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RESEARCH PAPER

Development of Fast-Disintegrating Pellets in a Rotary Processor

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ABSTRACT

The aim of the present work was to formulate fast-disintegrating pellets by direct pelletization in a rotary processor. Formulations containing kaolin or bentonite and lactose were agglomerated with or without the addition of crospovidone in an instrumented rotary processor. The effects of the excipients on the amount of wall adhesion, the size and size distribution, the disintegration time, and the shape of the agglomerates, as well as the content of agglomerates >2800 μm, were investigated. Further, pellets containing a model drug having a low aqueous solubility were prepared, and the drug dissolution profile was compared to that of pellets containing microcrystalline cellulose (MCC).

Formulations containing kaolin resulted in fast-disintegrating pellets. Pellets containing bentonite eroded, but did not disintegrate, and the formulations gave rise to large amounts of wall adhesion. The addition of crospovidone increased the water content at the end of liquid addition for all formulations, and resulted in slightly more spherical agglomerates. When comparing formulations containing kaolin and MCC, kaolin gave rise to wider size distributions and a higher amount of agglomerates >2800 μm, but the drug dissolution rate was much faster. Complete (100%) drug release was seen after 8 min with the kaolin formulation, whereas only 40% was released after 2 hr from the MCC formulation.

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INTRODUCTION

A fast disintegration of solid dosage forms leading to a fast release of the drug substance at the desired site in the gastrointestinal (GI) tract can offer advantages in terms of increased bioavailability and fast onset of the desired effect for gastro-resistant formulations. When working with gastro-resistant pellets, the focus is normally on the coating, but the behavior of the pellet itself is equally important. Microcrystalline cellulose (MCC) is traditionally used in aqueous pelletization processes. The multistep extrusion/spheronization process is most often used to prepare pellets, but other processes are available. Due to the unique pelletization properties of MCC, pellets can also be prepared in a single-step process in a rotary processor.[1–3] Since the mechanism of agglomerate formation in an extruder is fundamentally different from the gradual agglomerate growth obtained in a rotary processor, the optimal pellet formulation might also be expected to be different.

One disadvantage of MCC is that pellets containing MCC tend to swell in contact with liquid and do not disintegrate.[4–6] According to the model proposed by Kleinebudde,[5] MCC acts as a particulate undissolved gelling agent. During drying, the water is removed from the formed gel network, and the pellets shrink.[7] When the dry pellet is introduced to an aqueous system, the pellet swells and a reconstitution of the gel network occurs. The water within the swollen pellet becomes immobilized by the gel network, which leads to a slow release of the drug by diffusion through the pellet matrix. As a consequence, especially drug substances having a low aqueous solubility are released slowly from pellets containing MCC.[8] The mentioned model has been the subject of debate,[9] and other models exist to explain the role of MCC in pelletization.[10]

The addition of a "super disintegrant" has been shown to increase the release rate of the drug substance from a few pellet formulations containing MCC prepared by extrusion/spheronization,[11–14] but no general effect of super disintegrants on the release rate has been found. In a rotary processor, the addition of croscarmellose sodium as a disintegrant has been found to result in a faster release.[15] However, the addition of super disintegrants like crospovidone using water as granulation liquid was shown to be ineffective with regard to disintegration in extrusion/spheronization.[16] On the other hand, an addition of crospovidone was found to improve the quality of spheronization.[11] Therefore, the addition of a super disintegrant is indicated to be favorable since it will enhance the plasticity, thus improving the spheronization behavior.[11,17]

Identifying an excipient that could substitute MCC and give rise to fast-disintegrating pellets would be advantageous. Little has been published regarding the preparation of MCC-free pellets by aqueous agglomeration processes. Otsuka et al.[18] pelletized lactose, corn starch, and theophylline with an aqueous solution of hydroxypropylcellulose in a spheronizer. Scheler and Nürnberg[19] prepared MCC-free pellets by extrusion/spheronization using a formulation containing two types of povidone, silicium dioxide, and a drug substance using ethanol as the granulation liquid. Basit et al.[20] used a formulation containing 50% of a freely soluble drug substance, 30% of barium sulfate, and 20% of glyceryl monostearate for the preparation of pellets by extrusion/spheronization. The use of bentonite and kaolin as extrusion aids has been mentioned[17,21] without presenting experimental results. The preparation of MCC-free pellets by agglomeration in a rotary processor has not been described up to now.

Kaolin and bentonite are both naturally occurring forms of hydrated aluminum silicates that are insoluble in water. Kaolin is indicated not to swell appreciably in water, whereas bentonite swells to about 12 times its volume.[22] Kaolin is primarily used in oral formulations as a diluent in tablet and capsule formulations, but is also used as a suspending vehicle. Bentonite is primarily applied in suspensions and gels.[23] Bentonite and kaolin were examined in a mixture with MCC and lactose for extrusion/spheronization and found to improve plasticity for the formation of pellets.[24]

The aim of the present study was to investigate the use of hydrated aluminum silicates as potential pelletization aids for the production of fast-disintegrating pellets in a rotary processor.

