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Studies on Mixing of Pharmaceutical Powders

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Abstracts □ The mixing of salicylic acid and wheat starch powders was studied using a V-type mixer. After the optimum operating conditions of the mixer were examined, the mixing characteristics relating to dilution ratio, particle size of active ingredient and addition ratio of lubricants were investigated. The coefficient of variation was expressed by a power law relating to the dilution ratio and the particle size of active ingredient. Furthermore, the comparison of results with the theoretically estimated values of mixing index suggested that the mixing of cohesive pharmaceutical powders is a complex stochastic process and cannot be explained fully by a simple theory based on a complete random mixing.

Keywords □ Mixing- of multicomponent powders evaluation of homogeneity using a mixing index based on statistical analysis, Salicylic acid-powders mixed with wheat starch for homogeneity evaluation, Mixer-the optimum operating conditions of a V-type mixer, Lubricants—the effect of magnesium stearate and talc on the mixing.

The mixing operation of powder is one basic requirement in solid formulations for the preparation of a uniform homogeneity prior to final tableting or encapsuation in the pharmaceutical industry.

The importance of uniform drug distribution in the final dosage form is recognized by the official compendia[1], which requires a content uniformity check on all dosage units containing a certain weight or less of active ingredient. Recently, instances of excessive intertablet dose variation in commercial pharmaceutical products was brought to light[2], and many drug recalls have occurred because of unsatisfactory content uniformity. Problems of excessive dose variation generally appear to be confined to high potency, low dose drugs where a substantial portion of the weight of the final product is due to excipients employed as diluents, lubricants, disintegrants, etc.

Several published reviews on mixing dealt with various aspects of mixing mechanism, methods of sampling, mixture and mixer evaluations, and related statistical techniques.[3] Some articles were also published on mixing operations in V-type mixers.[4~6] These studies were concerned with the rates of mixing, the operatve mechanisms involved, and performance evaluations compaiing V-type mixers with other types of mixing equipment.

In pharmaceutical mixing operations where materials of different particle characteristics are encountered, it is insufficient to explain enoughly the mixing characteristics. Therefore, the current investigation was designed to study several factors involved in the mixing process: dilution method and its ratio dilution method and its ratio particle size distribution and lubricants, accounting for the physical properties of powders involved.

This paper reports the mixing of pharmautical powders of salicylic acid and wheat starch in a V-type mixer. The results were evaluated by the mixing index based on the complex random mixing.

EXPERIMENTAL METHODS

Materials

Salicylic acid powder of spectra grade was used as an active ingredient. It was used as received or its particle size was controlled by enlarging with the sublimation method and by micronizing with 100mm diameter ball-mill for 10 minutes. Also of corn starch, spectra grade potato starch, and lactose as diluents were employed as received. The wheat starch of special grade was used as the diluents in great quantities.

The magnesium stearate and talc powders of special grade were also used as received for lubricants. All other chemicals were of analytic grade unless specified otherwise.

Physical Properties

The particles size distribution of fine powders were measured by a conventional method of microscopy.[7] The particle size of sublimated salicylic acid was classified and determined by sieving with the standard sieves. Moreover, the angle of repose and the compressility relating to the flow properties of the mixtures of salicylic acid and wheat starch powders were measured fundamentally based on the method proposed by Carr.[8]

The physical properties are summarized in Table I. Fig. 1 shows the photographs of particles observed by a microscope. Wheat starch powder has spherical shape but salicylic acid powder is of cylindrical shape. The aspect ratio, the ratio of length to diameter is observed to be 12.0 for that as received and 2.4 for micronized powders.

Fig. 2 shows the frequency distribution of

Table I: Physical properties of pharmaceutical powders.

