Optimization of Size Distribution of Granules for Tablet Compression[1)]

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Particle size distribution of granules for tablet compression manufactured by a high-shear-mixer were examined, and the relationship between this size distribution and physical properties (*e.g.*, angle of repose, angle of spatula, loose bulk density, tapped bulk density, compressibility, hardness of tablets and weight variation of tablets) was determined. Optimization of particle size distribution was also carried out, taking the effects of hardness and weight variation into consideration.

The particle size distribution of granules for tablet compression could be expressed as a function of median particle size and standard deviation with a logarithmic normal distribution. The physical properties of granules for tablet compression and tablets were significantly affected by this factor. A contour diagram of the hardness of the tablets compressed with an autograph was consistent with that of compressibility. The contour diagram of the hardness of tablets compressed with a rotary tableting machine was different, however, and was found to be affected by both the fluidity of granules for tablet compression and compression speed. Furthermore, tablet hardness increased as the median particle size decreased, when the standard deviation was less than 1.0.

The physical properties of tablets could be predicted from the contour diagram of optimum particle size distribution of granules for tablet compression. As a result, the time spent making the tablet formulation could be reduced. It was found that the optimum ranges of median particle size and standard deviation were less than 150 μm and less than 1.0, respectively.

Key words tablet granulation; tablet hardness; high-shear-mixer; weight variation; logarithmic normal distribution; optimum granule size distribution

Hardness and weight variation are believed to be the main factors for evaluating physical properties of tablets. Although some information about these factors can be obtained from the properties of granules for tablet compression, exact values can so far only be determined by tableting. Many studies on the relationship between granulation methods and properties of granules for tablet compression have been reported.[2-4)] But most of these studies did not focus on the relationship between the granule properties for tablet compression and tablet properties. If these physical properties of tablets can be exactly predicted before tableting, the time spent on determining the optimum formulation can be reduced.

A sieving method is often used to measure the particle size distribution of granules because of its simplicity. The granules collected on each sieve can be weighed and evaluated.

In this paper granules manufactured by a high-shear-mixer were investigated, and the particle size distribution was analyzed by logarithmic-normal-distribution. The median particle size and the standard deviation obtained were used as distribution parameters for estimating the physical properties (*e.g.*, angle of repose, angle of spatula, loose bulk density, tapped bulk density, compressibility, hardness of tablets and weight variation of tablets). Optimization for particle size distribution was also carried out, taking the effects of hardness and weight variation into consideration.

Experimental

Materials The materials used for experiments were of Japan's pharmacopoeia grade. The formula of granules for tablet compression consisted of D-mannitol (45%), crystalline cellulose (20%), cornstarch (7%), low substituted hydroxypropylcellulose (20%), and hydroxypropylcellulose (8%).

Granulation A vertical granulator (FM-VG-10, Powrex Corporation) was used as the high-shear-mixer, and a flow coater (FL-Mini, Freund Industrial Co., Ltd.) understood as a fluidized bed dryer. A new speed mill (WP-10, Okada Seiko Co., Ltd.) was used as a breaker.

All of the materials (2 kg) were blended in a vertical granulator, purified water (0.88 kg) was added, and granulation followed for 10 min at 250 rpm. The resulting materials were then dried at an inlet temperature of approximately 70 °C for 60 min in the flow coater. All of the resulting materials were then passed through a 1.5 mm i.d. screen of the new speed mill.

Measurement of Particle Size Distribution Particle size distribution of granules for tablet compression was determined by sieve analysis in a series of 75 mm i.d. laboratory sieves of Japan's pharmacopoeia grade. Particle size distributions were expressed as cumulative probabilities.

Measurement of Physical Properties of Granules A powder tester (PT-E, Hosokawa Micrometrics Laboratory) was used to measure the physical properties of the powder (*e.g.*, angle of repose, angle of spatula, loose bulk density, and tapped bulk density). An electronic moisture balance (Shimadzu Corporation, Libror EB-280 MOC) measured loss on drying of granule under the following conditions: temperature, 70 °C; time, 30 min.

