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Fluid bed granulation of a poorly water soluble, low density, micronized drug: comparison with high shear granulation

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Abstract

A 2^{4-1} fractional factorial design was used to evaluate the effect of various process variables in fluid bed granulation, on the physico-chemical properties of granule and tablet containing a high dose, poorly water soluble, low density, and micronized drug. The process variables studied were inlet air temperature, inlet air flow, spray rate of the binder solution, and atomization air pressure. Tablets with identical composition, weight, size and hardness were also manufactured in a high shear granulator and their physical properties were determined and compared with those produced by the fluidized bed granulation method. Except for the granule size distribution, other physical properties of granulations and tablets produced in a fluid bed granulator are independent of the selected process variables within the study range. Both atomization air pressure and spray rate of the binder solution had strong impact on granule size distribution. Irrespective of the process conditions used in the fluid bed granulation, granules from this process were more porous, less dense and more compressible than the granules from the high shear granulation process. Comparable tablet dissolution rates to those prepared by the optimized high shear granulation method can be achieved by selecting the appropriate process conditions in fluid bed granulation. These results suggest that wet granulation tablets of a high dose, poorly water soluble, low density, micronized drug can be manufactured using a fluidized bed granulation method, with comparable tablet dissolution rates to those produced with an optimized high shear granulation method. © 2002 Published by Elsevier Science B.V.

Keywords: Fluid bed granulation; High shear granulation; High dose, poorly water soluble, low density, micronized drug; Granule size; Tablet dissolution

1. Introduction

Fluid bed granulation and drying offers several advantages over other multi-step granulation and drying processes. Mixing of dry powders, granu-

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lating and drying can be successively carried out within a single piece of equipment. Reduction in the manufacturing process steps results in overall shortening of manufacturing time. Fluid bed granulation and drying also reduces handling of raw materials, and hence, reduces operator exposure to irritating and/or toxic compounds.

The theory and techniques of fluidization have been known for many years and have been described extensively in the literature (Othmer, 1956; Zenz and Othmer, 1960; Scott et al., 1963). Fluidized bed technique has been used in pharmaceutical industry for drying (Vanecek et al., 1966), coating (Robinson et al., 1968), and recently granulating. Wurster (1959) first described granulation in the fluid bed. The design and operation of fluid beds for continuous production of tablet granulation was presented by Scott et al. (1964).

Fluidized bed granulation is a complex process in which both product and process variables affect the properties of granules at the same time. The product variables include the starting materials and their physicochemical properties (particle size, surface area, solubility in water), binder type and binder concentration. The process variables include inlet temperature of fluidizing air, fluidizing air velocity, atomization air pressure, addition rate of binder solution, nozzle height and spray angle.

The effect of starting materials on granule properties was previously studied (Schaefer and Worts, 1977, 1978a). Since granulation is induced by formation of liquid bridges between particles (Newitt and Cnoway-Jones, 1958), the final granule characteristics are influenced by the particle size, surface area and water binding properties of the excipients (Schaefer and Worts, 1977). However, the starting materials used in these studies were common excipients and hence, the results observed may not be the same as those when a significant amount of active is present in the formula. The problems encountered with fluid bed granulation of a formula containing a high amount of poorly water soluble, micronized active include, difficulty in fluidizing due to the powder being cohesive (Dussert et al., 1995) and poor wetting, which impairs binder efficiency (Dussert et al., 1995). The study on the effect of characteristics of the active on granulation properties was inconclusive (Sunada et al., 1998).

The effect of atomization air pressure and binder addition rate on final granule properties was studied with mixed results. While some authors have shown a decrease in granule size with increased atomization air pressure (Schaefer and Worts, 1977; Davies and Gloor, 1971; Gupte, 1973; Rouiller et al., 1975), others found no effect (Ormos et al., 1973). Similarly, several authors found that an increase in binder addition rate resulted in a larger granule size (Scott et al., 1964; Davies and Gloor, 1971; Rouiller et al., 1975) while Schaefer and Worts (1978a) reported studies that found no effect of this factor on the granule size.

Table 1
A 2^{4-1} fractional factorial design to study the effect of fluid bed granulation processing variables on physical properties of granules and tablets prepared with a high dose, water insoluble, low density, micronized drug

Experiment	Inlet air temperature (°C)	Inlet air flow (CMH)	Spray rate of binder solution (g/min)	Atomization air pressure (bar)
1	60	20	30	1.5
2	50	10	20	0.5
3	50	10	30	1.5
4	50	20	20	1.5
5	60	10	30	0.5
6	60	10	20	1.5
7	50	20	30	0.5
8	60	20	20	0.5