Powder	Mass mean diameter (μm)	Density (g/cm^3)	Shape	Flowability Repose angle (°)	Compressibility (%)	Cohesion[e]
Salicylic acid						
I [a]	112	1.44	Cylindrical	64~65	53	Cohesive
II [b]	45	1.44				
III [c]	210[d]	1.44				
IV [c]	385[d]	1.44				
V [c]	648[d]	1.44				
Diluents						
Wheat starch	21	1.38	Sphere	59~60	45	Cohesive
Corn starch	15		Sphere			
Potato starch	28		Sphere			
Lactose	20	1.53	Sphere			
Lubricants						
Magnesium stearate	14		Sphere			
Talc	16		Sphere			

a) as received, b) micronized for 10 min., c) enlarging by sublimated method, d) geometric mean of two sieve opening, e) judged by the values of repose angle and compressibility.

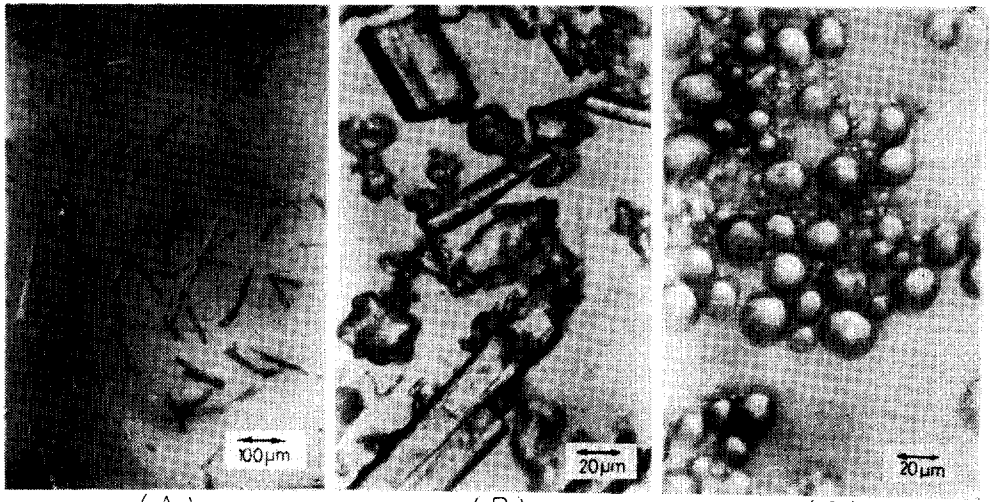

Fig. 1: Photographs of optical microscopy for salicylic acid and wheat starch powders.
A) Salicylic acid (as received), B) Salicylic acid (micronized for 10 min.), C) Wheat starch

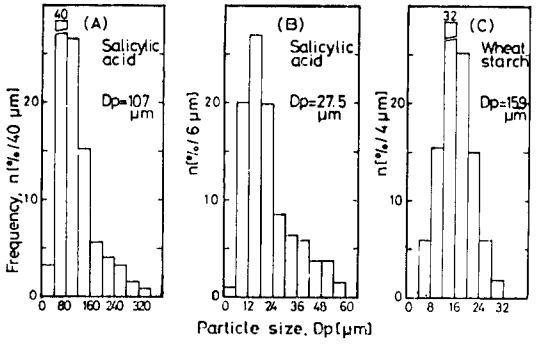

Fig. 2: Frequency distribution of particle size of samples based on number.
A) Salicylic acid (as received), B) Salicylic acid (micronized for 10 min.), C) Wheat starch.

particle size of salicylic acid and wheat starch powders. When the particle size distribution initially observed on the number basis was reduced to that based on the mass basis, the particle shape of each powder was taken an account to be cylinder for salicylic acid and sphere for wheat starch.

Mixing

The mixing was carried out in a V-type mixer made with stainless steel, its inner volume of 1.85 liter. The mixer was rotated at a desired speed controlled by a speed regulator. The multicomponent system consisted of salicylic acid as active ingredient and wheat starch as diluent with the dilution ratio predetermined. The charging was carried out through both sides of the V-type mixer, and each component was dilated during charging.

