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COMMUNICATION

Influence of Chopper and Mixer Speeds and Microwave Power Level During the High-Shear Granulation Process on the Final Granule Characteristics

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ABSTRACT

Although microwave drying technology has been used extensively, detailed studies in the pharmaceutical field are necessary to model the different operational parameters involved in microwave drying in combination with the high-shear granulation processes. The implications of the chopper and the mixer speeds during the granulation step and the microwave power level during the drying step on the final granule characteristics were investigated. α-Lactose monohydrate and microcrystalline cellulose were granulated at three different mixer and chopper speeds in a laboratory-scale high-shear mixer (Mi-Mi-Pro™) and dried at three microwave power levels. The dried granules were characterized by friability tests, particle size analysis, bulk and tapped density studies, and porosimetry. Neither the mixer speed nor the chopper speed had a significant influence on the granule friability, which was low for all batches produced. The selected materials and experimental conditions induced a very robust granulation process, but the granule size distribution was influenced by the microwave power level. The reciprocal relationship between the dust formation and the microwave power level was analyzed using a central composite factorial design. The amount of dust remained low in all batches, but it influenced some of the inherent density properties and the volume reduction behavior of the granulation mass. In almost all cases, the Carr index decreased slightly with increasing micro-

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wave power. The major granule characteristics were not changed when different mixer or chopper speeds were changed, although the mixer speed did alter the intragranular pore size distribution.
Key Words: *Factorial design; High-shear granulation; Microwave drying.*

INTRODUCTION

There is growing interest for microwave drying technology in granulation processes. The major advantages are a reduction of the drying time and the use of a single-unit process without batch transfer from the granulator to the dryer, therefore minimizing the risks of cross-contamination.

For the last purpose, different types of granulators, such as fluidized beds and high-shear mixers, have recently been modified to be able to use this drying technique. The technical difficulties in obtaining the correct microwave implementation are being acknowledged and were investigated by some researchers. Doelling et al. (1,2) described a fluidized bed dryer equipped with a microwave generator and the heat transfer to a model granulate. Waldron (3) developed a prototype high-shear mixer that was instrumented with a microwave generator.

Today, it is clear that not only the instrumental conditions, but also the dielectric properties of the products are very important and determine the microwave drying suitability and efficiency. Duschler, Carius, and Bauer (4) compared the drying behavior of some pharmaceutical excipients and compounds dried by simple convection and by microwave drying. They stressed the importance of continuous mixing during the drying phase to improve the dielectric heating efficiency. Vromans (5), who investigated the dielectric properties of α-lactose monohydrate and potato starch in a high-shear mixer, reported the necessity of the continuous mixing of microwave-transparent excipients such as starch to avoid the occurrence of ''hot spots'' during drying. Lactose, on the contrary, did not require this mixing since it is an energy-absorbing material.

Apart from these heat transfer problems, the implications of microwave drying on the final physical granule characteristics were studied only by Mandal (6). Mandal concluded that microwave radiation did not modify the surface properties of sulfathiazole/lactose granules, but he did not investigate the intragranular pore size distribution. Physical changes are important and should be controlled since they might eventually influence the tableting properties of the granulate. The aim of this study was to investigate the influence of the different experimental parameters in a high-shear granulation process (namely, chopper and mixer speeds during the wet granulation step and the microwave power level during the drying phase) on the final granule characteristics. The parameter settings were selected according to a central composite design, and the results were analyzed by polynomial model fitting.

MATERIALS AND METHODS

α-Lactose monohydrate (Pharmatose®-90 M, DMV, Veghel, The Netherlands) and microcrystalline cellulose (Avicel® PH-101, FMC, Caldic, Rotterdam, The Netherlands) were used as received. All granule batches were produced in a laboratory-scale, high-shear mixer (Mi-Mi-Pro™, Pro-Cept, Zelzate, Belgium), equipped with a 1.7-L capacity spherical bowl, a three-blade impeller, and a chopper to avoid the growth of oversize aggregates during the wetting phase.

