Wet Granulation in Rotary Processor and Fluid Bed: Comparison of Granule and Tablet Properties

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ABSTRACT

The aim of the present study was to investigate and compare granule and tablet properties of granules prepared by wet granulation in a rotary processor or a conventional fluid bed. For this purpose the working range of selected process variables was determined and a factorial study with 3 factors (equipment type, filler type, and liquid addition rate) and 1 covariate (fluidizing air flow rate) was performed. Two grades of calcium carbonate with different size and shape characteristics were applied, and the liquid addition and fluidizing air flow rates were investigated in the widest possible range. Dry mixtures of microcrystalline cellulose, polyvinyl povidone, calcium carbonate, and riboflavin, in a 10:5:84:1 ratio, were granulated in both types of equipment. The granulation end point was determined manually in the fluid bed and by torque measurements in the rotary processor. The filler type had a more pronounced effect on granular properties in the fluid bed, but the rotary processor showed a higher dependency on the investigated process variables. The rotary processor gave rise to more dense granules with better flow properties, but the fluid bed granules had slightly better compressional properties. Furthermore, the distribution of a low-dose drug was found to be more homogeneous in the rotary processor granules and tablets. Generally, wet granulation in a rotary processor was found to be a good alternative to conventional fluid bed granulation, especially when cohesive powders with poor flow properties or formulations with low drug content are to be granulated by a fluidizing air technique.

KEYWORDS: Wet granulation, fluid bed, rotary processor.

INTRODUCTION

Wet granulation is an important process in the formulation of solid dosage forms in the pharmaceutical industry. The main purposes of the granulation procedure are to enhance the flow properties of the powder blends and to decrease dust problems in the handling of the powder blends. Most often, fluid bed or high shear mixer granulation is used for the wet granulation of pharmaceutical formulations. An alternative to the conventional choice of equipment is the agitation fluid bed, in which an impeller is incorporated into the bottom of the fluidizing column.[1] A second, newer alternative for wet granulation of pharmaceutical powders is the rotary processor. This equipment is also a modified version of a fluid bed in which the diameter of the bottom of the fluidizing column has been increased and a rotating friction plate has been installed. The fluidizing air enters the fluidizing chamber through a small gap between the rotating friction plate and the wall of the product chamber. Several different names, such as rotary processor,[2] rotary fluidized bed,[3] rotary fluid bed granulator,[4] rotor fluidized bed granulator,[5] or fluid bed roto-granulator,[6] have been used in the literature. In this article, the term *rotary processor* is used. Most of the literature regarding wet granulation in a rotary processor has investigated the preparation of pellets by direct wet pelletization, as reviewed by Gu et al.[7] The effect of process variables[8,9] and formulation variables[10,11] on direct pelletization has been investigated, and the process has been compared with the conventional extrusion spheronization process for the formation of pellets.[12] In most of the literature, mixtures of microcrystalline cellulose (MCC) and lactose are used as starting materials and water is used as the binder liquid. Generally, direct pelletization in a rotary processor has been found to be a sensitive process that depends on suitable starting materials and a high degree of control over process variables. The water content at the end of the liquid addition has been found to be the most influential parameter in wet granulation in the rotary processor,[2] so a high level of control over this parameter is needed. One method by which this high level of control can be achieved is monitoring the torque of the rotation friction plate.[8]

Although the rotary processor has been commercially available for several decades, few researchers seem to have published studies of the preparation of granules in the rotary processor and the compression of these granules into tablets. Jäger and Bauer investigated and compared granulation in a rotary processor and a conventional fluid bed using the same formulation and process variables in both

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Table 1. Characterization of Starting Materials*

Excipient	Particle Size (μm)	Surface Area (m^2/g)	Pycnometric Density (g/mL)	Poured Bulk Density (g/mL)	Tapped Bulk Density (g/mL)	Carr Index (%)
Sturcal ($CaCo_3$)	9 (0.5)	2.90 ± 0.17	2.63 (0.01)	0.59 ± 0.00	0.88 ± 0.01	32.9 ± 0.9
Scoralit ($CaCo_3$)	29 (2)	0.49 ± 0.00	2.71 (0.01)	1.31 ± 0.01	1.69 ± 0.00	22.2 ± 0.5
MCC	123 (4)	—	1.57 (0.01)	0.38 ± 0.00	0.46 ± 0.00	17.0 ± 0.7
PVP	118 (2)	—	1.16 (0.05)	0.36 ± 0.00	0.43 ± 0.00	17.5 ± 0.6

*MCC indicates microcrystalline cellulose; PVP, polyvinyl povidone.

types of equipment.[4] They found that the very homogeneous ropelike movement of the powder bed in the rotary processor allows for considerably higher spraying rates than in a traditional fluid bed granulator, in spite of a lower air flow rate.[4] They explained that this resulted from the more intense and uniform material motion in the rotary processor, caused by the unique cooperation between the centrifugal forces, gravity, and the fluidizing air. Compared with granules from conventional fluid bed granulators, spherical granules from a rotary processor possess higher apparent densities, higher tapped and bulk densities, and lower porosities.[4] In another study,[3] the rotary processor was found to produce a better drug content uniformity for tablets, compared with literature findings from conventional fluid bed granules. This was found to be the case even at low active levels such as 1%.[3]

The aim of the current study was to directly compare rotary processor and fluid bed granulation in laboratory scale equipment and to investigate the effect of formulation and process variables on granule and tablet properties.