After the mixer was rotated at a certain speed throughout the study, it was stopped at predetermined each time interval. Then six spot samples, 1.0 gram each, were withdrawn from six different locations of the powder bed shown

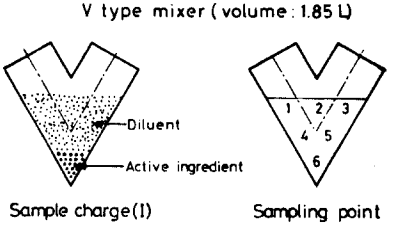

Fig. 3: Locations of sampling spot and charge pattern I.

in Fig. 3. The samples were assayed using a spectrophotometer.

Assay in Mixing

The salicylic acid content in a sample was assayed by the following method. The sample of the powder mixtures was dissolved in distilled water. Residual wheat starch was removed by centrifugation. An aliquot of filtrate was appropriately diluted with distilled water and 6.12% aqueous solution of ferric chloride was added at the ratio of ferric chloride solution 3 to filtrate 5 in volume, and then its content quantity was determined spectrophotometerically at the wavelength of 445nm.

Calibration curve and the reproducibility were made and checked from the same solution prepared from the accurately weighted amount of salicylic acid and wheat starch in the same proportion as used in the mixing studies.

Mixing Index

The degree of mixedness achieved was evaluated based on the coefficient of variation (CV) calculated from the experimental data. Several formulas on the theoretical degree of mixedness in a completely randomized mixture have proposed by many researcheres[9], but the evaluation in this work is grounded in the requirement of official compendia of drug[1], in which the content of tablet is within the limits between 95% and 105% or 90% and 110% of the average of active ingredient.

RESULTS AND DISCUSSION

The amount of a spot sample and the choice of wheat starch used in great quantities as diluent were examined previously to the experiments of mixing characteristics and the results were given in Tables Ⅱ and Ⅲ, respectively.

Even the small amount of sample below 1.0 gram was taken the high dilution ratio into consideration. Also, the wheat starch powder was selected as diluent because that its degree of mixedness had no significant difference of comparing with other diluents.

Table II: Effect of amount of sample.

Sample weight (g)	Coefficient of variation* (%)
0.2	3.8
0.5	2.8
1.0	2.3
2.0	2.0

* Value of CV at the equilibrium mixed state.

Table III: Effect of diluents.

Diluents	Coefficient of variation* (%)
Lactose	2.8
Wheat starch	2.3
Potato starch	2.0
Corn starch	2.5

* Value of CV at the equilibrium mixed state.

The mixing characteristics of the V-type mixer relating to operating conditions were examined based on the experimental variables shown in Table IV. Figs. 4, 5, and 6 give the plots of the coefficient of variation as function

Table IV: Experimental variables for optimizing of operation conditions of mixer.

Variables	Ranges	Optimum conditions
Rotatory speed (rpm)	10, 30, 50, 70	50
Charge ratio (%)	15, 22, 30, 42	30~40
Charge pattern**	Ⅰ, Ⅱ, Ⅲ	Ⅰ

* Charge ratio in volume means the ratio of feed powders to net volume of the mixer.

** Charge patterns Ⅰ, Ⅱ, and Ⅲ mean the filling of salicylic acid at the bottom, at the top, and at the intermediate as opposed to the wheat starch.

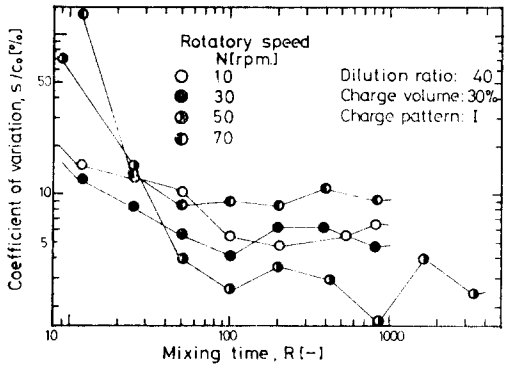

Fig. 4: Effect of rotatory speed on the mixing.

