Investigation of a 2-Step Agglomeration Process Performed in a Rotary Processor Using Polyethylene Glycol Solutions as the Primary Binder Liquid

Submitted: March 8, 2006; Accepted: June 11, 2006; Published: October 27, 2006

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ABSTRACT

The purpose of this research was to investigate the use of polyethylene glycol (PEG) solutions as the primary binder liquid in a 2-step agglomeration process performed in a rotary processor and characterize the resulting granules and their tableting characteristics. This was done by granulation of binary mixtures of microcrystalline cellulose (MCC) and either lactose, calcium phosphate, acetaminophen, or theophylline, in a 1:3 ratio, using a 50% (wt/wt) aqueous solution of PEG and water as the binder liquid. Formulations containing lactose were agglomerated using 5 different amounts of the PEG binder solution, giving rise to a PEG content in the range of 6% to 43% (wt/wt). The process outcome was characterized according to adhesion, yield, and water requirement, and the prepared granules were characterized according to size, size distribution, and flow properties as well as tableting properties. The agglomeration of all mixtures resulted in high yields of free-flowing agglomerates and gave rise to good reproducibility of the investigated agglomerate characteristics. The process allowed for the incorporation of 42.5% (wt/wt) PEG, which is higher than the percentage of PEG reported for other equipment. Tablets of sufficient strength could be prepared with all investigated excipients using 20% wt/wt PEG; higher PEG contents gave rise to adhesion and prolonged disintegration. In conclusion, agglomeration in a torque-controlled rotary processor using solutions of PEG as the primary binder liquid was found to be a robust process, suitable for the incorporation of high contents of PEG and/or drug compounds.

KEYWORDS: rotary processor, direct agglomeration, torque measurement, PEG binder liquid.

INTRODUCTION

In the present study, the use of aqueous solutions of polyethylene glycol (PEG), in high concentrations, for agglomeration in a rotary processor was investigated to determine the feasibility of the process and the characteristics of the prepared agglomerates.

The main application of PEG in pharmaceutical agglomeration processes has been as a meltable binder in melt agglomeration. Melt agglomeration is a simple agglomeration process where powder particles are combined to form larger particles with a meltable binder and sufficient mechanical agitation.

Obvious advantages of melt agglomeration compared with the traditional wet granulation are that, since no water is applied, no subsequent drying of the prepared agglomerates is needed, and that moisture-sensitive drugs and excipients can be applied. Furthermore, agglomerates containing solid dispersions of drugs with low aqueous solubility, giving rise to increased dissolution rates, can be prepared by melt agglomeration.[1,2] A disadvantage of melt agglomeration is the elevated equipment temperature of 75 to 120°C needed, which can make it difficult to achieve a sufficient and reproducible temperature control, and can create a burn risk for the operator. Furthermore, if the melted binder is sprayed on during the process, care must be taken to avoid clogging of the nozzle.

The other binders (besides PEG) typically used in melt agglomeration are glycerides, fatty acids, or waxes,[3] all with a melting point in the range of 50 to 100°C. The amount of meltable binder that can be incorporated into the agglomerates during melt agglomeration depends on the intragranular voids and thus on the densification of the agglomerates. Higher shearing forces will result in higher densification and lower maximum binder concentration. A high shear mixer has most often been applied in melt agglomeration, but other equipment (eg, coating pans,[4] blenders,[5] fluidized bed granulators)[6] has also been used. The maximum amount of binder that can be applied has been reported to be ~22% in a high shear mixer[7] and 30% in a fluid bed granulator.[6] Exceeding the maximum concentration leads to excessive adhesion and uncontrolled agglomerate growth.[8]

Recently, Vilhelmsen et al[8] found that the rotary processor was a good alternative to high shear mixers for melt agglomeration. The maximum incorporable amount of meltable binder was found to be ~28%, and the melt agglomeration

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process was simplified because of the possibility of faster cooling in the rotary processor than in the high shear mixer.[8] The rotary processor is basically a fluidized bed granulator equipped with a rotating friction bottom plate that increases the agitation of the powder bed. The equipment has, because of the unique combination of centrifugal, fluidizing, and gravitational forces, mostly been used for direct wet pelletization, as reviewed by Gu et al.[9] Excellent control of the agglomerate size has been reported for wet pelletization in the rotary processor via the use of the torque of the friction plate as the end point detection method,[10,11] but this was not achieved for melt agglomeration in the rotary processor.[8]

