



Research paper

Preparation of sustained release matrix pellets by melt agglomeration in the fluidized bed: Influence of formulation variables and modelling of agglomerate growth

Anette Pauli-Bruns*, Klaus Knop, Bernhard C. Lippold

Heinrich-Heine-Universität, Institut für Pharmazeutische Technologie und Biopharmazie, Düsseldorf, Germany

ARTICLE INFO

Article history:

Received 4 September 2009

Accepted in revised form 10 December 2009

Available online 22 December 2009

Keywords:

Fluidized bed

Melt agglomeration

Matrix

Pellets

Sustained release

Growth mechanism

Microcrystalline wax

ABSTRACT

The one-step preparation of sustained release matrix pellets, using a melting procedure in a fluidized bed apparatus, was tested in a 2³ full factorial design of experiments, using microcrystalline wax as lipophilic binder, theophylline as model drug and talc as additional matrix forming agent. The three influence parameters were (A) size of binder particles, (B) fraction of theophylline in solid particles and (C) fraction of microcrystalline wax in formulation. The response variables were agglomerate size and size distribution, dissolution time, agglomerate crush resistance, sphericity, yield and porosity.

Nearly spherical pellets comprising a smooth, closed surface could be obtained with the used method, exhibiting the hollow core typical for the immersion and layering mechanism.

The reproducibility was very good concerning all responses.

The size of agglomerates is proportional to the size of the binder particles, which serve as cores for pellet formation in the molten state in the fluidized bed. Additionally, the agglomerate size is influenced by the volume of the solid particles in relation to the binder particles, with more solid particles leading to larger agglomerates and vice versa. Dissolution times vary in a very wide range, resulting from the interplay between amount of drug in relation to the meltable matrix substance microcrystalline wax and the non-meltable matrix substance talc.

The change of binder particle size does not lead to a structural change of the matrix; both dissolution times and porosity are not significantly altered.

Agglomerate crush resistance is low due to the hollow core of the pellets. However, it is significantly increased if the volume fraction of microcrystalline wax in the matrix is high, which means that the matrix is mechanically better stabilized.

A theoretical model has been established to quantitatively explain agglomerate growth and very good accordance of the full particle size distributions between predicted and actual values could be shown. A low volumetric binder to solids ratio is compensated by a more porous layer. On the basis of this model, in-depth understanding on the mechanism and influence of product properties could be gained; and an a priori estimation of particle size distributions for new formulas can be performed, with densities, formula, and binder particle size distribution as input parameters.

© 2009 Elsevier B.V. All rights reserved.

1. Introduction

Pharmaceutical melt agglomeration is a well-described technique, which follows similar principles as wet agglomeration with binder solutions or solvents. In both cases, inter-particular bonding is achieved by wetting of powder particles or sticking of liquid droplets on their surface, and subsequent agglomerate formation

and growth by collision with further particles or agglomerates. In the case of wet agglomeration, the mass is subsequently dried to form solid bridges and to obtain the final product; in case of meltable binders, cooling leads to solidification of these.

In the pharmaceutical industry, agglomeration techniques using binder solutions are used frequently. However, melt techniques can offer some technical advantages. Due to the fact that the drying step is replaced by cooling, cost can be saved both in terms of energy and process time. Additionally, cooling can mostly take place in the same apparatus or on trays, whereas drying often requires the transfer to a fluid bed apparatus or a tray dryer.

A wide range of different functionalities of the agglomerated product and the respective tablets can be achieved by melt

* Corresponding author. Heinrich-Heine-Universität, Institut für Pharmazeutische Technologie und Biopharmazie, Universitätsstraße 1, 40225 Düsseldorf, Germany. Tel.: +49 69 380976094.

E-mail addresses: Anette.Pauli-Bruns@gmx.de (A. Pauli-Bruns), knopk@uni-duesseldorf.de (K. Knop), lippold.b@t-online.de (B.C. Lippold).

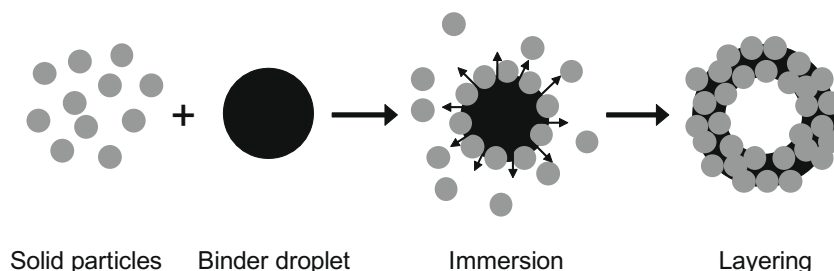


Fig. 1. Immersion and layering mechanism, after [39].

techniques; this comprises fast-dissolving tablets [1,2], scalable manufacture of solid dispersions [3–9], gentle processing of essential oils [10] or hygroscopic drugs [11–15], manufacture of effervescent tablets [16,17], sustained release tablets [18–22] or granules/pellets [3,23–32], taste masking [33], and preparation of floating delivery systems [34–38].

In principle, the same apparatuses used for agglomeration with binder liquids can also be used for melt agglomeration (high shear mixer, fluidized bed granulator, extruder). In some cases, modifications are needed, e. g. in fluidized bed apparatuses, where spraying of melts requires heated nozzle and tubing.

In general, agglomerate formation is a process that consists of the three steps nucleation (aggregation of primary particles), growth (aggregation of two or more nuclei, or further aggregation with primary particles), and breakage. These steps can occur subsequently or in parallel.

For melts, Schaefer [39,40] proposed two different mechanisms of nucleation, depending on whether the melt is distributed on the surface of the solid (distribution mechanism) or the solid is immersed into the surface of the liquid melt droplets (immersion mechanism, Fig. 1). Despite the fact that his work is based on high shear mixer experiments, similar mechanisms could also be observed in fluidized bed apparatuses [41–44]. The prevalence of one or the other mechanism is mainly dependent on the relative sizes of the solid particles and the molten binder droplets, further the binder viscosity, the shear forces and the interplay of these factors.

In case of nucleation by distribution, agglomerate growth will take place by coalescence of wetted nuclei [41–44]. In case of immersion, growth can either occur by subsequent coalescence [43,44] or by layering of primary particles [41,45,46] (Fig. 1) or a mixture of the two mechanisms [44], depending on apparatus, process and formulation variables. In case of the layering mechanism, which is the focus of this publication, the melt is forced outwards the agglomerate by capillary forces, where it leads to a sticky surface, and more primary particles are layered on, accompanied by formation of a cavity within the agglomerate [41,45,46].

The principle of sustained drug release by matrix formation using a non-water soluble waxy or fatty hydrophobic matrix has been described since the 1970s [47,48], initially for monolithic delivery systems. The interesting feature is that the hydrophobic matrix substance can also melt and serve as binder, thus exhibiting dual functionality in these products.

Over the decades, it has been shown that multiparticulate forms have a series of advantages over monolithic forms in sustained release [49]; pellets seem to be the most ideal form. Pellets are spherical agglomerates which exhibit a smooth, closed surface [42]. They should have an approximate size of 0.5–2 mm, a narrow size distribution, and sufficient mechanical stability for further processing. Different techniques for industrial manufacture of pellets based on melting matrices have been described with different apparatuses common to pharmaceutical industry: high shear mixers [27,28,50], rotary processors [51,52] and twin-screw extruders [53].

Melttable binders (or ingredients) are either added to the formula as solid products, and are molten in situ, or are molten prior to adding, with or without atomization, which offers a variety of options to design product properties [54].

Agglomerates formed by the immersion and layering mechanism in fluidized bed equipment have been described to be relatively spherical and smooth, thus meeting some of the desired properties of pharmaceutical pellets. The aim of the present work is to describe a simple one-step procedure for reproducible preparation of sustained release matrix pellets, using these mechanisms, to identify the critical parameters that influence product properties, and to gain an in-depth understanding on the underlying agglomerate formation and growth mechanisms, in order to be able to design product properties a priori.