Materials and Methods

Materials

MCC (Avicel, type PH102, FMC International, Cork, Ireland), calcium carbonate (Scoralit, Scora SA, Caffiers, France; and Sturcal L, Specialty Minerals, Lifford, UK), and polyvinyl povidone (Povidone) (PVP K-30, BASF, Ludwigshafen, Germany) were used as starting materials. All materials were of European Pharmacopoeia grade, as stated by the suppliers. The determined physical properties of the starting materials are shown in Table 1. Purified water was used as the granulation liquid. The droplet size characteristics of the atomized granulation liquid are shown in Table 2. Riboflavin (BASF) was used as the marker compound.

Experimental Design

A factorial designed study with 3 categorical independent variables (factors) and one continuous predictor variable (covariate) was performed. The 3 factors were investigated at 2 levels and the covariate was investigated at 2 levels for each of the combinations of the independent variables. Each experiment was performed in duplicate, giving a total of 32 granulation experiments. The included factors were the type of granulation equipment, the filler type (grade of calcium carbonate), and the liquid addition rate; and the covariate was the fluidizing air flow rate. The composition of the applied formulations is shown in Table 3, and the experimental setup is shown in Table 4. PVP was used as a dry binder, and water was used as a binder liquid to allow for torque-controlled end point determination in the rotary processor without changes in the composition of the prepared agglomerates.

The included response variables were loss of material (LOM), amount of oversized granules, granular bulk density and porosity, granular size and size distribution, granular flow properties (Carr index and tablet mass deviation), tablet crushing strength, tablet porosity, and tablet disintegration time. In addition, the distribution of drug marker in different size fractions was investigated.

The results were subjected to statistical analysis of covariance using the general linear models module in STATISTICA (Statistica, Version 7.0, StatSoft Inc, Tulsa, OK) to analyze the

Table 2. Droplet Size Determinations

Nozzle Type	Liquid Flow Rate	Mean Droplet Size ($d_{0.5}$) μm (n = 2)	Span* (n = 2)
Rotary processor	Low (30 g/min)	19.8 ± 0.1	1.60 ± 0.06
	High (55 g/min)	21.7 ± 0.1	2.74 ± 0.01
Fluid bed	Low (30 g/min)	25.6 ± 0.2	1.29 ± 0.01
	High (55 g/min)	27.3 ± 0.2	1.40 ± 0.04

*$(d_{0.9}-d_{0.1})/d_{0.5}$

Table 3. Composition of the Investigated Formulations*

Formulation: Blend A			Formulation: Blend B		
Material	Fraction (%)	Amount (g)	Material	Fraction (%)	Amount (g)
Avicel PH102	10	82.5	Avicel PH102	10	82.5
Povidone K-30	5	41.25	Povidone K-30	5	41.25
Sturcal L	84	693	Scoralit	84	693
Riboflavin	1	8.25	Riboflavin	1	8.25

*Total batch size: 825 g.

effect of the categorical independent variables (factors), controlling for the effects of the continuous predictor variable. Effects with a P value below .05 were denoted significant.

Fluid Bed Granulation

A Glatt GPCG-1 (Glatt GPCG-1.1; Glatt, Binzen, Germany) mounted with the fluid bed column was used. The starting materials (825 g) were mixed manually (preblend), sieved through a 0.5-mm sieve, and loaded into the equipment, which had been preconditioned for approximately 10 minutes. The inlet air temperature was set to 25°C, and the fluidizing air flow was set according to the experimental setup, listed in Table 4. The granulation liquid was sprayed onto the fluidized powder bed using a pneumatic atomizer at a 1.0-bar atomizing air pressure. The fluid bed nozzle (Schlick 970/0-S3, Düsen-Schlick GmbH, Coburg, Germany), equipped with a 1.0-mm tip orifice and a 6.5-mm air dome spacer ring, was placed in the lower nozzle inlet, which was approximately 15 cm above the resting powder bed. The liquid addition rate was set according to the experimental setup. The liquid addition was terminated once the agglomerates had reached a suitable size, judged visually by the operator. After the liquid addition, the granules were dried in the equipment by increasing the fluidizing air flow rate by 80% until the product temperature had risen to room temperature. The dried granules were placed in open containers and stored at room temperature.

Rotary Processor Granulation

A Glatt GPCG-1 (Glatt GPCG-1.1) mounted with the rotary processor inset, which was equipped with a cross-hatched friction plate, was used. The starting materials (825 g) were mixed manually (preblend), sieved through a 0.5-mm sieve, and loaded into the equipment, which had been preconditioned for approximately 10 minutes. The inlet air temperature was set to 25°C, and the fluidizing air flow was set according to the experimental setup, listed in Table 4. The air gap pressure difference was set to 2.0 kPa by elevating

Table 4. Experimental Setup for the 3 Categorical Independent Variables and the Continuous Predictor Variable*

