

Direct Pelletization in a Rotary Processor Controlled by Torque Measurements. III. Investigation of Microcrystalline Cellulose and Lactose Grade

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ABSTRACT

The aim of the present study was to investigate the use of different grades of microcrystalline cellulose (MCC) and lactose in a direct pelletization process in a rotary processor. For this purpose, a mixed 2- and 3-level factorial study was performed to determine the influence of the particle size of microcrystalline cellulose (MCC) (~60 and 105 μm) and lactose (~30, 40, and 55 μm), as well as MCC type (Avicel and Emcocel) on the pelletization process and the physical properties of the prepared pellets. A 1:4 mixture of MCC and lactose was applied, and granulation liquid was added until a 0.45 Nm increase in the torque of the friction plate was reached. All combinations of the 3 factors resulted in spherical pellets of a high physical strength. The particle size of MCC was found to have no marked effect on the amount of water required for agglomerate growth or on the size of the resulting pellets. An increasing particle size of lactose gave rise to more spherical pellets of a more narrow size distribution as well as higher yields. The MCC type was found to affect both the release of the model drug from the prepared pellets and the size distribution. Generally, the determined influence of the investigated factors was small, and direct pelletization in a rotary processor was found to be a robust process, insensitive to variations in the particle size and type of MCC and the particle size of lactose.

KEYWORDS: rotary processor, direct pelletization, torque measurement, microcrystalline cellulose.

INTRODUCTION

Direct pelletization has been reported to be an attractive alternative to the conventional extrusion/spheronization process for the preparation of pharmaceutical pellets or spheres,¹ and the subject has been reviewed previously.² In order for direct pelletization in a rotary processor to be an attractive alternative in an industrial perspective, a sufficient

robustness of the process is needed in terms of controllability, reproducibility, and insensitivity to variations in the starting materials.

The most influential parameter has been found to be the water content of the agglomerates at the end of liquid addition,³ thus all variables that influence the water content will affect the outcome of the process. Tight control of the water content is therefore needed in order to control and reproduce the process, and this has been proven possible by controlling the liquid addition end point by torque measurement.¹

Previously published studies regarding direct pelletization in a rotary processor have almost always used a formulation containing microcrystalline cellulose (MCC) and a filler. The most frequently applied grade of MCC for direct pelletization in rotary processors is Avicel PH101,^{1,4,5} but Avicel PH102^{3,6} and PH200⁷ as well as Emcocel 50M⁸ have also been applied.

The effect of the amount of MCC in the formulation has been investigated in several studies,^{3,7,9} and they all reported that increasing amounts of MCC facilitated the preparation of spherical agglomerates. When the liquid addition end point was controlled by torque measurements, the amount of MCC in the formulation was shown to have a major effect on the pellet size.⁹ The effect on pellet size was found to be most pronounced when low contents of MCC was applied, and 20% (wt/wt) was found to be the minimum amount needed in order for direct pelletization in a rotary processor to result in spherical agglomerates.⁹

Since the process has been found to be very sensitive to changes in the content of MCC, it might also be expected that the particle size of the applied MCC has an effect on the outcome of the pelletization process. Only one study included the effect of the particle size of MCC on direct pelletization in a rotary processor: Sienkiewicz et al⁷ investigated the effect of the 3 grades of MCC (Avicel PH101, PH102, and PH200) with different particle size on direct pelletization in a rotary processor. The authors found a marked difference in the ability to form spherical pellets between the various investigated combinations, and only half of them resulted in good pellets. Generally, the MCC particle size was found to have little effect on the process with the largest particle size grade being slightly superior to

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the smallest grade and about equal to middle grade. In the study, the liquid addition was continued until pellets of a certain size were produced, as judged visually by the operator.⁷ Since the water content at the end of liquid addition has been found to be the most influential factor in direct pelletization in rotary processors³ and small changes were found to change pellet characteristics significantly,⁹ the little effect of changing the MCC particle size found by Sienkiewicz et al⁷ may therefore be explained by unknown variations in the water content at the end of liquid addition.

MCC is derived from natural wood pulp, and differences in the chemical composition of MCC types prepared by different manufacturers will therefore exist. In order for direct pelletization to be characterized as a robust process, it should be insensitive to changes in the MCC type applied. No studies involving direct pelletization in a rotary processor were found in which the effect of MCC type was investigated.

The most frequently used filler in direct pelletization in a rotary processor is lactose monohydrate of a 200-mesh quality with an average particle size of approximately 40 μm .^{1,10} Other fillers, such as calcium phosphates,³ calcium carbonate, and mannitol,¹¹ as well as different grades of lactose, have also been investigated. Generally, the applied filler's ability to spheronize in a rotary processor is reported to be related to its particle size. Larger particle size fillers are more suitable, giving rise to, for example, higher yields and better reproducibility.^{3,7}

Previous studies show that direct pelletization in a rotary processor can be controlled with excellent reproducibility using the torque of the friction plate as liquid addition end point detection.^{1,9} This was shown using one MCC grade in combination with one lactose grade. In the current investigation 4 grades of MCC (2 types [Avicel and Emcocel] each in 2 particle sizes [~ 60 or $105 \mu\text{m}$]) were pelletized by direct pelletization in a rotary processor in which the liquid addition end point is controlled by torque measurements, in combination with lactose of 3 different particle sizes (30, 40, and $55 \mu\text{m}$), in order to investigate the effect of the applied starting materials on the process and

the characteristics of the resulting pellets. In order to stress the process and thus facilitate the determination of the effects of the investigated variables, a formulation containing the previously determined minimum MCC content of 20% wt/wt⁹ was chosen in the present study.