Because of the high water solubility of the smaller PEG grades, solutions of high concentration can be prepared. Aqueous solutions of PEG 6000 in high concentration were used successfully as the granulation liquid in a study of the effect of granulation methods on the loose density and compactability of granules.[12] Based on these findings and the literature published on melt agglomeration in rotary processors, it might be possible to prepare agglomerates with high contents of PEG without the use of elevated temperatures in a rotary processor. When suitable process conditions are used, the dissolved PEG binder will solidify in the rotary processor shortly after atomization because of the evaporation of water. This will prevent agglomerate growth by coalescence and thus give rise to a controlled nucleation by immersion of particles in the droplets and a slow agglomerate growth by distribution of PEG on the formed nuclei. After the addition of the PEG, subsequent increase of temperature or addition of water would lubricate the surface of the formed agglomerates and possibly lead to agglomerate growth by coalescence as well as smoothing of the surface and rounding of the shape of the agglomerate.

To test this hypothesis, binary mixtures of lactose and microcrystalline cellulose (MCC) were agglomerated in a rotary processor by a 2-step process in which different amounts of a 50% (wt/wt) aqueous PEG binder solution were applied as the primary binder liquid and water was applied as the secondary binder liquid. The water addition was discontinued once the torque of the friction plate had increased to the desired level (0.15 Nm). Furthermore, for 1 concentration of PEG, 3 other excipients, calcium phosphate, theophylline, and acetaminophen, were applied to investigate the effect of filler/drug properties. The process was characterized according to the amount of water needed for agglomerate growth to occur, the amount of adhesion, and the process yield. The agglomerates were characterized according to flowability, density, agglomerate size, and size distribution; and tablets prepared from the agglomerates were characterized by crushing strength, disintegration time, and uniformity of mass.

Materials and Methods

Materials

MCC (Avicel, type PH101, FMC International, Cork, Ireland), α-lactose monohydrate (Pharmatose type 200M, DMV International, Veghel, The Netherlands), acetaminophen and theophylline (BASF, Ludwigshafen, Germany), calcium phosphate (calcium hydrogen phosphate dihydrate), and PEG (PEG-6000, Clariant GMBH, Gendorf, Germany) were used as starting materials. Solutions of PEG and purified water were used as binder liquids. All materials were of European Pharmacopoeia[13] grade, as stated by the suppliers.

Agglomeration Procedure

A rotary processor (Glatt GPCG-1.1, Glatt GMBH, Binzen, Germany) equipped with a cross-hatched friction plate pattern was used for all the experiments. Temperature and flow rate of the fluidizing air were set to 40°C and 90 m^3/h, respectively, in all experiments. The starting materials (600 g) were mixed manually, sieved through a 0.5-mm sieve, and loaded into the equipment, which had been preheated by running empty for 12 minutes. After the fluidizing air flow was initiated, the air gap pressure difference was set to 2.5 kPa by elevating the friction plate, and the rotation of the friction plate was started and set to 900 rpm. The preweighed amount of PEG binder liquid was then sprayed tangentially into the moving powder at 30 g/min, using a pneumatic atomizer and a 1.0-bar atomizing air pressure. The nozzle was equipped with a 1.0-mm tip orifice and a 3-mm air dome spacer ring. Following the addition of the PEG binder liquid, purified water was added at 30 g/min until a 0.15-Nm increase in the torque of the friction plate was reached (computed as the difference between the current torque value and the minimum torque value, as previously described by Kristensen et al[10]). The process was continued for 3 minutes of wet massing and drying, and the prepared agglomerates were removed from the rotary processor and stored at room temperature in open containers.

Characterization

Starting Materials

The size distribution by volume of the starting materials was determined in triplicate by a Malvern 2601Lc laser diffraction particle sizer (Malvern Instruments, Malvern, UK), and the median particle diameter and the span were calculated. The span is defined as the difference between the diameters at the 90 and the 10 percentage points relative to the median diameter.