2. Materials and methods

2.1. Materials

Theophylline anhydrous (Ph.Eur.) (BASF AG, Ludwigshafen, Germany) was used as the model drug. Purified Talc (Ph.Eur.) was supplied by C.H. Erbslöh, Krefeld, and Microcrystalline Wax (Ph.Eur.) (TerHell 5603, Schümann Sasol, Hamburg, Germany) was used as lipophilic binder.

2.2. Methods

2.2.1. Characterization of primary materials

2.2.1.1. Laser diffraction. The particle size distributions by volume of theophylline and talc were determined in triplicate by Helos H1402/KF-Magic laser diffraction particle sizer (Sympatec GmbH, Clausthal-Zellerfeld, Germany) fitted with a dry powder feeder operating at 2 bar.

2.2.1.2. Sieve analysis of microcrystalline wax sieve fractions. Sieve analysis was conducted with a PC-controlled sieve station (AS 200 control, and software SP1000, version 1.07, Retsch, Haan, Germany), at an environmental temperature of 5 °C. Analytical sieves with 200 mm diameter and 50 mm height were used. Samples of approximately 30 g were preconditioned in a deep freezer. The sieves were vibrated permanently, amplitude 1.5 mm; complete separation was assumed when less than 0.1% of the mass on a sieve passes the sieve within a minute, which was the case after 10 min. Analysis was carried out in triplicate. Median and quartiles were calculated by linear interpolation of the cumulative mass fraction curve.

2.2.1.3. Pycnometric density. Pycnometric density was determined in triplicate by an AccuPyk 1330 gas displacement pycnometer (micromeritics, Norcross, USA) at 25 ± 0.1 °C, using helium purge. The sample was weighed into the 3.5-mL chamber such that it is filled at an approximate two-thirds level and was rinsed with

Helium for 10 cycles. Density measured is the mean of five measurements of the same sample.

2.2.1.4. Density of the melt. Approximately 5 g microcrystalline wax, accurately weighed, was transferred into a 10-mL measurement cylinder. The wax was molten on a water bath at 60 °C and the volume was taken for density calculation.

2.2.1.5. Melting range and peak temperature. The melting range and the melting peak temperature of the microcrystalline wax were estimated in triplicate by a DSC 821e differential scanning calorimeter (Mettler-Toledo GmbH, Gießen, Germany). A sample of about 3 mg was sealed in a 40- μ L aluminium pan with a hole, and scanned between 20 and 90 °C at a heating rate of 10 °C/min. Indium was used as calibration standard.

2.2.2. Formulation

As the binder content is limited by the process, but is not sufficient in terms of achieving long sustained release, an additional non-meltable matrix substance was needed, which had to be (a) non-meltable at processing temperatures (b) non-soluble in dissolution fluids and (c) available as fine particle size. Talc was chosen for this purpose. All batches were 500 g in size, composed of microcrystalline wax (meltable binder) and the solid powder mixture (theophylline + talc).

2.2.3. Preparation of microcrystalline wax sieve fractions

Microcrystalline wax was deep frozen to avoid smearing, and was subsequently sieved into size fractions through a 500- μ m sieve (Retsch, Haan, Germany) on a sieve station (Retsch AS200 control) in a cool room (5 °C) at the amplitude of 1.5 mm. For the center point experiments, the two fractions were blended at 1:1 ratio. Fractions are further referred to as S (<500 μ m), M (blend of the two fractions) and L (>500 μ m).

2.2.4. Fluid bed equipment

A fluidized bed granulator (GPCG-1, Glatt GmbH, Binzen, Germany), without inserts or spray nozzles, was used.

2.2.5. Agglomeration procedure

Ingredients were deagglomerated (microcrystalline wax: 1000- μ m sieve, theophylline: 315- μ m sieve) and filled into the container. For heating, inlet air temperature and fluidizing airflow were set to 70 °C and 70 m³/h, respectively. At a product temperature of 60 °C (after approximately 8 min), the inlet air heating was switched off. When product temperature had dropped to 50 °C, the apparatus was turned off and the pellets were put on trays for further cooling. Filters were shaken every 10 s for 10 s in alternating mode over the whole process.

2.2.6. Agglomerate characterization

2.2.6.1. Scanning electron microscopy. Whole and crushed agglomerates were analyzed. For crushing, agglomerates were quick-frozen with liquid nitrogen and subsequently broken. Pictures were taken by a scanning electron microscope (SEM) (LEO VP 1430, Carl Zeiss NTS GmbH, Oberkochen, Germany). The agglomerates were sputtered with gold in a Sputter Coater (Edwards S150B, GB-Crawley) at 17 °C, for 180 s before microscopy.

2.2.6.2. Sieve analysis. Sampling: the whole batch was poured onto a tray to form a cone. Using two cardboard cards, a segment of approximately 30 g size was taken. The analysis was carried out at room temperature. Apparatus and parameters were as described for sieve analysis of microcrystalline wax fractions (Section 2.2.1.2). The span is defined as the difference between the mass

diameters at the 75% and the 25% points relative to the mass median diameter.

2.2.6.3. Dissolution and MDT₈₀. A paddle apparatus Ph.Eur. was used. 1000 mL of 0.1 N HCl solution was used as dissolution medium. For dissolution from hydrophobic matrices, it is a prerequisite that the dissolution medium is able to wet the matrix and to penetrate the pores. Therefore, 0.2% Hypromellose Ph.Eur. (Pharmacoat 606, Syntapharm, Mülheim, Germany) was added to the medium as wettability enhancer to simulate the low surface tension of the gastric fluid [55]. The medium was degassed by ultrasonic treatment (Branson Sonifier, Gerhard Heinemann GmbH, Schwäbisch Gmünd, Germany) at 60% power, alternating mode, for 5 min, and subsequently stored in a vacuum cabinet (vacutherm, Kendro, Haunau, Germany) at $p \leq 10$ mbar for 1 h. Sampling was done via Reagent filters (Bran-Lübbe GmbH, Norderstedt, Germany). A piston pump (PVP80, Erweka Apparatebau GmbH, Heusenstamm, Germany) was used to transfer the medium to a photometer (Lambda 2, Perkin Elmer & Co GmbH, Überlingen, Germany), where concentration was measured at 243 nm. We used 10-mm Suprasil flow-through cuvettes (Hellma GmbH & Co. KG, Mühlheim/Baden, Germany) were used; the measurement interval was 5 min. Pellets of sieve fraction 800–1000 μ m were used for analysis. Measurements were carried out at 37 ± 0.5 °C, 50 rpm, sixfold.

2.2.6.4. Agglomerate crush resistance. Twenty pellets of each batch (sieve fraction 800–1000 μ m) were crushed with a texture analyzer (TA-XT2i, Stable Micro Systems, Haslemere, Great Britain). The flat punch was moved with a speed of 1 mm/s down on the pellet. The crushing strength was the first maximum appearing in the force-versus-displacement profile.

2.2.6.5. Sphericity. Agglomerates from the size fraction of 800–1000 μ m were placed on a desk illuminated with cold light (Leica KL1500DC, Leica Mikrosysteme Vertrieb GmbH, Bensheim, Germany). Pictures were taken with a digital camera (DC300F, Leica) through a stereo microscope (MZ 75, Leica), 1 pixel = 11.1 μ m. Image analyses were performed on at least 500 agglomerates, using imaging processing software (Leica QWin Standard Y2.8, Leica Microsystems Imaging Solutions Ltd., Cambridge, Great Britain). For each agglomerate, 64 Feret diameters are determined; the longest is defined as particle length. The aspect ratio is calculated as the particle length divided by the maximum width found at a 90° angle to the length.

2.2.6.6. Porosity of agglomerate layer. The porosity was determined by mercury porosimetry, using PASCAL 140 and 440 apparatuses (Thermo Finnigan Italia S.p.A., Rodano, Italy). A sample size according to the expected intrusion (approximately 0.5 g) was weighed into a dilatometer type CD3P (also Thermo Finnigan) and evacuated for 15 min in PASCAL 140. Pressure was increased at speed setting 5p up to 400 kPa and reduced again to minimum. After transfer to PASCAL 440, intrusion and extrusion curves were recorded from 0.1 to 400 MPa. Measurements were carried out in duplicate. Mercury (Suprapur) was procured from Merck KGaA, Darmstadt.