First, 100 g of both products were brought into the bowl and mixed with an impeller speed of 1000 rpm for 13 min. Mixer and chopper speeds were selected (Table 1), and the granulation liquid, 110 ml of demineralized water, was added at a constant rate of 10 ml · min^{-1} to the 200 g powder mix using a Dossimat™ pipette. Microwave-vacuum technology was applied to dry the granulation mass using a Divac™ 2.2 L vacuum pump (50 mbar; Leybold vacuum, Export, UK) and a microwave generator with adjustable power settings (Table 1). To avoid caking, the mixer remained functioning at a very low

Table 1

Levels of the Granulation Parameters

Levels	x_1 Mixer Speed (rpm)	x_2 Microwave Power (W)	Chopper Speed (rpm)
Lower (−)	250	50	1000
Base (0)	700	100	2000
Higher (+)	1150	150	3000

speed (50 rpm) during the drying phase. All experimental parameters were computer controlled and registered. The dried granules were passed through a 1.48-mm sieve to eliminate large agglomerates.

All granulation batches were divided into four equal fractions to determine the friability, the particle size distribution, the bulk and tapped densities, and the porosity. The friability of the granules was analyzed by introducing 10 g of the granules with a particle size between 250 and 1000 μm together with 200 glass beads (mean diameter 4 mm) in an Erweka-type friabilator for 16 min at a rotational speed of 25 rpm. After 400 rotations, the glass beads were removed, and the granules were sieved over a 250-μm screen. The friability value in percentage was calculated for each batch using the following equation: $F(\%) = 100 \times (P - P')/P$, where P is the initial weight of granules (10 g) and P' is the final weight after sieving over a 250-μm screen. The granule particle size distribution was determined with a laser diffraction analyzer (Malvern, Mastersizer, Worcestershire, UK). About 40 g of the granules were accurately weighed (W) and poured into a 100-ml graduated cylinder to determine the bulk and tapped densities. The bulk volume V and the tapped volume V' after 250 taps on a tap density apparatus (J. Englesman, Ludwigshafen, Germany) were used to calculate (in $g \cdot ml^{-1}$) the bulk density d and the tapped density D. The Carr index C values were calculated to study the compaction characteristics of the granulation mass. Porosity measurements of the 500–710 μm granule fraction, using a mercury porosimeter (Autopore® III 9420, Micromeritics, Norcross, GA), yielded the median pore diameter (μm), the porosity value (%), and the pore size distribution.

A two-factor, three-level face-centered central composite design (7) was applied to construct a second-order polynomial model to describe the effect of process parameters (x_1 = mixer speed and x_2 = microwave power level) on the dust formation (Table 1) at a certain chopper speed. The levels for each parameter are represented by a minus (−) sign for the lower level, a plus (+) sign for the higher level, and a zero (0) for the base level. TableCurve 3D (Jandel Scientific, SPSS, Erkrath, Germany) software was applied for the multiple regression analysis. The expected form of the polynomial equation is as follows: $y = b_0 + b_1x_1 + b_2x_2 + b_{11}x_1^2 + b_{22}x_2^2 + b_{12}x_1x_2$, where y is the response, x_n are the factors, and b_n are the coefficients characterizing the main (b_1,b_2), the quadratic (b_{11},b_{22}), and the interaction (b_{12}) effects. A positive sign for the coefficients refers to an increasing effect, while a negative sign indicates a decreasing effect on the corresponding response.

Table 2

Mean (±SD) Granule Friability (%), Porosity (%), and Mean Pore Diameter (μm) (n = 27)

	Mean	SD
Friability	3.6	2.0
Porosity	7.8	1.3
Mean pore diameter	3.4	2.4

RESULTS AND DISCUSSION

When the data of all batches produced were considered, neither the mixer speed nor the chopper speed had a significant influence on the granule friability. Besides, the friability was very low for all 27 batches (Table 2). Although the selected materials and the experimental conditions induced a very robust granulation process, the granule size distribution was influenced by the microwave power level. Increasing the microwave power level decreased the dust formation during the drying phase. The dust values were taken from the granule size distributions (% particles smaller than 190 μm). In Fig. 1, the dust formation at a chopper speed of 2000 rpm is expressed as a function of the microwave power and the mixer speed. Similar results were observed for chopper speeds of 1000 and 3000 rpm. At an intermediate mixer speed (750 rpm) during the wetting phase, a maximum dust-increasing effect was observed (Fig. 1), while at higher speeds, the dust particles reagglomerated on the surface of existing granule nuclei. This phenomenon was