The pycnometric densities of the starting materials were determined by an AccuPyc 1330 gas displacement pycnometer (Micromeritics, Norcross, GA) using helium purge

(n = 7). The poured and tapped densities were determined in duplicate using a European Pharmacopoeia[13] test for apparent volume, and the Carr's flowability index was calculated as previously described.[14]

Binder Liquid

The shear viscosity of the PEG binder solution was measured using a Rotovisco RV20 (Haake, Karlsruhe, Germany) as previously described.[15] The droplet sizes of the binder liquid and of water were determined using a Malvern 2600C particle sizer (Malvern Instruments) equipped with a 100-mm lens. The determinations were performed in duplicate as previously described.[16]

Agglomeration

The loss of material due to adhesion to the friction plate and the product chamber wall during each experiment was determined as the dry mass of the removable agglomerates relative to the mass of the applied starting materials. The yield was determined as the mass of the prepared agglomerates that could pass a 2000-μm sieve relative to the mass of the starting materials.

The size distribution of the granule fraction that had passed through a 2800-μm sieve was estimated by sieve analysis of a sample of ~75 g drawn from the entire batch using a Laborette 27 automatic rotary cone sample divider (Fritsch, Mainbernheim, Germany). Twelve ASTM standard sieves (Retsch, Haan, Germany) in the range of 180 to 2800 μm were vibrated for 10 minutes by a Fritsch analysette 3 vibrator (Fritsch) using an 8-mm amplitude. The granule size distributions were in good agreement with the log-normal distribution. Consequently, the mean granule size was described by the geometric weight mean diameter (d_{gw}) and the size distribution by the geometric standard deviation (s_g).

The poured and tapped densities were determined using a European Pharmacopoeia[13] test for apparent volume, and the Carr's flowability index was calculated as previously described.[14] Furthermore, the flowability of the prepared agglomerates was determined as described in the *European Pharmacopoeia*,[13] using a 10-mm outflow nozzle.

The shape and the surface structure were investigated using a scanning electron microscope (SEM) (JSM 5200, Jeol, Tokyo, Japan).

The agglomerates (<2000 μm) were, without further processing, compressed into 400-mg tablets using a single-punch tablet machine (Fette Excata 1/F, Fette GmbH, Schwarzenbek, Germany). The tablet machine was equipped with an 11.3-mm (1 cm^2) flat-faced punch and set to run at 60 compressions per minute using a 25-MPa (2.5-kN) compressional pressure. The punch was cleaned with a suspension of magnesium stearate in hexane between preparations. The prepared tablets were characterized according to crushing strength, disintegration time, and relative standard deviation of mass. The crushing strength was determined by a standard hardness tester (Schleuniger 8M tablet hardness tester, Schleuniger, Horgen, Switzerland), as an average of 10 tablets. The disintegration time was determined by the standard European Pharmacopoeia[13] method in 37°C water, as the average of 6 tablets. The uniformity of the tablet mass was investigated by determination of the relative standard deviation of the tablet mass based on the individual weight of 20 tablets. The tablets used for the characterization were randomly drawn.

Experimental Setup

By the use of a 2-step agglomeration process, mixtures of a filler (450 g) and MCC (150 g) were agglomerated in duplicate according to Table 1. A 50% wt/wt PEG binder solution was applied as the primary binder liquid; water was the secondary binder liquid. The water addition was

Table 1. Experimental Setup*

Batch ID†	Filler Type	Applied PEG Binder Solution‡ (g)	Concentration of PEG in Batch (% [wt/wt])	Total Batch Size (g)
A (1-2)	Lactose	75	5.90	637.5
B (1-2)	Lactose	150	11.1	675
C (1-2)	Lactose	300	20.0	750
D (1-2)	Lactose	600	33.3	900
E (1-2)	Lactose	900	42.9	1050
F (1-2)	Calcium phosphate	300	20.0	750
G (1-2)	Acetaminophen	300	20.0	750
H (1-2)	Theophylline	300	20.0	750

*PEG indicates polyethylene glycol.

†All batches contained 150 g of microcrystalline cellulose and 450 g of filler (n = 2).

‡50% (wt/wt) PEG 6000 in water.

discontinued once the torque of the friction plate had increased to the desired level (0.15 Nm).

The 16 agglomeration experiments were performed in a partial randomized order, with the effect of the amount of PEG being performed first.

The investigated variables were amount of adhesion and process yield, agglomerate size and agglomerate size distribution, agglomerate density and flowability, tablet crushing strength, tablet disintegration time, and uniformity of tablet mass.

