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Note

Correlation between loose density and compactibility of granules prepared by various granulation methods

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Abstract

The objectives of this study were to prepare the lactose granules by various granulation methods using polyethylene glycol 6000 (PEG 6000) as a binder and to evaluate the effects of granulation methods on the compressibility and compactibility of granules in tabletting. Lactose was granulated by seven granulation methods — four wet granulations including wet massing granulation, wet high-speed mixer granulation, wet fluidized bed granulation and wet tumbling fluidized bed granulation; and three melt granulations including melt high-speed mixer granulation, melt fluidized bed granulation and melt tumbling fluidized bed granulation. The loose density, angle of repose, granule size distribution, mean diameter of granules, and the tensile strength and porosity of tablets were evaluated. The compactibilities of granules were varied by the granulation methods. However, the difference in compactibility of granules could not be explained due to the difference in compressibility, since there was no difference in Heckel plots due to granulation methods. Among their granule properties, the loose density of granules seemed to have a correlation with the tablet strength regardless of the granulation methods.

Keywords: Wet granulation method; Melt granulation method; Compressibility; Compactibility; Loose density

1. Introduction

Due to their poor flowability and compaction heavier, pharmaceutical powders frequently request a granulation prior to tabletting. The optimal granulation method is selected for production of porous and free-flowing granules, which enable to form tablets with high mechanical strength at low compression pressure. Many researches have been conducted to demonstrate the influence of granulation method (Regnarsson and Sjögren, 1982) on the granule properties (Leuenberger, 1982; Jetzer et al., 1983, 1983a) or the tablet strength (Leuenberger and Jetzer, 1984; Wikberg

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and Alderborn, 1991; Zuurman et al., 1995; Adolfsson and Nyström, 1996), but few studies dealt with the linkage of these three using the same composition in formulation. One probable reason for the lack of such studies is the complexity of granulation system, since the effects of the properties of both the material and the granules are usually undistinguishable (Juppo et al., 1995; Juppo, 1996).

Binder (Symecko and Rhodes, 1995) is incorporated in the formulation to enhance the tablet strength and the tablets compressed from granules are known to have higher tensile strength than those compressed from powders. The addition method of binder could be mainly divided to the following two methods (1) a wet granulation with addition of a binder solution; and (2) a melt granulation with addition of meltable binder powder. Among binder polymers, polyethylene glycol 6000 (PEG 6000) has been often used as both a binder solution (Ford, 1983; Ukita and Murakami, 1994; Ronge et al., 1998), and a meltable binder (Schæfer et al., 1990; Chicco et al., 1997; Matsunaga et al., 1997) because of its physical properties.

The objectives of this study were to prepare the lactose granules by various granulation methods using PEG 6000 as a binder and to evaluate the effect of granulation methods on the compressibility and compactibility of granules in tabletting. The granulations were conducted by seven granulation methods — four wet granulations, i.e. wet massing granulation, wet high-speed mixer granulation, wet fluidized bed granulation and wet tumbling fluidized bed granulation; and three melt granulations, i.e. melt high-speed mixer granulation, melt fluidized bed granulation and melt tumbling fluidized bed granulation. Finally, the relationship between the granule property and the compactibility was discussed.

2. Materials and methods

2.1. Materials

Lactose (# 200, D.M.V., The Netherlands) as a model powder and PEG 6000 (PEG, Sanyo kasei Co., Japan) as a binder were used. The fed weight ratio of lactose to PEG was 10/1.

2.2. Wet granulation

2.2.1. Wet massing granulation (W-M-G)

Lactose (800 g) was massed in a planetary mixer (25 AMV-Qr, Dalton Co., Japan) with blades operating at 150 and 340 rev/min. The 50% aqueous binder solution containing PEG (80 g) was added as a continuous stream. The wet mass was then dried at 45°C in a tray oven for 5 h. The dried mass was fed into a comminuting mill (Power mill, P-3S, Dalton Co., Japan) fitted with a 0.8 mm orifice diameter screen and milled to produce the granules using knife-edges forward. The granules obtained were sieved through a 24-mesh screen, and any oversize granules were remilled using the above conditions and sieved again.

2.2.2. Wet high-speed mixer granulation (W-H-G)

Lactose (1000 g) was fed into a high-speed mixer (FS-GS-5DE, Fukae Powtec Co., Japan) and mixed at 550 rev/min of the main blade and 2000 rev/min of the chopper blade while the 50% aqueous binder solution containing PEG (100 g) was added instantaneously from the top of the vessel. The wet mass was then dried at 45°C in a tray oven for 5 h. The comminuting and sieving process was the same as W-M-G.

