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RESEARCH PAPER

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

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ABSTRACT

A factorial-designed study has been performed to investigate the effect of two formulation variables and three processing variables on size, size distribution, and friability of pellets made in a rotary processor by the wet granulation technique. The first are the microcrystalline cellulose content and the ratio of the amount of added water to the amount of microcrystalline cellulose in the powder mixture; the latter are the rotor speed, the spheronization time after water addition, and the water addition rate. Both formulation variables and the three processing variables have a major influence on pellet size and percentage loss in weight in the friability test. With the exception of the spheronization time, increasing an independent variable results in a wider size distribution. The wet granulation technique in the rotary processor has been judged to be a critical technique. However, if all variables are fully controlled, rather good reproducibility can be obtained.

INTRODUCTION

The currently popular method for producing pellets is the three-step process of extrusion, spheronization, and fluidized-bed drying. Consequently, this process, and especially the extrusion and spheronization step have been studied extensively. Nevertheless, alternative techniques were and are available (1). Due to technical imperfections, unsatisfactory results, lack of reproducibility, and so on, these techniques never made a major breakthrough in the pharmaceutical industry. However, technical improvements and excipients like microcrystalline cellulose have renewed the interest for these alternative production methods. Especially the "single pot" methods seem to be promising, i.e., the methods where pellets are produced, dried, and, if de-

sired, coated in the same piece of equipment. Two types of production machinery can be considered as promising for "single pot" pellet production: high-shear mixer-granulators and rotary processors. This article is focused on the rotary processors.

Using a rotary processor, several pellet production techniques can be applied. The most commonly used are powder layering and solution layering. Less customary, but even more interesting, is the wet granulation technique. This technique includes the conversion of a powder mixture containing the drug into spherical granules by spraying a binder liquid onto the powder mass, which undergoes a coil-wreath-shaped movement.

Recently, two papers describing the application of the wet granulation technique in a rotary processor have been published (2,3). Vecchio et al. (2) performed a limited number of experiments on the production of indobufen pellets in order to investigate the influence of the amount of microcrystalline cellulose and the nature of the filler material on several pellet characteristics. Rotor speed and process temperature were adjusted to obtain a regular spiral motion. Since the authors believe that these factors may influence the process, these variables should be kept constant or incorporated in the study as a variable.

Wan et al. (3) revealed the influence of the liquid spray rate and gap air pressure on the pellet size. These authors occasionally observed substantial wall adhesion of the wetted powder mass, which may be responsible for the poor reproducibility of the process.

Neither Vecchio et al. or Wan et al. mention the application of a wall coating or the use of one or more baffles. Both are a prerequisite to obtain a reproducible pelletization process.

The aim of this paper is to describe the influence of the major formulation and processing variables on size, size distribution, and friability of pellets made in a rotary processor by the wet granulation technique. Incorporation of the major formulation and process variables into one factorial designed study allows us to investigate the influence of each variable on several pellet characteristics, as well as to elucidate interactions between formulation variables or process variables or between formulation and process variables.

MATERIALS

α-Lactose monohydrate (Pharmatose®, type 200M, DMV, Veghel, The Netherlands), microcrystalline cellulose (Avicel®, type PH-101, FMC, Cork, Ireland), and 1% riboflavin (Produits Roche, Brussel, Belgium) were used as starting materials. All materials were of Ph. Eur. grade. Geometric mean diameters on a weight basis of 42 μm and 44 μm were found for, respectively, the α-lactose monohydrate and the microcrystalline cellulose as determined with an air jet sieve (type A320LS, Alpine, Augsburg, Germany). The geometric mean diameter on a volume basis of riboflavin was determined using the electrical sensing zone method (Coulter Multisizer II, Coulter Electronics, Luton, U.K.) and equaled 3.6 μm. Demineralized water was used as granulation liquid.

METHODS

Pellet Production Method

Riboflavin, lactose, and microcrystalline cellulose were dry mixed for 5 min in a Primax mixer (type M9, Küpper, Morenhoven, Germany) to break up any lumps and blend the mixture.

