ELSEVIER

International Journal of Pharmaceutics 198 (2000) 51–61

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Effect of process parameters on compressibility of granulation manufactured in a high-shear mixer

Sherif I. Farag Badawy *, Mark M. Menning, Mary Ann Gorko, Donna L. Gilbert

Pharmaceutical R and D, DuPont Pharmaceutical Company, Experimental Station, PO Box 80400, 19880-0400 Wilmington, DE, USA

Received 27 April 1999; received in revised form 27 September 1999; accepted 19 November 1999

Abstract

Various processing variables that can influence granulation characteristics of a lactose-based formulation were evaluated using a Plackett–Burman experimental design. These parameters were impeller speed, granulating solution addition rate, total amount of water added in the granulation step, wet massing time, moisture content of the granulation after drying, and screen size used for the dry milling. Results showed that granulation growth was enhanced by the increase in the amount of added water, high impeller speed, and short wet massing time. On the other hand, moisture content had the largest impact on granulation compressibility, followed by the wet massing time and impeller speed. Increasing moisture content of the granulation and decreasing wet massing time or impeller speed increased granulation compressibility. Increasing impeller speed and/or wet massing time decreased granule porosity and fragmentation propensity, which led to decreased granulation compressibility. Granulation compressibility was extremely sensitive to processing conditions. Tablets from all runs showed acceptable weight variation and friability, suggesting that the parameters evaluated had little effect on these responses in the ranges tested. © 2000 DuPont Pharmaceutical Company. Published by Elsevier Science B.V. All rights reserved.

Keywords: Granulation; High shear; Lactose; Compressibility; Porosity

1. Introduction

Wet granulation is a size enlargement process in which a liquid is used to achieve agglomeration of solid particles in a formulation. Agglomeration of solid particles in a pharmaceutical formulation improves their properties for tableting by rendering the particles free-flowing, non-segregating and suitable for compression (Kristensen, 1988). High-shear forces in high-speed mixers are widely used in the pharmaceutical industry for wet granulation. Several studies have investigated granulation parameters in high-shear mixers (Shaefer et al., 1986; Wehrle et al., 1993; Shiraishi et al., 1994). Processing parameters were shown to affect the growth rate of granules in the high-shear wet-granulation process. Granule agglomeration in-

* Corresponding author. Tel.: +1-302-695-9116; fax: +1-302-695-7592.

PII: S0378-5173(99)00445-7

creases with an increase in liquid saturation of the granules, which is enhanced by the continuous addition of granulating solution or by granule densification during processing. Granule densification is increased by high impeller speed and long wet massing time (Shaefer et al., 1986; Kristensen, 1988). Granulation parameters must be controlled in order to ensure the manufacture of a granulation with the desired particle size.

A robust compression process requires granulation with a high degree of compressibility and good flow characteristics. Compressibility of the granulation is of particular importance for the tableting (compression) process. Despite the large number of reports on the high-shear granulation process, the effect of the granulation parameters on the compressibility of the resulting granules is not well defined. The relationship between granulation parameters and granule compressibility is dependent, to a large extent, on the formulation and the consolidation mechanisms of the granulation during compression. During compression, the surface area of the granules increases and the separation distances between granules decrease. Wikberg and Alderborn showed that, for a lactose granulation, tablet strength was related to the degree of granule fragmentation during compression. They found that, for a series of granulations of the same composition, a higher degree of fragmentation propensity increased the volume reduction characteristics of the granulation upon compression, which in turn resulted in higher tablet strength. The increase in fragmentation propensity improves granulation compressibility. Fragmentation propensity is affected by granulation parameters that result in increased granule porosity (Wikberg and Alderborn, 1991, 1992a,b, 1993).

The aim of this study was to evaluate the effect of different processing parameters on the characteristics of a lactose-based granulation. Lactose granules fragment when subjected to compression forces and, therefore, undergo consolidation by a fracture mechanism (Juppo, 1996). A screening experimental design was used to identify critical parameters that influence granulation characteristics, including granule size and compressibility.

2. Materials and methods

2.1. Materials

Anhydrous lactose, NF, was the major component of the formulation (approximately 93% w/w) and was supplied by Quest International (Norwich, NY). Among other excipients in the formulation, povidone was used as a binder (2% w/w), and crospovidone as a disintegrant (2% w/w); both were supplied by International Specialty Products (Wayne, NJ). Magnesium stearate (1% w/w) was used as a lubricant (Mallinckrodt, St. Louis, MO).

