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Mixing of Pharmaceutical Powders and Granules. I. Effect of Grain Size on the Manufacturing Process

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Since the mixing of many kinds of granules is necessary for the manufacture of solid dosage forms, the determination of their mixing limit is very important. Equations to calculate the theoretical mixing degree were obtained by Lacey and Stange for homogenous particles and for particles with a grain size distribution in binary systems. However, it became clear that the theoretical values thus obtained are very different from the experimental ones for the mixing of two kinds of granules with different grain size distributions. Hence, by assuming space filling with target granules of small size and by utilizing the experimental mixing values, new equations were obtained.

The resulting theoretical values were in fair agreement with the experimental ones. Thus, it is considered that the mixing degree was affected not only by variation based on the random arrangements of particles, but also by the grain size distributions of the target particles in the mixing of granules with different grain sizes.

Keywords——mixing of powder and granule; analysis of grain size; determination of mixing degree; measurement of apparent and true density; target particle; complete mixing; grain size distribution; randomized mixing

The mixing of pharmaceutical powders and granules is essential for the preparation of solid dosage forms, and the quality of pharmaceutical preparations is affected by their mixing degree.

Since many kinds of granules are mixed in common preparations of tablets and capsules, the determination of their mixing limit is very important for proper control of the manufacturing process.

In this study, the mixing degree of two kinds of granules was determined experimentally as a basis for further theoretical consideration.

Experimental

Preparation of Granules——Granules of 24 and 32 mesh prepared by the usual wet granulation method were dried for 4 h at 60°C. Large granules of 24 to 28 mesh, and small ones of 32 to 35 mesh were obtained by suitable sieving.

The compositions of the granules are shown in Table I.

Analysis of Grain Size in Granules——A 100 mg portion of granules was weighed exactly in order to count the number of granules. The distribution of average weight was determined by repeating the experiment about two hundred times.

Determination of Mixing Degree——The two kinds of granules (40 g) in different combination ratios were mixed well in a compounding mixer, Merix type MW-2. Then, ten samples (1 g) were weighed accurately and dissolved in water to remove insoluble materials. The concentration of tartradin in the filtrate was measured spectrophotometrically to examine the relationship between standard deviation and mixing degree.

Measurement of Apparent and True Density——A mixture (40 g) of two kinds of granules placed in a 100 ml graduated cylinder was tapped well until no further decrease in volume was observed. The apparent density was calculated from the resulting volume. The true density was measured by means of a Beckman air comparison pycnometer, model 930.

Results and Discussion

Fig. 1 shows that, irrespective of the mixing ratio, an almost constant mixing degree was observed at a given rotation number.

Table I. Formulas of the Granules prepared for Mixing Experiments

Component	Large granules	Small granules
Lactose J.P.	180 g	180 g
Starch J.P.	5 g	20 g
Amicol C[a]	15 g	
15% Gelatin paste		38 g
Water	35 ml	
Tartradin[b]		100 mg

a) Gelatinized starch USP.
b) Additive used for obtaining constants of the target granules.

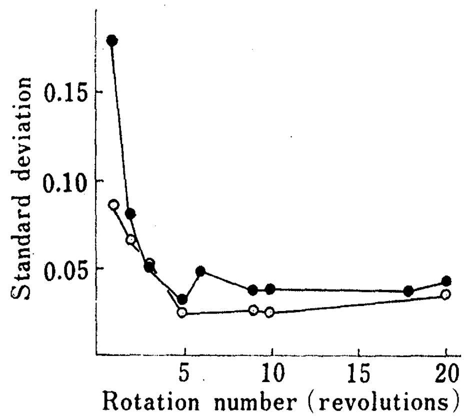

Fig. 1. Influence of the Number of Rotations on the Mixing Degree of Mixtures composed of Small and Large Granules

○, mixing ratio 3: 7; ●, mixing ratio 5: 5.