Table 2
Fluid bed granulation and drying process parameters

Experiment	Inlet dew point (°C)		LOD at the end of granulation (%)	Inlet air flow during drying (cfm)	Product temperature (°C)		Granulation and drying time (min)
	Set	Actual			Granulation	End of drying	
1	12.0	12.0	41.0	10–30	25–26	36	132
2	12.0	12.1	37.7	10–30	23–24	35	171
3	12.0	12.0	40.2	10–30	23–26	35	130
4	12.0	11.9	36.9	10–30	23–24	37	168
5	12.0	12.2	36.5	10–30	26–27	34	131
6	12.0	12.0	33.6	10–30	26–29	35	156
7	12.0	11.9	41.1	10–30	24–25	34	134
8	12.0	11.9	34.5	10–30	26–28	34	155

The fluidizing air velocity depends on the bed load, particle size and density (Davies and Richardson, 1963). Since the particle size changes gradually during granulation, the air velocity must be varied to keep the bed expansion constant. Hence, studying the effect of fluidizing air velocity is difficult unless it is only varied during the early granulation phase.

The inlet temperature of the fluidizing air influences the rate of evaporation which in turn affects the agglomeration by formation of liquid bridges during the granulation phase. In the drying phase, the inlet temperature of fluidizing air influences the drying time, which effects the extent of attrition (Scott et al., 1963; Zoglio et al., 1975). Hence, the inlet temperature may effect the granule size during both the granulation phase and the drying phase. Several authors (Davies and Gloor, 1971; Gupte 1973; Rouiller et al., 1975) have found that a rise in inlet temperature of fluidizing air resulted in decreased granule size.

The purpose of this study was to investigate the feasibility of producing tablets by fluid bed granulation technique of a high dose, poorly water soluble, low density, micronized drug that is currently manufactured using a high shear granulation method. The effect of various process variables including fluidizing air velocity, inlet temperature of the fluidizing air, binder addition rate and atomization air volume on the final granule properties was examined. In addition, granulations produced by the fluidized bed technique were compressed into tablets, and their physical properties were evaluated, and compared with those produced with high shear granulation method.

2. Materials and methods

2.1. Materials

Micronized drug substance was used in this study. Using Malvern Particle Size Analyzer, the particle size distribution values for the drug substance are 3.1 and 12.9 μm for d_{50} and d_{90}, respectively. The drug is practically insoluble in water at 9 μg/ml (pH 8.3) at room temperature. The bulk density and tap density values are 0.15 and 0.27 g/cm^3, respectively.

The granulation consisted of approximately 1 kg of dry solids of which 52% was active drug substance. An aqueous solution of a cellulose-based binder was used to granulate the dry components. Whatman 0.45 μm PTFE Autovial Syringeless Filters (Whatman Science, Ann Arbor, MI, USA) were used for sample filtration during dissolution testing. Ultra pure sodium lauryl sulfate (SLS) (JT Baker, Phillipsburg, NJ, USA) and Milli-Q water (Millipore Corp., Milford, MA, USA) were used to prepare the dissolution medium. HPLC grade methanol (EM Science, Bibbstown, NJ, USA), ultra pure SLS (JT Baker) and Milli-Q water (Millipore Corp.) were used in the preparation of the standard solution.

2.2. Fluid bed granulation

The 16 l fluid bed granulator used in this study was made by Niro Inc. (model MP-1, Aeromatic Fielder, AG). The humidity, temperature and flow of the inlet air were controlled. A spray nozzle by which the binder solution was atomized was located above the powder bed. The droplet size of the binder solution was controlled by the atomization air pressure and the spray rate of the binder solution.

Due to the high load, high bulk volume (low bulk density), and high static charge of the drug substance, the drug substance was first blended

Table 3
Particle size distribution of preblend

Screen size (mesh)	Screen opening (μm)	Percent retained (%)
30	595	18.5
50	297	27.6
100	150	23.2
200	75	23.1
400	37	7.6
Pan	<37	0.0
Total		100.0