2.2. Methods

2.2.1. Experimental design

Six variables were evaluated for their effect on granulation characteristics. These variables were: (1) impeller speed of the granulator; (2) granulating solution addition rate; (3) total amount of water added in the granulation step; (4) mixing time after complete addition of granulating solution (wet massing time); (5) moisture content of the granulation after drying; and (6) screen size used for milling of the dried granulation. These variables were screened with an eight run Plackett–Burman design shown in Table 1. Regression analysis of the data was carried out in SAS (Statistical Analysis System) by a linear model with no interactions. Analysis was done on the centered values of the factors (high level set to 1, low level set to -1). In the case of moisture content of the granulation and liquid addition rate, actual experimental values (not the target values) were used for the regression analysis.

2.2.2. Manufacturing process

Granulation was carried out in a TK-Fielder Spectrum Processor (SP-1) granulator at a batch size of 2 kg using an M8 impeller and a Christmas tree chopper design. Anhydrous lactose was blended with half of the quantity of crospovidone for 2 min in the granulator operating at impeller speed of 300 or 600 rpm and chopper speed of 3000 rpm. Povidone was dissolved in the granulating solution which was then added to the blend

Table 1
Plackett–Burman design for screening of processing parameters

Run number	Impeller speed (rpm)	Liquid addition rate[a] (g/min)	Total amount of water (g)	Wet massing time (min)	Moisture level after drying[b] (%)	Screen size for dry milling (inch)
1	600	200	225	1	2.0	0.024
2	300	200	225	3	0.8	0.032
3	300	100	225	3	2.0	0.024
4	600	100	185	3	2.0	0.032
5	300	200	185	1	2.0	0.032
6	600	100	225	1	0.8	0.032
7	600	200	185	3	0.8	0.024
8	300	100	185	1	0.8	0.024

[a] Target values. Actual values ranged from 90.8 to 143 g/min for the low level, and 186.8 to 216.5 g/min for the high level. Actual values were used for analysis.

[b] Target values. Actual values ranged from 0.64 to 0.73% for the low level and 1.92 to 2.54% for the high level. Actual values were used for analysis.

in the granulator at a rate of 100 or 200 g/min using a pressurized solution pot and a spray nozzle. The amount of water in the granulating solution represented 9.5 or 11.5% of the total solids in the granulator. Mixing was continued for 1 or 3 min after complete addition of the granulating solution (wet massing time). The granulation was dried in a Glatt WSG-3V fluid bed at 40°C inlet air temperature to a moisture content of approximately 0.8 or 2%. The dried granulation was milled using a Quadro 197S Comil through a screen of 0.032" or 0.024" opening diameter at 1000 rpm motor speed. The milled granulation was blended with the remaining quantity of crospovidone for 15 min in a 4 qt V-blender. Magnesium stearate was then added to the V-blender and blended for 5 min (Fig. 1). The lubricated granulation was compressed into 60 mg tablets using 7/32" round standard concave tooling.