An indirect measurement based on the extrusion curves, using intact agglomerates, was performed. This measurement principle has been described by Thommes [56]. A typical curve is depicted in Fig. 2. Upon mercury intrusion, first the inter-particle voids are filled (1). At a pressure of approximately 0.3 MPa (3 bar), which corresponds to an approximate pore diameter of 2.5 μ m, an abrupt intrusion increase is seen. Initially, the pores within the layer are filled; when the first pore with connection to the core is filled, the whole core will be filled with mercury (2). Upon extrusion, the mercury will leak from the pores within the layer, but not from the core (3). If a second pneumatic measurement with the same

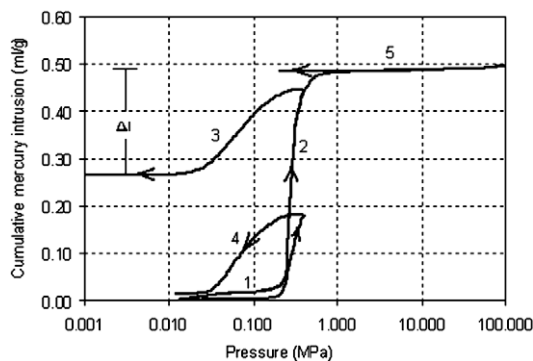


Fig. 2. Mercury intrusion and extrusion curves, example using batch O₃; 1 and 2: intrusion (first pneumatic measurement) 3: extrusion (first pneumatic measurement) 4: second pneumatic measurement, and 5: hydraulic measurement.

sample is done, inter-particle voids are already filled, and the pores within the layer are filled again, and to the same extent as what has leaked from the pores in the first measurement (4). Upon hydraulic (=high pressure) measurement of the same sample, also the smallest pores of the layer, which could not be filled by applying the maximum pneumatic pressure, are mercury filled (5). The difference between the maximum intrusion volume and the remaining mercury after extrusion (ΔI , dimension: mL/g) corresponds to the volume of pores in the layer. The porosity is calculated according to Eq. (1).

$$\varepsilon(\%) = \frac{\Delta I}{\frac{1}{\rho} + \Delta I} \cdot 100 = \frac{\Delta I}{V_{app}} \cdot 100 \quad (1)$$

ε is the porosity (%), ρ is the pycnometric density (g/mL), V_{app} is the apparent volume of layer.

2.2.7. Experimental design

On the basis of results obtained from preliminary experiments, a complete 2³ factorial design with one genuine repetition and three center points was performed giving a total of 11 experiments. The experiments were performed in a partially randomized order, and one center point experiment was carried out on each experiment day. The experimental design is shown in Table 1.

The response variables were median diameter (d_{50}), span, dissolution time MDT₈₀, agglomerate crush resistance, sphericity and porosity of the layer.

Data analysis was performed with UMetrics Modde 7.0 software (UMetrics, Umeå, Sweden).

3. Results and discussion

3.1. Material properties

Results from material characterization are summarized in Table 2. Due to stickiness, it was not possible to quantitatively separate

Table 1
Description of factors for the factorial design.

Independent variable	Low level (-)	Center point (0)	High level (+)
Particle size of microcrystalline wax (A)	S	M	L
Fraction of theophylline in solid particles ^a (B)	20%	42.5%	65%
Fraction of microcrystalline wax in formulation (C)	15%	20%	25%

^a The amount of talc in the solid particles (%) can be calculated as 100-B.

Table 2
Physical properties of the materials.

Material	Volume/mass median diameter (μm) ^a	Span	Pycnometric density (g/mL)	Density of the melt 60 °C (g/mL)	Melting (°C)	
					Range	Peak
Theophylline anhydrous	4.6	1.248	1.50	–	–	–
Talc	9.5	1.076	2.85	–	–	–
Microcrystalline wax	372.7 ^a	0.388	0.88	0.76	47–	58
	463.9 ^b	0.488				
	575.3 ^c	0.202				

^a Mass median diameter for microcrystalline wax, determined by sieve analysis; volume median diameter for talc and theophylline, determined by laser diffraction.

^b Fraction < 500 μm , coded 'S'.

^c Blend of fractions < 500 μm and > 500 μm , coded 'M'.

^d Fraction > 500 μm , coded 'L'.

wax particles <500 μm from >500 μm . Therefore, each fraction contains a small proportion of the other fraction. For full size distribution data of microcrystalline wax, refer to Fig. 3. At the center point (M), particle size distribution is wider than for the fractions S (-) and L (+).

3.2. Preliminary investigations

First investigations showed that nearly spherical pellets with a smooth surface (Fig. 4a and b) could be obtained with a very simple and short procedure. The binder particle size has to be much larger than the particle size of the solid particles, to achieve the immersion and layering mechanism, which results in the typical hollow pellets (Fig. 4c). Use of binder particles with a median size of 444 μm and theophylline with a high median particle size (81 μm) resulted in a high amount of fines and only a low proportion of pellets, which had a rough surface. Theophylline with a small median particle size (4.6 μm) resulted in a low amount of fines and smooth pellet surface. Median particle size of talc was 9.5 μm in both and the following experiments (Table 2). This reflects previous findings that the immersion mechanism is only prevalent if the solid particles to binder size ratio is low enough [40,46]. The binder content could be varied within a large range of about 12–28% of the total formulation, which is in good accordance with literature findings [41,46]. Below this range, the binder amount was not sufficient and a large amount of fines could be found; above this range, increased lump formation as well as deposition of pure molten binder on the granulator walls and on the bottom sieve were observed.

It was also seen that process variables were of minor influence, provided that the product temperature reached at least 60 °C, and the product is fully fluidized.

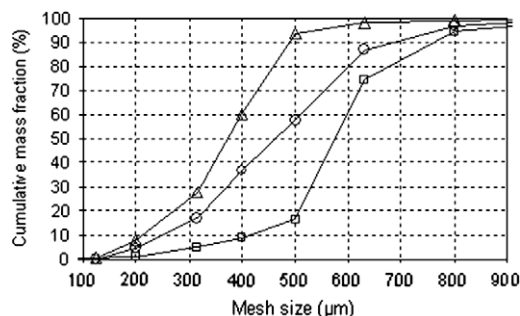


Fig. 3. Sieve data of microcrystalline wax fractions; mean ($n = 3$); Δ : 'S' (-), \circ : 'M' (0), \square : 'L' (+).

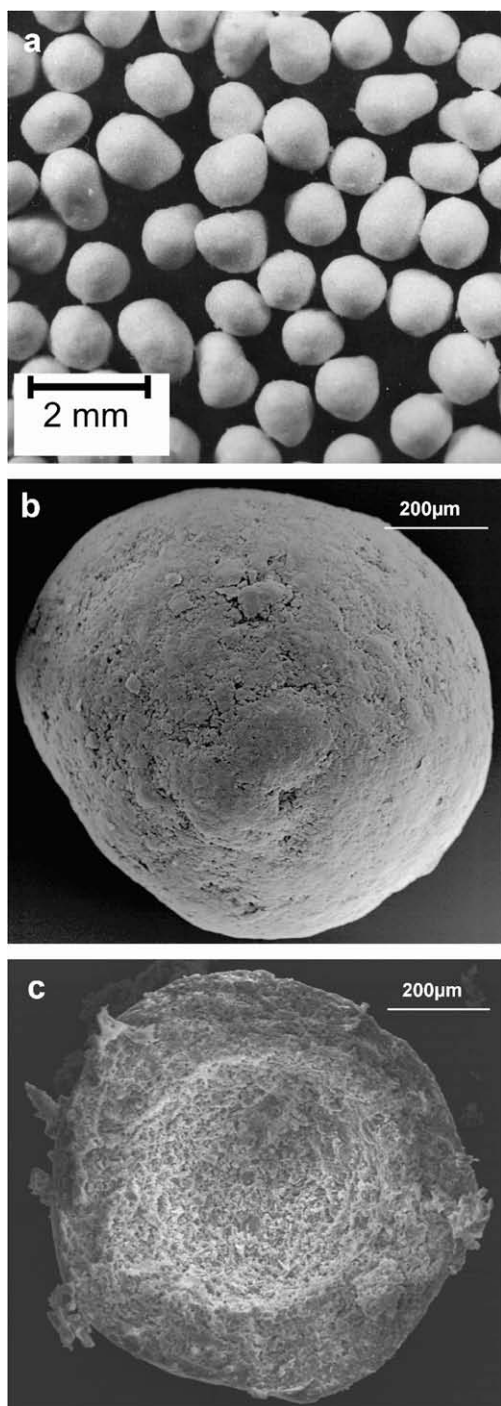


Fig. 4. (a) Photograph of pellets, sieve fraction 1000–1250 μm (composition: 16% microcrystalline wax, 42% theophylline, 42% talc). (b) SEM micrograph of a single pellet. (c) SEM micrograph of a crushed single pellet.