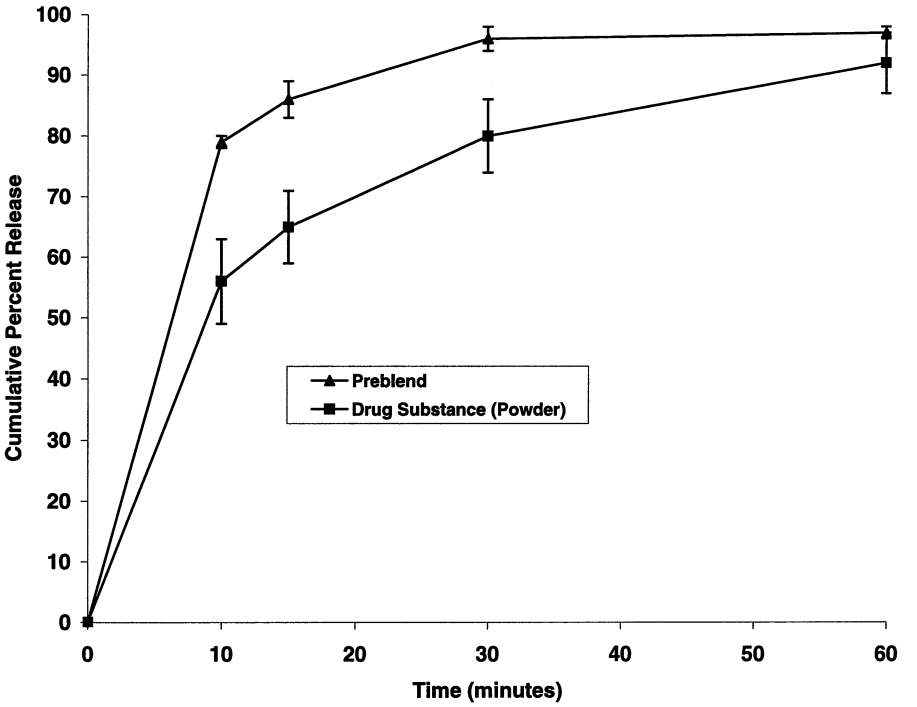


Fig. 1. Dissolution rates of the preblend and the pure drug substance (powder dissolution).

with the excipients, excluding the lubricant, in a 8 qt. V-blender (Patterson-Kelly Co., Stroudsburg, PA, USA). This preblend was then passed through a 16 mesh stainless steel screen (VWR Scientific, NJ, USA) and granulated in a fluid bed granulator with an aqueous binder solution.

2.3. Experimental design

This study involved a 2^{4-1} fractional factorial design. Inlet air temperature (during granulation and drying), inlet air flow during the addition of the binder solution, spray rate of the binder solution and atomization air pressure were evaluated as independent variables. The response variables included bulk and tap densities, and granule size distribution of dried, milled and unlubricated granulation, lubricated granulation compressibility, tablet disintegration time and dissolution. A statistical analysis of those response variables was performed using JMP Software (JMP 1.25, SAS Institute Inc., Cary, NC, USA). The fixed operating parameters included, (1) dew point of the inlet air; (2) the height of the spray nozzle; (3) the filter shaking cycle; (4) method of adding the binder; (5) batch size; and (6) Loss On Drying (LOD) value at the end of the granulation and drying. The matrix of the experiments is presented in Table 1.

The relatively low inlet air flow values were chosen in this study to avoid dispersing the fine

Table 4
Bulk/tap densities and Carr's index values of granulations manufactured by the fluid bed method

Experiment	Bulk density (g/cm^3)	Tap density (g/cm^3)	Carr's index
1	0.360	0.439	18
2	0.320	0.377	15
3	0.418	0.565	26
4	0.331	0.409	19
5	0.321	0.382	16
6	0.330	0.407	20
7	0.368	0.438	16
8	0.317	0.378	16

Table 5
Particle size distribution of granules from the fluid bed granulation process

Experiment	Granule size distribution		
	Granules >500 m (%)	Granules <105 μm	Geometric mean diameter (μm)
1	19.2	20.0	220
2	0.8	8.9	192
3	23.9	24.3	216
4	0.8	34.5	112
5	23.1	8.8	251
6	0.8	31.1	111
7	24.4	10.8	284
8	0.4	7.1	196

Table 6
Physical properties of compressed tablets prepared with fluid bed technique

Experiment	Compression force (kg)	Disintegration time (min)	Dissolved at 10 min (%)	Dissolved at 15 min (%)
1	742 (34)	12.6 (0.5)	44 (3)	55 (2)
2	789 (10)	13.1 (0.6)	46 (3)	60 (2)
3	676 (68)	15.3 (0.1)	41 (2)	56 (2)
4	705 (38)	12.9 (0.9)	35 (1)	45 (1)
5	714 (50)	12.5 (1.3)	48 (2)	62 (2)
6	802 (49)	14.5 (1.0)	26 (2)	36 (3)
7	930 (31)	16.4 (0.8)	44 (2)	56 (3)
8	808 (23)	17.2 (0.9)	50 (1)	71 (0)

(), Standard deviation (S.D.) of three determinations.

particles or scattering the drug in the upper part of the fluid bed. Upon completion of the binder solution addition, the inlet air flow was changed to maintain appropriate fluidization of the granulation bed. The inlet air flow during drying and other process parameters are summarized in Table 2.

2.4. Granulation in a high shear granulator

The high shear granulation process has been characterized in extensive optimization studies to produce tablets with acceptable physico-chemical, mechanical, and biopharmaceutical properties (data not shown). Factors examined included amount of granulating liquid added, granulating liquid delivery rate, and impeller and chopper speed. To compare the two manufacturing processes (i.e. fluid bed vs. high shear), a separate experiment was carried out in a high shear granulator (Gral 10L, GEI Processing, Towaco, NJ, USA) using the optimized wet granulation process. In this experiment, all the ingredients, except the lubricating agent, were added intragranularly and mixed for 3 min with impeller and chopper on setting 1. The binder was added as an aqueous solution at a rate of 50 g/min and then additional water was added at a rate of 100 g/min with impeller and chopper on setting 2 until desired power consumption reading was obtained. Drying was carried out in a Glatt Fluid Bed Dryer (Glatt WSG-3, Glatt Air Techniques, Ramsey, NJ, USA). Granulation of this batch was dried to the same LOD value as those of the fluid bed granulation batches.

