1
24	0	0	1
25	0	1	-1
26	1	1	1
27	0	-1	0
28	-1	-1	1
29	1	1	1
30	-1	1	1

X1 = rotor rotation speed (rpm) 150, 200, 250;
X2 = slit air flow rate (l/min) 100, 200, 300;
X3 = spray air rate (l/min) 10, 16, 22.

In each experiment, a mixture of previously milled caffeine anhydride and colloidal silicon dioxide equivalent to 150 g of caffeine was used as a drug filler. 300 g of anhydrous MCC beads were placed in the processing chamber and allowed to tumble for

1.0 min before spraying the binder solution. After spraying for 0.5 min the drug was added to the wetted mass at a screw rate of 5.0 rpm, keeping all the process parameters constant. At 24.5 min, addition of the drug was finished and spraying of the binder solution was continued at the same rate until 25.5 min. The spraying was continued at 25.5 min at a rate of 3.1 g/min. After the addition of 136.0 g of binder, the final pellets were taken out at 26.5 min and dried at room temperature (23 ± 2 °C) for 48 h.

3.3.4 Evaluation of initial beads and pellets

The initial beads were evaluated with respect to yield, size and size distribution, shape, surface morphology, bulk and tapped densities, flowability and friability. For evaluation of drug-layered pellets, percentage of drug loss during the preparation, drug in the expected yield fraction, expected yield as well as undersized and oversized pellets were also tested in addition to the above tests performed for initial beads (**I, II**). The expected yield fraction was used to characterise the shape, the surface morphology and the relevant physical and mechanical properties of the pellets.

Expected yield

The expected yield, undersized and oversized pellets as well as size and size distribution were determined by sieve analysis (Fritsch Analysette, Germany).

Loss of drug

The percentage of drug loss during the process and the percentage of drug in the expected yield fraction were determined spectrophotometrically at a wave length of 273 nm.

The percentage of drug loss during the process, drug in the expected yield fraction, expected yield and undersized and oversized pellets were calculated by using the following formulas:

Drug loss during the process (%)	=	[1- (AT/AM)] * 100	Eq. 1
Expected yield (%)	=	(L / M) * 100	Eq. 2
Undersized pellets (%)	=	(U / M) * 100	Eq. 3
Oversized pellets (%)	=	(O / M) *100	Eq. 4
Amount of drug in the expected yield fraction (%)	=	(AF / AM) * 100	Eq. 5

where

M	=	amount of total material used excluding moisture content
L	=	amount of expected pellet fraction in the total product excluding moisture content
U	=	total amount of undersized pellets in the product excluding moisture content
O	=	total amount of oversized pellets in the product excluding moisture content
AT	=	amount of drug present in the total product
AF	=	total amount of drug present in the expected yield fraction of the total product
AM	=	total amount of drug used

Bulk and tapped densities

The bulk and tapped densities were determined by the same method as used for the raw materials. The flowability and the angle of repose were measured by a flow-time and cone angle testing instrument (Pharma Test PTG, Pharma Test, Germany) with an 8- mm orifice. The flow rate was calculated by dividing the bead/pellet weight by the flow times. The angle of repose was measured by the instrument itself.

Friability

The friability of the beads/pellets was determined by weighing 20.0/10.0 g of beads/pellets and 20.0/10.0 g of glass beads (diameter about 2 mm) into a 100-ml container. The beads/pellets were mixed with the glass beads in a Turbula mixer (System Schatz, W.A. Bachofen, Switzerland) for 10 min and then sieved through a 250/450 μm sieve. The percent weight loss was then calculated. The measurements were made in triplicate.

Shape and surface roughness

The shape and surface roughness of both initial beads and drug-layered pellets were characterised using an optical microscopic image analysis system (Leach MZ6, Leica Imaging Ltd, Cambridge, England). The sample of the initial beads/pellets was spread on a two-sided adhesive tape with a spatula so as not to touch each other. The tape with the samples was placed in a glass Petri dish. At least 500 beads/pellets from each batch were measured from each experiment.