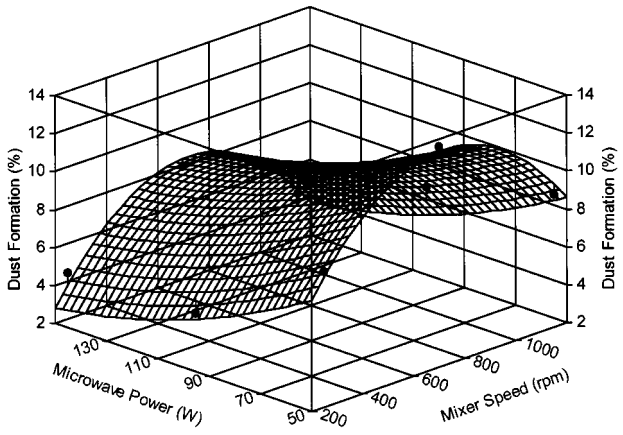

Figure 1. Dust formation as a function of the microwave power level and the mixer speed at a chopper speed of 2000 rpm.

Table 3

Randomized Matrix of the Two-Factor, Three-Level, Face-Centered Central Composite Factorial Design (at a Chopper Speed of 2000 rpm)

	Controlled Factors		Response Parameters					
			1000 rpm		2000 rpm		3000 rpm	
Trial	x_1 (rpm)	x_2 (W)	Measured y (%)	Predicted y (%)	Measured y (%)	Predicted y (%)	Measured y (%)	Predicted y (%)
1	−	−	7.2	7.1	9.1	8.8	9.0	9.6
2	−	0	4.4	4.8	4.6	5.5	6.1	7.0
3	−	+	3.9	4.1	4.5	3.8	3.9	2.4
4	0	−	10.4	11.3	13.6	13.3	13.0	11.8
5	0	0	9.2	8.9	10.2	10.1	11.6	9.8
6	0	+	8.7	8.0	8.0	8.4	2.8	5.8
7	+	−	9.2	8.9	9.0	9.6	8.6	9.2
8	+	0	6.4	6.3	7.0	6.3	6.9	7.8
9	+	+	4.9	5.3	4.5	4.7	5.9	4.4

statistically analyzed using a central composite factorial design. At every chopper speed, a polynomial equation was obtained after significance testing at the 95% confidence level.

At 1000 rpm,

$$y = 8.90 + 0.75x_1 - 1.65x_2 - 3.36x_1^2 + 0.79x_2^2 - 0.12x_1x_2 \qquad R^2 = 0.9490$$

At 2000 rpm,

$$y = 10.05 + 0.38x_1 - 2.48x_2 - 4.13x_1^2 + 0.81x_2^2 + 0.03x_1x_2 \qquad R^2 = 0.9668$$

At 3000 rpm,

$$y = 9.78 + 0.38x_1 - 3.01x_2 - 2.38x_1^2 - 1.03x_2^2 + 0.62x_1x_2 \qquad R^2 = 0.7734$$

These equations represent the effect of the processing factors x_1, x_2 on the dust formation y. To avoid the artifact caused by the different magnitude of the factors, coded levels were applied. For the three chopper speeds, the coefficient of the independent x_1 variable is positive (b_1 = 0.75, 0.38, and 0.38 for 1000, 2000, and 3000 rpm, respectively), which refers to its increasing effect on the corresponding response (more dust formation at higher mixer speeds). The coefficient of the independent x_2 variable is negative (b_2 = −1.65, −2.48, and −3.01), referring to a decrease in dust being formed due to shorter drying times (i.e., higher microwave power levels). Due to the negative quadratic effect of the mixer speed (b_{11} = −3.36, −4.13, and −2.38) caused by the reagglomeration of small dust particles, its main effect decreased again at higher mixer speeds. The quadratic effect of the microwave power level remains unclear. Table 3 summarizes the measured and the predicted dust formation values (%) for all chopper speeds. The reciprocal relationship between the dust formation and the microwave power level can be explained by the fact that, by increasing the microwave power from 50 W to 100 W and 150 W, the actual drying time was shortened from 90 to 50