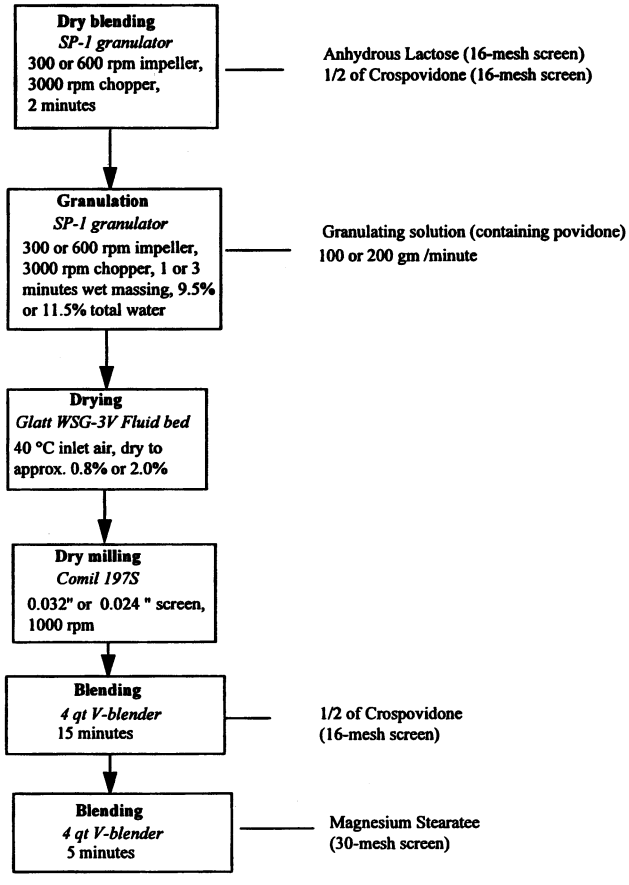

Fig. 1. Unit operations for manufacture of granulation from the various runs.

In addition to the 2 kg experimental-design batches shown in Table 1, three batches were manufactured using a TK Fielder PMA-65 granulator at 20 kg scale using a similar process. Chopper speed was 3000 rpm and impeller speed was 200 rpm, which represents the same impeller tip speed as the 300 rpm for the SP-1 granulator. The granulating solution was added to the granulator at a rate of 1000 g/min using a pressurized solution pot and a spray nozzle. The amount of water in the granulating solution represented 9.5% of the total solids in the granulator. Wet massing time was 0, 1, or 3 min. The granulation was dried in Aeromatic S2 fluid bed at 60°C inlet air temperature to a moisture content of approximately 1%. The dried granulation was milled using a Quadro 197S Comil through a screen of 0.032" opening diameter at 1000 rpm motor speed. The milled granulation was blended with the remaining quantity of crospovidone and magnesium stearate in a V-blender. The lubricated granulation was then compressed to 240 mg tablets using 11/32" round standard concave tooling.

2.2.3. Testing of granulation

2.2.3.1. Percent over size and particle size distribution. Percent oversize granulation was determined by passing the entire batch of dried granulation through 25-mesh screen. The weight percent of the granulation retained on the 25-mesh screen was taken as the percent oversize and was compared among the different batches. Particle size distribution of the final granulation was determined by mesh analysis using an Allen Bradley Sonic Sifter equipped with a series of six screens and a pan. An approximately 10 g sample was tested with a pulse setting of '5', sift setting of '5' and sifting time of 5 min.

2.2.3.2. Bulk and tapped density. Bulk density of the lubricated granulation was evaluated by determining the weight of 100 ml granulation in a graduated cylinder. The tapped density was deter-

mined using a Vankel tap density tester, Model 50-1200, which provides a fixed drop of one-half inch at a rate of 300 taps/min. A volume measurement was taken when the height of granulation in the 100 ml measuring cylinder reached a constant value (approximately 200–300 taps).

2.2.3.3. Moisture determination. Loss on drying (LOD) from a 5 g in-process sample during drying was measured at 105°C using a Computrac MAX 50 (Arizona Instruments).

2.2.3.4. Granulation compressibility. Compression profile of each granulation was obtained on an instrumented Korsch PH106 six-station tablet press using 7/32" round standard concave tooling (60 mg tablet weight). Tablets were compressed to a target weight of 60 mg using different compression forces ranging between 100–700 kg force. The resulting tablets at each compression force were tested for their weight and hardness using Vanderkamp VK200, Model 40-2000 hardness tester.

2.2.3.5. Weight variation and friability. Tablets compressed to a target weight of 60 mg also had a target hardness of 5 SCU. Tablets were tested for weight, hardness (Vanderkamp VK200 tester), thickness (Mitutoyo gauge), friability and disintegration time (USP methods). Weight variation of tablets was determined by calculating the S.D. of the weight of 20 tablets and was used to assess granulation flowability. Weight of tablets was monitored during the compression process.

2.2.3.6. Porosity. Pore-volume distributions of the granulations were determined for a sample of the granulation fraction retained on 100-mesh screen (particles >150 μm) by mercury intrusion porosimetry (Autopore III 9420, Micromeritics, Norcross, GA). Incremental pore volume was determined at different pressures ranging from 2500 to 60 000 psi corresponding to pore diameters between 120 μm to 0.003 μm. Equilibrium time was 10 s at each pressure. Pore volume distribution of tablets was also determined by a similar method.