The results were subjected to statistical analysis (analysis of variance) using STATISTICA software (Version 7.0; StatSoft Inc, Tulsa, OK) when possible. Effects with a P value below .05 were considered to be significant.

Results and Discussion

Starting Materials

The applied fillers/drugs were chosen to cover a wide range of physical properties to investigate the effect of the excipient on the process outcome. According to values from the literature,[13] the aqueous solubility of the fillers/drugs ranges from the freely soluble lactose, to the slightly or sparingly soluble theophylline and acetaminophen, to the practically insoluble calcium phosphate. The physical properties of the starting materials are listed in Table 2, and SEM images are shown in Figure 1.

Process Characteristics

The determined viscosity of the PEG binder solution was 38 mPa.s. Despite the high concentration, the pneumatic nozzle had no difficulties in atomizing the PEG binder solution into a suitable spray with a droplet size that would ensure a good and even distribution of the PEG in the powder bed. The average droplet size ($D_{0.5}$) was found to be 23.6 (± 0.2) μm for the PEG binder solution and 15.3 (± >0.1) μm for water.

Control over the water content of the fluidizing air in the rotary processor was not possible during the current investigation. It ranged from 4.2 to 8.9 g water per kg air. These variations affected the drying capacity of the fluidizing air and thus affected the water content in the powder bed. The process conditions were chosen according to a previously determined range of inlet air water content, to allow for complete removal of the applied water during the PEG binder solution addition. The changing conditions also affected the removal of moisture during the second phase of water addition. In the current experiments the water addition phase varied up to 50% (6 minutes) for repeated experiments. However, it has previously been reported that the application of torque measurements for the determination of the liquid addition end point in a rotary processor can compensate for random variation in the inlet air water and lead to good reproducibility of the agglomeration process.[10]

Although the applied excipients cover a wide range of particle sizes and water solubilities, the agglomeration process did not vary much. This might be explained by the initial nucleation step in which the application of the PEG solution diminishes the difference in the physical properties of the applied excipients. During the process, the powder mass settled quickly in the rotation friction plate in a rotating ropelike movement, indicating that fast initial agglomerate growth had occurred. This was even the case with acetaminophen, with a small particle size and low bulk density, which indicates that the process is suitable for granulation of cohesive powders with bad flow properties. Table 3 lists the results from the characterization of the process. The process was found to be reproducible and generally gave rise to low amounts of adhesion and high yields (Table 3). For 1 set of experiments using 11.1% PEG, however, high amounts of adhesion and thus lower yields were seen. Increasing the amount of PEG was found to decrease the amount of water needed in order for agglomerate growth to occur. This might in part be explained by the increased batch size that follows an increased addition of PEG, since it has been shown that an increased batch size decreases the amount of water needed for agglomerate growth to occur in a torque-controlled rotary processor.[10] Figure 2 shows a

Table 2. Characterization of the Applied Starting Materials

Excipient	Particle		Pycnometric Density	Poured Density	Tapped Density	Carr's Index
	Size (μm)*	Span*	(g/cc)*	(g/cc)†	(g/cc)†	%†
Microcrystalline cellulose	63 (0.2)	1.79 (0.04)	1.60 (0.003)	0.34 ± 0.00	0.43 ± 0.01	20 ± 1
Lactose	38 (0.2)	2.71 (0.02)	1.54 (0.001)	0.60 ± 0.02	0.77 ± 0.00	22 ± 1
Calcium phosphate	10 (0.1)	2.45 (0.02)	2.35 (0.002)	0.64 ± 0.04	0.96 ± 0.00	33 ± 2
Acetaminophen	11 (0.6)	3.42 (0.11)	1.29 (0.001)	0.19 ± 0.01	0.28 ± 0.01	34 ± 3
Theophylline	30 (0.4)	2.85 (0.06)	1.49 (0.002)	0.37 ± 0.00	0.48 ± 0.01	24 ± 1

*Mean (SD).

†Mean ± range.