One kilogram of powder blend was loaded into the inner bowl of the rotary processor (MP-1, Niro-Aeromatic, Bubendorf, Switzerland). The bowl wall was coated with a PTFE film (Scotch PTFE film tape, 3M, St. Paul, MN, USA) to prevent adhesion. One baffle directing the upper part of the powder mass downwards during the process was installed, thus preventing division of the wetted powder mass into two parts moving of different speeds. This baffle, together with the PTFE coating, ensured a coil-wreath-shaped movement of the moist mass in the inner bowl.

The rotor disk was operated at 550 rpm, and water was sprayed into the container at the indicated rate with the aid of a peristaltic pump (type 503S, Watson Marlow, Falmouth, U.K.) using 1.0 bar (ca. 1.10^5 Pa) of atomization pressure. Once all the water was sprayed, spheronization was performed at the specified rotor speed, i.e., 550 or 800 rpm.

After completion of the pellet formation, the pellets were dried at 50°C by lifting the inner container. The drying process was controlled by keeping a running check on the outcoming temperature of the fluidized bed dryer, and switching off the dryer when a specified end temperature T_e had been reached. This end temperature T_e corresponds to the sum of the wet bulb temperature and a quantity ΔT of 10°C.

Table 1

Low and High Levels for the Independent Variables

Independent Variable	Low Level	High Level
A. MCC content (%)	30	35
B. Water-MCC ratio	1.18	1.22
C. Rotor speed (rpm)	550	800
D. Spheronization time (min)	5	15
E. Water addition rate (ml/min)	30	60

A complete 2^5 study with eight replications was performed. The independent variables with their different levels are listed in Table 1.

Characterization of the Produced Pellets

Size and size distribution of three samples were determined by sieve analysis. Results were interpreted using the log-probability plot according to Martin (4). Therefore approximately equal classes of about 250 μm were used. After transformation of the frequency plot using probability units, a weighted linear regression was performed (5). This resulted in the first place in a geometric mean diameter on a weight basis (d_g), which is the particle size equivalent to 50% on the probability scale. Secondly, a range between the particle size equivalent to 16% on the probability scale and the particle size equivalent to 84% on the probability scale, denoted as range $d_{16\%}$-$d_{84\%}$, could be calculated using the geometric standard deviation (σ_g).

The friability was studied as described by Millili and Schwartz (6) using a metal friabilator with an abrasion wheel to reduce the electrostatic charges.

Statistical Analysis

The results for the pellet size, size distribution, and friability were analyzed by analysis of variance (ANOVA) using the SOLO statistical software (BMDP Statistical Software, Los Angeles, CA, USA).

In order to obtain data which were more normally distributed, a logarithmic transformation (7) was performed on the data for the geometric mean diameter and the range $d_{16\%}$-$d_{84\%}$. One unit was added to the friability data before the logarithmic transformation was applied in order to eliminate negative values.

Since second-, third-, or fourth-order interactions are not likely to exist (8), the results for these higher-order interactions together with the replications were used to determine the experimental error.

RESULTS AND DISCUSSION

Pellet Size and Size Distribution

From the results for the geometric mean diameter, given in Table 2, it is obvious that the size of the pellets changed if the independent variables were changed. Increasing an independent variable resulted in an increase in pellet size.

Following the agglomeration theory of Kristensen et al. (9), it could be expected that the microcrystalline cellulose content would influence the agglomerate plasticity directly, since microcrystalline cellulose is known to be a plastic material. There is also an indirect influence by an increase of the liquid saturation due to the consolidation undergone by the microcrystalline cellulose. Therefore, the microcrystalline cellulose content had a major influence on the limiting agglomeration size. The ANOVA report, given in Table 3, confirms that the microcrystalline cellulose content had a significant ($p < 0.001$) influence on the pellet size.