2.5. Moisture content of granules prepared by the fluid bed and the high shear granulator

The moisture content (expressed as LOD) during the fluid bed granulation and drying was followed by taking samples of approximately 2 g from the bed with a sampling probe. LOD values of various granule lots were determined using a Mettler Moisture Determination Balance (Model LJ16, Mettler Toledo, Switzerland) at 105 °C.

2.6. Bulk and tap densities of preblend and dried, milled and unlubricated granulations

Bulk and tap densities were determined using a 10 ml graduated cylinder. The bulk density was measured by carefully pouring the material into a pre-weighed 10 ml graduated cylinder and was calculated by dividing the weight of the material (g) by the volume (ml) occupied in the cylinder. The filled cylinder was then placed in a Vankel tap density tester (Model 50-1200, Vankel, Edison, NJ, USA) and tapped to constant volume. Both bulk and tap densities were measured in duplicate, reporting the average.

Table 7
Process variables observed in 2^{4-1} fractional factorial design on granule size distribution

Response variable	Process variable	*P* value
Granules passing through 140 mesh screen (%)	Atomization air pressure	0.0142
	Spray rate of binder solution	0.3039
	Inlet air temperature	0.9543
	Inlet air flow	0.4917
Granules retained on 35 mesh screen (%)	Spray rate of binder solution	0.0003
	Atomization air pressure	0.4483
	Inlet air temperature	0.4691
	Inlet air flow	0.2581
Geometric mean diameter (μ)	Spray rate of binder solution	0.0045
	Atomization air pressure	0.1108
	Inlet air temperature	0.4313
	Inlet air flow	0.6101

2.7. Particle size distribution of preblend and dried, milled and unlubricated granulations

An Allen Bradly Sonic Sifter (Model L3P, Allen Bradley, Milwaukee, WI, USA) equipped with a series of stainless steel screens and a fines collector was used for the determination of particle size distribution of the preblend and dried, milled, unlubricated granulation. The screens used were 30 (595), 50 (297), 100 (150), 200 (75), 400 (37) mesh (μm) and a fine collector pan for the preblend, and 35 (500), 50 (297), 80 (177), 100 (150), 140 (105) mesh (μm) and a fine collector pan for the dried, milled, unlubricated granulation. An approximately 6-gram sample was tested in duplicate with a pulse setting of 5, sift setting of 5 and sifting time of 5 min. The percent retained was calculated from the amount retained on each screen divided by the sample size. The geometric mean diameter was determined from the sieve analysis data (Fonner et al., 1981). The average of the two determinations was reported.

2.8. Scanning electron microscopy (SEM) of dried, milled and unlubricated granules

Granule surface characteristics were examined using a scanning electron microscopy (SEM, Model JEOL JSM 840). The granules were sprinkled onto a sample holder and approximately 60 nm of gold/palladium was vacuum evaporated onto their surface. The samples were then examined for surface characteristics.

2.9. Tablet manufacture

The dried, milled, and lubricated granulation blends from both fluid bed and high shear granulation processes were compressed into 1.2 g tablets on an instrumented Manesty single-station tablet press (Model F3, Manesty Machines Ltd., Liverpool, England) using 0.83×0.395 in. capsular shaped tooling. The compression forces required to achieve the target hardness (26