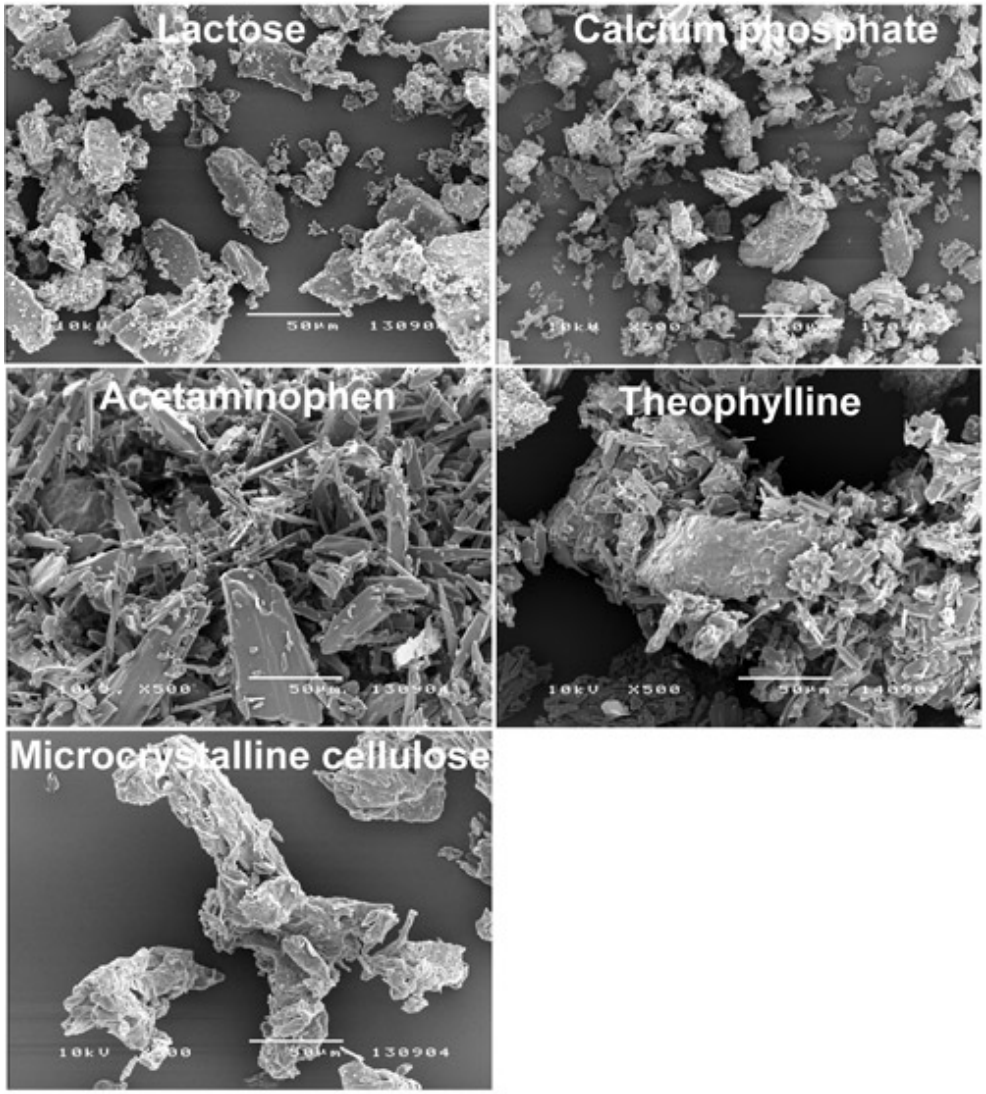

Figure 1. Scanning electron microscope images of the starting materials lactose, calcium phosphate, acetaminophen, theophylline, and microcrystalline cellulose (magnification ×500).

typical torque profile recorded during the agglomeration. Similar profiles were recorded for all agglomeration experiments. During the first part of the PEG binder addition, a small decrease is seen in the torque of the friction plate. This is caused by decreased friction in the bearings because of an increase in temperature. The torque level drops quickly

Table 3. Effect of the Applied Amount of PEG and Filler/Drug Type on Process Characteristics (Mean and Range of Repeated Experiments)*

Batch ID†	Content of PEG (% [wt/wt]/g)	Filler/Drug	Amount of Water‡ (g)	Adhesion (% [wt/wt])	Yield (% [wt/wt])
A	5.9/37.5	Lactose	409 ± 22	12 ± 1.5	88 ± 1.5
B	11.1/75	Lactose	252 ± 51	20 ± 3.4	79 ± 3.4
C	20/150	Lactose	144 ± 42	11 ± 2.6	89 ± 2.5
D	33.3/300	Lactose	116 ± 24	9.0 ± 0.6	90 ± 0.8
E	42.9/450	Lactose	45 ± 15	10 ± 3.1	89 ± 3.2
F	20/150	Calcium phosphate	166 ± 42	7.7 ± 0.3	90 ± 1.0
G	20/150	Acetaminophen	54 ± 13	3.4 ± 0.2	86 ± 1.0
H	20/150	Theophylline	148 ± 46	7.7 ± 0.3	89 ± 2.0

*PEG indicates polyethylene glycol.