The characteristics measured for each bead/pellet were area, minimum diameter (dmin and dmax), perimeter (perim) and convex perimeter (cperimeter). From the measured data, the roughness and shape parameters were derived. The shape parameters included sphericity (roundness and circularity) and oblongation (elongation, rectangularity, modelx). These parameters are shown below (Eqs. 6-11).

$$\text{Circularity} = 4*\pi*\text{area}/(\text{perim})^2 \quad \text{Eq. 6}$$

$$\text{Roundness} = (\text{perim})^2/(4*\pi*\pi\text{area}*1.064) \quad \text{Eq. 7}$$

$$\text{Elongation} = \text{dmax}/\text{dmin} \quad \text{Eq. 8}$$

$$\text{Rectangularity} = \text{area}/\text{dmin}*\text{dmax} \quad \text{Eq. 9}$$

$$\text{Modelx} = \text{perim}*\text{dmax}/4*\text{area} \quad \text{Eq. 10}$$

Roughness = Perim/cperim Eq. 11

The surface roughness was studied by scanning electron microscopy (Jeol JSM-840A, Jeol, Japan). Before taking the photograph, the sample of the beads/pellets was coated with gold in an argon atmosphere by an ion sputter coater (SDOO4, Baltzers Union, Liechtenstein).

3.3.5 Statistical analysis (**II-IV**)

Statistical evaluation was made using the Windows version of Systat 5.0. Modelling was performed by Modde for Windows (Version 3.0, Umeå, Sweden).

4. RESULTS AND DISCUSSION

4.1 Initial beads (I, II)

4.1.1 Mechanism of growth and formation (I)

The spherical bead/core formation mechanism consisted mainly of three phases. Nucleation is the phase where the initial processing materials were first wetted with water and well-formed nuclei were then produced by random collision and coalesence. The second phase, a transient region, consisted of coalescence between previously formed weak nuclei and layering of the filler over the well-formed nuclei. The final phase or the sphere growth region continued until the end of the process. Based on the formation and growth of MCC beads/cores, there were no great differences between the formulations tested. However, formulations (I and II), where MCC 50 μm and 15 μm were used as filler, layering rather than coalescence was found to dominate in the transition region as compared with MCC 90 μm and higher-density MCC 90 μm. This was attributed to their differences in size.

4.1.2 Effects of material variables on the properties of initial beads (I)

4.1.2.1 Size characteristics

The amount of initial beads in the fraction of 250-710 μm was considered as expected yield. The fractions larger than 1000 μm and smaller than 250 μm were classified as agglomerates and the powered fraction of the formulations, respectively. With increasing particle size of MCC as a filler the amount of expected yield and agglomerates (lumps) decreased. Exceptionally, the formualtion with high-density MCC (Emcocel HD90) as a filler produced a larger amount of agglomerates. The lumps in this case consisted of the accumulation of individual round granules instead of large irregular intact particles unlike other formulations (Table IV; **I**). The formation of agglomerates/lumps in experiments with Emcocel SM15 was mainly due to the addition to the body of the processing chamber, whereas in other formulations no adhesion to the processing

chamber occurred. The only beads smaller than 250 μm were formed with Emcocel SM15 as a filler.

4.1.2.2 Shape characteristics

The initial beads prepared with different grades of MCC as fillers were relatively spherical. The initial bead fraction 250-500 μm was more spherical than 500-700 μm, especially in formulations I and II. The image analysis results coincide with the visual results obtained by SEM that all formulation yielded a relatively smooth surface with no great deviations (Table V and Figure 4; **I**).

4.1.2.3 Packing characteristics

The bulk and tapped densities of the initial beads were positively related to the particle sizes of the microcrystalline cellulose grades used as filler. These results agree with the previous studies on wet granulation (Harwood and Pilpel 1968, Niskanen et al. 1990).

4.1.2.4 Flowability and friability

Flowability

The Hausner ratio measures the friction conditions in a moving powder mass, and a low Hausner value is a criterion of good granulation (Hausner 1967, Aulton and Banks 1978). An angle of repose < 30° can also be regarded as an indicator of good flowability of materials.