Experimental Design The median particle size (X1) and standard deviation (X2) of particle size distribution were selected as independent variables. Experiments of 9 formulations (#1—#9) were designed referring to a two-factor composite design, as shown in Table 1 in experimental units.[5-7)] An additional formulation (#10) was prepared to improve the reliability of polynomial regression equation for the physical properties of granules.

Preparation Granules for tablet compression, whose loss on drying was 2.65%, were classified according to particle size using sieves with the following mesh: 24, 32, 35, 42, 48, 60, 80, 100, 150, and 200, and the sample was then prepared following the experimental design with each granule classification.

Compression with Autograph Tablets (AG-tablets) were made with an autograph (AG-5000B, Shimadzu Corporation) under the following conditions: die, flat faced (10 mm in diameter); tablet weight, 300 mg; compression pressure, 24 kgf/mm^2; compression speed, 10 mm/min; and magnesium stearate, 0.5%.

Compression with Rotary Tableting Machine Tablets (R-tablets) were made with a Cleanpress (Correct 19, Kikusui) under the following

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Table 1. Composite Experimental Design for Two Factors

Formulation	D_{50} ($\times 100\,\mu m$) X1	σ X2
1	1.0	0.461
2	1.0	1.382
3	2.5	1.104
4	2.0	0.530
5	2.0	1.589
6	0.5	0.782
7	1.5	1.002
8	1.5	1.002
9	1.5	1.002
10[a]	1.0	0.921

a) Additional point to improve reliability of regression coefficient of $X1^3$ term.

conditions: die, convex surface (5 mm in diameter); tablet weight, 50 mg; compression thickness, 0.36 mm; rotating speed (compression speed), 30 rpm (about 40 mm/s); and magnesium stearate, 0.5%.

Measurement of Physical Properties of Tablets The weight of each of twenty tablets was measured to determine variation, and the result was expressed as three times the coefficient of variation (3 C.V.). The hardness of each of ten tablets was measured to calculate the mean value with a tablet tester (THP-4M, Schleuniger).

Results

Distribution Parameters The probability of a particle size with logarithmic normal distribution is expressed by probability density functions as follows[8]:

$$\phi(r)=1/(\sqrt{2\pi}\cdot\sigma\cdot r)\cdot\exp[-\{\ln(r)-\ln(D_{50})\}^2/(2\sigma^2)] \quad (1)$$

where $\phi(r)$ is the probability of a particle size, r (μm) is the particle size, D_{50} (μm) is the median particle size, and is standard deviation.

The cumulative probability density function to particle size (r) is calculated by integrating Eq. 1 as follows:

$$P(r)=1/\sqrt{2\pi}\cdot\int_0^r \exp[-\{\ln(r)-\ln(D_{50})\}^2/(2\sigma^2)] \quad (2)$$

where $P(r)$ is cumulative probability density to particle size.

The value of $P(r)$ can be measured using the sieving method. If the particle size distribution can be expressed as a logarithmic normal distribution, a regression line can be given with the probability paper.

Then, the $P(r)$ for each granule for tablet compression can be obtained practically by substituting this in Eq. 2. Median particle size and standard deviation were then obtained by the non-linear least squares method or the linear regression method. Figure 1 shows logarithmic normal plots on particle size distributions obtained from the measurement of granules for tablet compression. Their points fitted well on a line with a high multiple correlation coefficient. Using the parameters obtained with this slope and the y-intersect as initial values, the exact median particle size and standard deviation of each granule could be calculated using the non-linear least squares method, where the integral of Eq. 2 was determined by using the Hastings approximate equations as follows[9]:

$$Z=(\ln(r)-\ln(D_{50}))/\sigma \quad (3)$$

$$P(Z)=1/\sqrt{2\pi}\cdot\int_{-\infty}^{Z}\exp(-Z^2/2)dZ=G(Z) \qquad Z\geqq 0 \quad (4)$$