†Each batch contained 150 g of microcrystalline cellulose and 450 g of filler/drug.

‡Amount of water added after the PEG binder solution was added.

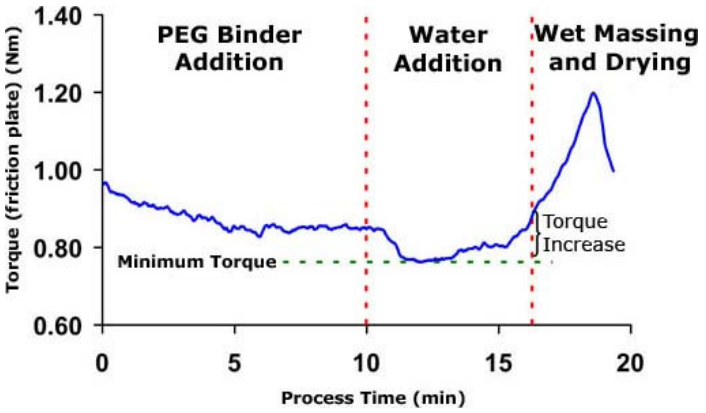

Figure 2. Torque profile recorded using batch C1. PEG indicates polyethylene glycol.

after the addition of PEG binder is stopped and the water addition is started, as can be seen in Figure 2. This can be explained by an increase in surface moisture that reduces the friction and facilitates the movement of the powder bed. Once the surface moisture is high enough for agglomerate growth by coalescence to occur, the friction and the torque signal increase, as shown in Figure 2. During wet massing, further growth as well as rounding of the agglomerates occurs. When the surface moisture of the agglomerates has been removed by the drying capacity of the fluidizing air, the interagglomerate friction decreases, leading to a sharp drop in the torque of the friction plate. No significant difference ($P > .29$) in the amount of water needed for agglomerate growth to occur was found for the applied excipients, although acetaminophen required less water, as indicated in Table 3. No correlation was found between the physical characteristics of applied drugs or filler and the amount of water needed for agglomerate growth to occur based on the torque profile and the amount of water needed. Taking into consideration the wide range of physical characteristics covered by the applied starting materials, the use of PEG binder solutions with high concentrations renders a robust process that is insensitive to the physical properties of the starting materials. An important factor in achieving this robust process could be the initial controlled nucleation and agglomerate growth. The SEM images of samples drawn at different time points (Figure 3) show the nucleating and agglomerate growth. After 1 minute, some agglomerates are formed, and after 5 minutes, all starting materials have been incorporated into nuclei or granules. During the rest of the PEG addition, further agglomerate growth is seen. Only a small increase in agglomerate size can be seen in Figure 3, but the surface of the agglomerates is smoother and the agglomerates appear denser. After wet massing and drying, the free-flowing agglomerates are rounded in shape; this roundness, in combination with the smooth surface and a particle size in the range of 500 to 1000 μm, makes them suitable for a subsequent coating process.