The poorest flowability was observed with Emcocel SM15, whereas in the case of respective initial core product, the direct measured flow rate, angle of repose and Hausner ratio values showed good flowability. In all formulations tested the initial beads of 250-500 μm had a higher flowability compared with 500-710 μm. Beads with high-density MCC produced the highest flowability, which correlates with their highest density, sphericity and surface roughness (Table VI; **I**).

Friability

The friability of the initial beads measured by the Turbula method was negligible. Only fractions 250-500 μm and 250-710 μm of formulations I and II had small percentage that was quite smaller in comparison to the upper limit. The friabilty of the other formulations was > 0.05%. (Table VI; **I**).

4.1.2.5 Limitations

The flow characteristics of different grades of MCC used as filler in preparing the initial beads created some limitations related to the process. The MCC grade (Emcocel SM15) had such a poor flow rate that it was a problem to feed it uniformly from the feeding device without external agitation. On the other hand, MCC grades Emcocel 90M and HD90 created quite an opposite problem due to their higher flow rate. Therefore, to maintain the same flow rate for the above two grades, an additional part was attached to the feeding device. However, the MCC grade Emcocel 50M, which was used as a filler in formulation II, was free from these problems.

4.1.3 Effects of process variables on the properties of initial beads (II)

Five process variables of potential importance with respect to the pharmaceutical quality of the intial beads were evaluated. The parameters studied were rotor rotation speed, slit air, spray air pressure, spray air rate and height of nozzle setting (Table 1; **II**).

4.1.3.1 Expected yield and mean diameter

The rotor rotation speed had a clear negative effect ($p < 0.001$), while the slit air flow rate ($p < 0.01$) and the spray air rate ($p < 0.05$) had a positive effect on the expected yield. When the rotor rotation speed was increased from 180 rpm to 280 rpm, the relative change of expected yield was in the range of –(32.4-90.3)%. As the slit air rates and spray air rates were increased from the lower to the higher, the relative changes in the expected yield were in the range of +(6.7-36.7)% and +(3.0-30.9)%, respectively. Rotor rotation speed ($p<0.001$), slit air flow rate ($p< 0.001$), and spray air rate ($p< 0.001$) were

also critical parameters affecting the mean diameter. Increasing the rotor rotation speed from 180 rpm to 280 rpm resulted in a relative change of +58.3% of mean diameter, while incresing the slit air flow rate from 140 l/min to 240 l/min (and spray air rate from 10 l/min to 16 l/min) resulted in a relative change of –26.5% (and –15.2%), respectively.

4.1.3.2 Bulk density

The process parameters statistically affecting the bulk densities of the initial beads were rotor rotation speed ($p < 0.001$), slit air flow rate ($p < 0.001$) and spray air rate ($p < 0.01$). The rotor rotation speed had a positive effect, and the slit air flow rate and spray air rate a negative effect on the bulk densities of the beads.

4.1.3.3 Shape and surface morphology

The shape of the beads was evaluated by measuring the sphericity (roundness and circularity) and oblongation (elongation, rectangularity, and modelx). For a perfectly round particle, the respective values are 1.

As regards quantitative values of roundness (Table 2 and 4; **II**), the rotor rotation speed ($p < 0.001$) had a negative effect, the slit air flow rate ($p < 0.01$) and spray air rate ($p < 0.05$) had a positive effect. As regards values of circularity, the rotor rotation speed ($p<0.001$) had a positive effect, and the slit air flow rate ($p < 0.001$) and spray air rate ($p<0.05$) had a negative effect. This shows that by increasing the rotor rotation speed and by decreasing the slit air and the spray air rate, more spherical beads can be obtained.

In case of oblongation, the rotor rotation speed and slit air flow rate had significant effect on the elongation and modelx, but not on the rectangularity of beads. Rotor rotation speed ($p < 0.001$) had a clear negative effect, and slit air flow rate ($p < 0.05$) a positive effect on the elongation. On the modelx values the rotor rotation speed ($p < 0.001$) had a negative and the slit air flow rate ($p < 0.01$) and spray air rate ($p < 0.05$) a positive effect. Consequently, increasing the rotor rotation speed resulted in a decrease in the elongation and modelx values, thus producing rounder beads.

The differences in the rectangular and roughness values of the experiments were negative for calculation of any significance (Table 2; **II**).

