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Theoretical Consideration on Dosage Variation[1)]

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Even if a random distribution of particles has been achieved in the practical process, a precise quantity of an active ingredient in individual dose units can not be always assured. This variation in the potency is attributed to a problem of mixing and related directly to the sampling error. Theoretical consideration indicates that the variance in the proportion of an active ingredient developed through sampling from a randomized bulk mixture is calculated with the following equations;

1. When the shape of particles is spherical

$$V\left\{\frac{g_A}{g}\right\}=\frac{P(1-P)\pi}{6g}\left\{PL_B^3d_B\left(1+\frac{9\sigma_B^2}{L_B^2}\right)+(1-P)L_A^3d_A\left(1+\frac{9\sigma_A^2}{L_A^2}\right)\right\}$$

2. When the shape of particles is cubic

$$V\left\{\frac{g_A}{g}\right\}=\frac{P(1-P)}{g}\left\{PL_B^3d_B\left(1+\frac{9\sigma_B^2}{L_B^2}\right)+(1-P)L_A^3d_A\left(1+\frac{9\sigma_A^2}{L_A^2}\right)\right\}$$

where, P is the proportion of an active ingredient, g the sample weight, d_A and d_B are the the densities of components, L_A and L_B the mean volume diameters of components, σ_A and σ_B the standard deviations of particle-sizes distributions of components; suffix A means the active component. The possible application of the result to suspension and emulsion has been discussed.

In order to attain an accurate dosage of a small amount of an active ingredient, it is important to consider problems of solid mixing. Although factors and properties associated with the particles themselves such as the size, shape and density of the particles, the roughness, electric charge of surface, surface energy, *etc.* play an important role in solid mixing, these are extremely complicated, and a considerable part of inventigations on mixing has been reported on the practical aspects of solid mixing, for instance the rate of mixing, the relative effiency of the mixing equipments, the variation in the potency attributed to a mixing process. Recently, Tawashi, *et al.*[3)] studied on the accuracy of dosage and found that the deviation in the proportion of an active ingredient occurred through several processes of tablets producing. Brochamnn-Hanssen and his co-worker,[4)] reporting on the dosage variation in tablets, found some disruption of uniformity occurred during the compressional process of the tablets and

1) Presented to the Kinki Branch Annual Meeting of the Pharmaceutical Society of Japan (Kyoto, November, 1962).
2) Location: *Juso-nishino-cho, Higashiyodogawa-ku, Osaka.*
3) R. Tawashi and P. Speiser, *Pharm. Acta Helv.*, **39**, 734 (1964).
4) E. Brochmann-Hanssen and J.C. Median, *J. Pharm. Sci.*, **52**, 630 (1963).

showed that one of the obvious sources of variability affecting the drug dosage was the variation in per cent composition. Train[5] also described the relation between mixing and the accurate dosage of drugs in view of statistical considerations and pointed out that the pharmaceutical aim should be to supply a precise quantity of an active ingredient in individual dose uints. Relating to this phenomenon, the equation derived by Stange[6] is significant to show the statistical aspects of the content of a potent drug in a unit dose taken from a truly randomized bulk mixture. However, in his study, the relationship between particle numbers and particle weights for sample solids was taken into fundamental considerations as a distiribution of particle-sizes necessary for derivation of the equation. This relationship is hardly observed directly by the conventional methods of sample of very fine particles, therefore, it is inconvenient to apply the result to the practical processes.

In the present paper, the relation between particle numbers and particle diameters was applied as the concept of the size-distribution of the components and then the equations concerning the variance in the proportion of an active component in a unit dose taken from a randomized bulk mixture were obtained here. The size-distribution of this kind is common in the field of micromeritics and obtained by measuring the particles at random along a given fixed line with a microscope. Furthermore, the result could be extended to suspension and emulsion.

Derivation of the Equation——Assuming a mixture of solids consisting of two components, A and B, the total weight is G wherein the weight of component A is G_A and that of B is G_B, thus

$$G=G_A+G_B \tag{1}$$

and the ratio of G_A to G is P which is given

$$P=\frac{G_A}{G} \tag{2}$$

As a rule particles are not of the same size, and certain distinction must be made with regard to the meaning of particle-size. When the frequencies of various particles are plotted against the mean of size-groups, the so-called "size-frequency" curve is obtained. From these data, the mean volume diameters[7] and the standard deviations[8] of particles for each component can be calculated, and these are L_A and L_B, σ_A and σ_B, respectively.