MATERIALS AND METHODS

Materials

MCC (Avicel, type PH101 and PH102, FMC International, Cork, Ireland and Emcocel, type 50M and 90M, Penwest, Danbury, CT), α -lactose monohydrate (Pharmatose type 125M, 200M, and 350M, DMV International, Veghel, The Netherlands), and riboflavin (BASF, Ludwigshafen, Germany) were used as starting materials. Purified water was used as binder liquid. All materials were of European Pharmacopoeia grade as stated by the suppliers.

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 water content on a dry mass basis was determined in duplicate by drying powder samples in an oven at 105°C until constant mass. For the lactose grades, water of crystallization is included in the estimated water content.

The pycnometric densities of the starting materials were determined by an AccuPyc 1330 gas displacement pycnometer (Micromeritics, Norcross, GA) using helium purge. The poured and tapped densities were determined in duplicate using the test for apparent volume as described in the European Pharmacopoeia, 4th ed.¹²

The determined physical properties of the starting materials are shown in Table 1, which lists the mean values of the repeated determinations and either range ($n = 2$) or SD ($n > 2$).

Table 1. Characterization of the Applied Starting Materials

Excipient	Particle		Pycnometric Density (g/mL)	Poured Density (g/mL)	Tapped Density (g/mL)	Water Content (% wt/wt)
	Size (μm)	Span				
Avicel PH101	61 \pm .3	1.75 \pm .01	1.596 \pm .003	0.33 \pm .01	0.41 \pm .01	4.0 \pm .1
Avicel PH102	106 \pm 1.6	1.77 \pm .01	1.590 \pm .003	0.36 \pm .01	0.44 \pm .00	4.0 \pm .1
Emcocel 50M	56 \pm .7	1.72 \pm .01	1.584 \pm .001	0.33 \pm .02	0.42 \pm .01	4.0 \pm .1
Emcocel 90M	105 \pm 3.1	1.74 \pm .01	1.594 \pm .002	0.34 \pm .01	0.41 \pm .00	4.1 \pm .2
Lactose 350M	31 \pm .3	2.23 \pm .21	1.536 \pm .001	0.47 \pm .03	0.79 \pm .02	5.1 \pm .2
Lactose 200M	41 \pm .1	2.65 \pm .19	1.536 \pm .001	0.55 \pm .02	0.82 \pm .01	5.0 \pm .1
Lactose 125M	56 \pm .5	1.75 \pm .17	1.537 \pm .001	0.68 \pm .02	0.86 \pm .00	4.8 \pm .2

Pelletization Procedure

A rotary processor (Glatt GPCG-1.1; Glatt, Binzen, Germany) described previously¹ was used in all experiments. Temperature and flow rate of the fluidizing air were set to 40°C and 90 m³/h (The humidity of the inlet air was not controlled and ranged from 4.7 to 5.5 g water per kg air). The starting materials (750 g) were mixed manually, sieved through a 1.0-mm sieve, and loaded into the equipment, which had been preheated by running empty for 12 minutes. Following initiation of the fluidizing air flow, the air gap pressure difference was set to 2.0 kPa by elevating the cross-hatched friction plate, and the rotation of the friction plate was turned on and set to 900 rpm. Purified water was sprayed tangentially into the moving powder at a rate of 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. The addition of liquid was continued until a 0.45 Nm increase in the torque of the friction plate was reached. The increase in torque was computed continuously as the difference between the current torque value and the minimum torque value.¹ Immediately after stopping the addition of liquid, samples were drawn in duplicate for the determination of the water content, and the nozzle was removed. Wet massing was continued for 6 minutes. The wet pellets were tray-dried at 40°C for 3 hours and stored at room temperature. For determination of the water content, the samples were dried in an oven at 105°C until constant mass, and the water content was calculated on a dry mass basis.

Characterization

The minimum torque level was computed as the lowest average of 100 consecutive data points (1 data point per second) and the torque increase rate as the applied torque increase (0.45 Nm) divided by the time span from when the minimum torque level is reached until the desired torque increase is reached, as shown in Figure 1.

The amount of adhesion was determined as the mass of the material that adhered to the friction plate and the product chamber wall after each experiment.

The amount of oversized pellets was determined as the pellets not able to pass through a 2800- μ m sieve and the yield as the pellet size fraction between 355 and 2000 μ m.