It has been observed previously that wet massing of cohesive powders and formulations, which demonstrated consolidation during the process, gave rise to a high sensitivity to the added amount of binder solution. So, it is not a surprise that raising the water–microcrystalline ratio from 1.18 to 1.22 had a major influence on the pellet size.

The extent of the consolidation depends not only on the properties of the formulation but also on the intensity of the agitation. Thus, it was to be expected that an increased rotor speed would lead to a higher degree of consolidation resulting in an increase in surface liquid, which promoted coalescence between colliding agglomerates. Consequently, the rotor speed had a significant ($p < 0.001$) effect on the pellet diameter.

The synergistic interaction between the microcrystalline cellulose content and the rotor speed reveals that consolidation due to a high rotor speed was more pronounced if the microcrystalline cellulose content was increased. The higher the microcrystalline cellulose content, the stronger the potential consolidation, and hence the larger the pellets were.

During the spheronization time after water addition, the pellet diameter seems to increase significantly ($p < 0.001$). These results indicate that even after 5 min ag-

Table 2

Results for the Geometric Mean Diameter (d_g), Size Distribution (Range $d_{16\%}$–$d_{84\%}$), and Friability

Experiment	d_g Mean (μm)	d_g 95% CL[a] (n = 3)	Range $d_{16\%}$–$d_{84\%}$ Mean (μm)	Range $d_{16\%}$–$d_{84\%}$ 95% CL[a] (n = 3)	Friability: Mean (%)
(1)	268	4.1	155	3.3	2.7
A	362	1.0	187	4.4	0.9
	355	1.6	177	1.4	1.0
B	363	9.2	215	23.9	1.5
AB	518	6.6	244	10.0	0.0
C	363	3.2	184	5.4	1.1
AC	503	6.9	244	13.7	0.1
BC	446	6.1	201	10.5	0.4
	387	2.7	175	2.5	1.0
ABC	611	4.7	232	3.8	0.0
D	330	1.3	147	2.6	1.8
AD	393	1.0	177	4.2	0.6
BD	385	0.4	187	2.4	1.0
ABD	421	1.2	198	2.1	0.4
	440	1.4	187	2.2	0.3
CD	403	2.9	170	1.2	0.7
	432	3.4	186	2.6	0.6
ACD	450	2.4	197	2.4	0.1
BCD	585	2.2	211	6.6	0.1
ABCD	623	0.6	198	10.9	0.0
E	372	8.5	216	21.5	1.5
AE	581	1.7	253	5.1	0.2
BE	515	4.1	329	7.7	0.5
	494	3.5	294	5.3	0.7
ABE	644	3.9	280	9.4	0.0
CE	441	3.0	207	2.2	0.4
ACE	875	15.3	330	2.0	0.0
	935	22.7	319	26.3	0.0
BCE	621	1.7	258	4.5	0.0
ABCE	1201	15.4	453	35.5	0.0
DE	412	2.7	213	0.7	1.0
	417	5.0	201	1.9	0.9
ADE	498	6.9	292	5.4	0.1
BDE	447	5.1	215	0.7	0.5
ABDE	697	42.1	246	12.9	0.0
CDE	603	11.2	257	9.3	0.0
ACDE	1119	10.8	341	26.4	0.0
BCDE	852	15.9	302	10.9	0.0
ABCDE	1368	14.0	364	47.1	0.0
	1341	18.8	364	49.4	0.0

[a]Value which has to be added to or subtracted from the mean to obtain the 95% confidence limits.

glomerate growth went on. On one hand, this can be attributed to a further densification of the pellets, which increased the liquid saturation, which in its turn promoted agglomeration. On the other hand, agglomerates would undergo a size reduction by attrition, breakage, or shatter, resulting in smaller particles. These smaller particles were then layered onto larger particles. This pellet growth proceeded until the moisture content reached a critical value, below which the rate of growth was negligible.