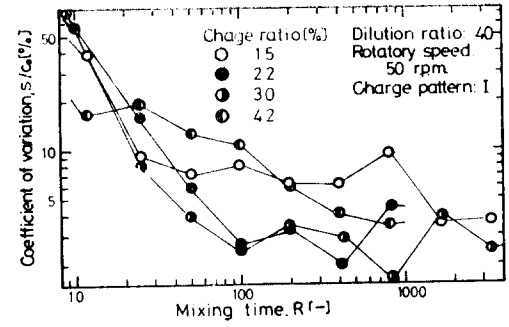

Fig. 5: Effect of charge ratio of feed on the mixing.

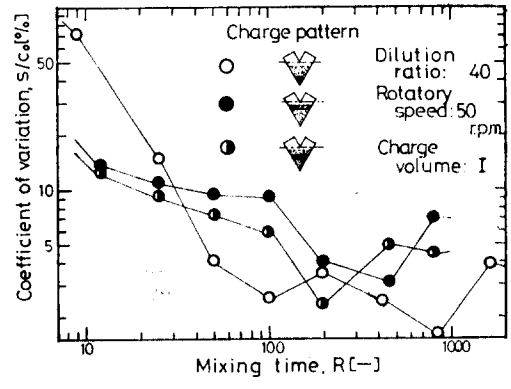

Fig. 6: Effect of charge pattern of feed on the mixing.

of the cumulative rotatory number relating to the rotatory speed, charge ratio in volume, and charge pattern, respectively.

The particles in the mixer are in disorder of an active three-dimensional motion under a certain operating conditions and at that time the mixing is considered to be progressed more rapidly and better. As the action of mixing and segregation was mutually occurred in mixing process as shown in Figs. 4, 5, and 6. Thus the optimum operating conditions within the ranges investigated are considered to be rotatory speed of 50 r.p.m., charge ratio of 30~40% in volume, and charge pattern of filling the active ingredient at the bottom of mixer as illustrated in Fig. 6. These conditions are similiar to data[9] of the practical mixer in the industrial field. The following experiments were carried out under above optimum conditions.

Mixing processes are generally considered as a random stochastic phenomena in nature. For a fully randomized two-component system of identical densities and particle size, the standard deviation σ was given the binominal distribution:

$$\sigma=(xy/N)^{1/2} \quad (1)$$

where x and y are the proportions of two ingredients and N is the number of partcles per sample taken.

Poole *et al.*[10] modified the expression developed by Stange[11] to account for the particle size distribution of a binary system:

$$\sigma=\left[\frac{x\cdot y}{M/\{y(\Sigma fw)_x+x(\Sigma fw)_y\}}\right]^{1/2} \quad (2)$$

where M is the mass of the sample taken from a mix and (Σfw) is the effective mean particle weight of the ingredient denoted by the subscript. Furthermore, the values of $(\Sigma fw)_x$ and $(\Sigma fw)_y$ are calculated based on the particle size distribution in Fig. 2.

As an example, the calculated standard deviation of a completely random mixture for micronized salicylic acid of 2.5% in powdered wheat starch with a sample size of 1.0gram would proceed as follows. The mean particle weights $(\Sigma fw)_x$ and $(\Sigma fw)_y$ are calculated to be 0.089

μg for salicylic acid ofxand 0.008μg for wheat starch of y. From these values, then the theoretically estimated standard deviation and coefficient of variation are calculated to be 4.60×10^{-5}, and 1.84%, respectively.

On the other hand, the total error in powder mixing experiments is generally attributed to the error in the analytical method, sampling, impurities, and mixing:

$$s_t^2=s_a^2+s_s^2+s_i^2+s_m^2 \quad (3)$$

where s^2 represents sampling variance and subscripts t, a, s, i, and m represent total, analytical method, sampling, impurities, and mixing respectively.