The size distribution of the pellet fraction that had passed through a 2800- μ m sieve was estimated by sieve analysis of a sample of approximately 75 g drawn from the entire batch using a Laborette 27 automatic rotary cone sample divider (Fritsch, Mainbernheim, Germany). A series of 12 ASTM standard sieves (Retsch, Hann, Germany) in the range of 180 to 2800 μ m was vibrated for 10 minutes by a Fritsch analysette 3 vibrator using an 8-mm amplitude. The

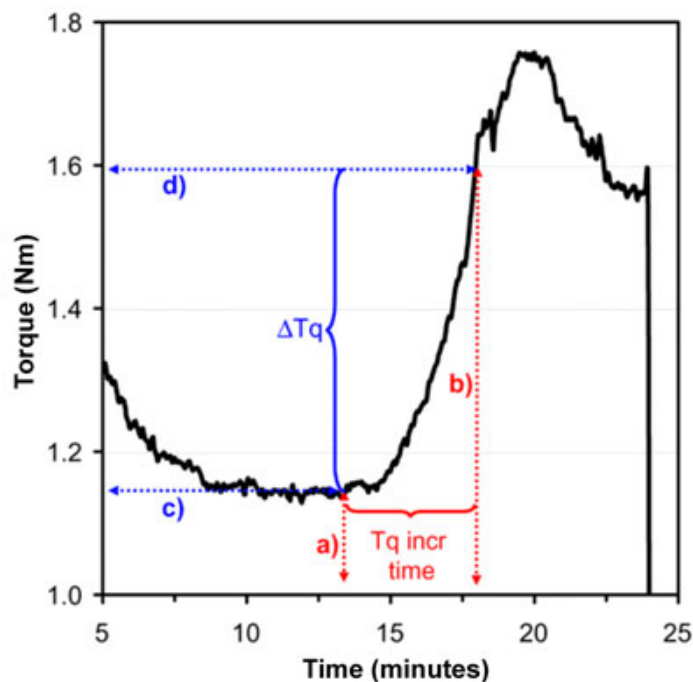


Figure 1. Torque profile from experiment with Avicel PH102 and Lactose 125M. Dashed line (A) time of minimum torque level, (B) termination of liquid addition, (C) minimum torque level, (D) torque at liquid addition termination.

pellet size distributions were in good agreement with the log-normal distribution. Consequently, the mean pellet size was described by the geometric weight mean diameter (d_{gw}), and the size distribution by the geometric standard deviation (s_g). The 900- to 1000- μ m fraction was saved and used for further characterization.

The pellet shape was studied by light microscopy and image analysis. The image analysis was performed as previously described.¹³ The shape of the agglomerates ($n \approx 100$) was characterized by their aspect ratio (length/width), which describes the deviation in shape from a circle to an ellipse, and by their roundness ($4\pi \times \text{area}/\text{perimeter}^2$), which is primarily a measure of surface irregularities. The image analysis was performed on one batch for each of the 12 experimental settings described below, and agglomerates from the 900- to 1000- μ m sieve fraction were applied. Further, pellets from the same fraction were studied using a scanning electron microscope (SEM) (JSM 5200, Jeol, Tokyo, Japan).

The crushing strength of the agglomerates from selected experiments was determined using an in-house apparatus.¹² The specific crushing strength (MPa) of 10 single agglomerates from the 900- to 1000- μ m fraction was calculated as the determined breaking force in Newton (N) divided by the cross-sectional area ($\pi \times \text{radius}^2$) of the assumed spherical agglomerates. The diameter of each of the agglomerates was determined using a digital height measuring device (Digital Indicator, type IDF-130, Mitutoyo Corporation,

Kawasaki, Japan). After each determination, the fragments were investigated visually to ensure that the measured force emanated from a break rather than a compression of the agglomerates.

Pellet disintegration was investigated in a standard tablet disintegration apparatus equipped with a 420- μm bottom sieve in 37°C 10⁻¹ M hydrochloric acid using the 900- to 1000- μm sieve fraction pellets. The test was discontinued after 30 minutes.

Dissolution tests were performed in duplicate in a Bio-Dis Extended Release Tester (VanKel Industries Inc, Edison, NJ) connected to an HP8452A Diode Array Spectrophotometer (Hewlett-Packard, Boeblingen, Germany). The dissolution temperature was 37°C, and the sample tubes moved with 20 dips per minute in 275 mL of 10⁻¹ M hydrochloric acid. Three hundred milligrams of pellets from the size fraction 900 to 1000 μm corresponding to approximately 3 mg of riboflavin were transferred to the sample tubes. Samples of dissolution medium were transferred to the spectrophotometer and back to the dissolution vessel through tubes, and the concentration of riboflavin was measured at 244 nm. The initial drug release (D_{ini}) was

determined as the release after 15 minutes, and the time of 50% drug release (T_{50}) was estimated by applying Equation 1 on the 20% to 75% drug release range.