Table 3

Analysis of Variance Table for Log Geometric Mean Diameter (Rounded Values)

Factor or Interaction	*df*	Effect ($\times 10^3$)	Mean Square ($\times 10^3$)	*F* Ratio	Prob > *F*
A	1	148.43	205.64	134.92	0.000
B	1	108.03	112.03	73.50	0.000
AB	1	-1.77	0.03	0.02	0.889
C	1	161.58	250.63	164.43	0.000
AC	1	34.54	11.44	7.51	0.011
BC	1	8.51	0.70	0.46	0.506
D	1	40.13	15.45	10.14	0.004
AD	1	-32.75	10.30	6.76	0.016
BD	1	-6.97	0.45	0.30	0.591
CD	1	35.84	12.33	8.09	0.009
E	1	188.65	341.64	224.15	0.000
AE	1	51.94	25.89	16.99	0.000
BE	1	3.61	0.13	0.08	0.777
CE	1	47.47	21.03	13.80	0.001
DE	1	5.37	0.28	0.18	0.674
Error	24		1.52		

Strong synergistic interactions can be noticed between the spheronization time after water addition and the microcrystalline cellulose content or rotor speed. The consolidation, which was more pronounced at high microcrystalline cellulose contents or high rotor speeds, was even much more pronounced if the consolidation could go on for a longer period.

In contrast with an earlier experience with pelletization in a high shear mixer-granulator (11), the water addition rate had a major influence on the pellet growth in the rotary processor, probably because in the latter there was no intense agitation to ensure the spreading of liquid, which was locally held by the powder mass. Due to its high water-containing capacity, the microcrystalline cellulose could hold the water locally, especially if high spray rates were used.

On the other hand, the influence of the water addition rate on the pellet size must be, at least partially, attributed to the differences in processing time. A lower water addition rate required longer processing times. During the process, water was removed by the air coming through the gap between the rotor disk and the inner wall. Thus, changing the water addition rate meant changing the amount of water added.

Strong interactions between the water addition rate and other independent variables were revealed by the ANOVA report. The chance of holding the water locally increased as the microcrystalline cellulose content increased. Therefore, a simultaneous increase of the microcrystalline cellulose content and the water addition rate resulted in large pellets, as was confirmed by the strong interaction between the microcrystalline cellulose content and the water addition rate. If a large amount of water was locally held due to a high water addition rate, and if at the same time a high rotor speed (i.e., fast and strong consolidation) was applied, locally a large amount of surface liquid was available for agglomeration. This led to a large increase in pellet size. A strong interaction between rotor speed and water addition rate was therefore found.

According to Hellén et al. (12), who refers to studies of Rowe (13) and Baert et al. (14), the size distribution of a pellet batch determined by sieve analysis can be considered to be acceptable and narrow if 90% of the pellets show a particle size between 0.7 and 1.4 mm. Although the pellets produced in these experiments are mostly smaller, and therefore difficult to judge by the norm of Hellén et al., the results obtained for the range $d_{16\%}$-$d_{84\%}$ (Table 2) indicate that narrow particle size distributions have been reached.

In Fig. 1 it can be seen that, generally, the size distribution became wider with increasing pellet size. The ANOVA report, presented in Table 4, reveals that with exception of the spheronization time after water addi-

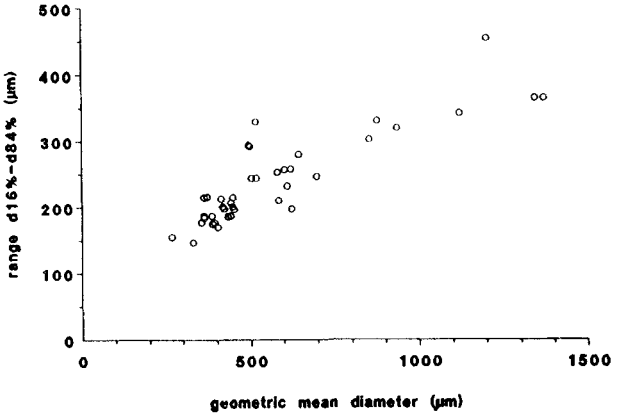

Figure 1. Range $d_{16\%}$-$d_{84\%}$ as a function of geometric mean diameter.

tion, increasing one of the independent variables led to an increase in the $d_{16\%}$-$d_{84\%}$ and hence resulted in a wider pellet size distribution.