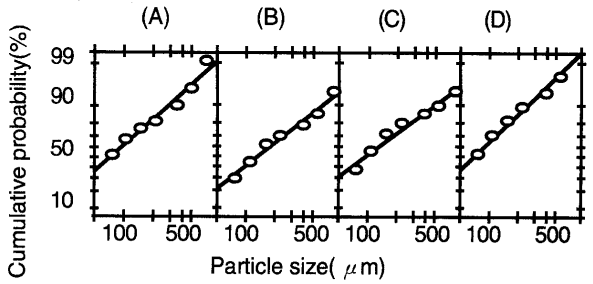

Fig. 1. Particle Size Distributions of Granules for Tablet Compression

(A) $D_{50}=64.2\,\mu m$, $\sigma=1.19$, $r=0.965$; (B) $D_{50}=125\,\mu m$, $\sigma=1.06$, $r=0.973$; (C) $D_{50}=94.7\,\mu m$, $\sigma=1.06$, $r=0.965$; (D) $D_{50}=67.7\,\mu m$, $\sigma=0.889$, $r=0.983$.

Table 2. Experimental Values of Response Variables

Formulation	Y1[a] (°)	Y2[b] (°)	Y3[c] (g/cc)	Y4[d] (g/cc)	Y5[e] (%)	Y6[f] (kgf)	Y7[g] (kgf)	Y8[h] (%)
1	38	60	0.576	0.728	20.9	11.6	3.54	1.93
2	47	66	0.532	0.775	31.4	13.0	3.15	3.06
3	40	57	0.580	0.739	21.5	12.3	3.08	2.75
4	39	40	0.625	0.722	13.4	10.7	2.57	1.50
5	39	55	0.647	0.767	15.6	11.2	3.59	3.19
6	43	64	0.517	0.730	29.2	12.4	4.67	3.55
7	41	53	0.624	0.763	18.2	10.9	3.57	2.54
8	42	53	0.618	0.763	19.0	11.8	3.84	2.68
9	42	54	0.625	0.760	17.8	11.2	4.00	2.53
10[i]	—	56	—	—	—	12.2	—	—

a) Angle of repose. b) Angle of spatula. c) Loose bulk density. d) Tapped bulk density. e) Compressibility. f) Hardness of AG-tablets. g) Hardness of R-tablets. h) 3 c.v. i) Additional point.

$$P(Z)=1/\sqrt{2\pi}\cdot\int_{-\infty}^{Z}\exp(-Z^2/2)dZ=1-G(Z) \qquad Z<0 \quad (5)$$

$$X=1/(1+0.2316419\cdot Z) \quad (6)$$

$$G(Z)=1/\sqrt{2\pi}\cdot\exp(-Z^2/2)\cdot(C_1\cdot X+C_2\cdot X^2+C_3\cdot X^3+C_4\cdot X^4+C_5\cdot X^5) \quad (7)$$

$C_1=0.319381530$ $C_2=-0.356563782$ $C_3=1.78147937$

$C_4=-0.1821255978$ $C_5=1.330274429$

Relationship between Particle Size Distributions and Physical Properties of Granules for Tablet Compression Physical properties of granules (*e.g.*, angle of repose, angle of spatula, loose bulk density, tapped bulk density, compressibility) were measured to estimate granule fluidity. The hardness and weight variation of the tablets were also measured. The compressibility was calculated by Eq. 3 as follows[10]:

$$C=100\cdot(P-A)/P \quad (8)$$

where C is compressibility, A is loose bulk density, and P is tapped bulk density. The weight variation of the tablets was expressed as a coefficient of variation.

These experimental values of response variables are summarized in Table 2. The optimum regression equations with third order term of X1 for each response variable were determined by multiple regression analysis[11,12] as summarized in Table 3. Co-linearlity between X1 and X2 was avoided by adding experimental point No. 10.