Then, a spot sample is taken from a bulk mixture mentioned above; the total number of partilces and the total weight of the sample are n and g, wherein the particle numbers and the weights of each component are n_A and n_B, g_A and g_B, respectively, thus

$$g=g_A+g_B \tag{3}$$

$$n=n_A+n_B \tag{4}$$

If the shape of particles is considered to be cubic; moreover the mean volume diameters of each component of the sample are given by l_A and l_B, the ratio of g_A to g is

$$\frac{g_A}{g}=\frac{g_A}{g_A+g_B}=\frac{n_A\cdot l_A{}^3\cdot d_A}{n_A\cdot l_A{}^3\cdot d_A+(n-n_A)\cdot l_B{}^3\cdot d_B} \tag{5}$$

where, d_A and d_B are densities of the components. The reciprocal of Equation (5) is

5) David Train, *J. Am. Pharm. Assoc.*, Sci. Ed., **45**, 265 (1960).
6) K. Stange, *Chem. Ing. Techn.*, **26**, 150, 331 (1954).
7) The mean volume diameter$=(\sum niLi^3/\sum ni)^{1/3}$, where Li is the mean of size-group, and ni is the number of particles in each group.
8) The standard deviation$=[\sum\{ni(Li^3-Lav^3)^2\}/\sum ni]^{1/6}$ in this study, where Lav is the mean volume diameter and others are the same as the mentioned above.

$$\frac{g}{g_A}=1+\left(\frac{n-n_A}{n_A}\right)\left(\frac{l_B^3\cdot d_B}{l_A^3\cdot d_A}\right) \tag{6}$$

The estimations of l_A, l_B and g_A/g are

$$E\{l_A\}=L_A \tag{7}$$

$$E\{l_B\}=L_B \tag{8}$$

$$E\left\{\frac{g_A}{g}\right\}=P \tag{9}$$

and from the theoretical view, the variances of n_A, l_A and l_B are given by

$$V\{n_A\}=np(1-p) \tag{10}$$

$$V\{l_A\}=\frac{\sigma_A^2}{n_A}\simeq\frac{\sigma_A^2}{np} \tag{11}$$

$$V\{l_B\}=\frac{\sigma_B^2}{n_B}\simeq\frac{\sigma_B^2}{n(1-p)} \tag{12}$$

where, p is the proportion of the particles number of component A to the total particles number of the bulk mixture. From Equations (7), (8), (9), (10), (11), and (12), the variance of Equation (6) is calculated as follows,

$$\begin{aligned}V\left\{\frac{g}{g_A}\right\}&=\left(\frac{L_B^3\cdot d_B}{L_A^3\cdot d_A}\right)^2V\left\{\frac{n-n_A}{n_A}\right\}+\left(\frac{n-np}{np}\right)^2V\left\{\frac{l_B^3\cdot d_B}{l_A^3\cdot d_A}\right\}\\&=\left(\frac{L_B^3\cdot d_B}{L_A^3\cdot d_A}\right)^2V\left\{\frac{n}{n_A}\right\}+\left(\frac{n-np}{np}\right)^2\left(\frac{d_B}{d_A}\right)^2V\left\{\frac{l_B^3}{l_A^3}\right\}\\&=\left(\frac{L_B^3\cdot d_B}{L_A^3\cdot d_A}\right)^2\left(\frac{n}{n^2p^2}\right)^2V\{n_A\}\\&\quad+\left(\frac{n-np}{np}\right)^2\left(\frac{d_B}{d_A}\right)^2\left[\frac{9L_B^4}{L_A^6}V\{l_B\}+\frac{9L_B^6}{L_A^8}V\{l_A\}\right]\\&=\left(\frac{L_B^3\cdot d_B}{L_A^3\cdot d_A}\right)^2\left(\frac{n}{n^2p^2}\right)^2np(1-p)\\&\quad+\left(\frac{n-np}{np}\right)^2\left(\frac{d_B}{d_A}\right)^2\left[\frac{9L_B^4}{L_A^6}\cdot\frac{\sigma_B^2}{n(1-p)}+\frac{9L_B^6}{L_A^8}\cdot\frac{\sigma_A^2}{np}\right]\\&=\left(\frac{L_B^3\cdot d_B}{L_A^3\cdot d_A}\right)^2\cdot\frac{(1-p)}{np^3}\left\{1+\frac{9p\sigma_B^2}{L_B^2}+\frac{9(1-p)\sigma_A^2}{L_A^2}\right\}\end{aligned} \tag{13}$$

and

$$V\left\{\frac{g}{g_A}\right\}=\frac{1}{P^4}\cdot V\left\{\frac{g_A}{g}\right\} \tag{14}$$