2.2.3. Wet fluidized bed granulation (W-F-G)

Lactose (4400 g) was fluidized in a fluidized bed granulator (FLO-5, Freund Sangyo Co., Japan) at 65°C of inlet air temperature. The 20% aqueous binder solution containing PEG (440 g) was sprayed using a two-fluid nozzle. The spray rate, the spray air pressure and the spray airflow were 70 ml/min, 1.7 kg/cm^2 and 170 Nl/min, respectively. The moisture content of granules during the operation was continuously monitored by an infrared moisture analyzer (DPA-M100, Okawara Co., Japan), which was equipped at the side of the fluidized bed granulator. The operating conditions such as inlet air temperature and airflow rate were controlled during granulation to reach at the

maximum moisture content of 7%. After spraying, the granules were dried until the temperature of the granules reached at 45°C.

2.2.4. Wet tumbling fluidized bed granulation (W-T-G)

Lactose (4400 g) was fluidized in a tumbling fluidized bed granulator (Spir-A-Flow, Freund Sangyo Co., Japan) at 60°C of inlet air temperature and mixed at 300 rev/min of the agitator and 150 rev/min of the rotator. The 20% aqueous binder solution containing PEG (440 g) was sprayed using a two-fluid nozzle. The spray rate, the spray air pressure and the spray airflow were 70 ml/min, 1.7 kg/cm^2 and 170 Nl/min, respectively. The moisture content of granules during the operation was continuously monitored by an infrared moisture analyzer (DPA-M100, Okawara Co., Japan), which was equipped at the side of the tumbling fluidized bed granulator. The operating conditions such as inlet air temperature and airflow rate were controlled during granulation to reach at the maximum moisture content of 7%. After spraying, the granules were dried until the temperature of the granules reached at 45°C.

2.3. Melt granulation

2.3.1. Melt high-speed mixer granulation (M-H-G)

Lactose (1000 g) and PEG (100 g) were fed into a high-speed mixer (FS-GS-5DE, Fukae Powtec Co., Japan) and mixed at 550 rev/min of the main blade and 2000 rev/min of the chopper blade in the vessel at 75°C for 15 min. The comminuting and sieving process was the same as W-M-G.

2.3.2. Melt fluidized bed granulation (M-F-G)

Lactose (4400 g) and PEG (440 g) were fluidized in a fluidized bed granulator (FLO-5, Freund Sangyo Co., Japan) at 80°C of inlet air temperature for 15 min. The airflow rate was controlled under visual observation of the powder flowability in the fluidized bed granulator. The melt granulation was finished when the granule temperature reached at 60°C.

2.3.3. Melt tumbling fluidized bed granulation (M-T-G)

Lactose (4400 g) and PEG (440 g) were fluidized in a tumbling fluidized bed granulator (Spir-A-Flow, SFC-5, Freund Sangyo Co., Japan) at 75°C of inlet air temperature and mixed at 300 rev/min of the agitator and 100 rev/min of the rotator. The airflow rate during granulation process and the end-point of granulation were the same as M-F-G.

2.4. Tabletting

Five hundreds milligrams of the granules was compressed by a reciprocating press (Autograph IS-5000, Shimadzu Co., Japan) using two flat-faced punches and a die 10 mm in diameter. Applied compression pressures were 640, 960, 1270, 1590, 2420 and 3180 kg/cm^2 and punch velocity was 10 mm/min.

2.5. Granule properties

2.5.1. Loose density

The loose density of granules was determined by pouring granules into a 100-ml glass cylinder. The granules were poured at 10 cm above the glass cylinder by a powder feeder. The cylinder was straightened up and the volume occupied by the granules was read to the nearest 1 ml. The loose density was taken as the quotient of the weight and the volume of granules. The mean of 3 determinants was taken as the loose density.

2.5.2. Mean granule diameter

The mean granule diameter was evaluated by a sieve analysis method using 10 sieves (1000, 840, 740, 500, 350, 250, 175, 105 and 75 μm). The sieves were tumbled with an automatic sieve shaker (Iida Co., Japan) for 3 min. The sieve load was 10.0 g. The fraction remaining of each sieve was weighed. The mean granule diameter was determined as 50% in diameter by plotting the cumulative percentage oversize against sieve size on log-probability graph.

2.6. Tablet properties

2.6.1. Tensile strength

Hardness of five tablets was measured with Schleuniger tester (6-D, Shuleuniger). The tensile strength for each tablet was calculated from the following equation, Fell and Newton (1968),

$$\sigma = \frac{2P}{\pi Dt}$$

where σ is the tensile strength, P is the hardness of the tablet, D is the tablet diameter, and t is the tablet thickness. The mean of 5 determinants was taken as the tensile strength. The tablet testing was carried out at 24 h after compression to allow for full elastic recovery. The tablet diameter and thickness were measured with a dial gauge with 10^{-3} mm divisions.

2.6.2. Tablet porosity

The tablet porosity (ε) was calculated from the following equation,

$$\text{Porosity}(\varepsilon) = \left(1 - \frac{\text{Apparent density}}{\text{True density}}\right) \times 100$$

where the apparent density was determined by dividing the tablet weight by the volume calculated from the tablet dimensions measured using a dial gauge. The mean of 5 determinants was taken as the porosity of tablets.