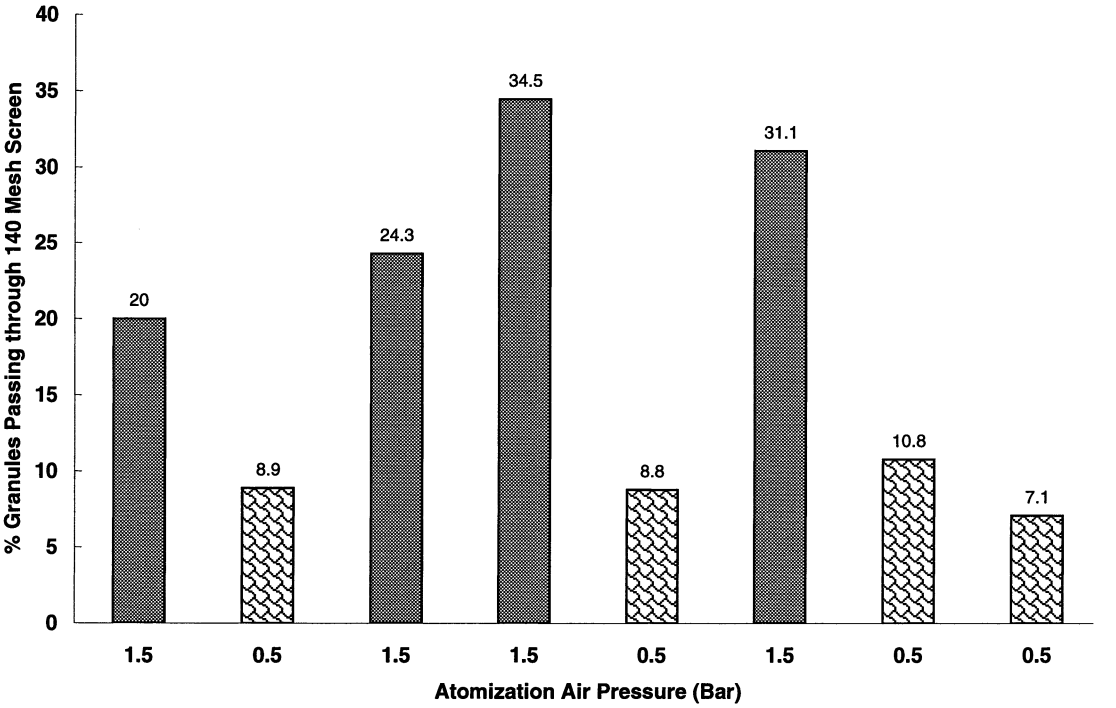


Fig. 2. Effect of atomization air pressure on percentage granules passing through the 140 mesh screen.

SCU) were recorded using a Universal Instrumentation Monitor Tablet Press Module, version 1.48 (Metropolitan Computing Cooperation, MCC, East Hanover, NJ, USA). The tablet hardness was determined using a Tablet Hardness Tester (Vanderkamp VK200, Vankel, Edison, NJ, USA).

2.10. Tablet disintegration

Tablet disintegration was determined in Purified Water, USP using a standard USP disintegration apparatus (Erweka ZT72, Erweka Instrument Corp.) at 37 °C. The average of three determinations were reported.

2.11. Dissolution

Multipoint dissolution test was conducted with either 600 mg drug substance (powder), or 1162.8 mg preblend (containing 600 mg drug) or one 600 mg strength tablet in 900 ml of 2% SLS at 37 °C using the USP Apparatus II (Paddle method). Ten milliliters of the sample were withdrawn from each vessel at 10, 15, 30, 60 and 90 min and an equivalent volume of dissolution medium was added to the dissolution vessel after each sampling. Samples were filtered through a Whatman autovial 0.45 μ PDVF, appropriately diluted, and analyzed at 250 nm by UV spectrophotometer (Model 8451A, Hewlett Packard). The paddles were rotated at 50 rpm followed by 150 rpm after 60 min. The reported data were the mean of three determinations.

3. Results and discussion

3.1. Physical properties of preblend

3.1.1. Bulk and tap densities

The bulk and tap densities of the preblend are 0.23 and 0.40 g/cm^3, respectively. The Carr's index calculated from the bulk and tap densities (42.5%) suggest a very poor flow of the preblend.

3.1.2. Apparent particle size

The apparent particle size distribution of the preblend is presented in Table 3. The geometric mean diameter of the preblend calculated from the particle size distribution data was 266.5 μm, indicating that drug particles are present in the preblend as agglomerates.

3.1.3. Dissolution rate

To maintain a 'sink condition', the dissolution medium contained 2% SLS. The solubility of drug in the dissolution medium at 25 °C is around 4 mg/ml. The dissolution rate of the preblend was compared with that of the drug substance (powder dissolution), and the results are presented in Fig. 1. The faster dissolution rate from the preblend could be due to the presence of the surface active agent and the superdisintegrant in the preblend.

3.2. Effects of fluidized bed granulation process variables on physical properties of granulation and compressed tablets

The success of granule formation depends upon the process variables associated with the fluid bed granulator. The values of the response variables in the eight experiments in the fractional factorial design are presented in Tables 4–6. The significant process variables at a 95% confidence level were determined. Except for the granule size distribution, other physical properties of the granulation and the compressed tablets are independent of the selected process variables within the study range.