Table 1

Physical Properties of the Excipients

Materials	Median Diameter (μm)	Span	Surface Area (m^2/g)	Particle Density (g/cm^3)	Poured Density (g/cm^3)	Tapped Density (g/cm^3)	Water Content (% w/w)	Swelling Volume (mL/g)
Kaolin	4.9	2.6	8.1	2.67	0.36	0.55	0.8	1
Bentonite	12	2.2	16.9	2.40	0.59	0.86	8.9	11
MCC	61	1.8	—	1.57	0.33	0.48	5.4	5
Lactose	41	2.7	—	1.54	—	—	5.5	—
Crospovidone	99	1.9	—	1.23	—	—	3.2	4.5

EXPERIMENTAL WORK

Materials

Kaolin [kaolin (heavy)] (ECC International, Cornwall, U.K.), bentonite (Ultramar Sievers & Co., Hamburg, Germany), α-lactose monohydrate (200M) (DMV International, Veghel, The Netherlands), crospovidone and riboflavin (BASF, Ludwigshafen, Germany), and microcrystalline cellulose (Avicel®, type PH-101, FMC International, Cork, Ireland) were used as starting materials. Purified water was used as binder liquid. All materials were of European Pharmacopoeia[25] 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, Worcestershire, U.K.), and the median particle diameter and the span were calculated. The span is defined as the difference between the diameters at the 90 and 10 percentage points relative to the median diameter. The water content on a dry mass basis was determined in duplicate by drying samples in an oven at 105°C until constant mass.

The apparent particle density, the poured and tapped densities, and the surface area were determined in duplicate. The apparent particle density was determined by an AccuPyc 1330 gas displacement pycnometer (Micromeritics, Norcross, GA, USA) using helium purge. The poured and tapped densities were determined using the test for apparent volume as described in the European Pharmacopoeia.[25] The BET multi-point surface area was determined by a Gemini 2375 surface area analyzer (Micromeritics, Norcross, GA, USA).

The swelling volume of kaolin, bentonite, and MCC was determined in duplicate according to "Identification B" for kaolin, heavy[25] as the apparent volume of a sediment produced by adding 2.0 g in 20 portions to 100 mL of a 10-g/L solution of sodium lauryl sulfate in a 100-mL graduated cylinder. The sediment was allowed to stand for 2 hr before reading the volume.

The determined physical properties of the starting materials are shown in Table 1, which lists the mean values of the repeated determinations. For the lactose, water of crystallization is included in the estimated water content.

Pelletization Procedure

An instrumented rotary processor (Glatt GPCG-1.1, Glatt, Binzen, Germany) described previously[3] was used for all the experiments. The instrumentation allows recording of the torque of the rotating friction plate, as well as the inlet and outlet air temperature, the product temperature, the fluidizing air flow rate, and the air gap pressure difference. Temperature and flow rate of the fluidizing air were set to 40°C and 100 m^3/hr, respectively, in all experiments. The starting materials were mixed manually, sieved through a 1.0-mm sieve, and loaded into the equipment, which had been preheated by running empty for 12 min. 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. Purified water was then sprayed tangentially into the moving powder at a rate of 25 g/min using a pneumatic atomizer with a 1.0-mm nozzle diameter, an air dome setting of position 3, and an atomizing air pressure of 2.0 bar. The liquid addition was continued until the torque increase (computed as the difference between the current torque value and the minimum torque value, as previously

described[3]) had reached the desired value. Immediately after stopping the liquid addition, samples were drawn in duplicate for the determination of the water content, and the nozzle was removed. Wet massing was continued for 2 min. The wet pellets were tray-dried at room temperature until constant mass was attained. For the determination of the water content, the samples were dried in an oven at 105°C until constant mass, and the water content was then calculated on a dry mass basis.

Characterization

The amount of adhesion was determined as the dry weight of the material that could be scraped off from the friction plate and the product chamber wall after each experiment, relative to the applied batch size.

The size distribution of the agglomerate fraction that had passed through a 2800-μm sieve was estimated by sieve analysis of a sample of about 75 g drawn from the entire batch using a Laborette 27 automatic rotary cone sample divider (Fritsch, Idor-Oberstein, Germany). A series of 12 ASTM standard sieves (Retsch, Düsseldorf, Germany) in the range of 180–2800 μm was vibrated for 12 min by a Fritsch analysette 3 vibrator (Fritsch, Idor-Oberstein, Germany) using a 7-mm amplitude. The agglomerate size distributions were in good agreement with the lognormal 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 900–1000-μm fraction was saved and used for further characterization.

The agglomerate shape was investigated by light microscopy and image analysis. Thirty to 40 agglomerates were drawn by scooping from the 900–1000-μm fraction and placed on an illuminated desk. Photographs were taken with a digital camera (MTI CCD72EX, DAGE-MTI, USA) connected to a 55-mm lens (Micro-Nikkor, Nikon, Tokyo, Japan) (magnification: 1 pixel = 20 μm) and image analysis was performed on the digital photographs using image processing and analysis software (Global Lab. Image version 2.20, Data Translation Inc., USA). The shape of the agglomerates ($n \approx 100$) was characterized by the aspect ratio (length/width), which describes the deviation in shape from a circle to an ellipse, and by the roundness ($4\pi \times \text{area/perimeter}^2$), which is primarily a measure of surface irregularities. Values of aspect ratio and roundness were calculated for each formulation using data from approximately 100 agglomerates (three photographs). Further, photographs of the same fraction were taken from selected experiments using a scanning electron microscope (SEM) (JSM 5200, Jeol, Tokyo, Japan).

The crushing strength of the agglomerates was determined using an in-house apparatus based on a Gefran pressure sensor (Sensori Industriali, Verona, Italy) with a 5-kg range and a piston speed of 50 μm/sec. The average crushing strength of 10 single agglomerates from the 900–1000-μm fraction was calculated.

The intragranular porosity of the pellets was estimated in duplicate on a sample of 3–4 g from the 900–1000-μm size fraction by a mercury immersion method as described previously.[26]

The pellet disintegration time was determined in 37°C 70 mM phosphate buffer (pH 6.8) using a tablet disintegration apparatus[25] modified with a 420-μm bottom sieve. Twenty agglomerates from the 900–1000-μm fraction were used for each determination, and the determinations were performed in triplicate. The disintegration time was defined as the time when two or less agglomerates were left on the bottom sieve.