Different drugs were also tested: pellets can also be obtained with nicotinamide and hydrochlorothiazide [57].

3.3. Scanning electron micrographs

Each batch was subjected to scanning electron microscopy; the presence of the typical hollow core as shown in Fig. 4c could be seen for each single batch. Twins were not seen. This supports the theoretical agglomeration and growth mechanism, after which each single agglomerate results from one single molten binder par-

Table 3

Results for the response variables median agglomerate size (d_{50}), inter quartile difference (I_{50}) and span (I_{50}/d_{50}), mean, $n = 3$.

Run no.	Level ^a	d_{50} (μm)	I_{50} (μm)	Span (I_{50}/x_{50})
2	(1)	625	249	0.399
8	a	989	296	0.299
10	b	675	276	0.409
6	ab	1143	314	0.275
1	c	522	165	0.317
9	ac	872	229	0.263
5	bc	560	205	0.365
3	abc	895	180	0.201
4	0 ₁	766	381	0.498
7	0 ₂	792	366	0.463
11	0 ₃	790	371	0.470

^a Letters indicate high level, (1) indicates all low levels, and '0' indicates center point.

tic. However, it has to be considered that only a few agglomerates were analyzed per batch, so if twins/multiple cores are not prevalent, they can still be present.

3.4. Agglomerate size

A good reproducibility (standard deviation = 14 μm , RSD = 1.8%) of the process as well as a good fit between the statistical model and experimental data ($r^2 = 0.994$) could be observed. For full agglomerate size data, refer to Table 3.

Increasing the particle size of the binder microcrystalline wax (factor A) leads to a highly significant increase in agglomerate size (Table 4). The particle size of the binder is therefore the most important parameter to control the size of the agglomerates. Quantitatively, when increasing the binder median diameter from $d_{50} = 373 \mu\text{m}$ (S) to $d_{50} = 575 \mu\text{m}$ (L), an average increase in agglomerate size of two times the effect calculated for factor A, $2 \times 189.6 \mu\text{m} = 379.2 \mu\text{m}$, occurs, i.e. the agglomerate size is increased by almost double the value of the increase of the diameter of the binder particles. The diameter of agglomerates should be the diameter of the original binder particle, minus some potential contraction that occurs when solid particles are immersed into the droplet, plus twice the thickness of the layer layered on the core. If the diameter of agglomerates increases to a stronger extent than the core particle in the inter batch comparison, this suggests that the thickness of the layer layered onto the binder droplet is not constant, as has been suggested by Abberger and Henck [42]. In fact, larger binder particles seem to have binding capacity for a thicker layer than smaller ones. This will be discussed in more detail in the modelling section.

Table 4

Effects of the independent variables in the factorial design in Table 3 on the response variables median agglomerate size (d_{50}) and span (I_{50}/d_{50}).

Factors and interactions	x_{50} (μm) ($r^2 = 0.994$)		Span (I_{50}/x_{50}) ($r^2 = 0.980$)
	Effect	p	Effect
Constant	784.5	–	0.3160
Sieve fraction of microcrystalline wax (A)	189.6	2.2×10^{-5}	–0.0563
Fraction of theophylline in solid particles (B)	33.1	0.0162	–0.0034
Fraction of microcrystalline wax in formulation (C)	–72.9	0.0009	–0.0294
AB	11.1	0.2510	–0.0181
AC	–18.4	0.0911	0.0020
BC	–17.9	0.0975	0.0001

Increasing the fraction of theophylline in the solid particles (factor B) will also give rise to an increased agglomerate size. An increased amount of theophylline comes along with a decreased amount of talc. As theophylline has a much lower pycnometric density than talc, increased amount of theophylline means that a larger volume of solid particles is available for layering, and is actually layered on the core binder droplets, resulting in larger agglomerates.

The fraction of microcrystalline wax in the formulation (factor C) is also a key factor for agglomerate size. The more binder is available, the smaller is the agglomerate size. As more binder means less solid particles per binder particle, a thinner layer is suggested as reason for this effect.

To summarize the results seen from factors B (fraction of theophylline in the solid particles) and C (fraction of microcrystalline wax in the formulation), a relative volume increase of solid particles compared to binder particles/droplets leads to a thicker layer which is layered on. This means that the amount of solid particles that can be bound/layered by a given particle is not a constant, but subject to the availability of solid material in the tested range of 15–25% microcrystalline wax. Ansari and Stepanek [46] tested a binary system of PEG 6000 and mannitol, in the range of 5–25%, and found that agglomerate size is a constant for a given initial binder particle size, but the amount of fines is increased at lower binder amounts. The fact that percentage is given as mass percentage, not volume, and different binder to solids particle size ratios might explain these differences.

3.5. Agglomerate size distribution

On comparison of particle size distribution of the binder particles with the agglomerates, it becomes clear that the distribution widens during agglomerate formation (data not shown). This indicates that the layer thickness is dependent on the initial binder (droplet) particle size also within one batch, with thicker layers for larger particles.

In terms of the response agglomerate size distribution, the center point variation is not a valid parameter for estimation of the variance, because it does not range in the middle of the values of the single runs. In contrast, it is significantly higher (Span $I_{50}/d_{50} = 0.475 \pm 0.020$, $n = 3$, and $I_{50}/d_{50} = 0.316 \pm 0.072$, $n = 8$, for center points and single runs, respectively). This is due to the fact that the binder (microcrystalline wax) had a broader particle size distribution at the center points, where a blend of two sieve fractions was used, than it had at the single runs, where single fractions of binder have been used. Therefore, p values were not calculated and no measure for the significance of effects is available. However, the very good reproducibility of center point experiments suggests that the variance of the data is in the order of a few percent, and the high $r^2 = 0.980$ (Table 4) indicates an adequate statistical model.

A negative effect is caused by the particle size of the binder microcrystalline wax (factor A). This is probably caused by the different size distribution of the binder particles themselves (Span of 'S' binder = 0.388, Span of 'L' binder = 0.202).

Table 6
Effects of the independent variables in the factorial design in Table 5 on the response variables Mean Dissolution Time 80% (MDT₈₀), agglomerate crush resistance and porosity.

Factors and interactions	MDT ₈₀ (min) ($r^2 = 0.957$)		Agglomerate crush resistance (N) ($r^2 = 0.957$)		Porosity (%) ($r^2 = 0.995$)	
	Effect	p	Effect	p	Effect	p
Constant	146.4	–	0.34	–	27.41	–
Sieve fraction of microcrystalline wax (A)	–4.5	0.7418	0.08	0.0008	0.33	0.4478
Fraction of theophylline in solid particles (B)	–101.5	0.0013	0.03	0.0308	1.92	0.0081
Fraction of microcrystalline wax in formulation (C)	54.8	0.0125	0.12	0.0002	–10.36	0.0000
AB	2.4	0.8596	0.00	0.8137	0.64	0.1803
AC	19.1	0.2067	0.05	0.0069	0.47	0.2958
BC	–25.1	0.1194	0.00	0.8107	0.89	0.0869

Table 5

Results for the response variables Mean Dissolution Time 80% (MDT₈₀), mean \pm standard deviation, $n = 6$, agglomerate crush resistance, mean \pm standard deviation, $n = 20$, and porosity, mean \pm standard deviation, $n = 2$.