Table II. Relation between Experimental Index and Theoretical Degree of Mixing of Small and Large Granules

Mixing ratio of small granules (weight)	Index of mixing (Standard deviation)			Theoretical degree of mixing by Lacey	Theoretical degree of mixing by Stange
0.1	0.039	0.045	0.032	0.0024	0.0083
0.2	0.038	0.015	0.020	0.0030	0.0118
0.3	0.023	0.025	0.034	0.0032	0.0144
0.4	0.026	0.032	0.038	0.0032	0.0165
0.5	0.035	0.045	0.040	0.0031	0.0180
0.6	0.037	0.050	0.058	0.0029	0.0183
0.7	0.057	0.052	0.056	0.0026	0.0180
0.8	0.059	0.055	0.061	0.0021	0.0165
0.9	0.059	0.062	0.068	0.0016	0.0123

Consequently, the rotation number of 10 was used for mixing unless otherwise stated. Table II shows the relationship between the experimental index and the theoretical degrees of mixing of small granules with large ones.

The mixing degree of homogenous particles in a binary system was evaluated theoretically on the basis of Lacey's assumption,[1] *i.e.*, the target particles were considered to be randomized in the ultimate mixing state. That is, the distribution of the target particles in these mixing samples based on a binomial distribution in the complete mixing state was calculated by Eq. 1:

$$\sigma_R = \sqrt{\frac{P(1-P)}{N}} \tag{1}$$

where N and P are the total number of particles, and the number ratio of target particles, respectively.

The number of particles per unit weight of the various size granules must be known to apply this theoretical equation for the estimation of mixing. The number of granules can be determined by grain size analysis as follows.

Microscopic and sieving methods are commonly used for the grain size analysis of granules. The former, however, requires many assumptions to obtain the number of particles with known diameter and weight, and the latter is inadequate for determination of the precise grain size distribution in granules as required for this study. The number of particles was directly measured by the method described in "Experimental."

Fig. 2 shows the weight distribution for various sizes of granules.

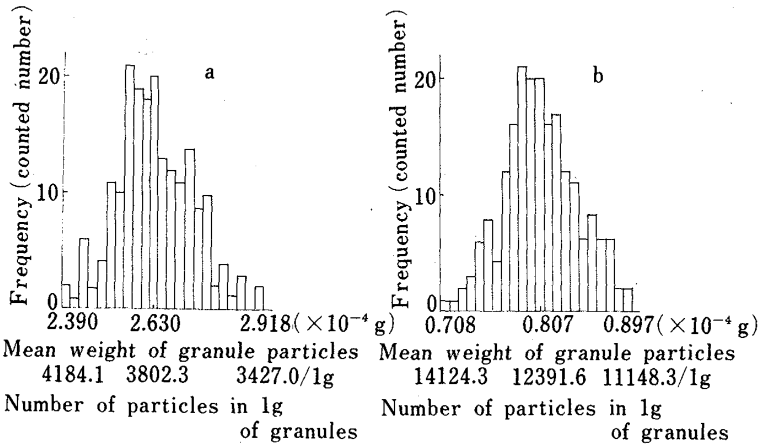

Fig. 2. Histograms of the Particle Size Distributions of Granules

a, large granules; b, small granules.

Since the number per weight is calculated from the weight of granules, its distribution can also be obtained. Skewness and kurtosis are shown in Fig. 2 as parameters of the normality of distribution.[2] As is shown in Table III, the distribution of particle weight in granules was normal at the 5% level.

TABLE III. Test of Normality in Size Distribution of Granules

	Large granules	Small granules
Skewness	1.410	0.384
Kurtosis	0.280	0.677
5% level (df ∞)	1.960	

In addition, the mean weight of particles and the standard deviation of two kinds of granules were calculated as shown in Table IV. The average and standard deviation of the number of particles per weight of both sizes of granules are also listed in Table IV.