Dissolution experiments were performed in duplicate in an Erweka DT 70 (Erweka, Düsseldorf, Germany) dissolution tester. Approximately 1000 mg of pellets or crushed pellets from the 900–1000-μm fraction were added to a dissolution chamber containing 900 mL 37°C 70 mM phosphate buffer (pH 6.8). Paddles rotating at 100 rpm were used, and 5-mL samples were drawn at 0.5, 1, 2, 4, 8, 15, 30, 60, 120, and 240 min. The dissolved amount of riboflavin was determined by UV-measurement at 444 nm using a Perkin-Elmer spectrometer (UV/VIS spectrometer, type Lambda 14P, Perkin-Elmer, Massachusetts) with a 1.0-cm cuvette and UV Winlab software (UV Winlab version 1.1, Perkin-Elmer, Massachusetts). The crushing of pellets was performed manually with a mortar and pestle.

The error bars represent the range, i.e., the difference between the results of two repeated experiments in Figs. 1–3 and 6, and the standard deviation of measurements on approximately 100 agglomerates from the same experiment in Fig. 4.

Experimental Setup

The experimental work was divided into three parts. In the first part, mixtures of lactose [75%

(w/w)] and 25% (w/w) of either bentonite or kaolin were compared. A batch size of 750 g was used. Two different torque increase levels (0.2 and 0.3 Nm) were applied for each mixture. Further, the effect of an addition of 5% (w/w) crospovidone and a corresponding reduction of the lactose content was investigated for all formulations. All experiments were performed in duplicate, giving a total of 16 experiments. In order to identify the most suitable formulation for the preparation of fast-disintegrating pellets, the effects of the different excipients on agglomerate size, size distribution and shape, water content at the end of liquid addition, wall adhesion, amount of oversized agglomerates (>2800 μm), agglomerate crushing strength, and disintegration time were investigated and subjected to statistical analysis (ANOVA) using STATISTICA software (Version 5.1, StatSoft, Oklahoma).

In the second part, the effects of batch size and friction plate rotation speed were investigated by performing a 2^2-factorially designed study with center point. A formulation containing 25% (w/w) kaolin, 70% (w/w) lactose, and 5% (w/w) crospovidone was chosen based on the findings of the first part. All experiments were performed in duplicate giving a total of 10 experiments. The investigated levels were 500 and 1000 g for the batch size and 600 and 1200 rpm for the rotation speed. The response variables were agglomerate size, size distribution and shape, wall adhesion, amount of oversized agglomerates (>2800 μm), and disintegration time. Statistical analysis was performed using STATISTICA software (Version 5.1, StatSoft, Oklahoma). The independent variables, batch size (BS) and friction plate rotation speed (RS), were coded (low level = −1, center point = 0, and high level = 1), and the individual response variables were fitted to the polynomial below by multiple linear regression:

$$y = b_0 + b_1 \times \mathrm{BS} + b_2 \times \mathrm{RS} + b_{12} \times \mathrm{BS} \times \mathrm{RS} \quad (1)$$

In the third part, two formulations containing either 25% (w/w) kaolin or 25% (w/w) MCC, 68% (w/w) lactose, 5% (w/w) crospovidone, and 2% (w/w) riboflavin were pelletized in duplicate to investigate the effect of a substitution of MCC with kaolin on the drug dissolution. Riboflavin was chosen as the model drug substance, because it has previously been used to investigate dissolution from pellets prepared by rotary processing.[8] A batch size of 750 g was used. In order to produce pellets with a mean diameter of approximately 1000 μm, a torque increase of 0.3 Nm was used with the kaolin formulation and 0.7 Nm with the MCC formulation.

RESULTS AND DISCUSSION

Preliminary Experiments

In preliminary experiments, the addition of the super disintegrants crospovidone, sodium starch glycolate (Explotab®), crosslinked sodium starch glycolate (Explotab CL®), or croscarmellose sodium (Ac-Di-Sol®) was visually found to improve the pelletization process. Crospovidone showed the best improvement and was therefore included in the first part. The composition of the formulation used in the first part was based on the findings from preliminary experiments in which the content of kaolin and bentonite, and/or crospovidone was investigated in a mixture with lactose. Kaolin and bentonite were investigated in the range of 15% to 30% (w/w) and crospovidone in the range of 0 to 10% (w/w). The preliminary experiments showed no clear effect of the content of the kaolin or the bentonite on the agglomerate size. Increasing the content from 15 to 25% (w/w) was seen to result in less variation between repeated experiments, but no positive effect was seen with a further increase. A maximum of 5% (w/w) crospovidone was chosen since a further increase was seen to produce more tumbling and less rope-like movement of the mass.

The preliminary experiments showed that wet massing for longer than 2 min after the end of liquid addition gave rise to a larger amount of fines caused by attrition of the agglomerates, primarily with formulations containing kaolin.

Effects of Excipients

The ability of the excipients to absorb water is supposed to affect the pelletization properties since a higher water content might increase the plasticity of the wetted mass. Contrary to kaolin, bentonite is able to absorb a high amount of water,[23] as illustrated by the water contents in Table 1. This explains why the bentonite formulations give rise to significantly ($p = 0.000$) higher water contents than the kaolin formulation at the same torque increase, as can be seen in Fig. 1. The addition of 5% (w/w) crospovidone results in a significant ($p = 0.000$) increase in the water content of approximately 8%