4.2 Drug-layered pellets (III, IV)

4.2.1 Effects of material variables on the properties of pellets (III)

4.2.1.1 Drug loss

The drug loss during the process was defined as the amount of active ingredient lost during the preparation of pellets due to adhesion to the body and/or leakage through the opening of the processing chamber. The results show that the drug loss during the process was lower in formulations with povidone (Plasdone K-29/32) than those with maltodextrins mainly at a lower concentration level. There was no clear difference in drug loss during the process between the maltodextrin grades tested.

The concentration of the binders had a negative effect on the size of the drug loss during the process ($p < 0.05$). With increasing binder concentration the size loss of the drug decreased. The effect of concentration was greater with Maltrin M100 than with Plasdone K-29/32 and Maltrin M040. The initial bead size had no significant effect on the drug loss (Table IV and Figure 3; **III**).

4.2.1.2 Expected yield

The expected yield was defined as the amount of pellets in fractions 630-1250 μm, 500-1000 μm and 350-800 μm, including process loss, loss due to the formation of agglomerates and undersized pellets. The results indicate that the lowest expected yield was obtained with Plasdone K-29/32 at a lower bead size and higher concentration level, followed by Maltrin M040 and M100. Plasdone K-29/32 at a lower concentration and higher bead size level gave the highest expected yield, and maltodextrins at a higher concentration and higher bead size level followed the same trend. For Plasdone K-29/32

and maltodextrins, this was mainly due to the formation of a smaller amount of agglomerates and undersized pellets, respectively.

4.2.1.3 Amount of drug in the expected yield fraction

The results indicate that the expected yield fractions for a higher binder concentration and lower bead size produced the smallest amount of active drug, and this was mainly due to the formation of a larger amount of oversized pellets (agglomerates). The response was opposite at higher concentration and bead size levels. The expected yield fraction with Plasdone K-29/32 at a lower concentration gave more active ingredient compared with maltodextrins. This could be due to the formation of more undersized pellets and greater drug loss during the process for maltodextrin.

4.2.1.4 Size and shape characteristics

Size and size distribution

The fraction below the minimum size of initial beads was regarded as undersized pellets. The pellets prepared with Plasdone K-29/32 yielded the smallest amount of undersized pellets (Table III; **III**). Formulations with Maltrin M100 were more prone to form undersized pellets than those with Maltrin M040 at lower concentrations, whereas at higher concentrations there was no big difference. This could be explained by the higher DE values of Maltrin M100 showing a smaller binding capacity, and thereby producing more undersized pellets at lower concentrations.

The concentration of the binder was more critical and had an opposite effect on the amount of undersized pellets ($p < 0.01$). The effect of binder concentration was more pronounced with maltodextrins ($p > 0.001$) than with Plasdone K-29/32. The initial bead size had no effect on this response (Table IV and Figure 4; **III**).

Plasdone K-29/32 was more inclined than the maltodextrin grades tested at higher concentrations to produce a larger amount of agglomerates, thus influencing the size of

the expected yield fraction and thus influenced the size of the expected yield fraction. Maltrin M100 produced less agglomerates than Maltrin M040.

The size distributions of the pellets were quite equal for all types of binders tested (Figure 3). Smaller initial bead size yielded a wider size distribution than a higher initial bead size. The size distribution of the final pellets was wider compared with the respective initial bead size distribution, which was more pronounced with smaller initial beads.