3. Results and discussion

3.1. Percent oversize and particle size distribution

Percent of the dried (unmilled) granulation retained on 25-mesh screen (oversize granulation) and the percent of the final granulation retained on 60-mesh screen were used to compare the extent of granule growth between the various runs. Percent oversize granulation was comparable for all runs except for run 1 and 6. The percent oversize granulation was 31.4%, and 23.2% for these two runs, respectively, compared to 6.7–13.9% for the other batches (Table 2). Mesh analysis results of the lubricated granulation showed a larger fraction of the granulation retained on the 60-mesh screen for runs 1 and 6 compared to other runs. Runs 1 and 6 have high impeller speed (600 rpm), a high level of the total amount of water (225 g) and low wet massing time (1 min). Therefore, this combination of parameters appears to have a pronounced effect on particle agglomeration, resulting in the observed increase in percent oversize granulation and the larger fraction retained on the 60-mesh screen regardless of the screen size used for milling. This conclusion is supported by the results of the regression analysis for the 40–60 mesh granulation fraction and percent oversize data (Table 4). Regression analysis showed that impeller speed, total amount of water, and wet massing time have the largest effect on granule size as shown by the large magnitude of their parameter estimates for the percent oversize granulation and the 40–60 mesh fraction models. The positive sign of the parameter estimates for the impeller speed and total amount of water indicates that the high level of these parameters leads to larger granule size. To the contrary, the negative sign for the wet massing coefficient suggests that shorter wet massing time results in larger granule size.

The effect of impeller speed and the amount of water on granule growth can be explained by their effect on the degree of liquid saturation of the granules during the granulation process. Granule growth by coalescence is very dependent on the degree of liquid saturation of the colliding parti-

Table 2
Results of granulation evaluation from the different runs

Run number	1	2	3	4	5	6	7	8
Unmilled granulation								
Percent oversize granulation (25 mesh)	31.4	7.3	10.0	6.7	9.9	23.2	7.1	13.9
Final Lubricated granulation								
Bulk density (g/ml)	0.70	0.69	0.69	0.75	0.64	0.71	0.72	0.66
Tapped density (g/ml)	0.79	0.81	0.78	0.83	0.75	0.83	0.84	0.78
Moisture content (%)	1.95	1.07	1.79	1.75	1.95	1.12	0.78	1.08
Mesh analysis (% w/w)								
40	5.8	2.2	1.4	3.8	2.4	5.4	1.3	1.2
60	53.4	19.1	29.6	30.4	19.6	45.0	23.5	19.9
80	21.5	24.6	29.8	27.3	21.2	23.4	25.4	24
100	5.7	12.2	11.6	10.9	9.7	7.2	10.7	10.8
200	9.5	38.4	24.6	24.8	32.9	14.8	32.7	34
325	2.6	3.4	2.43	2.57	11.8	3.5	6.1	8.8
Pan	1.5	0.1	0.56	0.29	2.5	0.7	0.2	1.3

cles. Depending on the degree of liquid saturation, the bonding strength between the colliding granules may be strong enough to resist the separating forces exerted by the impeller of the high-shear granulator. The higher degree of liquid saturation is associated with more free liquid on the granule surface which enhances granule coalescence. Liquid saturation, S, of an agglomerate of particles (granule) is given by the equation (Kristensen, 1988):

$$S = H(1-\varepsilon)\frac{\rho}{\varepsilon} \quad (1)$$

where H is the ratio of the mass of the liquid phase to the mass of solids in the agglomerate, ε is the porosity of the agglomerate, and ρ is the particle density. The effect of high impeller speed and high level of water on percent oversize granulation can, therefore, be described as the result of increased liquid saturation of the granulation. High amounts of water will increase the magnitude of H in the above equation, while higher impeller speed is expected to increase granule densification and hence decrease the porosity, ε, term and increase the density, ρ, term.

During the granulation process in a high-speed mixer, particles or small granules agglomerate due to coalescence, and larger granules are broken due to the mechanical forces acting on them (Shaefer et al., 1986). These two effects counteract each other and the net effect depends on several factors such as the nature of the formulation, impeller speed, liquid saturation, and granule size. Under the above experimental conditions, the effect of increased wet massing time appears to result in breaking of the large granules, as shown by the decrease of the oversize granulation and the granulation fraction retained on the 60-mesh screen.