Especially the water addition rate had a major influence on the pellet size distribution. Since an equal spreading of the liquid was not ensured at higher spray rates, agglomeration was less controlled, leading to pellets with a less equal size.

Increasing the rotor speed resulted in a relatively small increase in size distribution. An increase in the spheronization time seemed even to lead to a narrower pellet size distribution, although the effect of the spheronization time on the size distribution is not revealed as a significant one ($p = 0.148$) by the ANOVA report in Table 4. These observations can be explained by the rotor action on the agglomerates, which wore off or broke up into smaller particles. These smaller particles were layered onto other particles as spheronization went on, leading to a more homogenous size distribution. Increasing the rotor speed or the spheronization time enhanced this process.

If the results for the pellet size and pellet size distribution of the replications are compared to those of the original experiments, differences in the geometric mean diameter up to 60 µm and differences in the range $d_{16\%}$-$d_{84\%}$ up to 35 µm can be observed. Taking into account the major influences of all the independent variables on size and size distribution, as well as the major interactions between them, the pelletization process in the rotary processor can be classified as a critical but nevertheless reproducible one.

Friability

The results for the friability—i.e., the percentage loss in weight during the friability testing—are presented in Table 2. If these results are compared to those which can be found in the literature and which were obtained by comparable methods, the majority of the pellets seem to be strong enough to withstand rough handling. O'Connor and Schwartz (15), for instance, have report-

Table 4

Analysis of Variance Table for Log Range $d_{16\%}$-$d_{84\%}$ (Rounded Values)

Factor or Interaction	*df*	Effect ($\times 10^3$)	Mean Square ($\times 10^3$)	*F* Ratio	Prob > *F*
A	1	81.50	61.99	28.53	0.000
B	1	64.34	39.73	18.29	0.000
AB	1	-20.87	4.18	1.92	0.178
C	1	57.95	32.24	14.84	0.001
AC	1	30.38	8.86	4.08	0.055
BC	1	-15.81	2.40	1.11	0.304
D	1	-22.48	4.85	2.23	0.148
AD	1	-13.15	1.66	0.76	0.391
BD	1	-28.79	7.74	3.56	0.071
CD	1	24.67	5.84	2.69	0.114
E	1	157.80	239.05	110.02	0.000
AE	1	21.65	4.50	2.07	0.163
BE	1	4.51	0.20	0.09	0.767
CE	1	23.22	5.03	2.32	0.141
DE	1	9.05	0.78	0.36	0.553
Error	24		2.17		

ed values of 0.10% to 3.07% loss in weight for different pellet formulations processed by an extrusion–spheronization process containing different types of Avicel and theophylline. These authors have classified these pellets as hard ones. The friability of pellets produced by Hellén et al. (16) varied between 0.3% and 2.7%. Pellets with friability values < 1.7% have been judged by these authors as mechanically acceptable, e.g., for coating purposes.

In Fig. 2, a large decrease in % loss in weight can be observed as size increases from 250 to 600 μm.

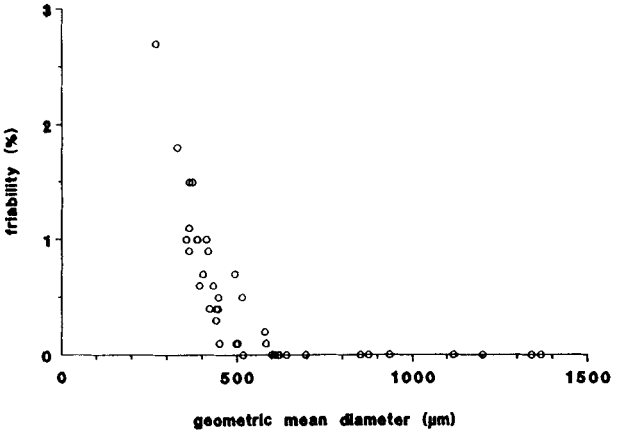

Figure 2. Friability as a function of geometric mean diameter.