Level	MDT ₈₀ (min)	Agglomerate crush resistance (N)	Porosity (%)
(1)	217.6 ± 21.66	0.23 ± 0.032	37.0 ± 1.49
a	137.2 ± 9.98	0.29 ± 0.064	35.1 ± 0.03
b	31.5 ± 1.22	0.16 ± 0.024	38.8 ± 0.38
ab	17.5 ± 0.72	0.24 ± 0.063	39.4 ± 0.13
c	310.7 ± 45.21	0.37 ± 0.030	16.5 ± 0.32
ac	363.7 ± 34.62	0.63 ± 0.075	12.6 ± 1.16
bc	81.2 ± 5.73	0.32 ± 0.042	19.8 ± 0.03
abc	86.8 ± 5.77	0.57 ± 0.098	20.5 ± 0.36
O ₁	114.9 ± 10.13	0.33 ± 0.064	26.2 ± 0.05
O ₂	103.4 ± 1.65	0.34 ± 0.050	26.6 ± 0.01
O ₃	145.7 ± 8.72	0.30 ± 0.037	27.1 ± 0.76

The second highest effect is caused by the fraction of microcrystalline wax in the formulation (factor C). The more microcrystalline wax is used, the narrower is the agglomerate size distribution. This interesting finding will also be discussed in the modelling section.

3.6. Dissolution

During dissolution testing, no visible destruction of the matrices occurs. For assessment of dissolution time, MDT₈₀ [58] is used as kinetic independent parameter. To exclude effects caused by agglomerate size, always the same sieve fraction (800–1000 μm) is used for the dissolution experiments. Results and effects are listed in Tables 5 and 6.

The dissolution times vary in a large range between 17 and 363 min. The two significant influence parameters are the fraction of theophylline in the solid particles (factor B), and the fraction of microcrystalline wax in the formulation (factor C); both results are a logical consequence of the drug to matrix ratio.

It is interesting to note that the particle size of microcrystalline wax (factor A) clearly shows no influence on the dissolution time; this indicates that the agglomerate structure is not altered by the size of binder particles.

Some of the batches ((1), a, b, O₁, O₂) showed a biphasic dissolution profile; a correlation to the factors could, however, not be established. Some in-depth investigations on this finding are described in [57].

3.7. Agglomerate crush resistance

Crush resistance is a relevant parameter for further processing like filling into capsules or sachets. The crush resistance measured ranges between 0.16 and 0.53 N, which is quite low. For all results, refer to Tables 5 and 6.

Crush resistance is mainly dependent on the stability of the matrix. For a high fraction of microcrystalline wax in the formulation (factor C), the solid particles are well linked by the high amount of available binder, and a relatively high crush resistance has been observed, despite the fact that the thickness of the layer around

the hollow core is smaller. Thus, the structure of the layer is more important than the thickness.

A similar effect can be deduced for the increase of theophylline amount in the solid particles (factor B): the more theophylline (comprising a relatively low density compared to talc), the more volume has to be bound by the same amount of binder. Therefore, the matrix is less stabilized, and crush resistance is reduced. Again, this happens despite a thicker layer layered on the hollow core.

Interestingly, the increase of particle size of microcrystalline wax also leads to increased crush resistance of pellets, despite a quantitatively unchanged composition of the matrix. One possible explanation could be that for smaller binder particles, the thickness of layered material is less. However, agglomerates of the same sieve fraction (800–1000 μm) were taken for the measurements, which should approximately have the same layer thickness.

A different possible explanation is that the smallest binder particles actually do not serve as seed for immersion, but are themselves layered on larger cores. These relatively smallest particles are smaller in absolute numbers at the lower level for binder particle size (<500 μm), than they are at the high level (>500 μm). Potentially, these larger layered binder droplets, which are contained in the matrix in addition to the binder material from the core, are better capable to supply additional matrix stabilization, than they are in case of smaller layered binder droplets. This hypothesis is supported by the fact that there is a highly significant interaction ($p = 0.0069$) between factors A and C, i.e. pellet crush resistance increase is much more pronounced at high binder levels in the formulation than at low level (refer also to Fig. 5).

3.8. Sphericity

The median shape factors determined were in the range of 1.06–1.10. No significant effect of any of the tested parameters on sphericity was found.

3.9. Yield

The yield of the experiments was within 70–91%. In the 2^3 factorial analysis, no significant effect of the variables on the yield was found.

3.10. Porosity

Porosity is determined to gain a deeper understanding of agglomerate structure and to aid theoretical modelling of pellet growth. Results are summarized in Tables 5 and 6.

Some very interesting results can be seen: binder particle size (A) has no effect on porosity; this indicates that no structural changes in

the matrix occur upon changes of binder particle size. Increase of theophylline fraction in solid particles (B) and decrease of binder amount (C), i.e. increase of solid particles to binder volume ratio, lead to a significantly increased porosity. As a larger volume has to be bound with the same volume of binder, less inter-particle voids can be filled and a more porous structure results. This shows that variable amounts of solid particles can be bound by the same binder particle/droplet, depending on availability of solid particles, and compensating with different porosity. This has already been postulated by Ansari and Stepanek [46] by theoretical modelling.

4. Theoretical model of agglomerate nucleation and growth

A theoretical model describing agglomerate growth helps to gain understanding on the effects of parameters, and facilitates formulation finding with new formulas. Different theoretical models have been established already [42,46].

Abberger and Henck [42] has described a model with good correlation to experimental data; however, this model is hardly suitable for prediction of agglomerate sizes, because a number of unknown parameters (fraction of sticky surface in total agglomerate surface, number of seeds, number distribution of seeds, shape of solid particles, apparent density of granules, critical size of binder particles above which these serve as seeds) have to be estimated and add uncertainty to the calculations. In addition, his model is based on the assumption that the layer thickness is a constant and not dependent on binder particle size; present data show that this is not the case. Additionally, theoretical considerations make it improbable that layer thickness is independent on initial droplet size. Schaafsma et al. [59] describes the process of agglomerate growth in the following way: at the beginning, liquid saturation is 100%; the liquid binder starts to move through inter-particle capillaries. On the surface, new particles are bound and new inter-particle capillaries are formed. The more the process advances, the more the liquid saturation will drop and the diameter of those inter-particle capillaries which are still liquid filled, becomes smaller and smaller. When the liquid saturation drops below a critical value, only very thin capillaries, which are not accessible for solid particles, are liquid filled. These capillaries are not accessible for solid particles any more and therefore, layering comes to a halt. The larger the seed particle/droplet, the more binder volume is available to fill the inter-particle capillaries of the layered solid particles. Until the critical value is achieved, a thicker layer should be layered on. Even if the critical end point is not achieved due to a lack of sufficient amount of solid particles, it can be assumed that the particles will stick on the stickiest agglomerates and will therefore be distributed in a way that the layer thickness is higher for larger seeds than for small ones. Once the critical value is achieved, no more layering occurs. If more solid particles are available, these are not bound and remain as fines, as seen by Ansari and Stepanek [46].

Based on the findings from the experimental data, and these theoretical considerations, a different model is established, based on the following assumptions:

1. Both core droplets and agglomerates are spherical; this is not exactly the case but simplifies the calculation.
2. The volume of the formed cavity is of the same size as the initial binder particle. It is known that the binder will expand upon melting by 13.5% in volume, and it has been postulated that some contraction occurs when solid particles are immersed into the surface [46]. However, the model is not very sensitive to this parameter; e.g. the 13.5% volume contraction only causes a 5.2% difference in diameter. For the sake of simplification, and because the quantitative extent of such contraction as well as its dependencies on formulation or other variables are unknown, this is not taken into consideration.

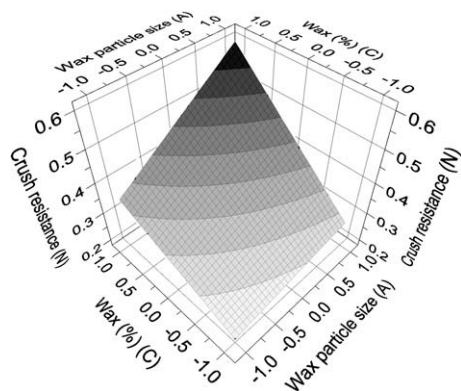


Fig. 5. Response surface plot of factors sieve fraction of microcrystalline wax (A) and fraction of microcrystalline wax in formulation (C) for the response pellet crush resistance; fraction of theophylline in solid particles (B): 42.5% (center point).