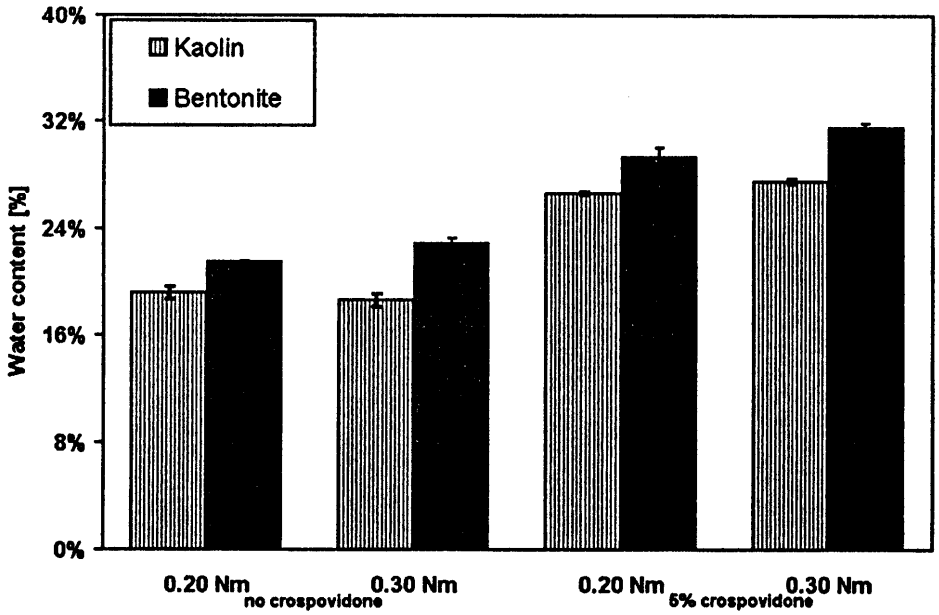

Figure 1. Effects of the level of torque increase (Nm) and the addition of crospovidone on the water content at the end of liquid addition.

(w/w), because crospovidone is able to absorb a large amount of water.[23] As expected, an increase in the torque level resulted in a significant ($p = 0.001$) increase in the water content. The water contents in Fig. 1 are markedly lower than the water contents, around 45% (w/w), found to be necessary in order to produce pellets with the same fraction of MCC instead of kaolin or bentonite in the same rotary processor.[27]

Figure 2 shows the total amount of material that adhered to the friction plate and chamber walls after each experiment. The bentonite formulations give rise to significantly ($p = 0.000$) more adhesion than the kaolin formulations. This might be due to the higher water contents of the bentonite formulations, but other differences in the physical properties (Table 1) might also contribute. Kaolin gave rise to low amounts of adhesion similar to that seen with MCC formulations. Unpublished data from previous experiments[27] with MCC formulations in the same rotary processor showed an adhesion around 10% (w/w). An increase in torque level gave rise to a small significant ($p = 0.000$) increase in the amount of adhesion, whereas the addition of crospovidone had no significant effect on the amount of adhesion.

The differences in the physical properties of the agglomerates are shown in Fig. 3. Kaolin formulations cause 10–20% (w/w) oversized agglomerates, and no clear effect of the torque increase level is seen for these formulations (Fig. 3a). The addition of crospovidone to kaolin is seen to decrease the variation in oversized agglomerates between the repeated experiments, but no significant effect of the addition of crospovidone on the average amount of oversized agglomerates is seen. Practically no oversized agglomerates are obtained with the bentonite formulations.

The bentonite gives rise to significantly ($p = 0.005$) smaller agglomerates than the kaolin (Fig. 3b). This is partly ascribed to a more pronounced shrinkage during drying of the agglomerates containing bentonite, because bentonite swells more than kaolin (Table 1). An increase in torque level as well as the addition of crospovidone results in significantly ($p = 0.000$) larger agglomerates for the bentonite formulation.

For the size distributions (Fig. 3c) no significant effects were found but the distributions are generally slightly wider than those obtained in previous experiments with MCC formulations, where the s_g values were found to be around 1.3.[27]

Figure 4 shows results on the agglomerate shape for formulations containing 75 or 70% (w/w) lactose, no or 5% (w/w) crospovidone, and 25% (w/w) of either kaolin, bentonite, or MCC. Analysis

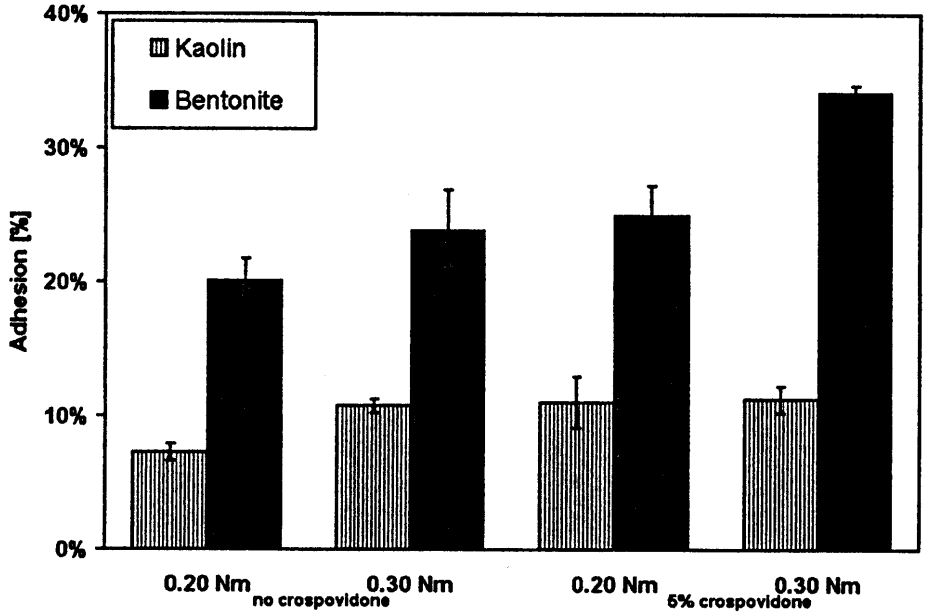

Figure 2. Effects of the level of torque increase (Nm) and the addition of crospovidone on the amount of adhesion [% (w/w)].

of variance showed significant effects for the type of excipients as well as the crospovidone content on both agglomerate shape (aspect ratio) ($p = 0.000$ and 0.003, respectively) and agglomerate smoothness (roundness) ($p = 0.000$ and 0.000, respectively). Figure 4a shows that formulations containing kaolin give rise to less spherical agglomerates than those containing bentonite. The addition of crospovidone causes more spherical agglomerates for both kaolin and bentonite. The most spherical agglomerates are obtained with the MCC formulation. Figure 4b shows similar effects, the smoothest agglomerates being obtained with the MCC formulation. Bentonite results in slightly smoother agglomerates than kaolin. Again, crospovidone has a slight positive effect on the smoothness. The effect of crospovidone on the agglomerate shape is ascribed to an increased plasticity of the mass caused by the swelling of the crospovidone (Table 1).