In all charts the error bars indicate the range of repeated experiments.

$$\text{Dissolved drug (\%)} = \text{Slope} \times \text{Square root (Time)} + \text{Intercept} \quad (1)$$

Experimental Setup

In all experiments, 750 g of mixtures of MCC, lactose, and riboflavin in a 20:79:1 ratio were used. A mixed 2- and 3-level factorial designed study was performed in duplicate in a randomized order giving a total of 24 experiments. The included factors were MCC type (Emcocel or Avicel) MCC size (~60 or 105 μm) and lactose size (~30, 40, and 55 μm). The experimental setup is listed in Table 2.

The included response variables were the minimum torque level, torque increase rate, water content at the end of liquid addition, amount of adhesion, yield, pellet size, pellet size distribution, pellet shape, pellet crushing strength, pellet disintegration time, and drug release characteristics.

Table 2. Applied Experimental Settings in the Mixed 2- to 3-level Factorial Study and the Results of the Pellet Characterization

Exp No.	Experimental Settings			Pellet Size and Size Distribution		Pellet Shape		Pellet Strength SCS (SD)
	MCC Type	MCC Size [†]	Lactose Size [‡]	d_{gw} (μm)	s_g	Aspect Ratio (SD)	Roundness (SD)	
1	A	S	S	1165	1.35	1.11(.050)	.953(.033)	19.6(2.0)
2	A	S	S	1063	1.38	-	-	-
3	A	S	M	1238	1.42	1.10(.036)	.945(.016)	19.3(1.7)
4	A	S	M	1001	1.46	-	-	-
5	A	S	L	1099	1.49	1.15(.058)	.933(.038)	18.3(1.2)
6	A	S	L	987	1.50	-	-	-
7	A	L	S	1405	1.34	1.11(.054)	.951(.034)	18.2(1.7)
8	A	L	S	1382	1.35	-	-	-
9	A	L	M	1231	1.43	1.10(.043)	.945(.025)	18.5(2.2)
10	A	L	M	967	1.37	-	-	-
11	A	L	L	1239	1.43	1.14(.054)	.906(.040)	17.4(2.2)
12	A	L	L	915	1.38	-	-	-
13	E	S	S	1017	1.27	1.11(.047)	.940(.029)	18.7(1.8)
14	E	S	S	986	1.29	-	-	-
15	E	S	M	998	1.33	1.10(.036)	.961(.018)	19.2(3.6)
16	E	S	M	1095	1.37	-	-	-
17	E	S	L	1041	1.38	1.13(.053)	.939(.031)	18.2(2.4)
18	E	S	L	958	1.41	-	-	-
19	E	L	S	1249	1.35	1.12(.045)	.946(.027)	16.7(1.5)
20	E	L	S	1156	1.32	-	-	-
21	E	L	M	1231	1.44	1.10(.052)	.946(.031)	16.5(2.5)
22	E	L	M	1000	1.41	-	-	-
23	E	L	L	1142	1.47	1.14(.063)	.930(.040)	16.0(1.9)
24	E	L	L	1089	1.49	-	-	-

*A indicates Avicel; E, Emcocel; d_{gw} , geometric weight mean diameter; s_g , geometric standard deviation; and SCS, specific crushing strength (MPa).

[†]S: ~60 μm , L: ~105 μm

[‡]S: ~30 μm , M: ~40 μm , L: 55 μm

Table 3. Resulting *P* and Factor Coefficient Values From the Statistical Analysis of Variance on the Investigated Response Variables*

Response Variable	MCC Type	MCC Size	Lactose Size (L)	Lactose Size (Q)
Minimum torque level	-	-	-	-
Torque increase rate	-	-	.01(±.020)	-
Water content (end liquid added)	-	.00(.004)	.00(±.006)	-
Adhesion	-	-	.00(±40.4)	.02(±14.4)
Yield	.00(.026)	.01(±.022)	.00(.079)	.02(.020)
Size (d_{gw})	-	.03(55.6)	-	-
Size distribution (s_g) [†]	.01(±.015)	-	.00(±.057)	-
Aspect ratio [†]	-	-	.00(±.013)	.00(±.012)
Roundness [†]	-	-	.02(.010)	-
Specific crushing strength [‡]	.01(±.50)	.00(±.84)	.04(.42)	-
Initial drug release (D_{ini})	.02	-	-	-
Time of 50% drug release (T_{50})	-	-	-	-

*L indicates linear effect; Q, quadratic effect; - indicates not significant effect ($P > .05$); d_{gw} , geometric weight mean diameter; and s_g , geometric standard deviation. Factor coefficient values appear in parentheses.

[†]Significant interaction ($P < .01$) between MCC type and MCC size was found.

[‡]Performed using data from one of the repeated experimental settings ($n = 1$).

