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Influence of binder properties, method of addition, powder type and operating conditions on fluid-bed melt granulation and resulting tablet properties

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The aim of the study was to investigate melt granulation in a laboratory scale fluid-bed granulator with respect to granule growth, granule properties and resulting tablet properties. The parameters investigated were method of addition of PEG (spray-on or addition as flakes), binder concentration, PEG type (3000, 4000 and 6000, sprayed-on), size (PEG 4000, added as three different sized flakes), powder type (two different sized lactose types and corn starch) and operating conditions (volume air flow and heating temperature). Addition of binder as flakes led to layering as a growth mechanism when the size of the flakes was high. Coalescence occurred when the size was low. Coalescence also occurred when spraying was the method of addition. Due to the greater viscosity of the PEG 6000 melt it produced bigger granules than 3000 or 4000. The influence of volume air flow was moderate and the influence of heating temperature in the range of 70–90 °C was very low with both methods of addition. The disintegration time of tablets from granules where PEG was added as flakes was shorter than from granules where PEG was sprayed-on. The latter method of binder addition led to tablets which did not disintegrate but eroded. This was apparently caused by formation of a binder matrix, which could not be destroyed by the disintegrant.

1. Introduction

Conventionally, granulation is performed as wet granulation, typically with aqueous solutions of binders. Wet granulation is well established. The two most important methods of wet granulation currently used in the pharmaceutical industry are fluid-bed granulation and granulation in high-shear mixers with subsequent fluid-bed drying [1]. Sometimes, wet granulation can cause problems. On the one hand, moisture can be incompatible with components of the formulation. On the other hand, the drying step has been claimed to be the time controlling step of a wet granulation or at least to be time consuming [2]. Therefore, a recent trend in granulating is to develop methods which do not need moisture or solvents. In addition to roller compaction, melt granulation is one such method.

Melt granulation with high-shear mixers has been investigated since 1990 mainly by Schaefer et al. [3]. Only a few papers deal with fluid-bed melt granulation [4–10].

According to Schaefer and Mathiesen [11], two different mechanisms of granule formation may be involved in melt granulation, depending on the binder particle size and the viscosity of the molten binder. Distribution of the molten binder on the surface of the solid particles will occur when the molten binder droplets are not larger than the solid particles. This leads to subsequent growth by coalescence. Immersion of the solid particles in the molten binder will occur when the molten binder droplets are larger than the solid particles. During melt granulation in high shear mixers, both mechanisms will be active simultaneously, because the binder droplets are comminuted by the high shearing forces, but normally one of the two mechanisms will be dominant.

Abberger and Henck [10] demonstrated that both these mechanisms occurred also in fluid-bed melt granulation of lactose and polyethylene glycol (PEG) 4000.

The study aimed to investigate the effects of method of addition of PEG, binder concentration, size, powder type and operating conditions (volume air flow and heating temperature) on granule growth with both mechanisms of granule formation, coalescence and layering. A further objective was to investigate the properties of the resulting tablets.

2. Investigations, results and discussion

2.1. Binder addition by spray-on

Fig. 1 shows the effect of PEG type and mass fraction when sprayed onto the powder bed on the median granule diameter d_{50} . It also shows the effect of initial powder size. 13% was the smallest amount of PEG which allowed granulation of GranuLac 200 without problems caused by filter clogging. 25.9% was the highest amount which could be added before defluidization took place. The same maximum concentration before uncontrollable growth took place was found by Schaefer [12], when he was granulating lactose with PEG 3000 in a high shear mixer.

As expected, the median diameter increased with increasing amount of PEG at all three types. With each PEG concentration, the highest median diameters were attained with PEG 6000. According to Ennis et al. [13], higher viscosity gives an increased potential for growth.

Schaefer and Mathiesen [14] found some median diameters were greater with PEG 3000 than with PEG 6000.