Table 2 lists the average crushing strength of single agglomerates, as well as the intragranular porosity and the disintegration time of agglomerates from formulations containing 70% (w/w) lactose, 5% (w/w) crospovidone, and 25% (w/w) of either kaolin, bentonite, or MCC. The strength of the agglomerates containing bentonite is seen to be slightly lower than that of the MCC formulation, whereas the kaolin formulation results in a much lower strength. The addition of crospovidone was found to have no effect on the crushing strength, in accordance with previous data.[12] The data in Table 2 indicate that the crushing strength might be related to the intragranular porosity of the agglomerates, since a lower porosity corresponds to a higher strength. The agglomerates containing MCC or bentonite have a denser structure than those containing kaolin due to the difference in swelling properties (Table 1), resulting in a more pronounced shrinkage during drying when the agglomerates contain MCC or bentonite. Accordingly, Kleinebudde[7] found that a shrinkage resulted in a lower porosity.

The disintegration test showed that the agglomerates containing kaolin disintegrated after approximately 15 sec (Table 2). The bentonite formulations did not disintegrate, but could be seen to swell and then slowly erode from the surface. Thus, the fact that kaolin does not swell appreciably (Table 1) could explain the rapid disintegration of the kaolin formulations. Although crospovidone is commonly used as a "super disintegrant,"[28] no clear effect of the addition of 5% (w/w) crospovidone on the disintegration time was found. This is in accordance with results obtained from extrusion/spheronization.[16]

Because of the high amount of adhesion and the slow disintegration seen with the bentonite formulations, kaolin was found to be the most suitable of

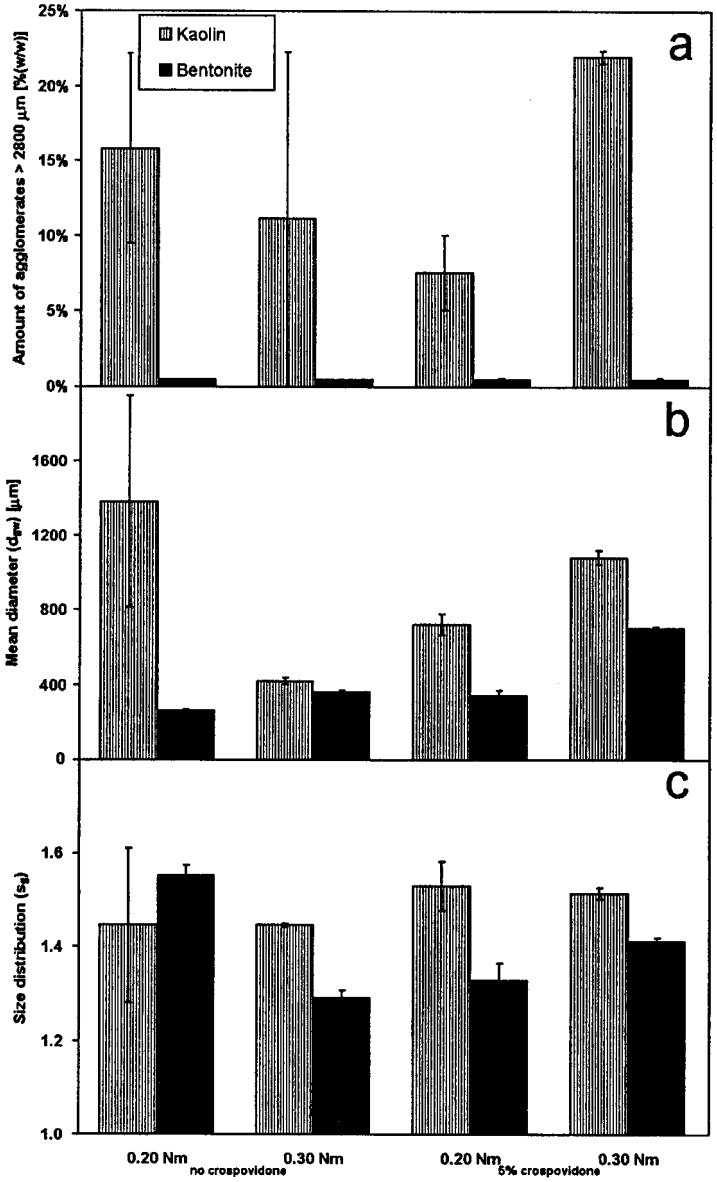

Figure 3. Effects of the level of torque increase (Nm) and the addition of crospovidone on (a) the amount of agglomerates >2800 µm, (b) the agglomerate size, and (c) the agglomerate size distribution.

the excipients for the formulation of fast-disintegrating pellets in a rotary processor. The addition of crospovidone to the kaolin formulation was advantageous, because it resulted in slightly rounder agglomerates without any negative effect on the agglomeration process or the physical properties of the agglomerates. Consequently, a formulation containing kaolin and crospovidone was applied for the remaining experiments.