Assuming the mean volume diameter and the mean density of the bulk mixture consisting of two components are L and d respectively,

$$P=\frac{G_A}{G}=\frac{N_AL_A^3d_A}{NL^3d}=\frac{L_A^3d_A}{L^3d}p \tag{15}$$

where, N and N_A represent the total number of particles and the number of particles of component A in the bulk mixture. Substitute Equations (13) and (15) into Equation (14),

$$\begin{aligned}V\left\{\frac{g_A}{g}\right\}&=\left(\frac{L_A^3d_A}{L^3d}\right)^4\left(\frac{L_B^3d_B}{L_A^3d_A}\right)^2\frac{p^4(1-p)}{np^3}\left\{1+\frac{9p\sigma_B^2}{L_B^2}+\frac{9(1-p)\sigma_A^2}{L_A^2}\right\}\\&=\left(\frac{d_Ad_B}{d^2}\right)^2\left(\frac{L_AL_B}{L^2}\right)^6\frac{p(1-p)}{n}\left\{1+\frac{9p\sigma_B^2}{L_B^2}+\frac{9(1-p)\sigma_A^2}{L_A^2}\right\}\end{aligned} \tag{16}$$

It is necessary to convert Equation (16) from the basis of particle number into that of particle weight, because of the complication of taking a sample by particle number.

Since,

$$g=nL^3d \tag{17}$$

$$\frac{P}{L_A^3d_A}+\frac{(1-P)}{L_B^3d_B}=\frac{1}{L^3d} \tag{18}$$

and from Equation (15),

$$(1-P)=\frac{L_B^3d_B}{L^3d}(1-p) \tag{19}$$

Equation (16) becomes

$$V\left\{\frac{g_A}{g}\right\}=\frac{P(1-P)}{g}\left\{\frac{L_A^3d_AL_B^3d_B}{L^3d}+\frac{9PL_B^3d_B\sigma_B^2}{L_B^2}+\frac{9(1-P)L_A^3d_A\sigma_A^2}{L_A^2}\right\}$$

$$=\frac{P(1-P)}{g}\left\{Pd_BL_B^3\left(1+\frac{9\sigma_B^2}{L_B^2}\right)+(1-P)d_AL_A^3\left(1+\frac{9\sigma_A^2}{L_A^2}\right)\right\} \tag{20}$$

Equation (20) represents a general solution to the proposed problem since it permits determination of the variance in the proportion of a given ingredient. It shows that the variance in per cent active ingredient which is brought about by taking a sample from a truly randomized bulk mixture is affected by the proportion of an active ingredient, P, the sample weight, g, the densities of components, d_A and d_B, the mean volume diameters of components, L_A and L_B, and the standard deviations of particle sizes distributions, σ_A and σ_B.

When the shape of particles is assumed to be spherical, Equation (21) is derived in the same manner.

$$V\left\{\frac{g_A}{g}\right\}=\frac{P(1-P)\pi}{6g}\left\{Pd_BL_B^3\left(1+\frac{9\sigma_B^2}{L_B^2}\right)+(1-P)d_AL_A^3\left(1+\frac{9\sigma_A^2}{L_A^2}\right)\right\} \tag{21}$$

Experimental

Apparatus——The apparatus used in this study was a V-type powder mixer having a drum volume of 5.8 liter and a rotative rate of 32 rpm.

Preparation of the Granules——The granules of lactose were prepared with starch paste by a conventional method. A portion of the granules was colored by spraying a methanol solution of a red dye. Table I liests the properties of granules used here.

Experimental Procedure——Colored granules of 150 g and white granules of 1350 g were weighed and put into a V-mixer. After 40 minutes mixing, the mixture was poured out. One hundred and fifty spot-samples of 2 g each were taken at random from the granules mixture. The granules of each samples were separated into two parts, colored and white portion, and weighed separately.