3. Results and discussion

To clarify the effect of granulation methods on the compactibility, the granules were prepared by seven granulation methods — four wet granulations including W-M-G, W-H-G, W-F-G and W-T-G; and three melt granulations including M-H-G, M-F-G and M-T-G, and compressed into tablets at various compression pressures. Fig. 1 shows the tensile strength of tablets as a function of compression pressure. The tensile strength increased with increase in compression pressure for all the tablets. In the wet granulation methods, the tensile strength was higher in the order of W-M-G, W-F-G, W-T-G, W-H-G at any compression pressure, while M-H-G, M-F-G, M-T-G in the melt granulation methods. These results indicated the compactibilities of granules varied due to the granulation methods.

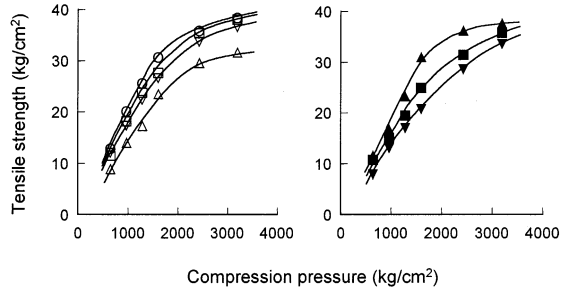

Fig. 1. Relationship between tensile strength of tablets, compressed with granules prepared by various granulation methods, and compression pressure. ○, W-M-G, △, W-H-G, □, W-F-G, ▽, W-T-G, ▲, M-H-G, ■, M-F-G, ▼, M-T-G.

Fig. 2 represents the Heckel plots for all the granules. The increase in compression pressure resulted in a continuous increase in ln $(1/\varepsilon)$ upto a certain constant value. However, there was little difference in compressibility of granules due to the granulation methods. The difference in compactibility of granules (Fig. 1) was not attributed to the difference in compressibility.

Table 1 shows the physical properties of granules prepared by the above various granulation methods. It can be seen that the angle of repose, granule size distribution and mean diameter of granules had not any special relation with compactibility. However, it seemed that the granules with low loose density showed high tablet strength.

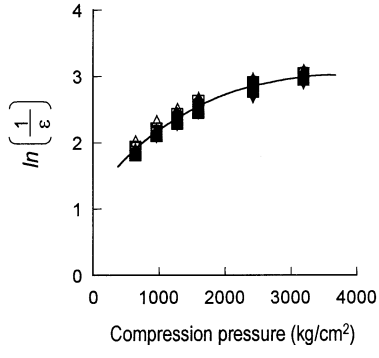

Fig. 2. Heckel plots for tablets compressed with granules prepared by various granulation methods. All the symbols correspond to Fig. 1.

Table 1
Granule properties prepared by various granulation methods

Angle of repose (°)	W-M-G	W-H-G	W-F-G	W-T-G	M-H-G	M-F-G	M-T-G
	40	37	37	40	39	37	41
Loose density (g/ml)	0.496	0.617	0.547	0.556	0.543	0.571	0.573
Size distribution (%)							
–/20 mesh	0	0	0	0	0	0	0
20/24	2.3	0	0	0.2	0.2	0.1	0.6
24/30	12.4	2.6	0.2	0.6	3.2	1.5	4
30/42	13.6	3.6	3.3	2.2	3.6	7	9.7
42/60	22.5	5.9	32.3	19.3	8.2	11.8	9.8
60/80	21	11	48.2	53.8	13.9	11.9	10.5
80/100	10	10.1	9.4	15.8	13.6	6.5	6
100/145	13	23.2	5.4	7.7	31.3	12.5	14.5
145/200	3.1	25.8	0.8	0.4	16.7	38.3	22.8
200/–	2.1	17.8	0.4	0	9.3	10.4	22.1
Mean diameter (μm)	254	201	229	212	140	110	106

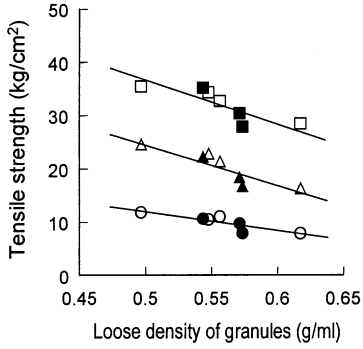

Fig. 3. Relationship between tensile strength of tablets and loose density of granules at various compression pressures. ○, 600 kg/cm^2, △, 1300 kg/cm^2, □, 2400 kg/cm^2. Open symbols, wet granulation methods; closed symbols, melt granulation methods.

Therefore, Fig. 3 exhibits the tensile strength of tablets as a function of the loose density of granules. The tensile strength decreased with increase in loose density of granules at the various compression pressures. Also, there was a similar relation regardless of the difference of granulation method. The line in Fig. 3 could be regarded as an intrinsic property line for materials used, which were lactose and PEG (weight ratio, 10/1).

The results suggested that the difference of the granulation method was not an essential factor affecting the compactibility of granules. The difference in the tablet strength might be probably concerned with another reason as the binder distribution in the granules, since the differences of granulation methods corresponded to the differences of addition methods of binder. We will clarify this point in near future.

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