Effects of Batch Size and Friction Plate Rotation Speed

In order to optimize the physical properties of the agglomerates further, the effects of batch size and rotation speed of the friction plate were investigated by the factorial design mentioned above. The statistical analysis showed significant effects of both independent variables on the mean diameter and the size

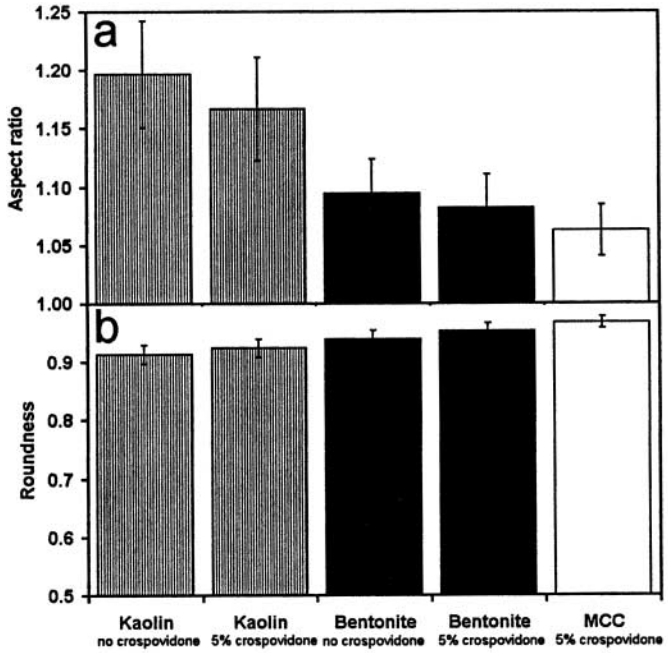

Figure 4. Effects of the excipients on (a) the aspect ratio and (b) the roundness of agglomerates from the 900–1000-μm fraction. Torque increase: 0.30 Nm for bentonite and kaolin, 0.70 Nm for MCC.

Table 2

Effects of the Excipients on the Crushing Strength, Intragranular Porosity and Disintegration Time of Agglomerates from the 900–1000-μm Fraction

	Crushing Strength		Intragranular Porosity		Disintegration Time	
	N	St. Dev.	%	Range	Sec	Range
Kaolin	2.7	0.3	16.9	±0.1	15	±5
Bentonite	10.2	1.2	8.9	±0.1	750[a]	±150
MCC	14.1	0.7	6.1	±0.1	n.d.[b]	—

[a]The agglomerates swelled and eroded slowly from the surface.
[b]No disintegration observed during 24 hr.

distribution, but no significant effects were found on either the adhesion, the amount of oversized agglomerates, or the disintegration time. The results from the statistical analysis are listed in Table 3, and the effects are illustrated in Fig. 5. The effects listed in Table 3 are the coefficients (b_0, b_1, b_2, b_{12}) in Eq. (1). The *r*-values in Table 3 indicate that the fit between the model and the data is better for the mean diameter than for the size distribution. Figure 5 shows that a good reproducibility of the repeated experiments was obtained.

As can be seen (Fig. 5a), a larger batch size results in a markedly smaller mean agglomerate size, and a higher rotation speed causes a slight increase in the mean agglomerate size. Figure 5b shows that the combination of a large batch size and a high rotation speed has to be avoided in order to obtain a narrow size distribution. An investigation of the shape, using light microscopy, revealed no clear effect of either batch size or friction plate rotation speed.

The results from part two have further documented that disintegrating pellets can be prepared

Table 3

Results from the Statistical Analysis

Factor	Mean Diameter (d_{gw}) (μm) $r = 0.975$		Size Distribution (s_g) $r = 0.882$	
	Effect	P	Effect	p
Constant	1183	—	1.43	—
(1) Batch size (g)	−533	(0.000)*	0.09	(0.003)*
(2) Rotation speed (rpm)	99	(0.015)*	0.08	(0.004)*
(1) × (2)	39	(0.227)	0.10	(0.002)*

*Significant at the $p < 0.05$ level.

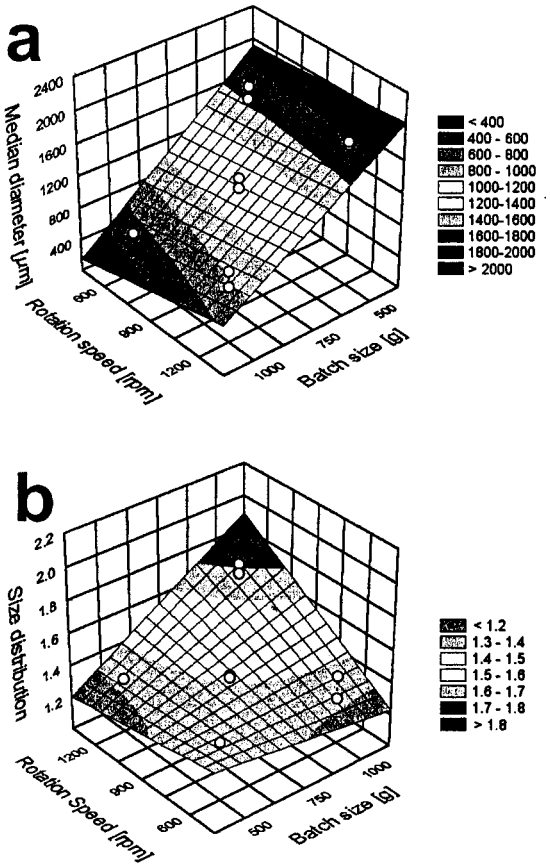

Figure 5. Effects of the friction plate rotation speed and the batch size on (a) agglomerate size, d_{gw}, and (b) agglomerate size distribution, s_g.

in a reproducible way using a formulation based on kaolin. If the combination of a large batch size and a high rotation speed is avoided, the process can be defined as robust since the amount of adhesion, the amount of oversized pellets, the disintegration time, and the size distribution are rather insensitive to variations in batch size and rotation speed. Further, the mean pellet diameter will be controllable by means of the torque increase. Since no optimal level of batch size and rotation speed could be established, the center point setting was used in the third part.