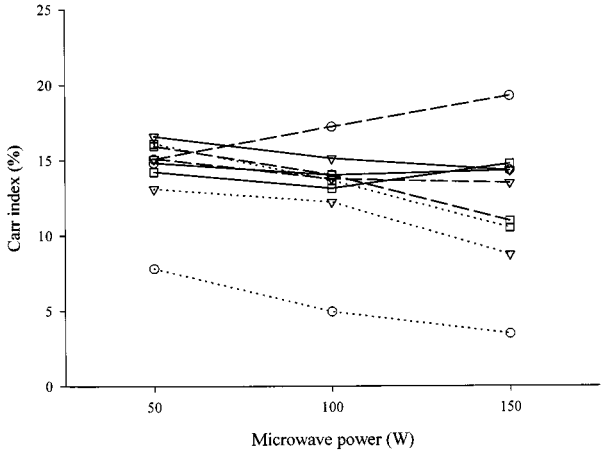

Figure 2. The Carr index as a function of chopper speed and microwave power level at a mixer speed of 250 rpm (○, chopper speed 100 rpm; □, chopper speed 100 rpm; □, chopper speed 100 rpm; . . . . , mixer speed 250 rpm; — — —, mixer speed 700 rpm; ____, mixer speed 1150 rpm).

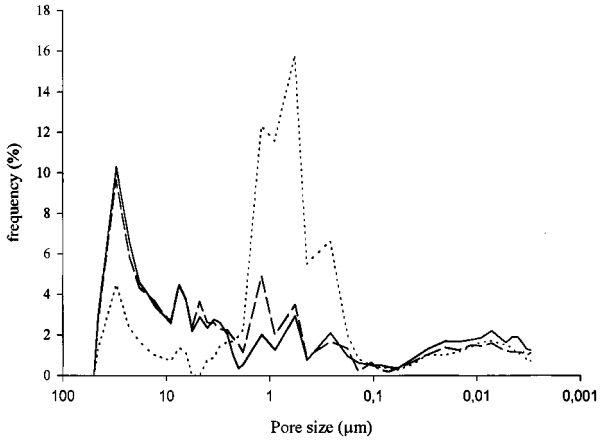

Figure 3. The pore size distribution of the batches produced with a chopper speed of 2000 rpm, a microwave power level of 100 W, and three different mixer speeds: . . . . , 250 rpm; — — —, 700 rpm; ____, 1150 rpm.

and 30 min, respectively. The low mixer speed (50 rpm) during this drying phase did prevent the formation of large lumps, but damaged the granules and so produced dust. Stirring during the drying phase is necessary, as suggested by Vromans (5), but should be performed with caution to avoid granulate break-up and dust formation.

Although in all batches the amount of dust was quite low, it still influenced some of the density properties and the volume reduction behavior of the granulated mass. In almost all cases, the Carr index decreased slightly with increasing microwave power (Fig. 2).

The total porosity of the granules and the median pore diameter did not change significantly with the different experimental conditions (Table 2). However, detailed investigation of the intragranular pore size distributions revealed three types of pores: macropores, mesopores, and micropores. Their sizes were 5 to 50 μm, 0.05 to 5 μm, and smaller than 0.05 μm, respectively. The pore size distribution was influenced by the mixer speed, but not by the chopper speed or the microwave power level. In Fig. 3, the pore size distribution of the batches produced at a chopper speed of 2000 rpm, a microwave power level of 100 W, and three different mixer speeds is shown as an example. At a mixer speed of 250 rpm, the mesopores were predominantly present, while at 700 and 1150 rpm, their importance decreased. The number of macropores increased slightly with increasing mixer speed, while the number of micropores was not altered.

These changes in the intragranular pore size distribution are very important, especially if granules are compacted into tablets. Selkirk and Ganderton (8,9) reported that the conditions during the granulation procedure influenced the intragranular pore size distribution and so affected the tablet pore structure. Wikberg and Alderborn (10) concluded that the granule characteristics before (i.e., pore size distribution) and during the compression phase (fragmentation and deformation propensity) are of decisive importance for the final structure and strength of the compact.

CONCLUSION

A high-shear granulation system was used in combination with microwave drying. Increasing the microwave power level shortened the drying step dramatically, but stirring during the drying phase remained necessary. The influence of mixer and chopper speed and microwave power level on the dust formation was analyzed using a central composite factorial design. The major granule characteristics were not changed when different mixer or chopper speeds were selected, but the mixer speed did alter the intragranular pore size distribution. During the selection of experimental parameters to obtain a robust granulation process, all aspects of the granulate quality have to be considered.

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