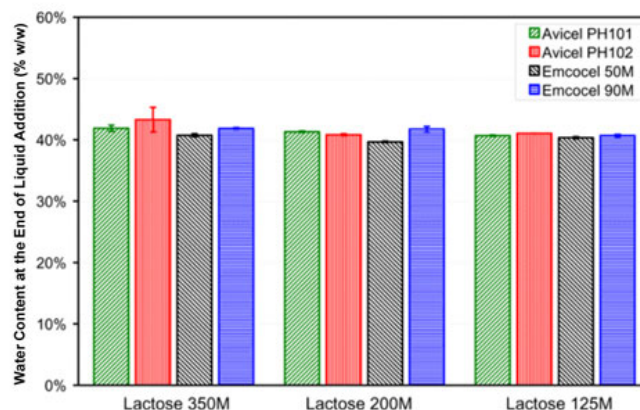
The results were subjected to statistical analysis of variance (ANOVA) using STATISTICA software (Version 6.0, StatSoft Inc, Tulsa, OK). Effects with a *P* value below .05 were considered significant. If no significant interactions were found, the analysis was repeated without interactions.

RESULTS AND DISCUSSION

Figure 1 shows a typical torque profile of the last part of the addition of liquid and the wet massing phase. The addition of liquid lasted from 16 to 26 minutes resulting in the addition of 500 to 800 g of water. Direct pelletization in a rotary processor is very sensitive to small changes in the water content at the end of the addition of liquid.¹ In the current experiments, the termination of the addition of liquid was controlled by torque measurements. Variables that affect the minimum torque level could therefore affect the outcome of the pelletization experiments. Previous studies¹ have shown that increasing the rotation speed of the friction plate as well as the inlet air temperature gave rise to a lower minimum torque level, because both led to an increased temperature and thus lower friction within the bearings of the friction plate. The minimum torque level was found to vary in the range of 1.11 to 1.25 Nm. Table 3 lists the *P* values found by the statistical analysis as well as the factor coefficient values for significant effects. No significant effects of any of the investigated variables were found on the minimum torque. This was to be expected since previous experiments¹ established no effect of a 2-fold increase in the batch size. Even though the minimum torque level was found to be unaffected by the applied formulation variables, it is still necessary to control the experiments by torque increase and not a set torque value owing to the low reproducibility of the minimum torque level.

As described in a previous study,¹ the torque increase starts when the agglomerate growth begins, and the torque increase rate indicates the relative speed by which the size enlargement proceeds. The statistical analysis showed a significant effect of the particle size of the lactose where the larger particle sized lactose 125M gave rise to a slower increase rate compared with the 2 other grades. Neither MCC type nor size had any statistical effect on the torque increase rate.

The water content of the agglomerates at the end of liquid addition ranged from 40% to 43% (wt/wt) as shown in Figure 2. On average, this water content corresponds to approximately 40% of the added liquid. Thus, the majority of the added liquid evaporates during liquid addition. Although no clear effects can be seen in any of the investigated parameters in Figure 2, the size of both MCC and lactose was found to have a significant effect (Table 3). The small effect can, however, be explained by the different moisture

**Figure 2.** Water content at the end of liquid addition.

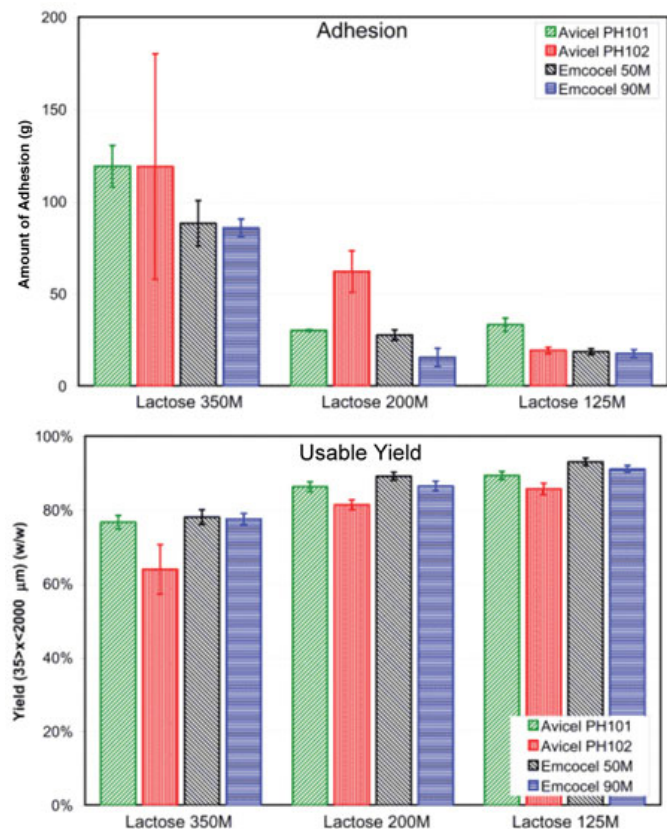


Figure 3. Amount of adhesion formed during pelletization and Usable Yield withdrawn from each experiment (% wt/wt of starting materials).