3.2. Granulation compressibility

Maximum hardness values were obtained from the compression profiles of the different runs and were used to compare the compressibility of the different granulations (Table 3). All granulations with higher moisture content showed increased compressibility and the maximum hardness values ranged between 8 and 10.4 SCU. This suggests that moisture content of the granulation has a pronounced effect on compressibility. Thus, granulations dried to the low moisture content showed lower compressibility except for run 8 which had maximum hardness of 8.2 SCU, comparable to the tablets with higher moisture content. Therefore, granulations from the different runs appeared to separate into two groups according to the maximum achievable hardness for the 7/32“ standard concave tablets. The first group showed

maximum hardness between 8 and 10.4 SCU and includes all runs dried to approximately 2% moisture together with run 8; the other group showed maximum hardness values between 4.1 and 4.7 SCU and includes the remaining runs dried to approximately 0.8% moisture.

Results of the regression analysis showed that moisture content has the largest effect on the maximum hardness, followed by the wet massing time and impeller speed. The negative sign of the coefficients for the wet massing time and impeller speed indicates that a low level of these parameters leads to more compressible granulation (Table 4). Granulation from run 8, which showed the highest compressibility among granulations dried to low moisture content, was manufactured using low impeller speed and short wet massing time (second and third most important parameters). Run 5, which showed the highest maximum hardness value among granulations, dried to a high moisture content, was also manufactured with low impeller speed and short wet massing time. Increasing the impeller speed and/or the wet massing time resulted in the decrease of granulation compressibility.

High impeller speed and long wet massing time can possibly decrease the granulation porosity by subjecting the granulation to high-shear forces for longer periods of time. Porosity of the granulation from runs 7 and 8 was determined by mercury intrusion porosimetry on a sample of the granulation with particle size greater than 150 μm. Pore volume for pores in the 1–8 μm diameter range was diminished for granulation from run 7, which was manufactured using high impeller speed (600 rpm) and long wet massing time (3 min), compared to run 8 (Fig. 2). These pores appeared to be critical for granulation compressibility, as shown by the remarkably higher compressibility of granulation from run 8. Tablets compressed using the more porous granulation showed reduced pore volume in the 1–4 μm pore diameter range compared to tablets compressed using the less porous granulation under the same compression force (Fig. 3). This finding illustrates the higher tendency of the more porous granulation to densify upon application of the compression force resulting in closer packing of the particles and, consequently, elimination of pores in the 1–4 μm range. In contrast, granulation from run 7 showed a peak at 2 μm, suggesting a lower tendency for densification upon compression. This is consistent with the finding by Wikberg and Alderborn, (1993) that demonstrated wider and bimodal pore-size distribution for the tablets compressed from granulation with low porosity compared to the narrower and smaller pore-size distribution for tablets compressed from the more porous granulation. The reduced porosity of the granulation from run 7 resulted in a decreased fragmentation propensity and volume reduction behaviour of the granulation which led to decreased granulation compressibility. Consequently, tablets compressed from the granulation with lower pore volume showed lower tablet hardness than tablets manufactured using more porous granulation.

The effect of wet massing time on granulation compressibility was also evaluated at 20 kg scale in the PMA-65 granulator. The experiments were conducted at the low impeller speed based on the results from the SP-1 experiments, which showed that high impeller speed decreased granulation compressibility. The granulation was dried to a target moisture content of approximately 1% since this was found to be the equilibrium moisture

Table 3
Results of compression experiments for the different runs

Run number	1	2	3	4	5	6	7	8
Maximum Hardness for 7/32'' tablets (SCU)	8.8	4.7	9.1	8.0	10.4	4.9	4.1	8.2
Weight variation for 7/32'' tablets of 5 SCU hardness (S.D.)	0.39	0.46	0.36	0.29	0.47[a]	0.31	0.39	0.42
Friability for 7/32'' tablets of 5 SCU hardness (%)	0.02	0.17	0.27	0.19	0.19[a]	0.06	0.08	0.06

[a] Tablets of 8 SCU hardness.