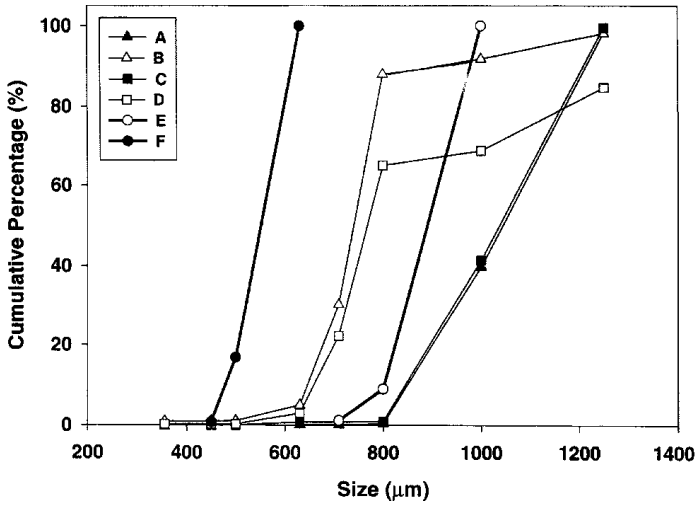


Figure 3. Size distribution of pellets containing povidone and maltodextrin. A: pellets with Plasdone K-29/32 at higher binder concentration and larger bead size (▲), B: pellets with Plasdone K-29/32 at higher binder concentration and smaller bead size (∇), C: pellets with Maltrin M100 at higher concentration and larger bead size (■), D: pellets with Maltrin M100 at higher concentration and smaller bead size (□), E: large beads (○), F: small beads (●) (**III**).

Shape

All formulations yielded relatively spherical pellets, and the drug-layered pellets were less spherical than the corresponding MCC beads. The drug-layered pellets were less spherical and rougher than the respective MCC beads. Formulations with a higher initial

bead size and lower binder concentration yielded more spherical and smoother pellets than the other ones. Pellets with Maltrin M040 were rougher than those with other binders used (Table III and Figure 2; **III**).

4.2.1.5 Packing characteristics and flowability

Packing properties

The pellets with Maltrin M040 exhibited lower bulk densities than the pellets with other binders. The bulk densities of the pellets with Plasdone K-29/32 were quite equal to those with Plasdone K-29/32. The lowest bulk densities of the pellets with Maltrin M040 were mainly due to their rough surface. In the case of M100 the effect was quite opposite.

Flowability

Pellets with Plasdone K-29/32 and Maltrin M100 were better flowing than those with Maltrin M040. One of the reasons could be the rough surface of the pellets prepared with M040. Based on the flowability of the respective pellets, the binders studied were ranked as M100 > Plasdone K-29/32 > M040 (Table III; **III**).

Both independent variables concentration and initial bead size had a significant inverse effect on the flowability of the pellets. With increasing concentration and initial bead size the flowability of the pellets decreased. The higher flowability of the pellets with small bead size was assumed to be due to the higher flowability of the small initial beads used (Table IV and Figure 6; **III**)

4.2.1.6 Friability

With the exception of maltodextrins (Maltrin M040 and M100) at a lower concentration (12% w/w) and smaller bead size, all binders produced pellets within an acceptable range of values. Plasdone K-29/32 yielded stronger pellets compared with the maltodextrin grades. Pellets prepared with Maltrin M100 were slighly more friable than

those with Maltrin M040. The difference between the friability values of the pellets could be due to their different DE values (Table III; **III**).

With increasing binder concentration and initial bead size, the friability of the pellets decreased. The concentration of the binder ($p < 0.01$) and the size of the initial beads ($p < 0.05$) had a negative effect on the friability of the pellets. The effect of binder concentration and initial bead size was more evident with Plasdone K-29/32 than with maltodextrins. This was thought to be due to the higher tendency of Plasdone K-29/32 to form agglomerates.

4.2.2 Effects of process variables on the properties of pellets (IV)

The feasibility of the centrifugal granulating process for preparing drug-layered pellets using microcrystalline cellulose beads as substrates and a sparingly water-soluble drug as a filler has been reported in previous sections. Three process variables which were found to have a significant effect on the quality of the MCC beads prepared in the same equipment were studied using 3^3 full factorial design. The results are presented in Table 2 (**IV**). The summary of the fitted models and statistical analysis with estimated effects are shown in Table 3 (**IV**).

4.2.2.1 Drug loss during the process

The main ingredients used for the preparation of pellets were powdered drug and MCC beads. There is no possibility of loss of MCC beads due to leakage through the opening of the processing chamber except adhesion to the body of the chamber, whereas drug loss probably occurred by both ways. The drug loss during the process could be reduced by controlling the process parameters. In the literature, yields of 90% are regarded as acceptable in a corresponding drug layering process (Vuppala et al. 1997). In our study, the drug loss was 5-10%.