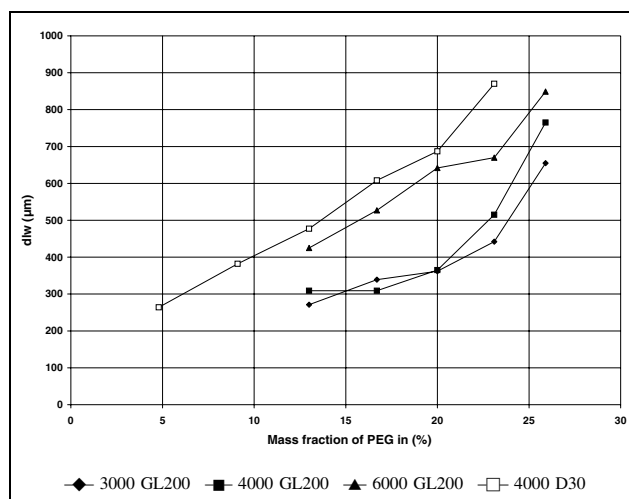


Fig. 1: Effect on the median diameter of granules of lactose type, PEG type and mass fraction when sprayed onto the powder bed

They attributed this to poorer distribution of the higher viscosity PEG. Despite the low shear forces in a fluid-bed, the distribution of binder in these experiments was facilitated by a high PEG temperature of 90 °C in combination with atomization. Schaefer and Mathiesen [15] investigated the effect of product temperature on granule growth of lactose and PEG 3000 or 6000. They found slower growth at the higher temperature of 120 °C than at 50 °C, due to the effect of temperature on viscosity.

It can be concluded, that the theory of Ennis is valid, when the binder is adequately distributed.

The gradient of the growth curves with PEG 3000 and 4000 in the range from 20 to 25.9% is high, and markedly higher than with PEG 6000.

Schaefer [12] found exponential growth which led to a doubling of the mean diameter within a small range of PEG 3000 concentration from about 22 to 25%.

Due to the larger particle size of lactose D 30, the resulting granule size was greater than with GranuLac 200. With D 30, granulation was feasible at a lower PEG concentration of 4.8%, and this can be explained by the larger size of the starting powder, which gave fewer problems caused by filter clogging.

The granule properties, poured volume (V_0), tapped volume (V_t), compressibility (C) and angle of repose (α) were investigated. Despite the differences in granule size, the differences in compressibility were small. The angle of repose was greatest at the lowest concentration with each PEG type due to a higher proportion of particles smaller than 100 μm . Variation of air flow volume in the range of 40–60 m^3/h with 20% PEG 4000 had only minor influence on granule size.

Variation of the temperature of the fluidizing air in the comparatively small range of 70–90 °C with 20% PEG 4000 had no influence.

Table 1 shows, that crushing strength and disintegration time increased with increasing concentration of PEG 4000, as expected. The differences between the two mechanisms of granule formation will be discussed below.

2.2. Addition of binder as flakes

PEG 4000 was added as flakes in three different sizes (Table 2) and increasing concentrations from 9.1 up to 28.6%.

Fig. 2 shows the granule growth with lactose GranuLac 200 and increasing PEG concentration with the three different sizes of PEG flakes and with corn starch.

With the coarse flakes, the median granule diameter reached a maximum with 23% PEG, and with greater con-

centrations it declined. Abberger and Henck [10] were able to show that this behaviour occurs when layering is the growth mechanism.

Up to 23%, the median diameter of granules with the coarse flakes was twice that of granules where PEG 4000 was added as an atomized melt. This is in accordance with previous findings [10].

The differences between medium and coarse flakes were comparatively small.

With the fine flakes, defluidization occurred with concentrations greater than 23%.

With the fine flakes, the growth behaviour and the median diameters attained were like those when PEG was sprayed-on; they were significantly smaller than with the coarse or medium sized flakes. This finding can be explained by the fine flakes melting rapidly and behaving like spray droplets; this is in accordance with Schaefer and Mathiesen [11], who investigated the effect of PEG type and size in a high-shear mixer. They found significantly smaller granule sizes when PEG 3000 or 6000 were added as fine powder, than when they were added as coarse powder or flakes. The differences in granule size between coarse powder and flakes were also small.

These authors [11] stated, that the viscosity of the molten binder is one of the controlling factors for the occurrence of one or other of the two mechanisms. Due to the low shear forces in an air suspension, the layering mechanism can occur with lower viscosities of molten binder than in a high shear mixer.

With corn starch, granulation was feasible, when 30% PEG < 100 μm were added to the medium flakes. Without this additive, it was not feasible due to filter clogging. The fine PEG melted rapidly and bound considerable amounts of corn starch, which would otherwise have led to filter clogging. Investigating granules of the fraction 1250–2000 μm , (PEG concentration 16.7%) were found that the granules have a nearly spherical shape and smooth surfaces.

Table 3 shows the poured and tapped volume, compressibility and angle of repose. As in the series where PEG was sprayed-on, the flowability with the two lowest concentrations was quite poor, due to the amount of material smaller than 100 μm .