Angle of Repose: Figure 2A shows the contour diagram of the angle of repose. The value of the angle was

Table 3. Optimum Regression Equation for Each Response Variable Determined by Multiple Regression Analysis

Coefficient	Regression coefficient value							
	Y1 (°)	Y2 (°)	Y3 (g/cc)	Y4 (g/cc)	Y5 (%)	Y6 (kgf)	Y7 (kgf)	Y8 (%)
b_0	31.35	68.18	0.4747	0.6700	28.28	10.020	5.929	3.440
b_1 (X1)	—	—	0.2322	−0.0621	−24.76	6.139	−2.638	−2.737
b_2 (X2)	19.58	—	−0.1277	0.0463	22.37	0.924	—	1.430
b_3 (X1X2)	−9.77	7.14	0.0753	—	−10.30	—	2.094	—
b_4 ($X1^2$)	2.14	−21.53	−0.0846	−0.0228	9.04	−6.432	—	0.734
b_5 ($X2^2$)	—	—	—	—	—	—	−1.486	—
b_6 ($X1^3$)	—	6.55	—	—	—	1.672	—	—
$r^{a)}$	0.966	0.940	0.949	0.966	0.936	0.927	0.914	0.950
$s^{b)}$	0.892	3.00	0.0202	0.00647	2.96	0.373	0.308	0.247
$F_0^{c)}$	23.3**	15.1**	9.1*	23.4**	7.09*	7.62*	8.50*	11.5**

a) Multiple correlation coefficient. *b*) Standard deviation. *c*) Observed F value (mean square regression). * $p<0.05$; ** $p<0.01$.

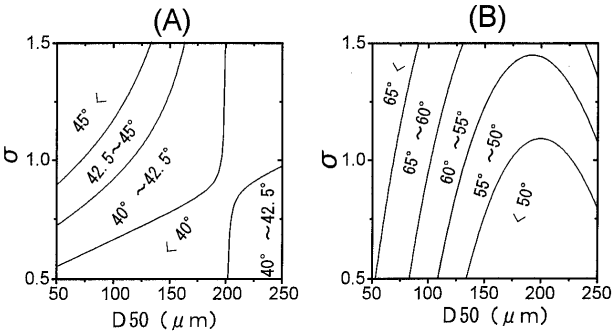

Fig. 2. Contour Lines of Angle of Repose (A) and Spatula (B) as a Function of D_{50} and σ

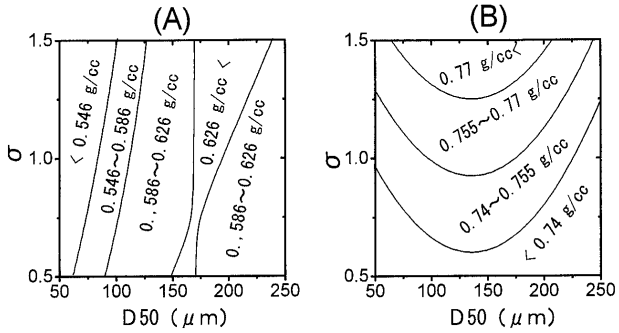

Fig. 3. Contour Lines of Loose (A) and Tapped (B) Bulk Density as a Function of D_{50} and σ

influenced by median particle size and the standard deviation of particle size distribution. The value increased as the median particle size became smaller and the standard deviation became larger. But when the median size was about 200 μm, there existed a minimum region.

Angle of Spatula: Figure 2B shows the contour diagram of the angle of spatula. The value of this angle was similar to that of the angle of repose. But when the median particle size was about 150 to 200 μm, there existed a minimum region.

Loose Bulk Density: Figure 3A shows the contour diagram of the loose bulk density. The value was little influenced by the standard deviation of particle size distribution, but there existed a maximum region in the range of about 150 to 200 μm of median particle size.

Tapped Bulk Density: Figure 3B shows a contour

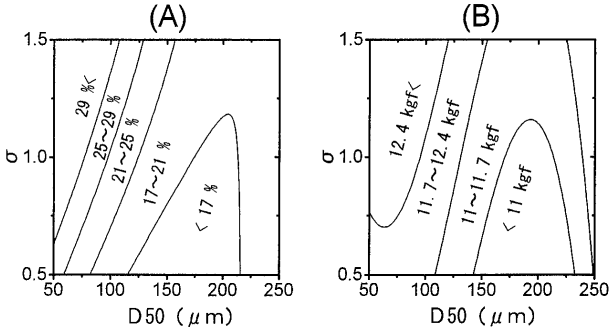

Fig. 4. Contour Lines of Compressibility (A) and Hardness of AG-Tablets (B) as a Function of D_{50} and σ

diagram of the tapped bulk density. The value was influenced by the median particle size and standard deviation of particle size distribution. The value increased as the standard deviation became larger, and there existed a maximum region at about 150 μm of median particle size.