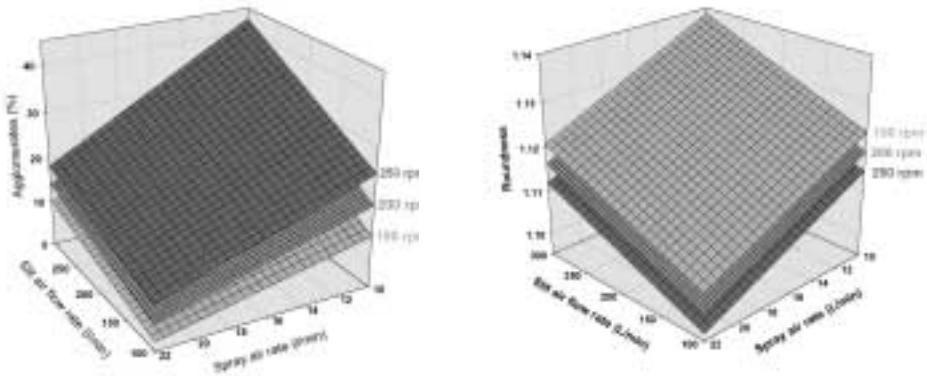
The statistical analysis shown in Table 3 (**IV**) indicated that the rotor rotation speed ($p < 0.01$) and slit air flow rate ($p < 0.001$) were important parameters affecting the drug loss

during the process. Both parameters had a positive effect on the drug loss. The effect of slit air was more pronounced than that of rotor rotation speed.

4.2.2.2 Formation of agglomerates

Agglomeration is a common processing problem in preparing pellets by the drug layering technique. Generally the problem of agglomeration could be minimised by controlling the critical process parameters. The statistical analysis shown in Table 3 (**IV**) indicates that all three parameters studied (rotor rotation speed $p < 0.001$, slit air flow rate $p < 0.001$ and spray air rate $p < 0.001$) had a significant influence on the formation of agglomerates during the pellet preparation. As shown in Figure 4, the amount of agglomerates was positively affected by the rotor rotation speed and the slit air flow rate, and negatively by the spray air flow rate. With increasing rotor rotation speed, the slit and spray air rates and the amount of agglomerates increased. By increasing the spray air rate from the lowest to the highest level the amount of agglomerates decreased. An obvious explanation is that a higher rotor rotation speed and slit air flow rate wetted the initial beads more due to the leakage of fine filler drug powder through the opening of the processing chamber, while increasing the spray air rate the overwetting of the pellets decreased.

(i) (ii)



(iii)

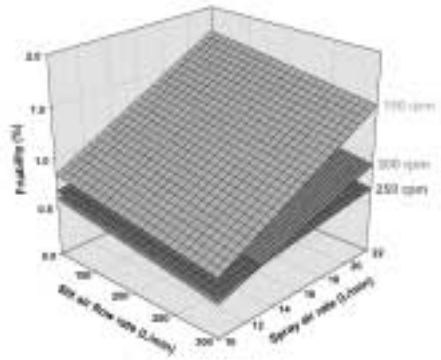


Figure 4. Surface plots representing the effects of slit air flow rate and spray air rate on the amount of agglomerates (**i**), roundness (**ii**) and friability (**iii**). Key: The rotor rotation speeds are 150 rpm (A), 200 rpm (B) and 250 rpm (C).

4.2.2.3 Bulk density

The process parameters affecting the bulk densities of the pellets were rotor rotation speed ($p < 0.01$), slit air flow rate ($p < 0.01$) and spray air rate ($p < 0.001$) (Table 3; **IV**). The rotor rotation speed and the spray air rate had a positive effect and the slit air flow rate a negative effect on the bulk densities of the pellets. Of the process parameters studied, the rotor rotation speed was dominant.

The effect of spray air rate on the bulk density of the pellets was inverse to that found previously with the initial MCC beads (see Section 4.1.3.2). This could be due to, e.g., only water being used as wetting agent without any binder in the preparation of MCC beads. MCC could not agglomerate until it was fully wet and had achieved plastic properties. The wetter the MCC powder was, the denser and rounder beads were obtained. In the preparation of drug-layered pellets, layering of drug powder over the initial beads depends mainly on the binding capacity of the binder. Overwetting of the surface of the initial beads with the binder solution enhances their agglomeration, resulting in irregular and rough pellets. As the spray air rate was increased, overwetting of the surface of the pellets decreased, and this obviously resulted in smoother and rounder pellets.