TABLE IV. Size Distribution Statistics of Granules

	Large granules	Small granules
Mean particle weight	2.63×10^{-4} g	0.807×10^{-4} g
Standard deviation	1.98×10^{-4} g	0.835×10^{-4} g
Mean number in 1 g	3806.16	12415.5
Standard deviation of number in 1 g of granules	584.2	148.7

The numbers in mixtures of granules (1 g) with various combination ratios were calculated from the results shown in Table IV. The variation of number for theoretical mixing obtained from this calculation was converted to the variation of weight by means of Eq. 2:

$$\sigma_{\mathrm{OW}} = \frac{W_{\mathrm{S}}\sqrt{NP(1-P)}}{W} \qquad (2)$$

where σ_{OW} is the standard deviation of the weight ratio for the small granules, W_{S} is the average weight of the small granules, and W is the sample weight (1 g).

These results are shown in Table II. Evidently, the experimental values are significantly larger than the calculated ones.

Stange[3] has proposed Eq. 3 to calculate the mixing degree of two kinds of powders with a grain size distribution by assuming random mixing in the same manner as suggested by Lacey.

$$\sigma_X^2 = \frac{PQ}{g}[P\cdot\gamma_Q(1+C_Q^2)+Q\cdot\gamma_P(1-C_P^2)] \qquad (3)$$

Here, σ_X^2 is the dispersion in the mixing, P and Q are the weight ratios of the two kinds of powders, g is the sample weight, γ_P and γ_Q are the average particle weights of the two powders, and C_P and C_Q are the variation coefficients in the grain size distribution of mixing powders. The variation at various mixing ratios was obtained by applying these parameters to the mixing of two kinds of granules of different size.

There was a substantial difference between the theoretical and experimental values, as shown in Table II. The apparent and true densities of the two kinds of granules used in this experiment are shown in Table V. From these results, it appears that the mixing degree is not affected by separation based on the difference of density or the interaction between the two kinds of granules during the mixing, and the theoretical mixing degree of Lacey and Stange does not seem to reflect the experimental values. Hence, we attempted to obtain an expression for the limit of the mixing degree compatible with the practical mixing data.

The mixing ratio of granules and the number of granules in the mixture must affect the mixing degree. The ultimate mixing state can be regarded as a random situation by assuming space filling by the target granules of small size. The mixing degree can be calculated as follows by replacing the experimental and theoretical values with the values shown in Table VI.

TABLE V. True and Apparent Densities of Granules

	True density	Apparent density
Small granules	1.52 g/ml	0.59 g/ml
Large granules	1.49 g/ml	0.64 g/ml

TABLE VI. Parameters for Theoretical Equation for Calculating the Degree of Mixing

	Observed numbers	Estimated numbers	Difference
Numbers of target granules[a]	x	n	e_1
Total numbers of granules[b]	y	m	e_2
Number ratio	X	M	ΔM

a) Number of small granules in various weight ratios.
b) Assuming small granules substituted in apparent volume of mixing system.

$$\Delta M^2 = (X-M)^2 = \left(\frac{x}{y}-\frac{n}{m}\right)^2 = \left(\frac{e_1+n}{e_2+m}-\frac{n}{m}\right)^2$$

$$= \frac{(e_1-e_2M)^2}{(e_2+m)^2} \doteqdot \frac{e_1^2-2e_1e_2M+e_2^2M^2}{m^2}$$

The variations are estimated as follows by assuming the variation of the number of small granules in 1 g and that with random mixing to be σ_N^2 and σ_0^2 respectively.

$$Ee_1^2 = \sigma_N^2M_w^2 + \sigma_0^2$$

$$Ee_2^2 = \sigma_N^2$$

$$Ee_1 = Ee_2 = 0$$

Further, the above equation may be approximated by Eq. 4, because $M \fallingdotseq M_W$.

$$E\Delta M^2 = \frac{\sigma_0^2 + 2\sigma_N^2 M_w^2}{m^2} \quad (4)$$

Eq. 5 is derived by converting Eq. 4 to weight variation.

$$\sigma_w = \frac{\overline{w}_S \sqrt{E\Delta M^2}}{W} \quad (5)$$

Here, $\overline{w}_S$ and W are the particle weight and total weight, respectively. σ_N^2 can be calculated from the standard deviation shown in Table IV, because it represents the variation of the number of small granules in 1 g. Since σ_0^2 is the variation caused by the randomization of the target particles in small granules, the value of σ_0^2 can be calculated by estimating the number of particles present in the mixture of small granules.