	Categorical Independent Variables			Continuous Predictor Variable
Batch	Equipment	Calcium Grade	Binder Addition Rate†	Fluidizing Air Flow‡
1a-b	RP (–1)	Sturcal (–1)	Low (–1)	Low (40)
2a-b	RP (–1)	Sturcal (–1)	Low (–1)	High (50)
3a-b	RP (–1)	Sturcal (–1)	High (1)	Low (45)
4a-b	RP (–1)	Sturcal (–1)	High (1)	High (60)
5a-b	RP (–1)	Scoralit (1)	Low (–1)	Low (35)
6a-b	RP (–1)	Scoralit (1)	Low (–1)	High (45)
7a-b	RP (–1)	Scoralit (1)	High (1)	Low (40)
8a-b	RP (–1)	Scoralit (1)	High (1)	High (60)
9a-b	FB (1)	Sturcal (–1)	Low (–1)	Low (60)
10a-b	FB (1)	Sturcal (–1)	Low (–1)	High (70)
11a-b	FB (1)	Sturcal (–1)	High (1)	Low (60)
12a-b	FB (1)	Sturcal (–1)	High (1)	High (90)
13a-b	FB (1)	Scoralit (1)	Low (–1)	Low (30)
14a-b	FB (1)	Scoralit (1)	Low (–1)	High (40)
15a-b	FB (1)	Scoralit (1)	High (1)	Low (35)
16a-b	FB (1)	Scoralit (1)	High (1)	High (60)

*Values in parentheses were used in the statistical analysis. RP indicates rotary processor; FB, fluid bed.
†Low: 30 g/min; high: 55 g/min.
‡Flow in m^3/h.

the friction plate, and the rotation of the friction plate was started at 900 rpm. The granulation liquid was then sprayed tangentially into the moving powder using a pneumatic atomizer at a 1.0-bar atomizing air pressure. The liquid addition rate was set according to the experimental setup. The rotary processor nozzle (Schlick 970/0-S3, Düsen-Schlick GmbH) was equipped with a 1.0-mm tip orifice and a 3-mm air dome spacer ring. The granulation end point was determined by torque measurements, and the water addition was terminated when a 0.15-Nm increase in the torque of the friction plate was reached. The torque increase was computed as the difference between the current torque value and the minimum torque value, as described elsewhere.[8] After the liquid addition, the granules were dried in the equipment by increasing the fluidizing air flow rate by 80% until the product temperature had risen to room temperature. After drying, the prepared agglomerates were stored in open containers at room temperature.

Tablet Manufacture

The granules were compressed, without lubrication, into 600-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 with a 100-MPa (10 kN per cm^2) compressional pressure. The compression force was measured on the lower punch and set by adjusting the downward movement of the upper punch. The prepared tablets were characterized according to uniformity of mass (relative SD), specific crushing strength (SCS), tablet porosity, and disintegration time.

Determination of Droplet Size

The droplet size and size distribution (span) were determined in duplicate for both the rotary processor and the fluid bed nozzles using a Malvern 2600 C Particle Sizer (Malvern Instruments Ltd., Malvern, Worchestershire, UK) equipped with a 100-mm lens. The determinations were performed as described above.[13]

Characterization of Starting Materials and Granules

The size distribution by volume of the starting materials was determined in triplicate by a Malvern 2601Lc laser diffraction particle sizer (Malvern Instruments), and the median particle diameter and range of repeated experiments were reported.

The pycnometric density of the starting materials was determined by an AccuPyc 1330 gas displacement pycnometer (Micromeritics, Norcross, GA) using a helium purge (n = 6).

The poured (p_o) and tapped bulk densities (p_k) of the starting materials, preblends, and granules were determined in duplicate using the test for apparent volume as described in the European Pharmacopoeia 4th edition, and the Carr index (K) was calculated according to Equation 1:

$$K = \left(\frac{pk - p0}{pk}\right) \bullet 100\% \qquad (1)$$

The granular porosity (ε), including inter- and intragranular voids, was calculated according to Equation 2:

$$\varepsilon = 1 - \left(\frac{p^k}{p}\right), \qquad (2)$$

where p is the pycnometric density of the applied preblend of the starting materials (g/mL).

The surface area of the calcium carbonates was determined in duplicate by the Brunauer-Emmett-Teller (BET) multipoint method (Gemini 2375 Surface Area Analyzer, Micromeritics.)

The LOM due to adhesion and filter penetration was determined as the difference in mass between the starting materials and the granules relative to the mass of the starting materials. The amount of the oversized granules (>2800 μm) was determined 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 ~80 g drawn from the entire batch using a Laborette 27 automatic rotary cone sample divider (Fritsch, Idar-Oberstein, Germany). A series of 9 ASTM standard sieves (Retsch, Haan, Germany) in the range of 75 to 2000 μm were vibrated for 10 minutes by a Fritsch analysette 3 vibrator (Fritsch) using a 3.5-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 SD (s_g).

Granules from selected experiments were investigated using a scanning electron microscope (SEM) (JSM 5200, Jeol, Tokyo, Japan).

The content of riboflavin was determined by UV measurement. Granule samples of approximately 0.15 g were dispersed in water and filtered, and the UV absorbance was measured at 444 nm (UV spectrometer UV-160A, Shimadzu, Kyoto, Japan). The content was determined in 3 fractions: fines (smaller than 125 μm), medium granules (between 125 μm and 355 μm) and large granules (larger than 355 μm).