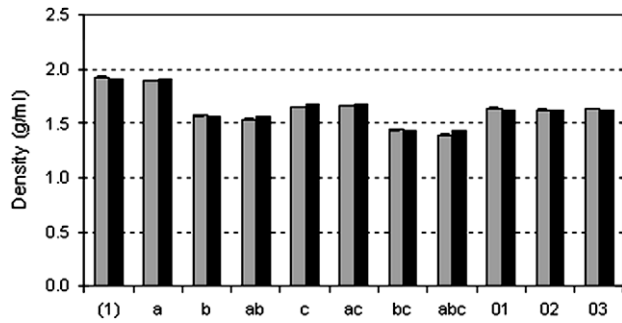


Fig. 6. ■: Pycnometric density of agglomerates, mean ± SD (n = 3); ■: calculated densities from formula and the pycnometric densities of the ingredients.

3. The composition of the matrix is identical to the composition of the formula, or, in other words, the liquid saturation has not reached the critical minimum value. This means that no relevant amount of fines remains from the process, which would lead to a selective lack of solid particles in the agglomerates, compared to the formula. For confirmation that this assumption is valid, the pycnometric densities of agglomerates are compared with the calculated density from the formula (Fig. 6). As the binder density is much lower than the density of the solid particles, a significant amount of fines

would result in lower agglomerate densities than theoretical. This is not the case; theoretical and actual densities are in very good accordance.

Based on these assumptions, the volume of the layer which is formed can be expressed as:

$$V_2 - V_1 = f \cdot V_1 \tag{2}$$

where V_1 and V_2 are the volumes of the binder particle and the resulting agglomerate, respectively; f is the ratio of total layer volume to binder volume, and is dependent on the volumes of the materials, and the total volume of air trapped in the layer:

$$f = \frac{V_{binder} + \sum V_{solid\ particles} + V_{air, layer}}{V_{binder}} \tag{3}$$

where V_{binder} and $V_{solid\ particles}$ are the respective total volumes in the formula, and are derived from the pycnometric densities of the substances, and their mass in the formula. $V_{air, layer}$ is the total air volume contained in the layer.

Arithmetic transformation of Eq. (2) and expression of volumes by using radii, assuming a perfect sphere, leads to

$$r_2 = r_1 \cdot \sqrt[3]{f + 1} \tag{4}$$

Using this equation, theoretical particle size distributions can be calculated for each batch. The comparison of theoretical versus actual size distributions is shown in Fig. 7.

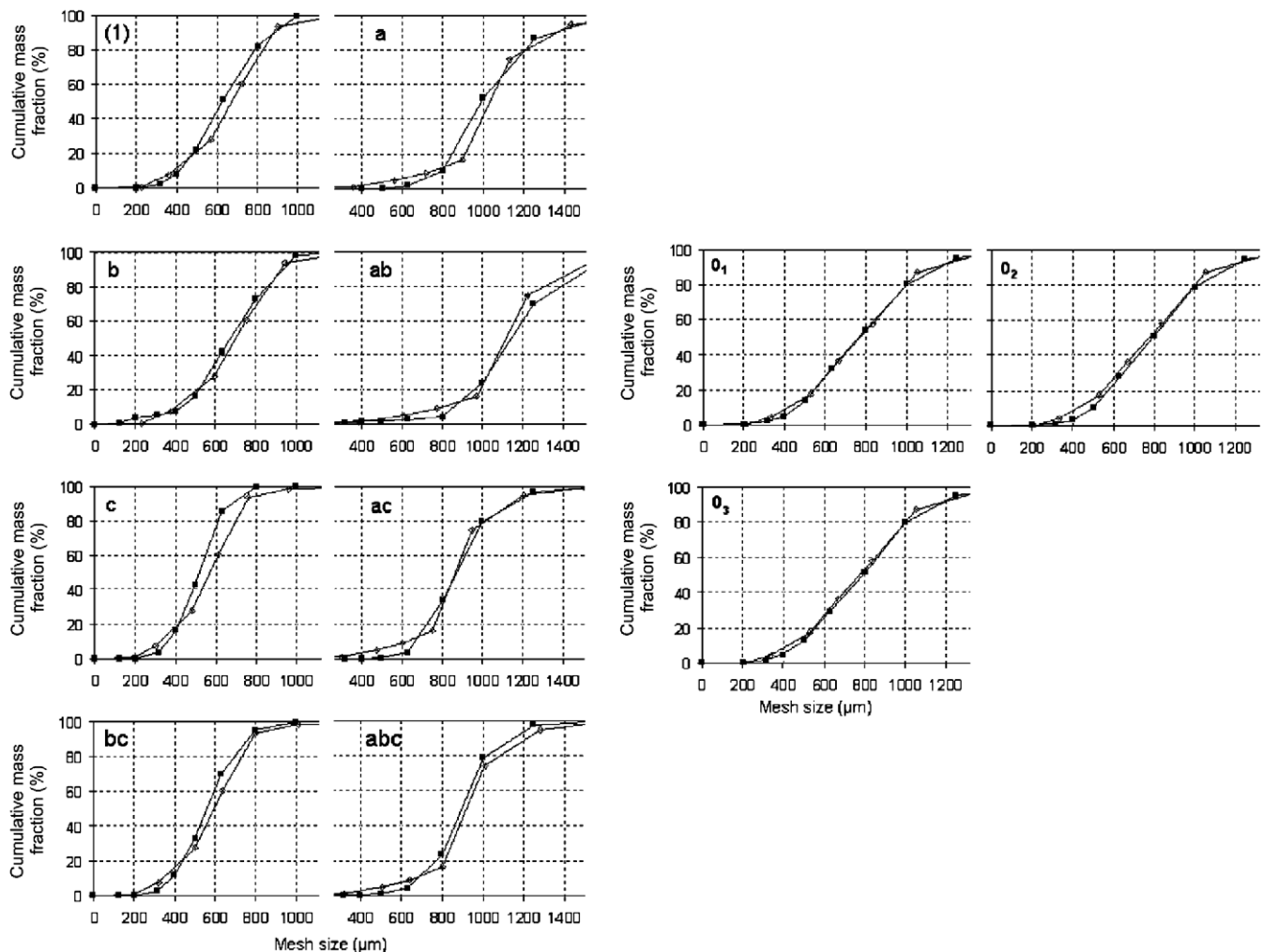


Fig. 7. Particle size distribution from sieve data (■, mean, n = 3) and from theoretical model (◇).

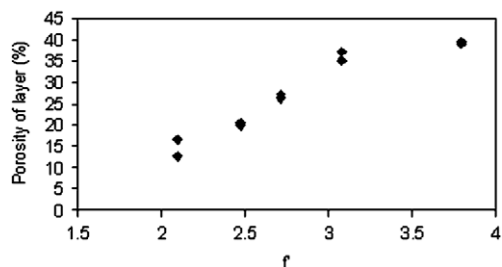


Fig. 8. Porosity of pellet layer versus f plot.

The data curves of theoretical and actual size distribution are in very good accordance for all tested batches; it is shown that this model is capable to predict particle sizes of agglomerates. Also, despite the simplification assumptions made for the model, the accuracy of agglomerate size prediction is very exact. The only parameters needed for such a prediction are the pycnometric densities of the components, the formula, and the porosity of the layer. The porosity is the only factor that is not known a priori; however, it is known to be dependent on the solid particles to binders ratio. By calculating the layer volume to binder volume ratio f without considering the air trapped in the layer after the following equation

$$f = \frac{V_{\text{binder}} + \sum V_{\text{solid particles}}}{V_{\text{binder}}} \quad (5)$$

and by referring to the correlation of f to porosity, as depicted in Fig. 8, a rough estimate can be made.

The model also explains why those batches with a lower binder amount exhibit a wider size distribution: based on the distribution of less binder per particle, a more porous layer is formed. This increases the ratio f , which leads to a wider size distribution.