content of the starting materials, as listed in Table 1, as well as the different amounts of adhesion formed during the experiments. Figure 2 shows excellent reproducibility despite variations in the liquid addition time and the humidity of the inlet air when the 2 largest lactose grades were applied. Ranges between repeated experiments were below 0.2% wt/wt (~2 g water). Higher ranges between repeated experiments were found when the lactose with the smallest particle size was applied. This result can again be explained by the large differences in the amount of adhesion when the small lactose grade was applied in combination with the previous finding that the batch size has a significant influence on the water content at the end of liquid addition.¹ The amount of adhesion formed in the preformed experiments can be seen in Figure 3. The amount of adhesion formed on the cross-hatched friction plate and the walls of the product chamber were not influenced by the size or type of MCC, whereas a significant effect was seen for the lactose size. Increasing the particle size of lactose caused a decrease in the amount of adhesion, as shown in Figure 3. If the movement of the mass is insufficient for a good distribution of the added liquid, adhesion will form on the walls of the product chamber. Fillers, such as lactose, show better flow properties with increasing particle size. Larger grades are therefore less prone to local overwetting caused

by an insufficient movement of the powder mass. This might explain the observed effect of the lactose particle size on the amount of adhesion. Owing to the increased amounts of adhesion formed with decreasing particle size of the lactose, the yield of pellets from each experiment was also significantly affected by the particle size of lactose, as shown in Figure 3. Further, the yield was also found to be significantly affected by both MCC type and size, with Emcocel and the small particle size giving rise to yields that were a few percentage points higher than those found with Avicel and the large particle size MCC. In order to avoid adhesion and increase the yield during processing of small or poorly flowing powder blends, baffles could be installed on the central cone or on the sides of the product chamber, directing the movement of the powder mass toward the friction plate. This would increase the shear forces acting on the powder and could lead to a more homogeneous distribution of water.

The results of the investigated parameters on pellet characteristics are listed in Table 2. Direct pelletization in the rotary processor is a very sensitive process with regards to changes in the amount of MCC applied, especially at low MCC content used in the current investigation. It could therefore be expected that different grades of MCC applied in the current investigation would also have an effect on the pellet size. However, from Figure 4, which shows the effect

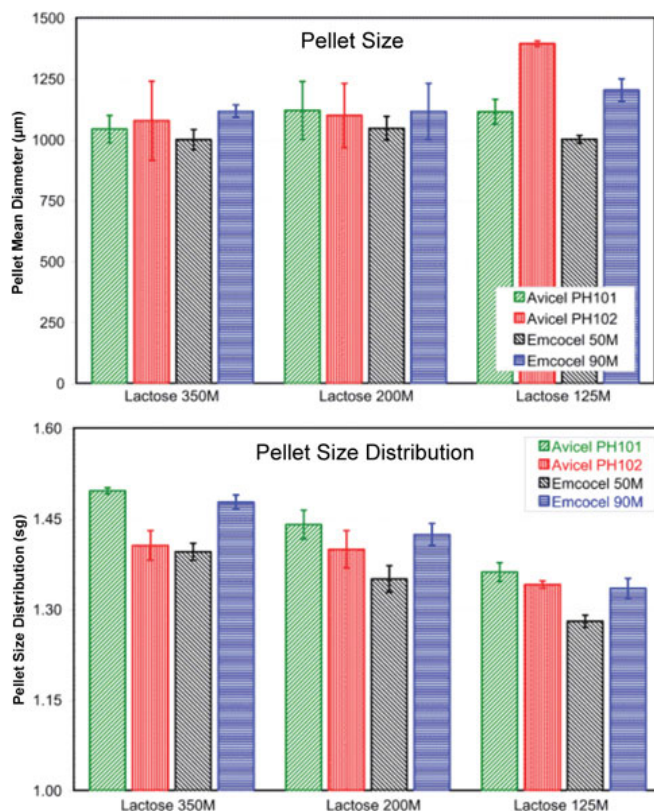


Figure 4. Pellet mean diameter (d_{gw}) and pellet size distribution (s_g).