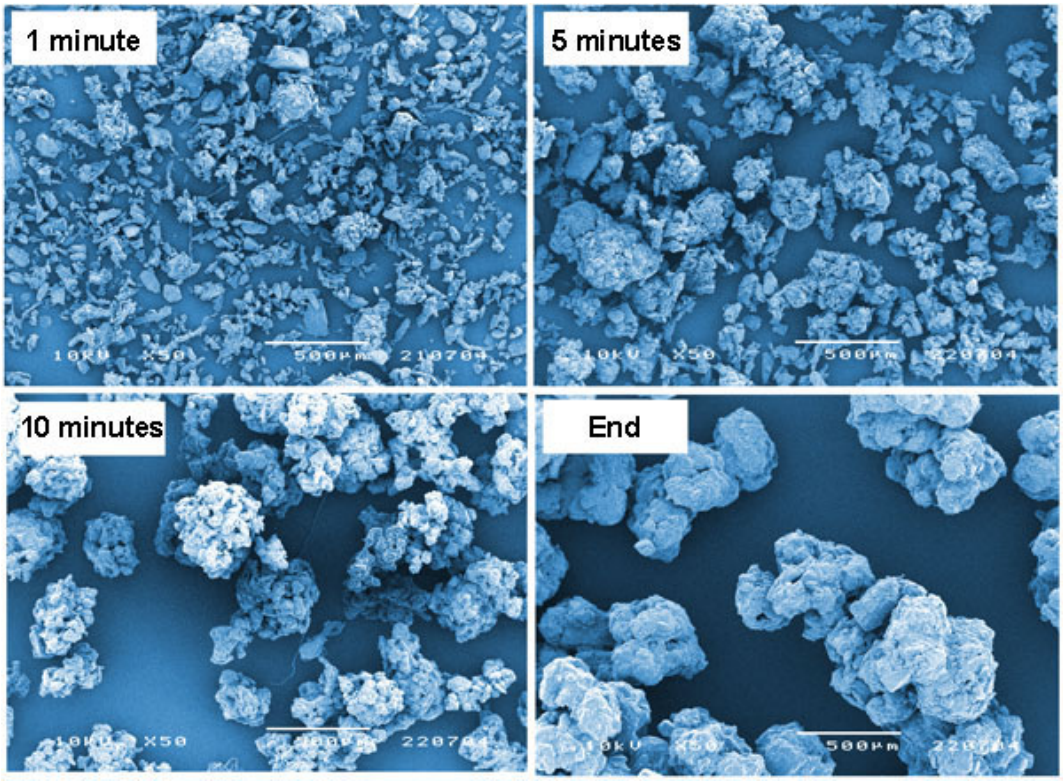

Figure 3. Scanning electron microscope images of agglomerates from batch C1 after 1 minute, 5 minutes, and 10 minutes of polyethylene glycol binder addition and after the water addition (End) (magnification ×50).

Table 4. Effect of the Applied Amount of PEG and Filler/Drug Type on Agglomerate Characteristics (Mean and Range of Repeated Experiments)*

Batch ID†	Particle Size d_{gw} (μm)	Size Distribution s_g	Poured Density (g/cc)	Tapped Density (g/cc)	Carr's Index (%)	Flowability (sec/100 g)
A	514 ± 15	1.46 ± 0.03	0.72	0.79	9	7.8 ± 0.1
B	678 ± 28	1.42 ± 0.03	0.76	0.78	3	8.9 ± 0.2
C	774 ± 44	1.39 ± 0.04	0.75	0.79	6	7.8 ± 0.1
D	381 ± 39	1.46 ± 0.01	0.54	0.62	12	10.5 ± 0.2
E	395 ± 5	1.41 ± 0.01	0.50	0.61	17	12.5 ± 0.3
F	836 ± 80	1.40 ± 0.01	0.94	0.99	5	6.4 ± 0.2
G	1010 ± 30	1.44 ± 0.04	0.68	0.71	4	10.9 ± 0.3
H	414 ± 21	1.46 ± 0.03	0.89	0.98	9	11.8 ± 0.3

*PEG indicates polyethylene glycol.

†Each batch contained 150 g of microcrystalline cellulose and 450 g of filler/drug. Fillers are listed in Table 1.

Agglomerate Properties

The physical properties of the prepared agglomerates are listed in Table 4. Good reproducibility was found for all the repeated experiments. No clear effect of the content of PEG could be seen on the agglomerate size, although the high-content batches D and E gave rise to smaller values than did the low- and medium-content batches. Good reproducibility was found for the agglomerate size distribution as well, as indicated in Table 4. The values ranged from 1.35 to 1.49, which is similar to those reported for both direct pelletization[17] and melt agglomeration[8] in the rotary processor. The good reproducibility in terms of agglomerate size and size distribution shows that torque control of the end point is feasible for the investigated process and indicates that the size of the agglomerates can be controlled by varying the torque increase level applied. As previously mentioned, no clear correlation was found between the torque increase and agglomerate size when traditional melt agglomeration was performed in the rotary processor.[8] However, based on the current investigation, such a correlation might exist for the 2-step agglomeration process applied here. This correlation is not general and will depend on the physical properties of the starting materials. However, it might be possible to prepare free-flowing agglomerates of a controlled size by applying the proper torque end point value for each of the investigated materials.