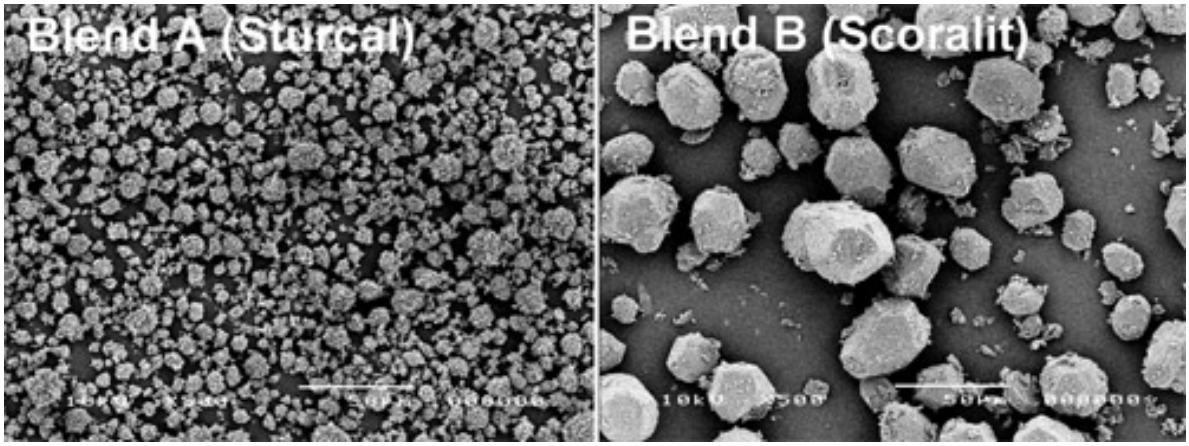

Figure 1. Scanning electron microscope pictures of the applied calcium carbonate grades Sturcal (Blend A) and Scoralit (Blend B). Magnification ×500.

Characterization of Tablets

SCS of the tablets was determined as the crushing strength divided by the cross-sectional area of the tablets. SCS for each batch was calculated as an average of 20 randomly drawn tablets. The crushing strength of the tablets was determined by a standard tablet hardness tester (Schleuniger 8M tablet hardness tester, Schleuniger, Horgen, Switzerland). The tablet height, applied to calculate the cross-sectional area and the tablet volume, was determined using a digital height-measuring device (Digital Indicator, type IDF-130, Mitutoyo Corporation, Kawasaki, Japan). The tablet porosity was calculated according to Equation 3:

$$\varepsilon tablet = 1 - \left(\frac{\left(\frac{m_{tablet}}{p} \right)}{v_{tablet}} \right) \qquad (3)$$

where m_{tablet} is the tablet mass (g), p is the pycnometric density of the applied preblend of the starting materials (g/mL), and v_{tablet} is the tablet volume (mL).

The tablet uniformity of mass was determined as the relative SD of 20 randomly drawn tablets.

The tablet disintegration time, an average of the disintegration times of 6 randomly drawn tablets, was determined by the standard European Pharmacopeia[14] method in 37°C demineralized water. The tablet friability was determined by the standard European Pharmacopeia[14] method using 10 randomly drawn tablets.

Images of the tablets were made with a digital camera (Infinity X, DeltaPix, Maalov, Denmark) equipped with a 60-mm lens (60mm f/2.8D AF Micro-Nikkor, Nikon, Tokyo, Japan).

Results and Discussion

Two different grades of calcium carbonate were chosen as model fillers. The physical properties of the starting materials are shown in Table 1, and the particle shapes of the applied calcium carbonate grades are shown in Figure 1. Because of the small particle size and irregular surface structure of Sturcal L, Blend A can be characterized as cohesive, whereas Blend B is more free-flowing because of the larger particle size and regular particle shape of Scoralit.

A series of preliminary experiments were performed to establish the lowest and highest rates of liquid addition and fluidizing air flow that would result in a successful granulation with both types of equipment and formulations. The criteria for a successful granulation were visible agglomerate growth within 20 minutes of liquid addition and low amounts of adhesion and oversized granules, as well as a good movement or fluidization of the powder blend throughout the process. Figure 2 shows the working areas as they appear when the determined boundary points are

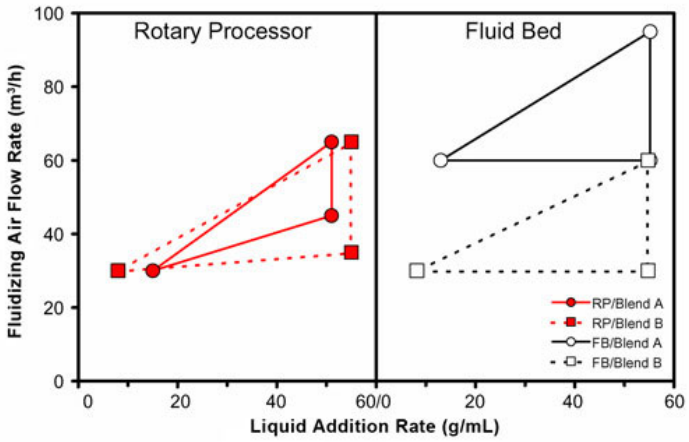

Figure 2. The determined working ranges of the RP and the FB. RP indicates rotary processor; FB, fluid bed.