Dissolution

Figure 6 shows that the drug release rate from the MCC formulation is markedly lower than that from the kaolin formulation. After 240 min, only 63% was released from the intact MCC formulation. The release from the MCC formulation showed a linear relationship between the released amount of drug and the square root of time, in accordance with previous results for MCC pellets produced in a rotary processor.[8] No disintegration of the MCC pellets was observed during the dissolution experiment, not even with continued stirring for 24 hr. After the experiment, the pellets were swollen and could easily be deformed. Accordingly, preliminary experiments with formulations containing MCC, lactose, and other super disintegrants like sodium starch glycolate (Explotab®) or croscarmellose sodium (Ac-Di-Sol®) showed no disintegration of the pellets.

For the kaolin formulation, a complete drug release is seen after 8 min, in accordance with the rapid disintegration of these pellets. A crushing of the MCC pellets is seen to enhance the drug release rate significantly, but the release rate is still slower than that seen from the kaolin pellets. This indicates that the small fragments of the crushed MCC pellets are still swelling, resulting in a delayed release of the drug.

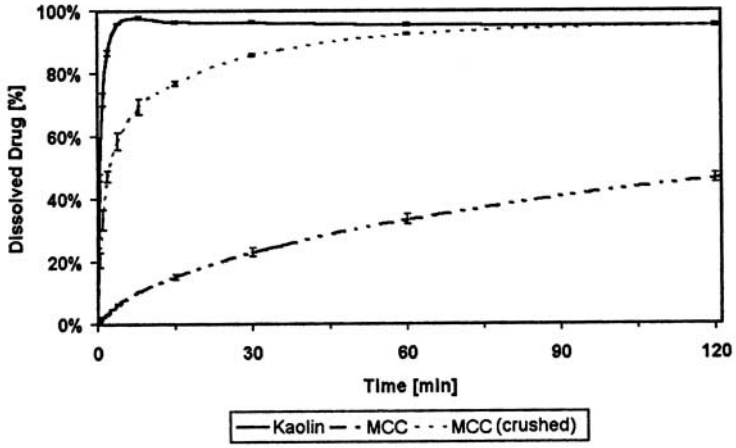

Figure 6. Effect of the excipient on the dissolution of riboflavin from the 900–1000-μm fraction of pellets.

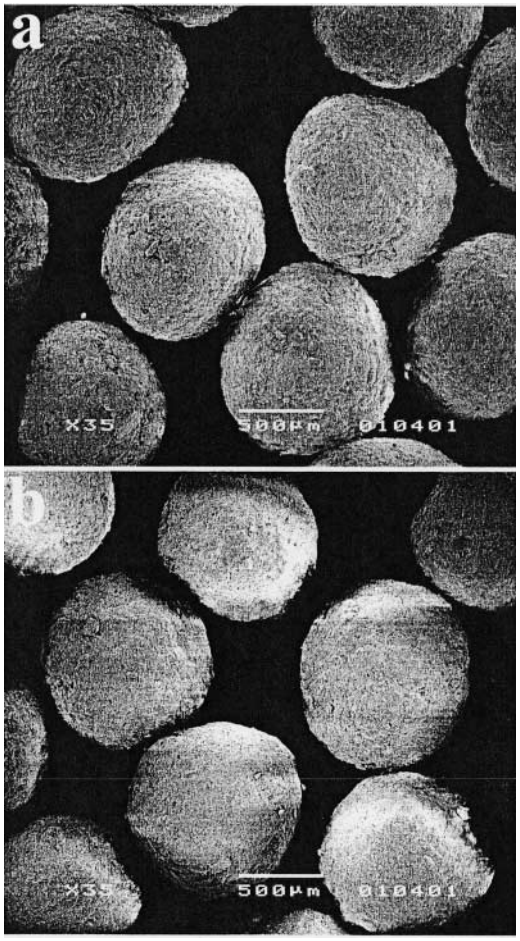

Figure 7. SEM images from the 900–1000 μm fraction of pellets containing (a) kaolin and (b) MCC.

Figure 7 indicates that the kaolin formulation gives rise to pellets of an acceptable sphericity compared with the MCC formulation. The MCC formulation was found to give rise to a lower amount of oversized agglomerates (less than 1% compared to approximately 15%) and a narrower size distribution ($s_g = 1.2$ compared to 1.6) than the kaolin formulation.

CONCLUSIONS

Water-insoluble hydrated aluminum silicates like kaolin or bentonite can be used as potential pelletization aids replacing MCC. Kaolin was found to be the most promising candidate for a pelletization aid, because it allows the formulation of fast-disintegrating and fast-releasing pellets.