Table 4
Regression analysis data for the Blackett–Burman experimental design

Variable	Parameter Estimate (P value)					
	Impeller speed	Liquid addition rate	Total amount of water	Wet massing time	Moisture level after drying	Screen size for dry milling
Maximum hardness	−0.729 (0.25)	−0.065 (0.91)	−0.436 (0.39)	−1.035 (0.19)	2.249 (0.11)	−0.213 (0.62)
Weight variation	−0.045 (0.10)	0.060 (0.12)	−0.008 (0.45)	0.001 (0.90)	−0.003 (0.79)	0.001 (0.88)
Friability	−0.039 (0.26)	−0.010 (0.76)	−0.0001 (0.99)	0.040 (0.27)	0.049 (0.27)	0.023 (0.41)
% Oversize	3.430 (0.22)	0.320 (0.89)	4.260 (0.18)	−5.938 (0.14)	0.922 (0.67)	−1.856 (0.38)
Bulk density	0.026 (0.10)	−0.012 (0.31)	0.003 (0.61)	0.015 (0.18)	−0.002 (0.74)	0.001 (0.80)
Tapped density	0.021 (0.02)	−0.009 (0.07)	0.002 (0.19)	0.014 (0.03)	−0.019 (0.03)	0.002 (0.15)
40–60 mesh fraction	9.409 (0.08)	−1.220 (0.63)	7.433 (0.10)	−5.827 (0.13)	4.210 (0.23)	−1.043 (0.55)
80–200 mesh fraction	−7.630 (0.03)	−0.512 (0.56)	−5.053 (0.05)	7.623 (0.04)	−4.589 (0.07)	0.691 (0.34)
>325 mesh fraction	−1.773 (0.27)	1.657 (0.40)	−2.427 (0.20)	−1.811 (0.27)	0.369 (0.79)	0.345 (0.74)

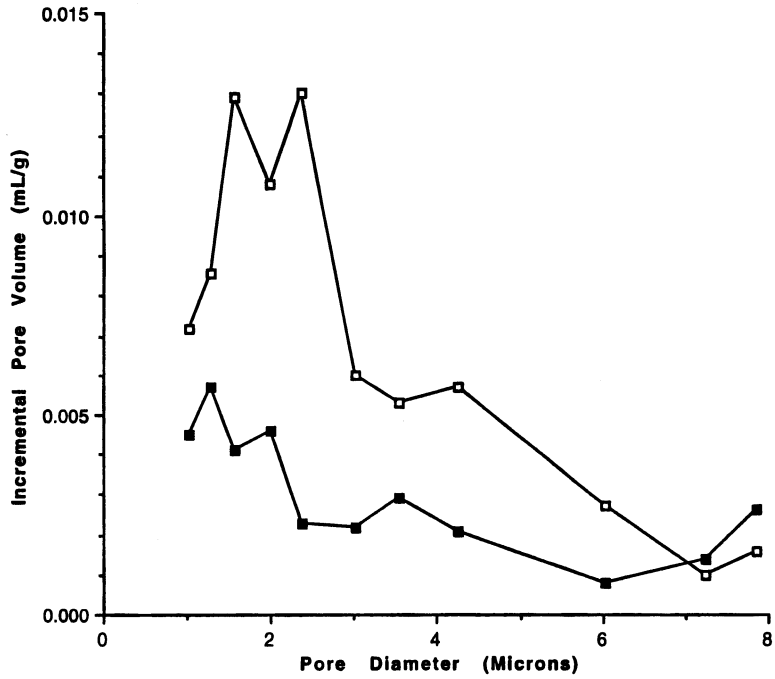

Fig. 2. Pore volume distribution determined by mercury intrusion porosimetry for granulations manufactured using different parameters. (■), run 7; (□), run 8.

content for the granulation at ambient conditions. Other parameters (amount of water, liquid addition rate and screen size) were arbitrarily selected as they were shown in the SP-1 experiments to have minimal effect on granulation characteristics. Compressibility of granulation manufactured in the PMA-65 granulator was also dependent on wet massing time. Granulation compressibility decreased as the wet massing time increased from 0 to 3 min (Fig. 4), indicating that the effect of wet massing time at this scale is similar to the SP-1 batches. Similar to the SP-1 batches, granulation manufactured using long wet massing time in the PMA-65 granulator showed a relatively low fragmentation tendency. Scanning electron microscopy of tablets compressed using granulation manufactured in the PMA-65 granulator with 3 min wet massing time showed a more preserved outline of granules than tablets compressed using the more compressible granulation from run 8 in the above SP-1 experiments (Fig. 5).