3.3. Particle size of the granulation

The percent granules passing through 140 mesh

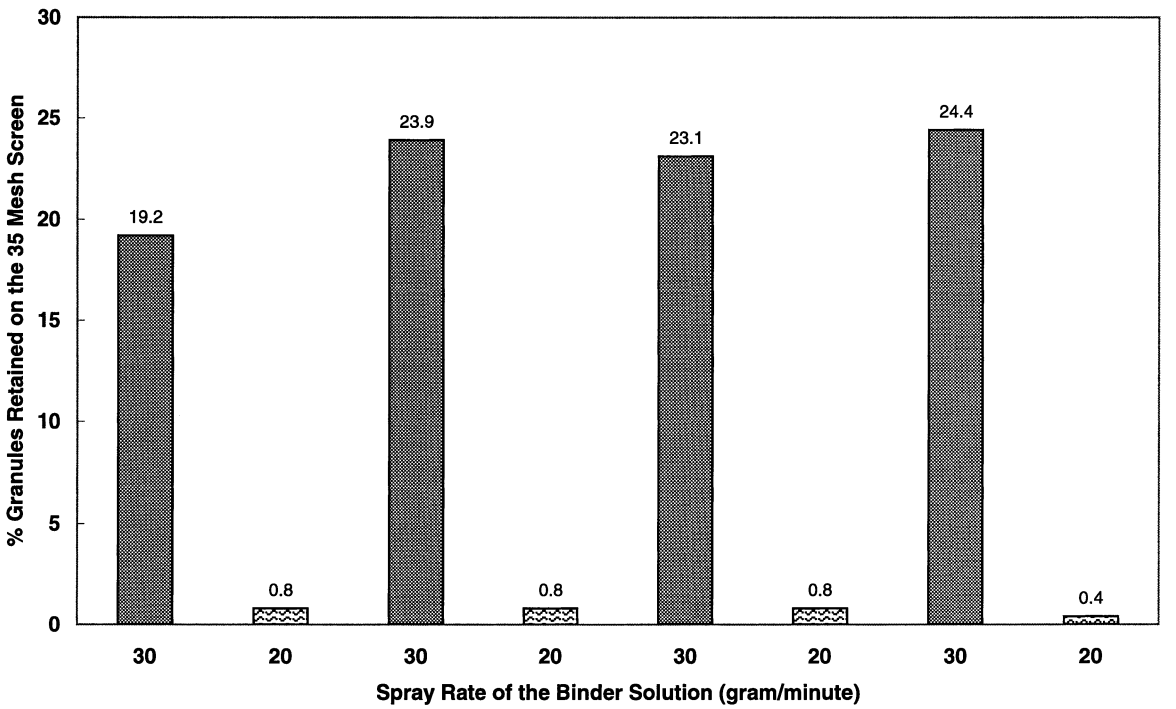


Fig. 3. Effect of spray rate of the binder solution on percentage granules retained on the 35 mesh screen.

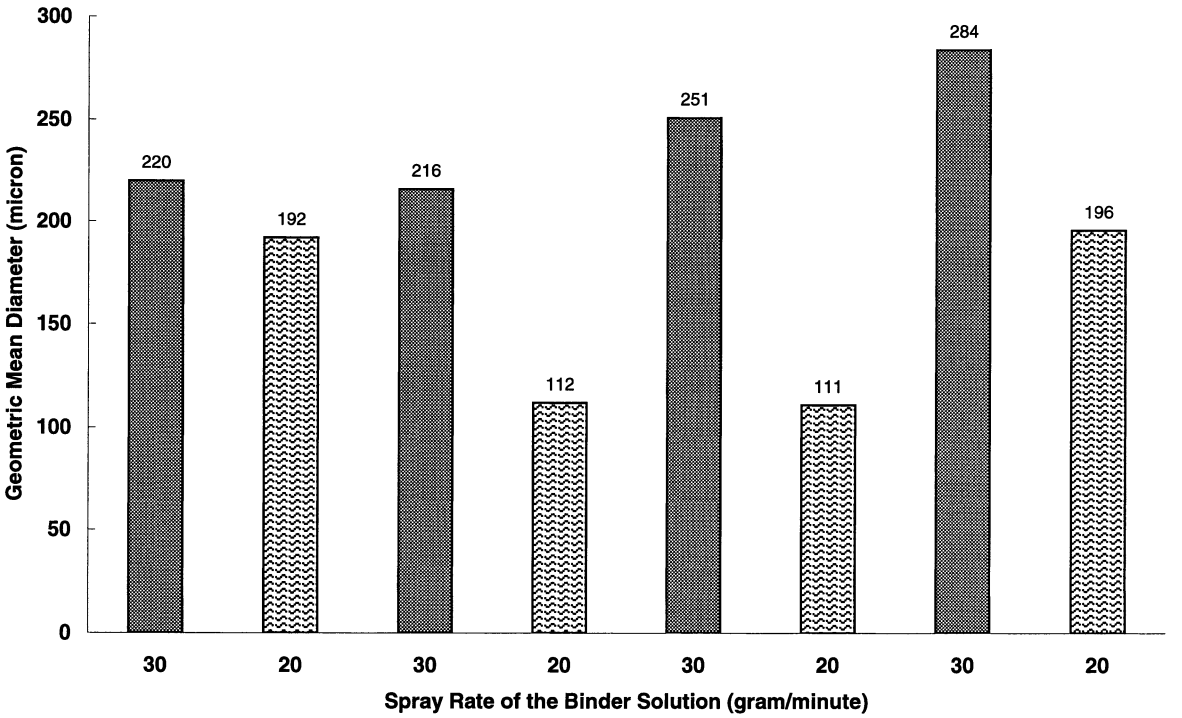


Fig. 4. Effect of spray rate of the binder solution on the geometric mean diameter of the granulation.