REFERENCES

1. Vertommen, J.; Kinget, R. The Influence of Five Selected Processing and Formulation Variables on the Particle Size, Particle Size Distribution, and Friability of Pellets Produced in a Rotary Processor. Drug Dev. Ind. Pharm. **1997**, *23* (1), 39–46.
2. Holm, P.; Bonde, M.; Wigmore, T. Pelletization by Granulation in a Roto-processor RP-2. Part 1. Effects of Process and Product Variables on Granule Growth. Pharm. Technol. Eur. **1996**, *8* (8), 22–36.
3. Kristensen, J.; Schaefer, T.; Kleinebudde, P. Direct Pelletization in a Rotary Processor Controlled by

Torque Measurements. I: Influence of Process Variables. Pharm. Dev. Technol. **2000**, *5* (2), 247–256.
4. Kleinebudde, P. Shrinking and Swelling Properties of Pellets Containing Microcrystalline Cellulose and Low Substituted Hydroxypropylcellulose: II. Swelling Properties. Int. J. Pharm. **1994**, *109* (Sep 5), 221–227.
5. Kleinebudde, P. Crystallite-Gel-Model for Microcrystalline Cellulose in Wet-Granulation, Extrusion, and Spheronization. Pharm. Res. **1997**, *14* (Jun), 804–809.
6. Ghebre-Sellassie, I. *Pharmaceutical Pelletization Technology*; Marcel Dekker: New York, 1989.
7. Kleinebudde, P. Shrinking and Swelling Properties of Pellets Containing Microcrystalline Cellulose (MCC) and Low Substituted Hydroxypropylcellulose (L-HPC): I. Shrinking Properties. Int. J. Pharm. **1994**, *109* (Sep 5), 209–219.
8. Vertommen, J.; Kinget, R. Influence of Five Selected Processing and Formulation Variables on the Release of Riboflavin from Pellets Produced in a Rotary Processor. STP Pharma Sci. **1996**, *6* (5), 335–340.
9. Ek, R.; Newton, J.M. Microcrystalline Cellulose as a Sponge as an Alternative Concept to the Crystallite-Gel Model for Extrusion and Spheronization. Pharm. Res. **1998**, *15* (4), 509–512.
10. Fielden, K.E.; Newton, J.M.; O'Brien, P.; Rowe, R.C. Thermal Studies of the Interactions of Water and Microcrystalline Cellulose. J. Pharm. Pharmacol. **1988**, *40*, 674–678.
11. Lövgren, K. Disintegrants and Fillers in the Manufacture of Spheres—Their Influence on Dissolution Rates and Binding Properties. Labo-Pharma—Probl. Tech. **1984**, *32* (339), 110–114.
12. Lövgren, K.; Bogentoft, C. Influence of Different Disintegrants on the Dissolution Rate and Hardness of Furosemide Granules Prepared by Spheronization Technique. Acta Pharm. Suec. **1981**, *18*, 108–109.
13. Schröder, M.; Kleinebudde, P. Influence of Formulation Parameters on Dissolution of Propyphenazone Pellets. Eur. J. Pharm. Biopharm. **1995**, *41* (6), 382–387.
14. Nürnberg, E.; Wunderlich, J. Manufacturing Pellets by Extrusion and Spheronization (Part II). Pharm. Technol. Eur. **1999**, *11* (3), 30–34.
15. Neumerkel, O.; Sakr, A.; Süss, W. Studies of the Production and Testing of Fluidized-Bed Rotor Granules with Modified Release. Pharmazie **1999**, *54* (11), 837–839.
16. Schröder, M.; Kleinebudde, P. Development of Disintegrating Pellets Obtained from Extrusion/Spheronization. Pharm. Sci. **1995**, *1*, 415–418.
17. Lövgren, K. Pellet Preparation. In *Industrial Aspects of Pharmaceutics*; Sandell, E., Ed.; Swedish Pharmaceutical Press: Stockholm, 1993; 210.
18. Otsuka, M.; Gao, J.; Matsuda, Y. Effect of Amount of Added Water During Extrusion–Spheronization Process on Pharmaceutical Properties of Granules. Drug Dev. Ind. Pharm. **1994**, *20* (19), 2977–2992.
19. Scheler, S.; Nürnberg, E. Optimierung Eines Sphäronisationsprozesses für die Herstellung Lipase-Haltige Extrusionpellets mittels Faktorieller Versuchsplanung. Pharm. Ind. **2000**, *62* (3), 236–242.
20. Basit, A.W.; Newton, J.M.; Lacey, L.F. Formulation of Ranitidine Pellets by Extrusion–Spheronization with Little or No Microcrystalline Cellulose. Pharm. Dev. Technol. **1999**, *4* (4), 499–505.
21. Fielden, K.E.; Newton, J.M. Extrusion and Extruders. In *Encyclopedia of Pharmaceutical Technology*; Swarbrick, J., Boylan, J.C., Eds.; Marcel Dekker: New York, 1992; Vol. 5, 395–442.
22. Harwood, R.J.; Luber, J.R.; Sunbery, E.W. Antacids and Clay Products. In *Pharmaceutical Dosage Forms—Disperse Systems*; Liebermann, H.A., Rieger, M.M., Banker, G.S., Eds.; Marcel Dekker: New York, 1989; 205–229.
23. Kibbe, A.H. *Handbook of Pharmaceutical Excipients*, 3rd Ed.; Pharmaceutical Press: London, 2000.
24. Law, M.F.L.; Deasy, P.B. Effects of Common Classes of Excipients on Extrusion–Spheronization. J. Microencaps. **1997**, *14* (5), 647–657.
25. *European Pharmacopoeia*, 3rd Ed.; Council of Europe: Strasbourg, 1997.
26. Johansen, A.; Schæfer, T. Effects of Interactions Between Powder Particle Size and Binder Viscosity on Agglomerate Growth Mechanisms in a High Shear Mixer. Eur. J. Pharm. Sci. **2001**, *12*, 297–309.
27. Kristensen, J.; Schaefer, T.; Kleinebudde, P. Direct Pelletization in a Rotary Processor Controlled by Torque Measurement. II: Effect of Changes in the Content of Microcrystalline Cellulose. AAPS Pharm. Sci. **2000**, *2* (3), article 24 (http://www.pharmsci.org/).
28. Gordon, M.S.; Rudraraju, V.S.; Dani, K.; Chowhan, Z.T. Effects of the Mode of Super Disintegrant Incorporation on Dissolution in Wet Granulated Tablets. J. Pharm. Sci. **1993**, *82* (2), 220–226.