3.3. Bulk and tapped density of granulation

Results of the regression analysis showed that impeller speed has the largest effect on bulk density followed by the wet massing time. These parameters showed a positive sign for the estimate of their coefficients. This is consistent with the above discussion that high impeller speed and wet massing time result in lower granulation porosity and, therefore, higher bulk density. In addition, the tapped density of the granulation showed a similar trend for the effect of wet massing time and impeller speed. It is noteworthy that both bulk and tapped density showed a correlation with the maximum hardness values. Runs 8 and 5, which showed the highest maximum hardness

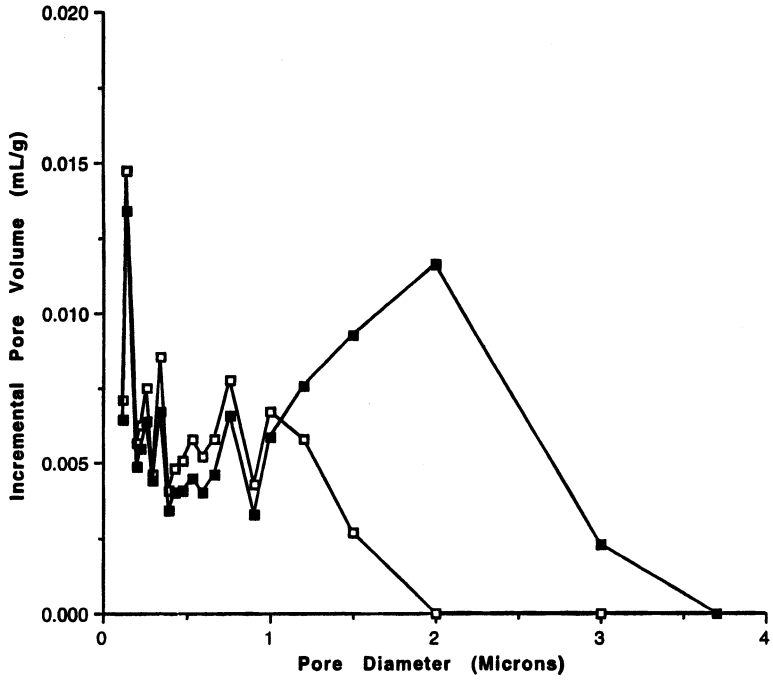

Fig. 3. Pore volume distribution determined by mercury intrusion porosimetry for tablets manufactured using different parameters. (■), run 7; (□), run 8.

among granulations with low and high moisture content, respectively, demonstrated the lowest bulk and tapped density among the eight runs.

3.4. Weight variation and friability

Weight variation and friability data were acceptable for all the runs. S.D. for the weight of tablets compressed to a target weight of 60 mg and hardness of 5 SCU was < 0.47 mg for all runs, indicating acceptable flow properties of the granulation. Friability was $< 0.3\%$ for the tablets from all runs. Regression analysis showed low values of all parameter estimates for the weight variation and friability models, suggesting little effect of the evaluated parameters on these two responses.

4. Conclusions

Granulation compressibility of a lactose-based formulation was very sensitive to change in pro-

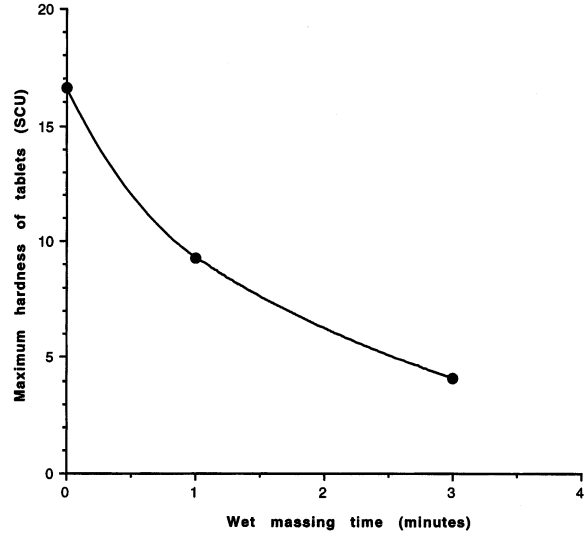

Fig. 4. Effect of wet massing time on compressibility of granulation manufactured in the PMA-65 high-shear granulator. Tablet weight, 240 mg; diameter, 11/32''.