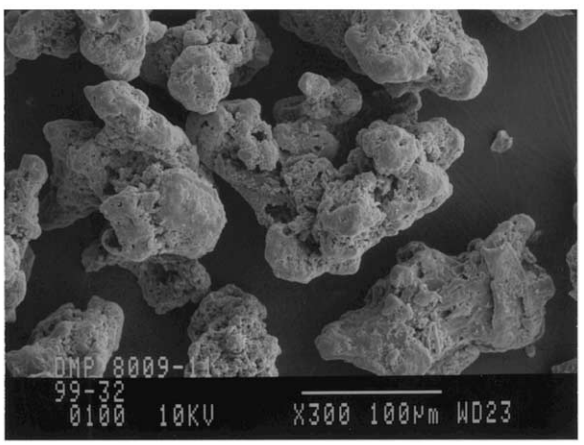
screen (<105 μm, defined as fines), the percent granules retained on 35 mesh screen (>500 μm, defined as coarse particles), and the geometric mean diameter were used to characterize the granule size distribution. The analysis of variance of the granule size distribution data (Table 5) clearly shows that the most important process variables are the atomization air pressure and the spray rate of the binder solution. The inlet air temperature and inlet air flow have little effect on the granule size. Table 7 shows those process variables and their P values on the particle size of the granulation.

Atomization of the binder solution occurs in the binary nozzle head, at which point the liquid binder and air converge to form fine droplets of aqueous binder. The degree of atomization of the binder solution is controlled by the air-to-liquid mass ratio in the nozzle head. Several authors (Davies and Gloor, 1971; Gupte, 1973; Rouiller et al., 1975) reported that increased atomization air pressure, and consequently, increased air-to-liquid mass ratio resulted in a decrease in granule size. Fig. 2 illustrates the effect of atomization air pressure on the percent granules passing through 140 mesh screen. Regardless of the other process variables, granulation prepared at an atomization pressure of 1.5 bars, which corresponded to a higher air-to-liquid mass ratio, produced more fines (20.0–34.5% granules <105 μm) than that manufactured at 0.5 bar ($<11\%$ fines). The increase in the percentage fines is attributed to the finer spray droplet formation of the binder solution as a result of increasing the air-to-liquid mass ratio in the atomization process, resulting in the formation of weaker binder–powder bridges. Since granule formation in a fluidized bed is a balance of size enlargement and size reduction, weak liquid bridges on the surface of starting materials would not be able to hold the powder

together making up a particle and thus allowing the size reduction process to predominate.

Figs. 3 and 4 illustrate the effects of binder solution spray rate on the percentage of granules retained on the 35 mesh screen (coarse particles) and the geometric mean diameter of the granulation, respectively. Overall, an increase in the spraying rate of the binder solution led to a corresponding increase in the granule size (both percentage coarse and geometric mean diameter). As summarized by Wan et al. (1995) higher spray rate allows a greater number of droplets to be sprayed onto the starting material per unit time. This resulted in an increased number of liquid bridges and hence larger granule size. With a lower spray rate, binder solution evaporated more rapidly and binding of particles was reduced. In addition, the longer granulation time as a result of a low spray rate exposed granules to attrition forces resulting in smaller granules.

(A)



(B)

Fig. 5. Surface characteristics of granules produced by the high shear granulation method (a) and by the fluid bed technique (b).

3.4. Comparison of physical properties of granules and compressed tablets manufactured with fluid bed technique and high shear granulation method

The bulk densities of the granulations prepared with the fluid bed technique ranged from 0.32 to 0.42 g/cm^3. This value was significantly smaller than that of the granulation prepared in a high shear granulator (0.59 g/cm^3).

The bulk density of a granulation is primarily dependent upon granule size, granule size distribution, granule shape and cohesive forces (Davies and Gloor, 1971). Smaller granules, such as those generated by the fluid bed granulation process (geometric mean diameter averaged 198 μm), have a low free-fall velocity and a high surface-to-mass ratio. The combination reduces the amount of granule movement as the sample granulation is poured into a cylinder for bulk density measurement. In addition, the greater cohesiveness of smaller particles produces an arching or bridging of the granules within the cylinder. An increase in the granule size by the high shear granulation process (geometric mean diameter was 284 μm) reduces the particulate interactions due to a lower surface-to-mass ratio. The resultant decrease in granulation void spaces is manifested by a higher bulk density value. However, it is felt that the bulk density increase with an increase in the average granule size, as seen in the high shear granulation process, is not solely attributable to the free-fall velocity and surface effects of the granules. Instead, the primary effect is the greater degree of wetting of the powder bed by the high shear granulation method. The greater wetting ability of the binder solution in a high shear granulator not only results in an increase in the average granule size but also produces a denser granulation (Davies and Gloor, 1971).