A small, but systematic discrepancy between theoretical and actual data can be seen for the smallest particles of each batch, where more small agglomerates are predicted than actually exist. This is a hint that the smallest binder particles do not serve as nuclei, but are themselves layered onto the binder, or that the smallest binder particles stick to fluidized bed container walls or filters.

It has to be noted that this model is valid as long as all particles are bound, and no considerable amounts of fines remain; or, in other words, liquid saturation does not fall below the critical value under which no further layering can occur. From the experimental data, this is at least valid in the f range between 2.1 and 3.1.

5. Conclusion and outlook

The preparation of sustained release matrix pellets, using a melting procedure in a fluidized bed apparatus, was tested in a 2^3 full factorial design of experiments, using microcrystalline wax as lipophilic binder, theophylline as model drug and talc as additional matrix forming agent.

Nearly spherical pellets comprising a smooth, closed surface, could be obtained with the introduced method, exhibiting the hollow core typical for the immersion and layering mechanism.

The reproducibility at the center point, which was carried out three times, was very good concerning all responses.

The size of agglomerates is mainly dependent on the size of the binder particles, which serve as cores for pellet formation in molten state in the fluidized bed, small particles leading to small agglomerates, large particles leading to large agglomerates. A second influence variable is the volume of the solid particles in relation to the binder particles. This volume is a function of the amount of solid substances (drug and non-melttable excipients) in the formulation, and their respective densities. The more volume

of solid particles per binder particle is available, the larger agglomerates will result at the same initial droplet size.

The width of agglomerate size distribution is mainly dependent on the size distribution of the initial binder particles. Also a low proportion of binder in the formulation will cause a wider size distribution.

Dissolution times vary in a very wide range, resulting from the interplay between amount of drug in relation to the melttable matrix substance microcrystalline wax and the non-melttable matrix substance talc.

The change of binder particle size does not lead to a structural change of the matrix; both dissolution times and porosity are not significantly altered.

Agglomerate crush resistance is low due to the hollow core of the pellets. However, it is significantly increased if the volume fraction of microcrystalline wax in the matrix is high, which means that the matrix is mechanically better stabilized. Larger binder particles can also cause a better crush resistance for pellets at the same size, despite identical matrix composition. This phenomenon is not yet fully understood and offers the possibility for further optimization with melttable or non-melttable mechanical stabilizers.

Porosity is dependent on the binder to solid particles ratio; the more binder is available to bind a certain amount of solid particles, the more inter-particle voids are filled, which results in a lower porosity of the layer.

A theoretical model has been established to quantitatively explain agglomerate growth, and very good accordance of the full particle size distributions between predicted and actual values could be shown. On the basis of this model, it could be seen that the amount of solid particles bound by a primary particle/droplet is variable and is a function of the binder to solids volume ratio within the formulation; within the tested range of f air values between 2.1 and 3.1, all solid particles are bound, compensating the lower amount of available binder for low binder to solids ratios with increased porosity of the layer. This also leads to a widened agglomerate size distribution.

Acknowledgements

Glatt GmbH is gratefully acknowledged for providing the GPCG-1.

References

- [1] G. Abdelbary, P. Prinderre, C. Eouani, J. Joachim, J.P. Reynier, P. Piccerelle, The preparation of orally disintegrating tablets using a hydrophilic waxy binder, *Int. J. Pharm.* 278 (2004) 423–433.
- [2] B. Perissutti, F. Rubessa, M. Moneghini, D. Voinovich, Formulation design of carbamazepine fast-release tablets prepared by melt granulation technique, *Int. J. Pharm.* 256 (2003) 53–63.
- [3] J. Breitenbach, Melt extrusion: from process to drug delivery technology, *Eur. J. Pharm. Biopharm.* 54 (2002) 107–117.
- [4] J.L. Ford, M.H. Rubinstein, Formulation and ageing of tablets prepared from indomethacin-polyethylene glycol 6000 solid dispersions, *Pharm. Acta Helv.* 55 (1980) 1–7.
- [5] R. Kinget, R. Kemel, Preparation and properties of granulates containing solid dispersions, *Acta Pharm. Technol.* 31 (1985) 57–62.
- [6] N. Passerini, B. Albertini, M.L. González-Rodríguez, C. Cavallari, L. Rodriguez, Preparation and characterisation of ibuprofen-poloxamer 188 granules obtained by melt granulation, *Eur. J. Pharm. Sci.* 15 (2002) 71–78.
- [7] A. Seo, P. Holm, H.G. Kristensen, T. Schaefer, The preparation of agglomerates containing solid dispersions of diazepam by melt agglomeration in a high shear mixer, *Int. J. Pharm.* 259 (2003) 161–171.
- [8] D. Yang, R. Kulkarni, R.J. Behme, P.N. Kotiyani, Effect of the melt granulation technique on the dissolution characteristics of griseofulvin, *Int. J. Pharm.* 329 (2007) 72–80.
- [9] T. Vilhelmsen, H. Eliassen, T. Schaefer, Effect of a melt agglomeration process on agglomerates containing solid dispersions, *Int. J. Pharm.* 303 (2005) 132–142.
- [10] K. Ukita, T. Murakami, Preparation of essential oil loaded granule by melt granulation, *Drug Dev. Ind. Pharm.* 20 (1994) 901–992.
- [11] J. Bretkreutz, M. Bornhöft, F. Wöll, P. Kleinbudde, Pediatric drug formulations of sodium benzoate: I. Coated granules with a hydrophilic binder, *Eur. J. Pharm. Biopharm.* 56 (2003) 247–253.