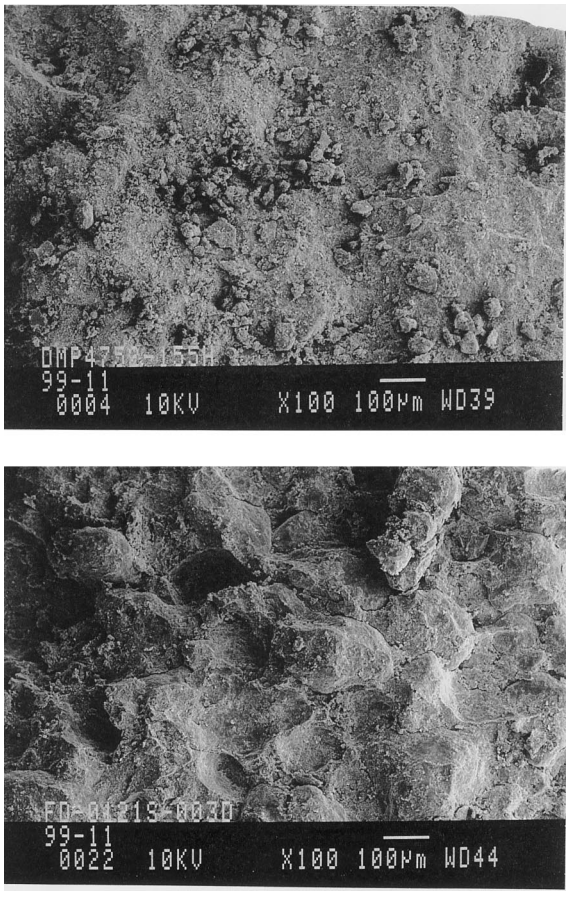

Fig. 5. Scanning electron micrographs of broken surface of tablets compressed using more compressible (top) and less compressible granulation (bottom).

cessing conditions. Moisture content of the dried granulation has the largest effect on the maximum hardness, followed by the wet massing time and impeller speed. Choice of processing parameters for a lactose formulation is critical in developing a manufacturing process that yields granulation with acceptable compressibility. On the other hand, granulation flow was more tolerant to a wider range of processing parameters as shown by the acceptable weight variation for the tablets from all runs.

Acknowledgements

The authors would like to thank L. Abrams and R. Maynard for the useful discussions and help with porosimetry measurements.

References

Juppo, A.M., 1996. Change in porosity parameters of lactose, glucose and mannitol granules caused by low compression force. Int. J. Pharm. 130, 149–157.

Kristensen, H.G., 1988. Agglomeration of powders. Acta Pharm. Suec. 25, 187–204.

Shaefer, T., Holm, P., Kristensen, H.G., 1986. Comparison between granule growth in a horizontal and a vertical high-speed mixer: II: granulation of lactose. Arch. Pharm. Chem. 14, 17–27.

Shiraishi, T., Kondo, S., Yuasa, H., Kanaya, Y., 1994. Studies on the granulation process of granules for tableting with a high-speed mixer: I: physical properties of granules for tableting. Chem. Pharm. Bull. 42 (4), 932–936.

Wehrle, P., Nobelis, P., Cuine, A., Stamm, A., 1993. Response surface methodology: an interesting statistical tool for process optimization and validation: example of wet granulation in the high-shear mixer. Drug. Dev. Ind. Pharm. 19 (13), 1637–1653.

Wikberg, M., Alderborn, G., 1991. Compression characteristics of granulated materials: IV: the effect of granule porosity on fragmentation propensity and the compactibility of some granulations. Int. J. Pharm. 69, 239–253.

Wikberg, M., Alderborn, G., 1992a. Compression characteristics of granulated materials: V: mechanical properties of individual granules assessed by diametral compression, in granulations with different volume reduction behaviour. STP Pharm. Sci. 2 (4), 313–319.

Wikberg, M., Alderborn, G., 1992ab. Compression characteristics of granulated materials: VI: pore size distribution, assessed by mercury penetration, of compacts of two lactose granulations with different fragmentation propensities. Int. J. Pharm. 84, 191–195.

Wikberg, M., Alderborn, G., 1993. Compression characteristics of granulated materials: VII: the effect of intragranular binder distribution on the compactibility of some lactose granulations. Pharm. Res. 10 (1), 88–94.