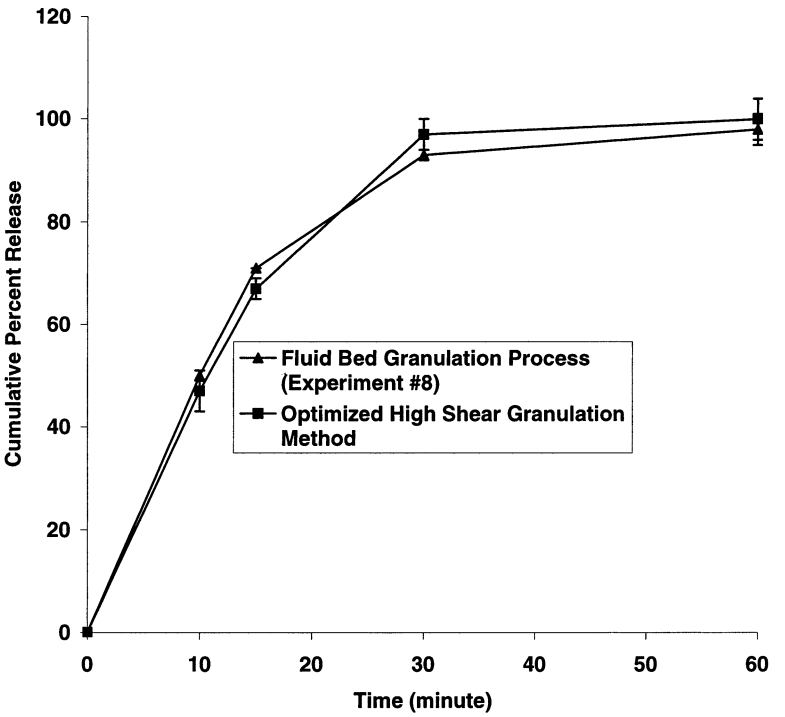


Fig. 6. Comparative dissolution profiles of wet granulation tablets manufactured with the fluid bed technique and the high shear granulation method.

Of greater interest, however, is the flow property of the granulation manufactured with the two methods. Granule size distribution, granule shape and granule density are the three critical factors affecting the flowability of granules. As expected, the high shear granulation process produced granules with better flow properties (Carr's index of 13) than the fluid bed granulation method (Carr's index of 15–26, Table 4). However, except for the granulation in Experiment #3, based on the Carr's index values, the other seven granulations should provide fair to good flow on a rotary tablet press (Fiese and Hagen, 1986).

The compression force required to form a tablet of identical hardness was 676–930 (Table 6) and 2956 kg for the granulations manufactured with the fluid bed and the high shear granulation method, respectively, an indication of a higher compressibility associated with the fluid bed granulation. The difference in the granulation compressibility could be attributed to the difference in the granule porosity, as indicated by the SEM (Fig. 5). Granules manufactured with the high shear granulation method are more rounded and denser with fewer fines (Fig. 5a), a direct result of the mechanism of granule formation in a high shear granulator. Generally, during the high shear granulation, agglomeration of the particles by liquid bridging occurs initially. Further granule growth results from cutting, compaction and adhesion of the agglomerates that lead to hardening and densification. On the other hand, the SEM picture (Fig. 5b) shows that the granules from the fluid bed granulation are more loosely aggregated, more irregular in shape, and appear to be more porous. In this process, granule growth is initiated by the formation of small nuclei consisting of particles held together by pendular or funicular bridging by the atomized binder solution. Further growth results from coalescence of the nuclei (Schaefer and Woerts, 1978b).

Although different granulation processes influ-

ence the granulation and tablet properties, the tablet dissolution rate achieved with the optimized high shear granulation method can be duplicated by appropriate adjustment of process variables in the fluid bed granulation method (Fig. 6).

4. Conclusions

In the fluid bed granulation process, granules are formed when the powders, wetted by the atomization binder solution, adhere to one another as contact is made in the heated fluidizing medium. The physical properties of granulation manufactured by this process are dependent on both the individual formulations granulated and the various process variables associated with the process. This study has shown that spray rate of the binder solution and the atomization air pressure are the most important factors affecting granule size distribution. As the spray rate of the binder solution increased, the ability of the solution to wet and penetrate the powders was enhanced, resulting in a larger granule size (reflected by the greater geometric mean diameter value and larger percentage of granules > 500 μm). On the other hand, increased atomization air pressure produced more granules of < 106 μm, due to the finer droplet formation of the binder solution as a result of increasing air-to-liquid mass ratio in the atomization process. The process variables in the fluid bed granulation method had little effect on the other physical properties of the granulation and tablets within the study range.

Irrespective of the processing conditions used in the fluid bed granulation method, granules from this process are generally more porous, bulkier, and more compressible than those from the high shear granulation process. Moreover, fluid bed granulation and drying process reduces the handling of raw materials, and hence, minimize operator exposure to irritating compounds, in this case, the drug substance.

This study demonstrated that wet granulation tablets of a high dose, poorly water soluble, low density, micronized drug could be manufactured using fluid bed technique. With a proper adjustment of process variables, dissolution rate of the tablet from the fluid bed granulation method is comparable to that from the optimized high shear granulation process. However, processibility of the granulation from the fluid bed technique at larger production scale needs to be assessed.

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