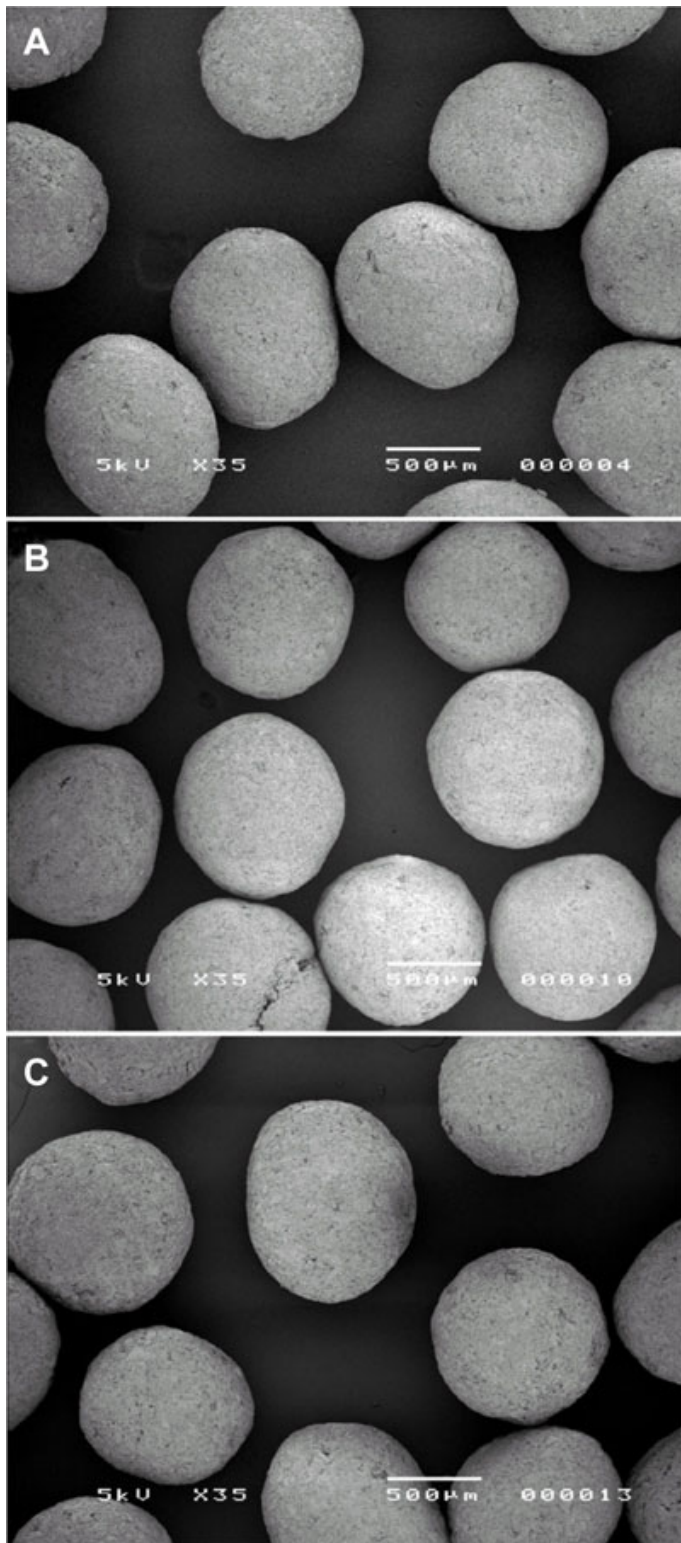


Figure 5. SEM photomicrographs of pellets prepared with Avicel PH101 and Lactose: (A) Lactose 350M, (B) Lactose 200M, and (C) Lactose 125M.

of the investigated variables on the pellet mean diameter, it can be seen that only a small difference was found, indicating that direct pelletization in a rotary processor controlled by torque measurements is a robust process. The mean pellet size ranged only 200 µm for 11 of the 12 in-

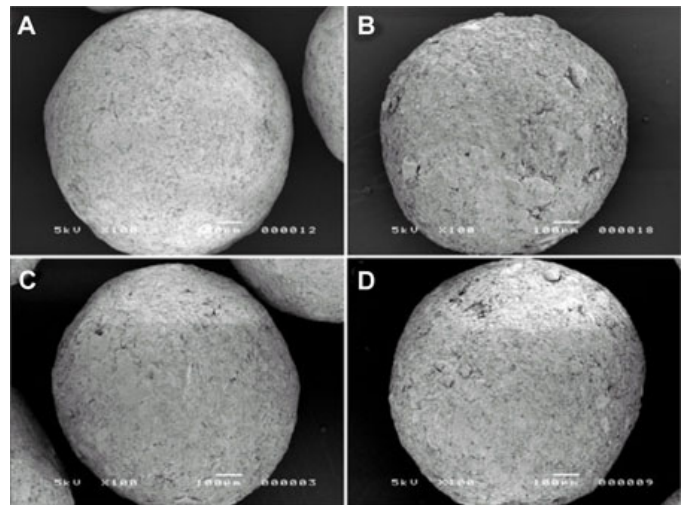


Figure 6. SEM photomicrographs of pellets prepared with Lactose 200M and MCC. (A) Avicel PH101, (B) Avicel PH102, (C) Emcocel 50M, or (D) Emcocel 90M.

vestigated formulations. Only the combination of Avicel PH102 and Lactose 125M differed markedly from the other settings. Pellets containing MCC will shrink during drying.¹⁴ A smaller degree of shrinkage with this combination might explain the observed effect on pellet size, although other unknown factors could also be involved. The statistical analyses did show a significant effect of the particle size of MCC, as listed in Table 3, with increasing size giving rise to larger pellets. This effect is mainly due to the high value of the above-mentioned combination of Avicel PH102 and Lactose 125M.

The particle size distribution (s_g) of the prepared pellets is shown in Figure 4. The MCC type and the particle size of lactose as well as the interaction between MCC type and size were found to have a significant effect.