Pellets with a size of 600 μm or larger did not have any measurable loss in weight during the friability testing. The decrease in friability with increasing pellet size may be attributed to the decrease in pellet surface as the size of the pellets increased. Investigating the process of extrusion and spheronization, Ligarski et al. (17) have also observed an increase in pellet hardness as the size of the pellets increased.

Besides the correlation between size and hardness, these authors found a positive correlation between the hardness of the pellets and the rotor speed during spheronization. The ANOVA report in Table 5 reveals a negative correlation, not only between the rotor speed and the % loss in weight in the friability test, but between every independent variable and the % loss in weight during the friability testing. Since an increase in one of the independent variables increased the size and since friability decreased with increasing size, this observation agrees with the expectations.

If the F ratios for the dependent variable geometric mean diameter are compared to those for the dependent variable friability, it can be seen that for the friability the F value is proportionally high for the microcrystalline cellulose content and low for the water addition rate. It must be concluded that the microcrystalline cellulose contributed greatly to the pellet strength. On the other hand, the water addition rate did not lead to those hard pellets, which could be expected on the basis of the influence it had on the geometric mean diameter. This

Table 5

Analysis of Variance Table for Log (1 + % Friability) (Rounded Values)

Factor or Interaction	*df*	Effect ($\times 10^3$)	Mean Square ($\times 10^3$)	*F* Ratio	Prob > *F*
A	1	-182.68	311.47	143.65	0.000
B	1	-101.67	99.22	45.76	0.000
AB	1	30.00	8.64	3.98	0.057
C	1	-157.71	238.77	110.12	0.000
AC	1	66.04	41.87	19.31	0.000
BC	1	40.63	15.84	7.31	0.012
D	1	-50.00	24.00	11.07	0.003
AD	1	48.33	22.42	10.34	0.004
BD	1	27.32	6.97	3.21	0.086
CD	1	-6.46	0.40	0.18	0.671
E	1	-125.21	150.50	69.41	0.000
AE	1	43.54	18.20	8.39	0.008
BE	1	27.29	7.15	3.30	0.082
CE	1	26.07	6.34	2.93	0.100
DE	1	11.87	1.35	0.62	0.437
Error	24		2.17		

is probably the consequence of an unequal spreading of the water, resulting in pellets with a less homogeneous strength, which led to some more friable pellets.

Since increasing the rotor speed or the spheronization time after water addition led to stronger consolidation, and hence stronger agglomerates, it is not surprising that an increase in one of these independent variables decreased the friability. The strong interactions between the rotor speed or spheronization time after water addition and the microcrystalline cellulose content elucidate that the decrease in friability due to the consolidation by the rotor speed or spheronization time after water addition was much more pronounced if the microcrystalline cellulose content was increased.

CONCLUSIONS

All the independent variables had a major influence on the pellet size and the % loss in weight in the friability test. Increasing an independent variable resulted in an increase in size and less loss in weight in the friability test. With the exception of the spheronization time after water addition, increasing an independent variable resulted in a wider size distribution. Increasing the spheronization time seemed to lead to a narrower size distribution, but this effect was not significant ($p = 0.148$).

Generally, it can be stated that if the size was increased, the size distribution became wider and the % loss in weight in the friability test was reduced.

If one would like to increase one of the independent variables, it is not preferable to increase the water addition rate. Increasing the water addition rate resulted in an increase in pellet size but resulted at the same time in a wider size distribution, and this in a much larger extent than if one of the other independent variables had been increased. Furthermore, increasing the water addition rate led to little decrease in friability compared to the decrease in friability obtained by increasing another independent variable.

Taking into account the major effects of the independent variables on the dependent variables and the strong interaction terms, it must be concluded that the process is critical. Although the process is critical, rather good reproducibility could already by obtained at this stage of the investigations.

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