Compressibility: Figure 4A shows the contour diagram of compressibility. Compressibility is considered to be a factor affecting the fluidity of powders, and the powder with high compressibility often clogs in the hopper. The contour diagram of compressibility was similar to that of the angle of spatula.

Relationship between Particle Size Distributions and Physical Properties of Tablets Hardness of AG-Tablets: Figure 4B shows the contour diagram of the hardness of AG-tablets. This value increased as the median particle size became smaller and as the standard deviation of particle size distribution became larger, and there existed a minimum region in a range of about 150 to 200 μm of median particle size. Thus, the contour diagram of the hardness of AG-tablets was similar to that of angle of the spatula and compressibility.

Hardness of R-Tablets: Figure 5A shows the contour diagram of the hardness of R-tablets. The value increased as the median particle size became smaller, and there existed a maximum region in a range of about 0.5 to 1.0 of the standard deviation of particle size distribution.

Weight Variation of R-Tablets: Figure 5B shows the contour diagram of the weight variation of R-tablets. The value of the variation increased as the median particle size became smaller and as the standard deviation of particle

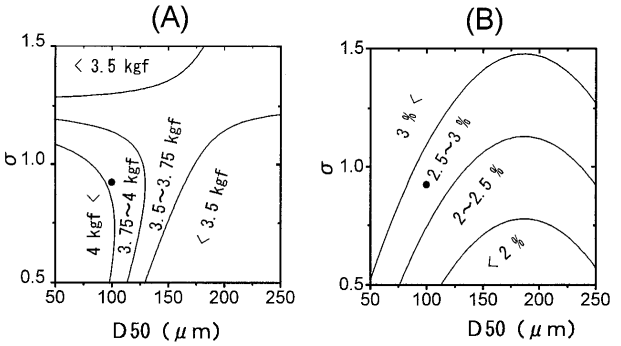

Fig. 5. Contour Lines of Hardness of R-Tablets (A) and Weight Variation (B) as a Function of D_{50} and σ

● represent $D_{50}=100\,\mu m$ and $\sigma=0.921$.

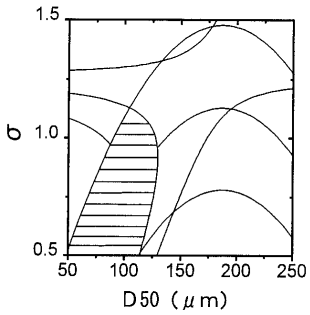

Fig. 6. Optimum Region of Hardness and Weight Variation as a Function of D_{50} and σ

size distribution became larger, and there existed a minimum region in a range of about 150 to 200 μm. Thus, the contour diagram was similar to those of the angle of spatula, compressibility, and the hardness of AG-tablets.

Discussion

The angle of spatula, compressibility, the hardness of AG-tablets and the weight variation of R-tablets had a minimum value in the range of about 150 to 200 μm of median particle size with small standard deviation of particle size distribution. That is, the granules in this region were considered to have excellent fluidity and poor compressibility. Most of the granules in this region were therefore thought to be regularly shaped primary granules with high density.

In the region where median particle size was less than 150 μm, the angle of repose, on the other hand, the angle of spatula, compressibility, the hardness of AG-tablets, and the weight variation of R-tablets became larger as the standard deviation increased and the median particle size decreased. The granules in this region were thus assumed to have poor fluidity and excellent compressibility, and to be a mixture of irregularly shaped primary granules with low density and powder.

In the region where median particle size was more than 200 μm, the angle of spatula, compressibility, the hardness of AG-tablets and the weight variation of R-tablets became larger as the standard deviation increased and the median particle size increased. Granules in this region were viewed as having poor fluidity and excellent compressibility, so that, most were believed to be irregularly shaped secondary granules.