The bulk densities and flow properties were influenced by the content of PEG. Higher contents gave rise to lower poured and tapped densities and a higher Carr index, as can be seen in Table 4. Although differences in the physical properties of the agglomerates were seen, they were generally small, and all agglomerate batches could be characterized as free-flowing and as such eligible for capsule filling or compression.

Tableting Properties

The uniformity of mass was good for all batches, and only the acetaminophen batch G gave rise to a relative standard deviation above 1% (Table 5). The higher deviation found for this batch might be explained by the large size of these agglomerates, which had an average particle size of 1000 μm. Tablets could be prepared from all but batch E without further processing. For batch E, with a PEG content of 42.9%, adhesion of material or tablets to the lower punch happened frequently. The problem might be reduced if the agglomerates were mixed with a glidant and an antiadhesive agent,

Table 5. Physical Properties of the Prepared Tablets—Effect of the Content of PEG and Filler/Drug Type (Mean and SD)*

Batch ID†	Content of PEG (%[wt/wt]/g)	Filler/Drug	Tablet Mass, Relative SD (%) (n = 10)	Crushing Force (N) (n = 10)	Tablet Disintegration (min) (n = 6)
A	5.9/37.5	Lactose	0.53	32 (2.1)	>0.2 (ND)
B	11.1/75	Lactose	0.61	42 (1.9)	3.1 (0.3)
C	20/150	Lactose	0.77	56 (3.2)	7.9 (1.6)
D	33.3/300	Lactose	0.29	84 (2.8)	13.8 (0.2)
E‡	42.9/450	Lactose	0.91	105 (7.8)	>15 (ND)
F	20/150	Calcium phosphate	0.79	67 (5.1)	9.2 (3.5)
G	20/150	Acetaminophen	1.42	48 (5.7)	11.6 (4.4)
H	20/150	Theophylline	0.53	84 (3.9)	>15 (ND)

*PEG indicates polyethylene glycol; ND, not determined.

†Each batch contained 150 g of microcrystalline cellulose and 450 g of filler/drug.

‡The punches needed frequent cleaning during tableting, because of adhered material.

but if tablets are to be prepared, the results indicate that the content of PEG should be kept well below 42%.

The crushing force of the tablets prepared with the same compression force was significantly ($P < .03$) influenced by the content of PEG, as can be seen from Table 5. As might be expected, increasing the PEG content gave rise to stronger tablets, because of the waxy nature of the PEG. Similar results were found for disintegration time, with an increase in PEG resulting in a prolonged disintegration time. The tablets containing 42.5% PEG showed almost no disintegration during the 15 minutes of the test. The tablets prepared with 5.9% PEG had a very rapid disintegration of 10 to 15 seconds. This can be explained by the swelling and disintegrating effect of the added MCC, which is stronger than the binding properties when PEG is applied in small amounts. The 4 different drugs/fillers applied all gave rise to sufficiently strong tablets. The fact that strong tablets were prepared, even with the highly elastic acetaminophen, indicates that the investigated process is robust and suitable as a granulation procedure for the preparation of tablets. For the applied fillers/drugs the disintegration time could be seen to follow the crushing force (Table 5). The long disintegration times seen indicate that the applied compressional force was not optimal and should be decreased to result in acceptable tablets for all materials.

Process Perspective

The investigated process might be an interesting alternative to melt agglomeration for the preparation of tablets containing solid dispersions or solutions. The process can be applied to incorporate a higher content of the meltable binder than has previously been published for melt agglomeration[7] in high shear mixers and rotary processors.[8] Furthermore, the investigated process can be used to prepare tablets with a high drug content of a bulky, poor-flowing drug with poor compression characteristics, as was shown with acetaminophen.

CONCLUSIONS

Agglomeration in a torque-controlled rotary processor using solutions of PEG as the primary binder liquid was found to be a robust process. The process can be applied for the preparation of agglomerates with a high drug content and physical properties suitable for further processing, such as coating, capsule filling, or compression. The process allowed for the incorporation of up to 42.5% wt/wt PEG and can therefore be used as an alternative to melt agglomeration with hydrophilic meltable binders.

ACKNOWLEDGMENTS

Glatt Norden Aps is acknowledged for financial support in the acquisition of the Glatt GPCG rotary processor.

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