Table I. Properties of Granules

Ingredient	Mean particle size (cm)	Standard deviation of particle-size distribution (cm)	Density	Particle shape
Colored lactose granule	0.14	0.017	1.37	nearly spherical
White lactose granule	0.14	0.017	1.37	nearly spherical

Results and Discussion

The unbiased variance[9] relating to the proportion of colored granules was obtained from the data of spot-samples, that was 1.22×10^{-4}. As the error of the analysis in this experiment is very small, the variance observed here seems to be composed of two main factors due to mixing and to sampling. The variance due to mixing is incompleteness of mixing, while the variance due to sampling means the variation caused by taking a sample from a perfect mixture represented by a random distribution of the particles. Since, $L_A=L_B$, $d_A=d_B$ and $\sigma_A=\sigma_B$ here, Equation (21) simplifies to

$$V\left\{\begin{matrix} g_A \\ g \end{matrix}\right\}=\frac{P(1-P)\pi L_A{}^3 d_A}{6g}\left(1+\frac{9\sigma_A{}^2}{L_A{}^2}\right) \qquad (22)$$

The variance due to sampling was calculated using Equation (22), and this was 1.003×10^{-4}. Compared the unbiased variance, 1.22×10^{-4} with the variance due to sampling, 1.003×10^{-4}, the granule mixture studied here appears to be randomized almost completely, whereas the standard relative error is

$$\frac{\sqrt{1.00\times10^{-4}}}{0.1}\times100=10(\%)$$

It will be seen that for a 10 per cent dispersion of granules having a diameter of 0.14 cm and a sample of 2 g, the confidence levels will be as follows: 68.3 per cent of samples would have less than a 10 per cent error in the proportions of 0.1, and in like manner 95.5 per cent of samples would have less than a 20 per cent error, while 99.7 per cent samples would have less than a 30 per cent error in the proportions of 0.1. To reduce the errors for each confidence level to reasonable limits, the granules must be reduced in size. Fig. 1 illustrates the relationship between the mean particle size and the variance in the proportion of an ingredient based on Equation (22), where $P=0.1$, $g=2$ g, $d_A=1.37$, and $\sigma_A=0.017$ cm. It is apparent that the granules should be reduced in size from 0.14 cm to 0.035 cm in order to keep the unit dose, based on a perfect mixing operation alone, within 4 per cent error of the correct dose for 95.5 per cent of the products and within 6 per cent error for 99.7 per cent of the products, because the standard relative error is

$$\frac{\sqrt{4.0\times10^{-6}}}{0.1}\times100=2.0(\%)$$

This discussion is essentially similar to that of Train.[5]

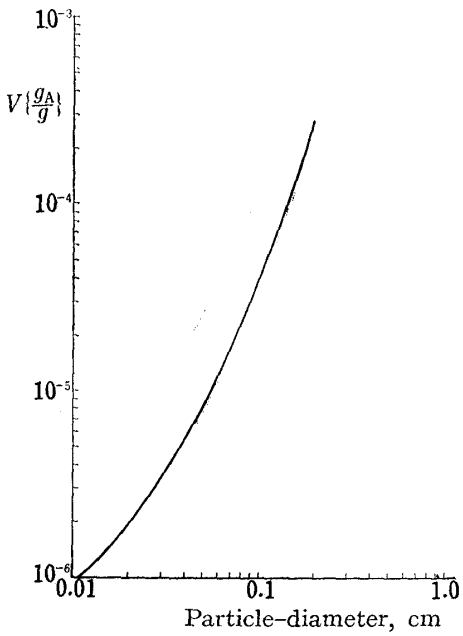

Fig. 1. Relationship between the Mean Particle Size and the Variance in the Proportion of an Ingredient based on Equation (22).
$P=0.1$, $g=2$ g, $d_A=1.37$, $\sigma_A=0.017$ cm

Theoretical studies on the variance of a truly randomized mixture have been reported by many researchers. Lacey[10] considered the uniform size particles as components and expressed the result

9) The unbiased variance $=\frac{1}{m}\sum_{i=1}^{m}(C_i-C)^2$ where m is the sample number, C_i is the proportion of colored granules in each sample, and C is the theoretical proportion of colored granules.