Table 5. Resulting *P* and R^2 Values From the Statistical Analysis for the Investigated Process and Granule Response Variables*

Variable	LOM R^2 0.746	Bulk Density R^2 0.960	Granular Porosity† R^2 0.965	Carr Index R^2 0.774	Relative SD Mass‡ R^2 0.734	$d_{(gw)}$ ∫ R^2 0.663	$s_{(g)}$ ‖ R^2 0.753
Air flow	0.757	0.075	0.150	0.196	0.344	**0.034**	0.078
(A) Equipment	**0.000**	**0.000**	**0.000**	**0.000**	0.062	**0.002**	**0.002**
(B) Filler type	0.099	**0.000**	**0.000**	0.125	0.858	0.991	**0.000**
(C) Addition rate	0.114	**0.008**	**0.004**	0.512	0.863	0.111	0.166
A * B	0.132	**0.009**	0.051	**0.007**	**0.023**	**0.008**	0.749
A * C	**0.016**	**0.003**	**0.010**	0.077	0.071	**0.010**	0.388
B * C	0.917	0.356	0.794	0.141	0.548	0.077	0.761
A * B * C	0.963	0.426	0.453	0.696	0.650	0.119	0.186

*Bold values indicate significant effect ($P < .05$). LOM indicates loss of mass during granulation.
†Porosity including inter- and intragranular voids.
‡Relative SD of tablet mass (n = 20).
∫Mean diameter.
‖Size distribution.

connected. The application of settings outside of the determined working areas will give rise to problems such as blocking of the bag filters, insufficient fluidization of the powder bed, lengthy process times, adhesion, and snowball formation. The values of liquid addition and fluidizing air flow rate used in the factorial designed study were chosen to give the widest possible range with a minimal difference of 10 m^3/h between the high and low levels of fluidizing air flow. The determined working ranges are valid for only the applied process and formulation variables, and changes in parameters like batch size or inlet air temperature will shift the working range batch size. The similar working range of liquid addition rate for the 2 types of equipment (approximately 10-55 g/min), seen in Figure 2, contradicts previous suggestions that the increased agitation of the powder bed in the rotary processor would allow for higher liquid addition rates.[4] These findings were not based on laboratory scale equipment, which might explain the difference. For each combination of equipment, filler type, and liquid addition rate, a different range of fluidizing air flow rates was found, as shown in Figure 2. Blend A required a higher fluidizing air flow rate than Blend B for successful fluidization in the fluid bed. This could be expected since Blend A contains the small, irregularly shaped calcium carbonate grade, whose cohesive nature can be seen in the high Carr index and low bulk density, as listed in Table 1. The fact that only a small difference in the working range was found for the rotary processor could suggest that granulation in the rotary processor is less sensitive to the flow properties of the powder bed than is conventional fluid bed granulation, and that the rotary processor might be able to successfully granulate powder blends that are too cohesive for fluid bed granulation.

Two different nozzles and 2 different liquid addition rates were applied in the present investigation. Only a minor difference in the droplet size was found, as listed in Table 2. Possible effects on the investigated response variables due to differences in droplet size could therefore be disregarded.

The amount of binder liquid needed for agglomerate growth to occur ranged from 100 to 500 g with a maximum difference between repeated experiments of approximately 30 g. This shows the necessity of using the torque or visual end point determination method and not adding a certain amount of binder liquid. Generally only a small effect of liquid addition rate and fluidizing air flow rate was seen in both types of equipment. An effect of the applied blend was seen in both types of equipment, with Blend A needing approximately 300 g in the rotary processor and approximately 500 g in the fluid bed, whereas Blend B needed approximately 150 g in the rotary processor and approximately 100 g in the fluid bed.

High yields are important, especially from an industrial perspective. LOM due to either adhesion to the equipment walls or filter penetration during the granulation procedure is nevertheless inevitable. The average LOM was 8% in the fluid bed and 20% in the rotary processor. Statistically significant effects were found for the equipment type as well as for the interaction between equipment type and liquid addition rate, as listed in Table 5. The high LOM in the rotary processor is caused by material adhering to the rotating friction plate. In the present experiments a plate with a cross-hatched pattern was used. Application of a smooth plate might reduce the high LOM found in the rotary processor. Higher liquid addition rates gave rise to higher LOM in the rotary processor but not in the fluid bed, which explains the significant interaction between equipment type and liquid addition rate, listed in Table 5. High amounts (15%) of oversized granules were found in the rotary processor for batches prepared from Blend B at high liquid addition rates and high air flow rates (batches 8a and 8b). All other experiments produced no or less than 1% oversized granules and, because of the lack of response, no statistical