4.2.2.4 Pellet flow rate

As seen in Tables 2 and 3, both rotor rotation speed ($p < 0.001$) and spray air rate ($p < 0.001$) had a significant positive effect on the flow rate of the pellets. With increasing rotor rotation speed and spray air rate the flow rate increased.

4.2.2.5 Shape and surface morphology

One of the main goals in pellet preparation is to produce spherical round particles, which contribute to successful coating and, thus, are optimal for controlled-release products. Good flow characteristics of particles during coating and accurate metering of granules, e.g. in capsule filling, are clearly dependent on the roundness of the particles.

Roundness is often defined by E*quation 7* (Section 3.3.4). By this definition for a perfectly round particle the roundness value is one. For the MCC beads the value was 1.061. Concerning the quantitative values of roundness, the rotorrotation speed ($p < 0.05$) and spray air rate ($p < 0.001$) had a negative effect,the slit air ($p < 0.001$) a positive effect (Figure 4; Section 4.2.2.2). This means that by increasing the rotor rotation speed and spray air rate, and by decreasing the slit air flow rate, more spherical and rounder pellets could be prepared. In this case, the effect of the spray air rate on the roundness was opposite to that on the shape of MCC beads. The reasons could be the same as for the bulk density of the pellets.

The surface roughness properties of the pellets measured by image analysis exhibited no significant differences. However, the SEM micrographs representing the pellets of the corner points of the full 3^3 factorial design shown in Figures 3 (**IV**) and 4 (**IV**) indicate that the pellets with a rounder shape had a relatively smoother surface than the less round ones.

4.2.2.6 Friability

As seen in Table 3 (**IV**), both the rotor rotation speed ($p < 0.001$) and the spray air flow rate ($p < 0.001$) had a statistically significant effect on the friability of the pellets. The rotor rotation speed had a negative and the spray air rate a positive effect on the friability (Figure 4; Section 4.2.2.2). At the highest rotor rotation speed, however, the spray air rate had virtually no effect on the friability. Change in spray air rate at the lower level of rotor rotation speed influenced the friability to a greater extent than the respective change at the higher speed (Figure 4; Section 4.2.2.2). This can be explained by the fact that as the rotor rotation speed is higher, the initial beads become wetter due to the loss of drug and thus nullify the effect of the spray air.

4.2.2.7 Interactions

Some significant paired interactions can be seen between the process parameters tested (Table 3; **IV**). Slit air rate and spray air rate were shown to interact with the formation of

agglomerates, bulk density and friability. Significant paired interactions related to bulk density were also found between all process parameters tested.

5. CONCLUSIONS

On the basis of the present results, the following conclusions can be drawn:

1. The centrifugal granulating process is a convenient method of manufacturing microcrystalline cellulose (MCC) initial beads (substrates). As regards process-related advantages and limitations, the formulation with MCC 90M as a seed material and MCC 50M as a filler seems to be more acceptable than the other ones.

2. Nucleation, coalescence, abrasion transfer and layering are the major mechanisms of the formation and growth of MCC beads in the centrifugal granulating technique.

3. The selection of binder for use in preparing drug-layered pellets in the centrifugal granulating process should be made with care. With povidone (Plasdone K-29/32) and maltodextrins (Maltrin M100 and M040) as aqueous binders, satisfactory drug-layered pellets based on MCC initial beads can be prepared. Binder concentration and bead size are critical material variables in processing the pellets. MCC initial beads of a larger size and a binder concentration as low as possible should be chosen for better reproducibility.

4. The effects of important process variables, i.e. rotor rotation speed, slit air (fluidized air) flow rate and spray air (atomizing air) rate, should be taken into account in preparing acceptable MCC initial beads and subsequent drug-layered pellets. The present process parameters can have a great influence on the physical and pharmaceutical characteristics of the MCC beads and subsequent drug-layered pellets such as yield, size, size distribution, shape, flowability and friability.

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