A plot of bulkiness against the weight ratio of small granules in the mixture is shown in Fig. 3.

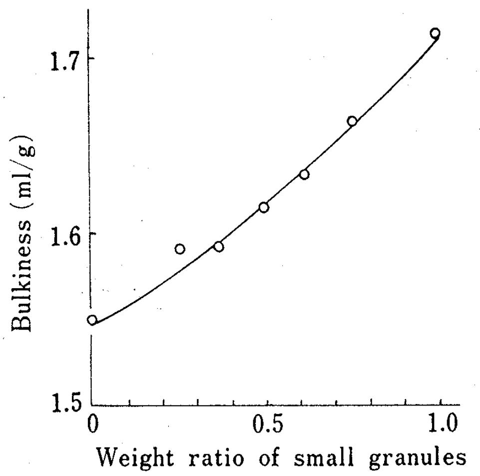

Fig. 3. Bulkiness Distribution in Mixtures of Small and Large Granules

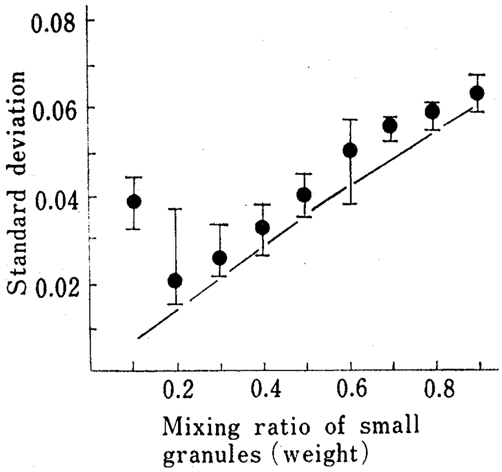

Fig. 4. Theoretical and Experimental Mixing Degree Values at Various Mixture Ratios

The points represent the median and vertical bars represent the standard deviations. The solid line is the theoretical standard deviation calculated from σ_0^2, σ_N^2, Eq. 4 and Eq. 5.

The filling number N_S of the small granules can be calculated by means of Eq. 6:

$$N_S = \frac{V_{app} \times d_{app}}{\overline{w}_S} \quad (6)$$

where V_{app} is the bulkiness for a given mixing ratio, d_{app} is the apparent density of the small granules, $\overline{w}_S$ is the mean weight per particle of the small granules. Hence, σ_0^2 can be calculated from Eq. 7.

$$\sigma_0^2 = \frac{(N_S - N_T)}{N_S} N_T \quad (7)$$

N_T is the number of target particles.

σ_W can be determined by substituting σ_0^2 and σ_N^2 into Eq. 4 and Eq. 5. As shown in Fig. 4, the experimental values were found to be in fair agreement with the theoretical ones in the mixing ratio range of 0.2 to 0.9 on plotting σ_W for various mixing ratios. Thus, the mixing degree in the final mixing state calculated on the basis of the above assumption reflects well the experimental values, and it seemed that the mixing degree was dependent not only on the variation based on the random arrangements of particles as suggested by Lacey and Stange, but also on the mixing of the different grain size distributions of the target particles in the mixing of granules with different grain sizes.

References and Notes

1) P.M.C. Lacey, *J. Appl. Chem*, **4**, 257 (1954).
2) G.W. Snedecor, "Statistical Methods," The Iowa State College Press, 1950.
3) K. Stange, *Chemie. Ingenier. Technik*, **35**, 580 (1963).