analysis was performed. The experiments that gave rise to high amounts of oversized granules also resulted in a large mean granule size. Figure 3 shows the effect of the investigated variables on granule size and size distribution. Because of the large amount of oversized granules and the large granule size found with batch 8, the applied torque increase, used to determine the end point of liquid addition, was not optimal for this batch. Generally, good reproducibility of the granule size was achieved for the repeated experiments. Only a small effect of the investigated variables can be seen in the fluid bed, where the mean diameter ranges from 215 to 295 µm. The lack of effect could be expected since the granulation process was terminated when a certain size was achieved, judged visually by the operator. In the rotary processor, where the end point was controlled by torque measurements, the granule size ranged from 200 to 850 µm. The good reproducibility between repeated experiments indicates that torque measurements can be used to determine the end point in rotary processor granulation. The statistical analysis gave rise to significant effects, as shown in Table 5. They are difficult to interpret because of the different methods by which the size was controlled in the 2 equipment types. It is clear that a wider size range of granules is obtainable in the rotary processor than in the fluid bed. This is an advantage, especially if the granules are intended for further processing, such as enteric coating or taste masking. The size distribution of the prepared granules, shown in Figure 3, also showed good reproducibility. Significant effects were found for equipment and filler type, with the rotary processor giving rise to lower s_g values, and thus a more narrow size distribution. Blend A, which used the more cohesive filler type, gave rise to wider particle size distributions for both types of equipment. A lower amount of fines in the granules from the rotary processor might explain the more narrow size distribution obtained with this equipment. The lower amount of fines in the rotary processor might be explained by a higher amount and a more homogeneous distribution of liquid at the surface of the granules, which would promote the coalescence between fines and granules. It might have been expected that higher amounts of fines would be seen in the rotary processor because of attrition during drying due to the contact between granules and the rotating friction plate. The fact that no increased attrition was seen in the rotary processor might be explained by the adhesion of material to the friction plate, which would reduce the friction between the plate and the granules.

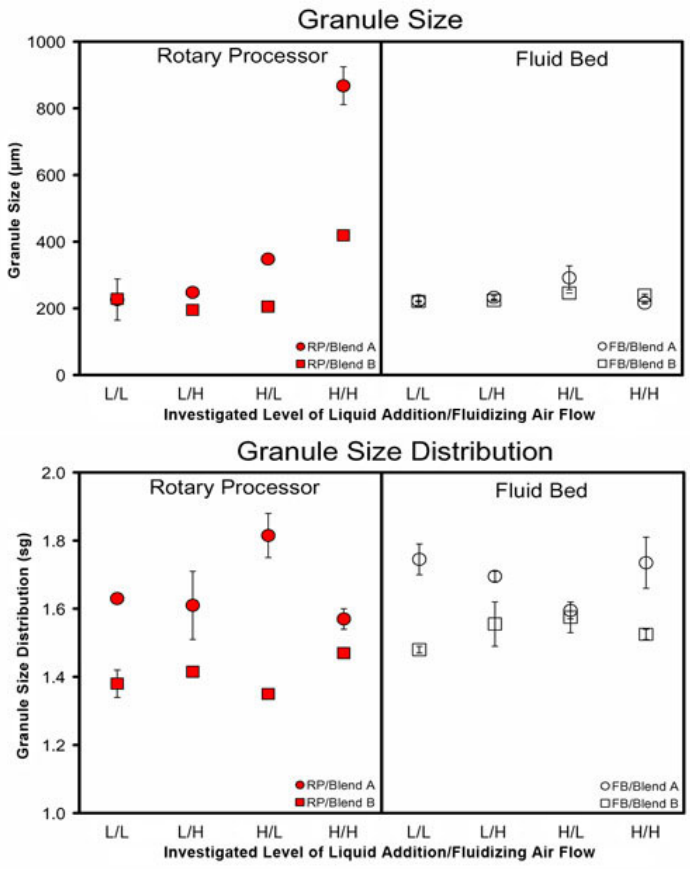

Figure 3. Effects of the investigated variables on granule size and granule size distribution. RP indicates rotary processor; FB, fluid bed; L, low; H, high. Error bars indicate the range of repeated experiments.

A great effect of the increased agitation of the powder bed in the rotary processor is seen in the determined bulk densities. The average bulk density of the rotary processor batches was approximately 0.9 g/mL compared with 0.6 g/mL in the fluid bed. This corresponds to a 30% decrease in volume when changing from the fluid bed to the rotary processor. The statistical analysis gave rise to several significant effects, as listed in Table 5. Blend B gave rise to higher bulk densities than Blend A, which could be expected because of the higher bulk density of filler (Scoralit), listed in Table 1, in this blend. A higher liquid addition rate was also found to increase the bulk density. This effect was most pronounced in the rotary processor, which explains the significant interaction found between equipment and liquid addition rate. The granular porosity was significantly lower in the rotary processor because of the increased agitation. An average of 60% was found in the rotary processor and 70% in the fluid bed. Filler type and liquid addition rate also gave rise to significant effects, as listed in Table 5. Based on the SEM pictures, it might be expected that Blend A would give rise to lower porosities than Blend B. However, because of the irregular particle shape of the filler in Blend A, Blend B gave rise to porosities that were statistically significantly lower than those of Blend A.