Photomicrographs give evidence for the postulated growth mechanism, a characteristic cavity in the interior of the cut granule corresponding to the PEG flake which acted as a seed. Due to the low shear forces in a fluid-bed, this cavity remained throughout the granulation.

Table 1: Properties of tablets (GranuLac 200, PEG 4000)

	Mass fraction of PEG (%)						
	9.1	13.0	16.7	20.0	23.1	25.9	28.6
Spray-on							
Crushing strength (N)		102 (6)	125 (4)	135 (3)	141 (3)	145 (6)	
Disintegration time (min)		5'17" (23")	9'35" (30")	11'14" (10")	12'16" (13")	12'52" (11")	
Fine flakes							
Crushing strength (N)	87 (7)		113(4)		135 (4)		
Disintegration time (min)	2'26" (5")		6'17" (7")		8'42" (13")		
Medium flakes							
Crushing strength (N)	54 (2)	96 (7)	118 (9)	133 (7)	128 (2)	131 (11)	133 (6)
Disintegration time (min)	1'01" (15")	5'39" (49")	7'43" (45")	8'31" (7")	8'26" (29")	9'22" (21")	9'44" (24")
Coarse flakes							
Crushing strength (N)		73 (5)		127 (7)		131 (3)	
Disintegration time (min)		2'46" (32")		7'23" (25")		8'54" (5")	

Table 2: Particle size distribution of PEG 4000 flakes

Fine (d_{1w} 108 μm)	Upper bound (μm)	100	125	160	250	315		
	Rel. amount (%)	50.7	12.1	16.6	16.3	4.3		
Medium (d_{1w} 390 μm)	Upper bound (μm)	100	200	250	315	500	800	1000
	Rel. amount (%)	10.4	11.7	5.4	10.5	34.8	24.4	2.8
Coarse (d_{1w} 549 μm)	Upper bound (μm)	100	200	315	500	800	1250	
	Rel. amount (%)	2.4	4.6	7.3	36.1	35.6	14.0	

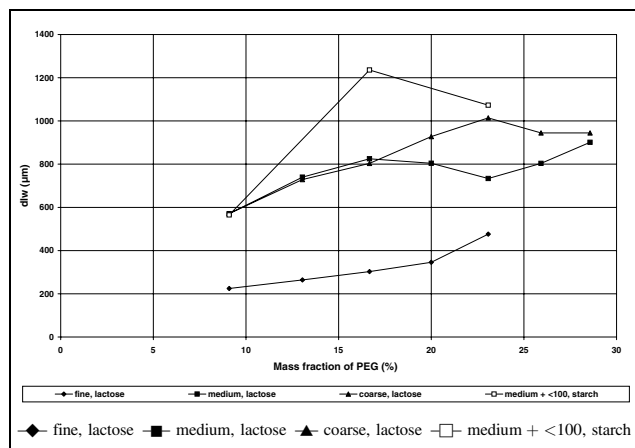


Fig. 2: Effect on the median diameter of granules of powder type, PEG 4000 size and mass fraction when added as flakes

The effect of volume air flow in the range of 40–80 m³/h was tested at a mass fraction of 20% of the medium sized flakes. The median diameter increased moderately with volume air flow. It is assumed, that more liquid PEG was squeezed out from the interior of the granule, leading to a greater area of the granule surface which was sticky. In fluid-bed wet granulation, this effect has been described previously [16].

Again, variation of heating temperature in the range from 70 to 90 °C had no effect.

Table 3: Properties of granules (PEG added as flakes)

Powder type, PEG size	Mass fraction of PEG in %						
	9.1	13.0	16.7	20.0	23.1	25.9	28.6
Lactose, fine							
V ₀ (ml/100 g)	165	173	175	170	156		
V _t (ml/100 g)	145	153	155	151	139		
C (%)	12	12	11	11	11		
α (°)	43	41	40	37	35		
Lactose, medium							
V ₀ (ml/100 g)	144	151	153	156	153	155	152
V _t (ml/100 g)	121	133	136	141	138	141	137
C (%)	16	12	11	10	10	9	10
α (°)	52	45	39	37	38	35	35
Lactose, coarse							
V ₀ (ml/100 g)	146	141	144	156	161	157	160
V _t (ml/100 g)	117	121	125	139	147	142	144
C (%)	20	15	13	11	9	10	10
α (°)	53	46	45	39	36	36	35
Corn starch, medium + <100							
V ₀ (ml/100 g)	170		164		133		
V _t (ml/100 g)	154		152		120		
C (%)	10		7		10		
α (°)	41		31		37		

Table 1 shows the crushing strength and the dissolution time in relation to PEG particle size and concentration. The values show the grand means, while the values in brackets show the standard deviation s_{in} within the two batches [17]. Crushing strength and dissolution time increased with increasing PEG concentration, as expected. The differences between the two mechanisms were similar to those in previous work [10]. Disintegration time tended to be shorter with increasing flake size for each concentration.