In the region where median particle size was less than 150 μm and the standard deviation was less than 1.0, the hardness of R-tablets was maximized; the granules in this region were supposed to have excellent fluidity and compressibility. Thus, most were considered to be regularly shaped primary granules with low density.

In the contour diagram of hardness of AG-tablets, the left side of the 12.4 kgf line was upward. This portion of the line might be inaccurate, since this left position was the border of the estimated region. In general, the left side of the 12.4 kgf line should go down similar to the 29% line of compressibility in Fig. 4A.

The contour diagram of the hardness of R-tablets was inconsistent with that of the hardness of AG-tablets. This was assumed to be due to the difference of compression speed between R-tablets and AG-tablets, as well as to the fluidity of granules.

The points where median particle size was 100 μm and standard deviation was 0.921 are plotted in Fig. 5. Tablets with these features were actually manufactured, and their physical properties were measured. Their hardness and weight variation was 3.89 kgf and 2.78%, respectively, these values coincided well with the analytical values in the contour diagram.

Figure 6 shows the optimum region for the particle size distribution of granules for tablet compression, where the coefficient of the weight variation of R-tablets was within 3%, and the hardness of R-tablets was more than 3.75 kgf.

The optimum region for granules for tablet compression was where the median particle size was less than 150 μm and the standard deviation was not more than 1.0, when R-tablets were manufactured.

This experiment did not take into account the influence of granule formulation and manufacturing method, so that, it is not possible to compare the granules on this basis. But these contour diagrams showed the region of optimum granule particle size distribution, and indicated the objective for a subsequent examination by high-shear-mixer to compare granules of the same formulations made under different manufacturing conditions. The patterns of these contour diagrams will not greatly change, even if granules of different formulation are compared, because the physical property of those manufactured by a high-shear-mixer is influenced only by the size and/or shape of the particle.

Conclusion

Particle size distributions of granules for tablet compression produced with a high-shear-mixer were expressed as a function of median particle size and standard deviation using legalistic-normal-distribution.

The relationship between these distribution parameters and the physical properties of granules for tablet compression were estimated.

The physical properties of tablets could be predicted from the contour diagram of optimum particle size distributions of granules for tablet compression, resulting in a reduction of the time spent in determining the optimum formulation. As far as the formulation in this paper is concerned, it was found that the optimum median particle size was less than 150 μm, and the optimum standard

deviation was not more than 1.0 when R-tablets were manufactured.

References and Notes

1) A part of this work was presented at the 6th International Symposium on Agglomeration of Japan, Nagoya, 1993.
2) Vojnovic D., Moneghini M., Rubessa F., *Drug Dev. Ind. Pharm.*, **20**, 1035—1047 (1994).
3) Nyqvist H., *Acta Pharm, Suec.*, **19**, 413—420 (1982).
4) El-Gindy N. A., Samaha M. W., El-Maradny H. A., *Drug Dev. Ind. Pharm.*, **14**, 977—1005 (1988).
5) Asao M., Kusunoki T., Ando T., Nakanura T., "Jikken Keikakuho," Nikkagiren, Tokyo, 1973, pp. 313—346.
6) Takayama K., The Proceedings of the Hoshi University, **26**, 11—18 (1984).
7) Takai T., Takayama K., Nambu N., Nagai T., *Chem. Pharm. Bull.*, **32**, 1942—1947 (1984).
8) Itai S., *Funtai Kougaku Kaishi*, **24**, 89—100 (1987).
9) Itai S., Nagai T., *Chem. Pharm. Bull.*, **33**, 1641—1651 (1985).
10) Carr, *Chemical Engineering*, **Jan. 18**, 166—167 (1965).
11) Takayama K., Nambu N., Nagai T., *Chem. Pharm. Bull.*, **31**, 4496—4507 (1983).
12) Takayama K., Nagai T., *Chem. Pharm. Bull.*, **37**, 160—167 (1989).