- [12] J. Breitkreutz, F. El-Saleh, C. Kiera, P. Kleinebudde, W. Wiedey, Pediatric drug formulations of sodium benzoate: II. Coated granules with a lipophilic binder, *Eur. J. Pharm. Biopharm.* 56 (2003) 255–260.
- [13] R. Thies, P. Kleinebudde, Melt pelletisation of a hygroscopic drug in a high shear mixer – Part 1. Influence of process variables, *Int. J. Pharm.* 188 (1999) 131–143.
- [14] R. Thies, P. Kleinebudde, Melt pelletisation of a hygroscopic drug in a high shear mixer – Part 2. Mutual compensation of influence variables, *Eur. J. Pharm. Sci.* 10 (2000) 103–110.
- [15] R. Thies, P. Kleinebudde, Melt pelletization of a hygroscopic drug in a high shear mixer. Part 3. Effects of binder variation, *Chem. Pharm. Bull.* 49 (2001) 140–146.
- [16] F.M. Yanze, C. Duru, M. Jacob, A process to produce effervescent tablets: fluidized bed dryer melt granulation, *Drug Dev. Ind. Pharm.* 26 (2000) 1167–1176.
- [17] J. Hamdani, A.J. Moes, K. Amighi, Development and in vitro evaluation of a novel floating multiple unit dosage form obtained by melt pelletization, *Int. J. Pharm.* 322 (2006) 96–103.
- [18] P. Flanders, G.A. Dyer, D. Jordan, The Control of drug release from conventional melt granulation matrices, *Drug Dev. Ind. Pharm.* 13 (1987) 1001–1022.
- [19] H. Guirgis, B. Broegmann, A. Sakr, Hot melt technology – effect of manufacturing method on tablet characteristics, *Pharm. Ind.* 63 (2001) 499–507.
- [20] H. Heinemann, W. Rothe, Verfahren zur Granulierung von pulverförmigen Tablettenmassen, *Deutsches Patent* DT 2127683, 1975.
- [21] M. Kojima, H. Hakagami, Preparation of the controlled-release matrix tablets of theophylline with micronized low-substituted hydroxypropyl cellulose by a fluidized hot-melt granulation method, *STP Pharma Sci.* 11 (2001) 145–150.
- [22] H. Qiu, X. Mei, Formulation and evaluation of sustained-release pellets of ketoprofen by melt pelletization, *Zhongguo Yaoxue Zazhi* 41 (2006) 287–290.
- [23] M. Grassi, D. Voinovich, M. Moneghini, E. Franceschinis, B. Perissutti, J. Filipovic-Grcic, Preparation and evaluation of a melt pelletised paracetamol/stearic acid sustained release delivery system, *J. Control. Release* 88 (2003) 381–391.
- [24] J. Liu, F. Zhang, J.W. McGinity, Properties of lipophilic matrix tablets containing phenylpropanolamine hydrochloride prepared by hot-melt extrusion, *Eur. J. Pharm. Biopharm.* 52 (2001) 181–190.
- [25] C.M. McTaggart, J.A. Ganley, A. Sickmueller, S.E. Walker, The evaluation of formulation and processing conditions of a melt granulation process, *Int. J. Pharm.* 19 (1984) 139–148.
- [26] P. Schmidt, J. Prochazka, Über die Herstellung von Retardgranulaten durch Granulatformung, *Pharm. Ind.* 38 (1976) 921–926.
- [27] L.J. Thomsen, Prolonged release matrix pellets prepared by melt pelletization – IV. Drug content, drug particle size, and binder composition, *Pharm. Technol. Europe* 6 (1994) 19–24.
- [28] L.J. Thomsen, T. Schaefer, J.M. Sonnergaard, H.G. Kristensen, Prolonged release matrix pellets prepared by melt pelletization – I. Process variables, *Drug Dev. Ind. Pharm.* 19 (1993) 1867–1887.
- [29] G.J. Vergote, C. Vervaet, I. Van Driessche, S. Hoste, S. De Smedt, J. Demeester, R.A. Jain, S. Ruddy, J.P. Remon, An oral controlled release matrix pellet formulation containing nanocrystalline ketoprofen, *Int. J. Pharm.* 219 (2001) 81–87.
- [30] D. Voinovich, M. Moneghini, B. Perissutti, J. Filipovic-Grcic, I. Grabnar, Preparation in high-shear mixer of sustained-release pellets by melt pelletisation, *Int. J. Pharm.* 203 (2000) 235–244.
- [31] D. Voinovich, M. Moneghini, B. Perissutti, E. Franceschinis, Melt pelletization in high shear mixer using a hydrophobic melt binder: influence of some apparatus and process variables, *Eur. J. Pharm. Biopharm.* 52 (2001) 305–313.
- [32] F. Zhou, C. Vervaet, J.P. Remon, Matrix pellets based on the combination of waxes, starches and maltodextrins, *Int. J. Pharm.* 133 (2001) 155–160.
- [33] M. Kidokoro, K. Sasaki, Y. Haramiishi, N. Matahira, Effect of crystallization behavior of polyethylene glycol 6000 on the properties of granules prepared by fluidized hot-melt granulation (FHMG), *Chem. Pharm. Bull.* 51 (2003) 487–493.
- [34] K. Chansanroj, G. Betz, H. Leuenberger, A. Mitrejev, N. Sinchaipanid, Development of a multi-unit floating drug delivery system by hot melt coating technique with drug–lipid dispersion, *J. Drug Deliv. Sci. Technol.* 17 (2007) 333–338.
- [35] J. Goole, K. Amighi, F. Vanderbist, Evaluation and floating enhancement of levodopa sustained release floating minitables coated with insoluble acrylic polymer, *Drug Dev. Ind. Pharm.* 34 (2008) 827–833.
- [36] V.F. Patel, N.M. Patel, Influence of drug-to-lipid ratio & release modifier on dipyridamole release from floating lipid granules, *Drug Deliv. Technol.* 8 (2008) 22, 24, 26–27.
- [37] S.T. Prajapati, L.D. Patel, D.M. Patel, Formulation and in vitro evaluation of floating matrix tablets of domperidone: influence of combination of hydrophilic and hydrophobic matrix formers, *J. Pharm. Chem.* 2 (2008) 54–59.
- [38] J. Hamdani, J. Goole, A.J. Moes, K. Amighi, In vitro and in vivo evaluation of floating riboflavin pellets developed using the melt pelletization process, *Int. J. Pharm.* 323 (2006) 86–92.
- [39] T. Schaefer, C. Mathiesen, Melt pelletization in a high shear mixer. IX. Effects of binder particle size, *Int. J. Pharm.* 139 (1996) 139–148.
- [40] T. Schaefer, Growth mechanisms in melt agglomeration in high shear mixers, *Powder Technol.* 117 (2001) 68–82.
- [41] T. Abberger, Influence of binder properties, method of addition, powder type and operating conditions on fluid-bed melt granulation and resulting tablet properties, *Pharmazie* 56 (2001) 949–952.
- [42] T. Abberger, J.O. Henck, Kornbildungsmechanismen bei der Schmelzgranulierung in der Wirbelschicht und ihre Auswirkungen auf die Tablettierung, *Pharmazie* 55 (2000) 521–526.
- [43] T. Abberger, A. Seo, T. Schaefer, The effect of droplet size and powder particle size on the mechanisms of nucleation and growth in fluid bed melt agglomeration, *Int. J. Pharm.* 249 (2002) 185–197.
- [44] A. Seo, P. Holm, T. Schaefer, Effects of droplet size and type of binder on the agglomerate growth mechanisms by melt agglomeration in a fluidized bed, *Eur. J. Pharm. Sci.* 16 (2002) 95–105.
- [45] Y. Haramiishi, Y. Kitazawa, M. Sakai, K. Kataoka, Study on fluidized melt-granulation. I. Examination of the factors on the granulation, *Yakuga. Zasshi* 111 (1991) 515–523.
- [46] M.A. Ansari, F. Stepanek, Formation of hollow core granules by fluid bed in situ melt granulation: modelling and experiments, *Int. J. Pharm.* 321 (2006) 108–116.
- [47] C.M. Prasad, G.P. Srivastava, Study of some sustained release granulations of aspirin, *Ind. J. Hosp. Pharm.* 8 (1971).
- [48] L. Starha, M. Chalabala, Die höheren Fettsäuren und ihre Glycerinester in den peroralen Arzneien mit prolongierter Wirkung, *Acta Fac. Pharm.* 21 (1972) 171–194.
- [49] F. Stanislaus, H.J. Huber, Different drug delivery systems in bioavailability studies, in: B.W. Müller (Ed.), *Controlled Drug Release*, Wissenschaftliche Verlagsgesellschaft, Stuttgart, 1987, pp. 56–68.
- [50] L.J. Thomsen, T. Schaefer, H.G. Kristensen, Prolonged release matrix pellets prepared by melt pelletization – II. Hydrophobic substances as melttable binders, *Drug Dev. Ind. Pharm.* 20 (1994) 1179–1197.
- [51] T. Vilhelmsen, J. Kristensen, T. Schaefer, Melt pelletization with polyethylene glycol in a rotary processor, *Int. J. Pharm.* 275 (2004) 141–153.
- [52] T. Maejima, T. Osawa, K. Nakajima, M. Kobayashi, Preparation of spherical beads without any use of solvents by a novel tumbling melt granulation (TMG) method, *Chem. Pharm. Bull.* 45 (1997) 518–524.
- [53] C. Reitz, P. Kleinebudde, Spherization of solid lipid extrudates, *Powder Technol.* 189 (2009) 238–244.
- [54] P. Kleinebudde, K. Knop, Direct pelletization of pharmaceutical pellets in fluid-bed processes, in: A.D. Salman, M.J. Hounslow, J.P.K. Seville (Eds.), *Granulation*, Elsevier, Amsterdam, London, 2007, pp. 779–814.
- [55] B.C. Lippold, A. Ohm, Beeinflussung der Benetzbarkeit von Arzneistoffpulvern durch Tenside, *Polymere und Magensaft*, *Acta Pharm. Technol.* 32 (1986) 20–25.
- [56] M. Thommes, *Analyse der Porenstruktur von Dragees*, *LaborPraxis* (2000).
- [57] A. Pauli, Herstellung von Retardmatrixpellets durch Schmelzagglomeration in der Wirbelschicht, *Cuvillier Verlag*, Göttingen, 2005.
- [58] B.C. Lippold, *Biopharmazie – Eine Einführung zu den wichtigsten Arzneiformen*, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, 1984.
- [59] S.H. Schaaafma, P. Vonk, P. Segers, N.W.F. Kossen, Description of agglomerate growth, *Powder Technol.* 97 (1997) 183–190.