Scott et al. [18] investigated the two mechanisms of granule growth described by Schaefer and Mathiesen [11] in a high-shear mixer with PEG 1500 and calcium carbonate. They found it likely that pouring molten PEG on a powder batch leads to nucleation via the immersion mechanism and addition of PEG as flakes to nucleation via the distribution mechanism. Droplet size has to be considered

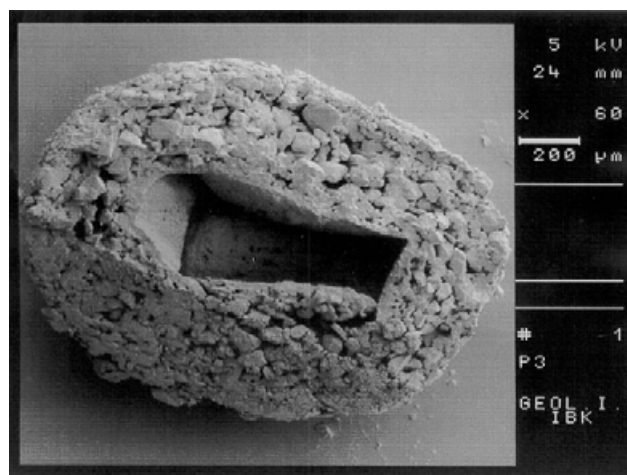


Fig. 3: Cut granule from the layering mechanism after 11' granulation duration

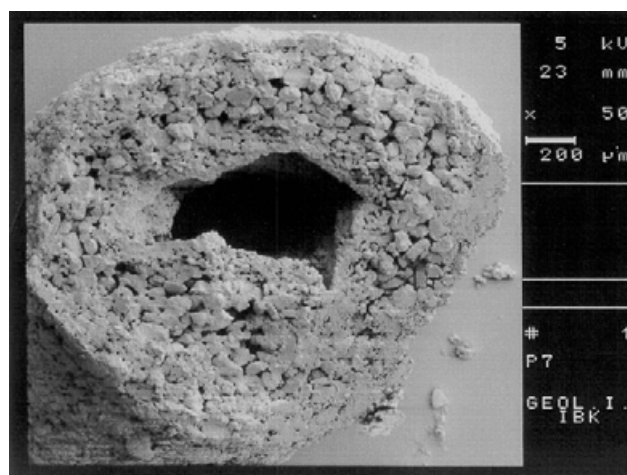


Fig. 4: Cut granule from the layering mechanism after 19'30'' granulation duration

in determining whether addition of molten PEG leads to the immersion or the distribution mechanism. In previous work, [10] it was shown by thermomicroscopy, that spraying molten PEG onto a powder led to the distribution mechanism.

Scott et al. [18] postulated, that the Schaefer and Mathiesen immersion mechanism leads to a very dense system containing little air. SEM micrographs indicate that this postulation has to be modified for fluid-bed granulation. Only the wall of the granules was very dense. In conclusion, it seems likely that the effect of adding meltable binders as flakes is strongly influenced by the granulation method, whether fluid-bed or high shear granulation.