The image analysis gave rise to aspect ratios from 1.10 to 1.15 and roundness values from 0.91 to 0.96. Significant effects of the particle size of lactose on both aspect ratio and roundness were found (Table 3). The small Lactose 350M gave rise to the highest aspect ratios and consequently deviated more in shape from a circle to an ellipse. It also had the lowest roundness values, indicating more surface irregularities. However, as can be seen from the SEM photomicrographs in Figure 5, the differences are small. Although no significant effect was found, an investigation using SEM indicated that the surface of pellets containing the large MCC particle size was less smooth compared with those containing the small particle size, as shown in Figure 6. As is evident from the SEM pictures in Figures 5 and 6, all experiments resulted in pellets sufficiently spherical for coating processing independent of the applied grades of MCC and lactose.

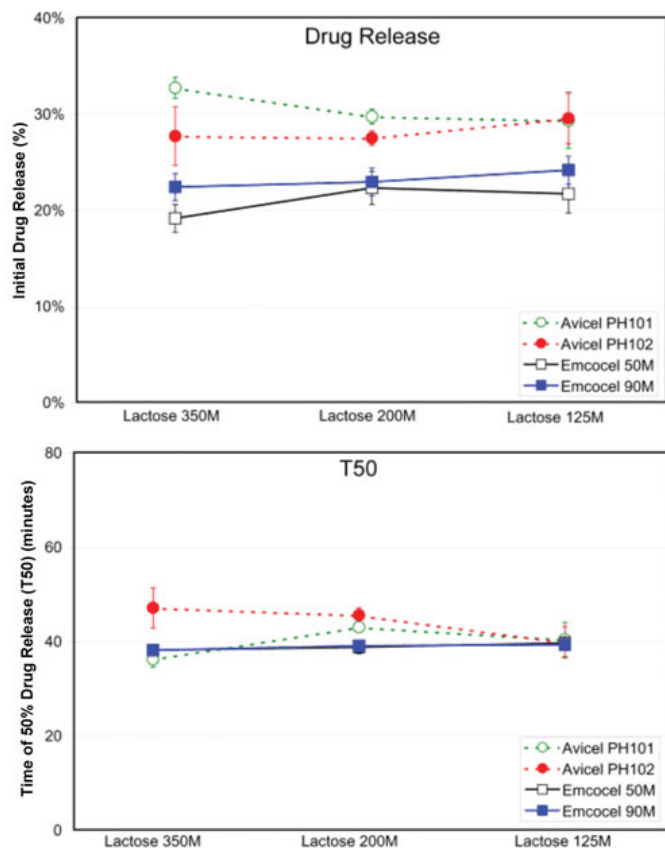


Figure 7. Effect of the investigated grades of MCC and lactose on initial drug release (D_{ini}) and calculated time of 50% drug release (T_{50}).

The specific crushing strength of single pellets showed high values, ranging from 16 to 20 MPa. The statistical analysis showed significant effects of both MCC type and size as well as the grade of lactose, as listed in Table 3. Although significant effects were found, the pharmaceutical relevance is small since only a 0.8 MPa difference in SCS between the 2 particle sizes of MCC and a 0.5 MPa difference between the types of MCC and the lactose grades were found. Owing to their high strength, all the prepared pellets should be able to withstand further processing such as coating and capsule filling.

The drug release from MCC pellets prepared by direct pelletization in rotary processors has been shown to be prolonged¹³ and to follow a square root time release mechanism.⁴ In the current investigation, a complete drug release (>95% wt/wt) occurred after approximately 4 hours. The release profiles could all be fitted well ($r > 0.99$) by Equation 1 in the range where 20% to 75% release. The initial release (D_{ini}) and the calculated time of 50% drug release (T_{50}) are shown in Figure 7. Pellets prepared with Avicel were found to have a significantly larger D_{ini} , but because of a slower release rate (slope in Equation 1), the T_{50} for the Avicel pellets was not significantly longer compared with the Emcocel pellets. It has been proposed that

MCC acts as a particulate undissolved gelling agent during the formation of the pellets.¹⁵ Once dry, MCC pellets are introduced to an aqueous system, and the pellet will take up water and swell and the gel-network will reconstitute. This process will, in turn, immobilize the movement of water within the pellet core and lead to a slow drug release. A difference in the rate and extent of water uptake and swelling of the different types of MCC applied might explain the difference in the determined initial drug release and drug release rate. The reconstituted MCC gel-network was found to have a high physical integrity and even after 24 hours was strong enough to maintain the shape of the original pellet. The high strength of the pellets was also obvious from the disintegration experiments, since no disintegration was observed during any of the disintegration experiments.

CONCLUSIONS

Changes in the particle size of both MCC and lactose as well as the type of MCC were found to have statistically significant effects on the pelletization process and the physical properties of the prepared pellets. However, because the determined effects were generally small and of low pharmaceutical relevance, direct pelletization in a rotary processor controlled by torque measurement was found to be a robust process insensitive to changes of the physical properties of the applied excipients. Since all combinations of the applied excipients produced strong spherical pellets in acceptable yields, changes between different particle sizes as well as manufacturers of the applied standard excipients can be made to a large extent, without markedly changing the physical properties of the prepared pellets. As a result, direct pelletization in a rotary processor controlled by torque measurement is a highly interesting tool in the development of novel pellet formulations.

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