10) P.M.C. Lacey, *Trans. Inst. Chem. Engrs.* (London), **21**, 53 (1943).

using particle number in spot sample. Buslik[11] dealt with multi-size powder, but no concern of multiple density. Therefore, these results can not be applied to the practical problems. With regard to the practical meaning, Stange's equation[6] is the most useful when the relationship between particle weights and particle numbers of the components as a particle-size distribution can be observed. If the components have uniform size, his equation is simplified to

$$V\left\{\frac{g_A}{g}\right\}=\frac{P(1-P)}{g}\{P\bar{\gamma}_B+(1-P)\bar{\gamma}_A\} \tag{23}$$

where, $\bar{\gamma}_A$ and $\bar{\gamma}_B$ are average particle weights of component A and B. Equation (23) coincides with Equation (20) and (21) of this study, when the standard deviations σ_A and σ_B are zero.

Oyama,[12] Yano,[13] Michaelis,[14] Rose,[15] Adams[16] and Weidenbaum[17] reported on the expression of degree of mixing to find the optimum operating conditions experimentally. These are suitable to estimate the mixing speed but not to calculate the variance caused by taking a spot sample from a randomized bulk mixture.

Concerning the dosage variation, as previously mentioned, Train[5] calculated the variance of active component proportion in a unit dose using a binominal distribution. Unfortunately, his conception can be applied only to the preparation having uniform particle size and uniform particle density. The present study, as a special case, can be extended to suspention and emulsion. It can be assumed that the particle diameter of the dispersed medium is zero, Equation (20) for cubic particles of the dispersed phase, *e.g.* suspension, becomes

$$V\left\{\frac{g_A}{g}\right\}=\frac{P(1-P)^2 d_A L_A^3}{g}\left(1+\frac{9\sigma_A^2}{L_A^2}\right) \tag{24}$$

and Equation (21) for spherical particles, *e.g.* emulsion, becomes

$$V\left\{\frac{g_A}{g}\right\}=\frac{P(1-P)^2\pi d_A L_A^3}{6g}\left(1+\frac{9\sigma_A^2}{L_A^2}\right) \tag{25}$$

Assuming that one of the smallest doses in pharmaceutical suspensions is 0.1 mg of an active ingredient and this is to be presented as a drop dose unit, 50 mg, for instance an ophthalmic suspension, the dilution P is 0.002. To be the same confidence levels as the preceding example,

$$\frac{\sqrt{V\left\{\frac{g_A}{g}\right\}}}{0.002}\times 100=2.0, \qquad V\left\{\frac{g_A}{g}\right\}=1.6\times 10^{-9}$$

from Equation (24)

$$1.6\times 10^{-9}=\frac{0.002(1-0.002)^2\cdot d_A\cdot L_A^3}{0.05}\left(1+\frac{9\sigma_A^2}{L_A^2}\right)$$

here, to assume that the drug has a density of 1.5 and very little deviation of particle-size distribution,

11) D. Buslik, *Bull. Am. Soc. Test Mat.*, **66**, 92 T (1950).
12) Y. Oyama and K. Ayaki, *Kagaku Kogaku* (*Chem. Eng. Japan*), **20**, 148 (1956).
13) T. Yano and Y. Sano, *Kagaku Kogaku* (*Chem. Eng. Japan*), **29**, 214 (1965).
14) A.S. Michaelis, V.Puzinauskas, *Chem. Eng. Prog.*, **50**, 604 (1954).
15) H.E. Rose, *Trans. Inst. Chem. Engrs.* (London), **37**, 47 (1959).
16) J.F.E. Adams and A.G. Baker, *Trans. Inst. Chem. Engrs.* (London), **34**, 91 (1956).
17) S.S. Weidenbaum and C.E. Bonilla, *Chem. Eng. Prog.*, **51**, 27 (1955).

$$L_A^3 = 2.68 \times 10^{-8}$$

and

$$L_A = 30(\mu)$$

The mean particle size should be less than 30 μ to attain an accurate dosage.

As previsouly mentioned, the above calculations have been based on a condition of true randomization in a heterogeneous system. However, it is not always easy to obtain perfect mixing in the practical processes of pharmaceutical manufacture, one should pay attention on the additional errors such as incompleteness of mixing, segregation by vibration, flocculation or aggregation of dispersed phase by settling, *etc.*

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