3 Experimental

3.1. Materials

Starting materials were lactose Ph.Eur. grade GranuLac 200 (Meggler, Wasserburg, Germany) with a $d_{50,3}$ of 38 μm [19], lactose Ph.Eur. grade D 30 (Meggler, Wasserburg, Germany) with a $d_{50,3}$ of about 115 μm [19] and corn starch Maisita 21005 (Avena, Wien, Austria) with a $d_{50,3}$ of 12 μm and a geometric standard deviation s_g of 2.3 [20]. PEG 3000 (Merck-Schuchardt, Hohenbrunn, Germany), 4000 Ph.Eur. grade (Brenntag, Wien, Austria) and 6000 (Merck-Schuchardt, Hohenbrunn, Germany) were used as meltable binders. The binders were characterised by Differential Scanning Calorimetry (DSC) with a DSC-7 and Pyris software for Windows NT (Perkin-Elmer, Norwalk, Ct., U.S.A.) using perforated aluminum samplepans (25 μl). Sample masses for quantitative analysis were 1–3 (± 0.0005) mg (Ultramicroscales UM3, Mettler, Greifensee, Switzerland). Nitrogen 99.990% (20 ml min^{-1}) was used as purge gas. Calibration of the temperature axis was carried out with benzophenone (mp 48.0 °C) and caffeine (mp 236.2 °C). The heating rate was 10 K min^{-1} . The onset of the melting peak for PEG 3000 was 57.9 °C, for 4000 58.4 °C and for 6000 59.7 °C (mean values of three determinations for each type). PEG 4000 flakes as supplied were comminuted to three different sizes, referred to as fine, medium and coarse. The resulting size distributions were determined by sieve analysis, and d_{1w} was calculated according to DIN 66141. Table 2 shows the size distributions of the three batches. Croscarmellose sodium NF grade Ac-Di-Sol was supplied by FMC Europe (Brussel, Belgium).

3.2. Equipment

An instrumented [21] fluid-bed granulator STREA-1 (Aeromatic-Fieldler, Bubendorf, Switzerland) was employed in the experiments.

3.3. Granulating procedure

Each granulation was performed in duplicate. The individual values are the mean of two experiments.

3.3.1. Binder addition by spray-on

Batch size: 400 g lactose, increasing amounts of PEG from 20–140 g; temperature of PEG: 90 °C; spray rate: 16.1 g/min (s.d. 0.4 g/min); atomizing air pressure: 0.8 bar; nozzle diameter: 1.1 mm; heating temperature: 90 °C; volume air flow: 30–40 m^3/h , increased to 50 m^3/h after end of spraying. At the beginning of spraying, the temperature in the vessel reached about 44 °C, and at the end it was 53–63 °C. The product was cooled to about 40 °C in the vessel, then taken out and cooled to room temperature on trays.

3.3.2. Addition of binder as flakes

Batch size: 400 g lactose or corn starch, increasing amounts of PEG from 40–160 g; heating temperature: 90 °C; volume air flow: 30 m^3/h in the mixing phase (8–11 min) to avoid filter clogging. At the end of this phase, the temperature in the vessel reached about 58–59 °C. Then air flow volume was increased to 50 m^3/h for 5 min. At the end of this period, the temperature in the vessel reached about 65–70 °C. In the subsequent cooling phase, volume air flow was increased to 60 m^3/h . When the temperature in the vessel was below 48 °C, volume air flow was decreased to 40 m^3/h . When the temperature fell to 38 °C, the process was stopped. The product was allowed to cool to room temperature on trays.

3.4. Granule characterization

3.4.1. Size distribution

The size distribution was determined by sieve analysis, and d_{1w} was calculated according to DIN 66141.

Batch size: 300.0 g; sieve machine: S + S (Retsch, Haan, Germany); sieves: 100, 200, 315, 500, 800, 1250, 2000 and 3150 μm according to DIN 4188; amplitude: 65; operating time: 12 min for the four coarsest sieves, 25 min for the four finer ones.

3.4.2. Poured and tapped volume, compressibility

Poured and tapped volume were determined using a STAV 2003 tapping apparatus (Engelsmann, Ludwigshafen, Germany). 100.0 g were tapped 1000 times. Each result is the mean of two determinations. Compressibility was calculated according to Schwartz et al. [22].

3.4.3. Angle of repose

The angle of repose was measured according to Pilpel [23]. Each result is the mean of five determinations.

3.4.4. Scanning electron microscopy

Micrographs were taken using a DSM 940A (Zeiss, Oberkochen, Germany) after sputtering by a Polaron E5100. with gold/palladium.

3.5. Tableting

The granules <2000 μm were mixed with 3% croscarmellose-sodium NF using a Turbula-mixer (Bachofen, Basel, Switzerland) at 26 min^{-1} for 20 min.

Press: PW 20 hydraulic press (Weber, Remshalden, Germany); die: 13 mm (Specac, Kent, United Kingdom); load cell: C 9 (Hottinger-Baldwin, Darmstadt, Germany); amplifier: MVD 2405 (Hottinger-Baldwin, Darmstadt, Germany); tablet mass: 500 mg (± 5 mg); pressing force 10 kN (± 0.5 kN). After 24 h aging, crushing strength was tested with 6 tablets (Schleuniger crushing strength tester) and disintegration time was tested according to Ph.Eur.

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