The granular flow properties are another important parameter in an industrial perspective. They are influenced by parameters such as granular density, shape, and surface structure. The Carr index is often applied to quantify the

flow properties. Lower Carr index values indicate better flow properties. The statistical analysis revealed a significant effect of equipment type as well as a significant interaction between equipment and filler type, as listed in Table 5. The rotary processor gave rise to values around 10%, whereas the fluid bed gave rise to values around 15%. No effect of filler type was seen in the rotary processor, but Blend B gave rise to significantly higher values in the fluid bed. This explains the significant interaction found between these 2 factors. Figure 4 shows the shape and surface structure of selected granules at low liquid addition and high fluidizing air flow rates for both types of equipment and blends. The differences in size and shape of the fillers are obvious in the SEM pictures, but no clear difference in the shape of the granules could be seen. Better flow properties of the granules prepared in the rotary processor did not give rise to a smaller relative SD of the mass of the prepared tablets, which might have been expected. The lack of correlation between Carr index and uniformity of tablet mass can partly be explained by the difference in granule size. The largest rotary processor granules were observed to leave the die because of the movement of the feeder. This might cause a less uniform filling and thus a larger deviation of the tablet mass. The statistical analysis showed a significant effect of the interaction between equipment and filler type. This was caused by higher values for Blend A in the rotary processor. Although significantly higher values were seen in the rotary processor for Blend A, all batches showed acceptable uniformity of mass, with maximum values of approximately 1.4% (relative SD).

SCS of the tablets prepared on the single-punch tablet machine was not significantly influenced by the equipment and process variables. Only the filler type gave rise to a significant effect ($P = .049$). A clear distinction between the 2 blends could be seen in the fluid bed, whereas the effect was less clear in the rotary processor, as listed in Table 6. Although no significant effects were found, it can be seen from the data in Table 6 that the crushing strength of tablets prepared in the rotary processor can be modified by changing the liquid addition rate and fluidizing air flow, to a much larger extent than is possible in the fluid bed and that tablets can be prepared with similar tablet strength using the 2 types of equipment. Table 6 also lists the tablet porosity. A significant effect ($P < .000$) of the blend is clear for both types of equipment. Generally, a good correlation between tablet strength and tablet porosity can be seen. The tablets showed short disintegration times, between 0.5 and 2 minutes, except tablets from batch 7 (4.5 minutes). No correlations between the tablet disintegration and tablet strength or porosity could be seen, as might have been expected. This was also the case for the tablet friability, as listed in Table 6. This might be explained by the disintegrating effect of the MCC present in both investigated blends.

A homogeneous distribution of the active substance in the granules is important to achieve a good content uniformity.

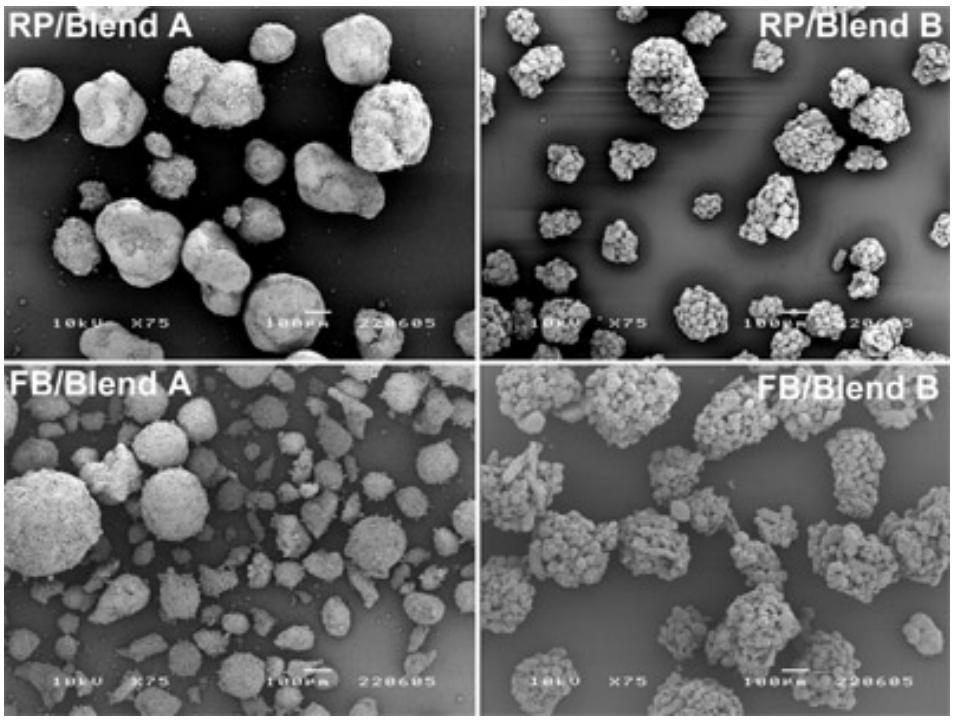

Figure 4. Scanning electron microscope pictures of granules from batches 2, 6, 10, and 14, all with low liquid addition and high fluidizing air flow rate. Magnification ×500. RP indicates rotary processor; FB, fluid bed.

Table 6. Determined Tablet Properties*

Batch	Specific Crushing Strength (MPa)	Friability (% wt/wt)	Disintegration Time (seconds)	Porosity (%)
1	0.391 (0.02)	2.15 ± 0.05	31 (1)	36 (0.6)
2	0.512 (0.07)	1.29 ± 0.07	41 (1)	33 (0.9)
3	0.748 (0.09)	0.78 ± 0.09	119 (9)	31 (0.9)
4	0.606 (0.08)	0.95 ± 0.02	51 (5)	32 (0.9)
5	0.497 (0.02)	1.16 ± 0.08	58 (4)	27 (0.5)
6	0.640 (0.03)	1.01 ± 0.02	38 (1)	24 (0.3)
7	0.408 (0.02)	1.23 ± 0.11	23 (1)	26 (0.2)
8	0.966 (0.12)	0.74 ± 0.06	278 (8)	22 (1.2)
9	0.670 (0.03)	1.55 ± 0.03	65 (<1)	34 (0.3)
10	0.557 (0.03)	0.95 ± 0.03	68 (3)	35 (0.3)
11	0.720 (0.05)	2.77 ± 0.17	78 (3)	33 (0.2)
12	0.692 (0.04)	1.17 ± 0.07	49 (4)	33 (0.2)
13	1.012 (0.07)	1.32 ± 0.10	67 (3)	26 (0.6)
14	1.052 (0.04)	1.28 ± 0.12	74 (2)	25 (0.4)
15	1.033 (0.03)	1.34 ± 0.09	70 (5)	25 (0.3)
16	0.892 (0.02)	1.21 ± 0.07	69 (4)	25 (0.4)

*The table lists the average and (SD) or ± range. See Table 4 for experimental settings.

In the present investigation, 1% of a marker drug was added to investigate the distribution in 3 size fractions. The content in each fraction is listed in Table 7. The statistical analysis of the content of drug in the fractions showed a significant effect of the equipment ($P = .038$) for the fines, whereas no significant effect was found for the other 2 fractions. The average content of drug in the fines was 1.1% in the rotary processor and 2.1% in the fluid bed granules, with the theoretical content being 1.0%. The better distribution of the drug in the rotary processor granules could also be seen visually, with a more intense and homogeneous color compared with the fluid bed granules. Furthermore, spots of what appeared to be the marker drug could be seen in the surface of the fluid bed tablets, as shown in Figure 5. The fact that the higher agitation in the rotary processor leads to a more homogeneous distribution of small quantities of drug is consistent with findings from the literature.[3]

Table 7. Distribution of Marker Drug in the Investigated Size Fractions*

	Drug Content (% wt/wt) in Each Granule Fraction		
Batch	Fines (<125 μm)	Medium Granules (125-355 μm)	Large Granules (>355 μm)
1	0.91	0.54	0.37
2	1.44	1.12	0.86
3	1.36	0.67	0.78
4	0.48	0.23	0.11
5	1.26	1.18	0.86
6	1.64	0.52	0.77
7	1.02	0.81	0.52
8	1.09	0.63	0.85
9	2.22	0.91	0.37
10	2.16	0.73	0.20
11	1.08	0.68	0.37
12	2.85	0.75	0.49
13	2.14	0.33	0.79
14	1.60	0.51	0.85
15	2.48	0.76	1.00
16	1.91	0.58	0.68

*Theoretical content: 1.0%. See Table 4 for experimental settings.

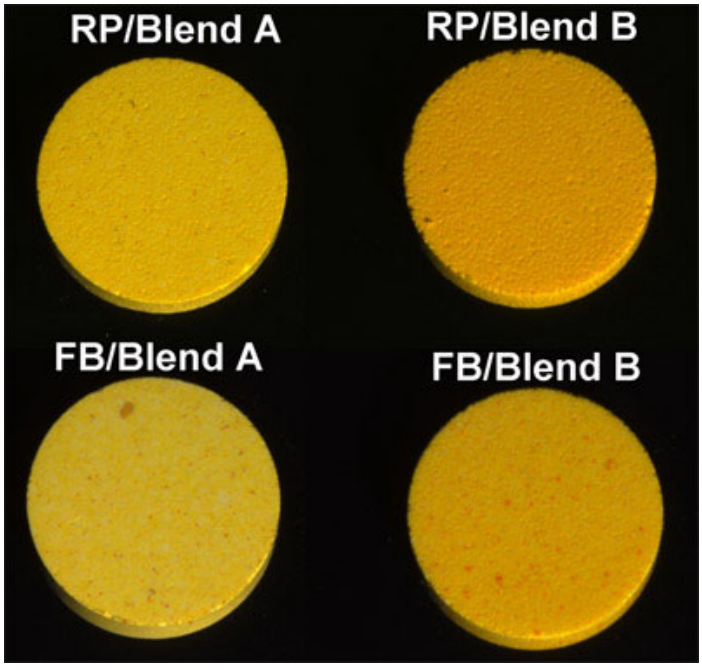

Figure 5. Digital images of tablets from batches 2, 6, 10, and 14, all with low liquid addition and high fluidizing air flow rate. RP indicates rotary processor; FB, fluid bed.

CONCLUSIONS

Compared with granulation in the fluid bed, wet granulation in the rotary processor was found to offer better maneuverability in terms of the obtainable granule size and was less influenced by the flow properties of the starting materials.

Similar tablet characteristics were found in the investigated types of equipment, although the tablets prepared with less dense fluid bed granules were slightly harder.

The applicable range of liquid addition rates was found to be similar in the rotary processor and in the fluid bed.

Generally, wet granulation in the rotary processor was found to be a good alternative to conventional fluid bed granulation, particularly when cohesive powders with poor flow properties or formulations with low drug content are to be granulated by a fluidizing air technique.

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