For simplicity, the total error in these studies is considered to be attributed to the error due to mixing, The sample standard, s was obtained experimentally from the results of several samples. Because of the limited sampling, the measured variability, s is only as estimate of the true variability of the population. When the population is normally distributed, the distribution of the sample variance follows the chi-square distribution and the variance of sample s^2 is:[12]

$$s^2=\sigma^2/n\text{-}1\cdot x^2_{n-1,\alpha} \quad (4)$$

where σ^2 is the population variance and χ^2_{n-1}, α is the value of chi-square distribution for the degree of freedom n-1 and the confidence level α, respectively.

Based on a pharmacopial standard, the acceptable standard deviation σ_A with a 99.7% confidence level within 10% of the mean content of an active ingredient is calculated using the assumption of normal distribution as follows:

$$\pm 3\sigma_A=\pm 0.10\ C_0=(\text{tolerance})(\text{mean}) \quad (5)$$

Where C_0 represents the mean content concentration of active ingredient. Thus the acceptable standard deviation σ_A may be fixed at any desired tolerance. Therefore, the target value on

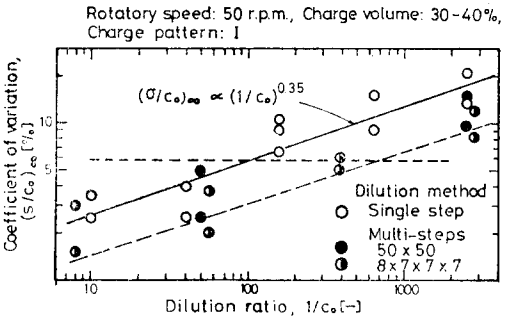

Fig. 7: Relationship between the dilution ratio and the coefficient of variation under equilibrium mixed state.

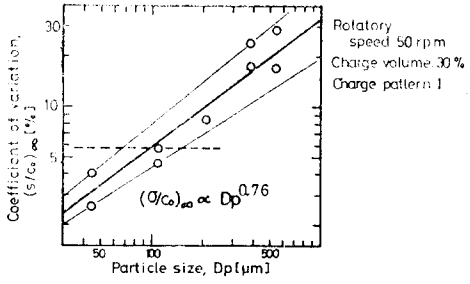

Fig. 8: Relationship between particle size of active ingredient and coefficient of variation under equilibrium mixed state.

the degree of mixedness is derieved from above Eqs. (4) and (5) as follows:

$$s/C_0=0.10/3\cdot(x^2_{n-1},\ \alpha/n-1)^{1/2} \quad (6)$$

In this work, the target value may be calculated to be ranged from 1.11% to 5.79% within the 99.0% confidence level. The level 5.79% may be considered to be the acceptable mixing index and it is also expressed in following Figs. 7 and 8.

Fig. 7 gives the plots of the coefficient of variation as a function of dilution ratio under the equlibrium mixed state, where the plots of open circle indicate the case diluted to accertain dilution ratio by a single step and the plots of closed circle indicates the case repeatedly diluted by the two steps in 50 by 50 instead of diluting at a time to the dilution ratio 2500 and the plots

of semicircle indicate the case diluted by four steps in $8\times7\times7\times7$ in the same manner of dilution method at two steps. Fig. 7 shows that the degree of mixedness becomes worse with the increase of dilution ratio. In the case of high dilution ratio, it also shows that the degree of mixedness is improved and approached an acceptable homogeneity by diluting of mutiple steps, the acceptable level could be extended to the high dilution ratio of about 1000.

Fig. 8 gives the plots of the coefficient of variation as a function of particle size for salicylic acid powder of active ingredient under the equlibrium mixed state. As the particle size decreases, the degree of mixedness becomes better. It is considered as its reason that the decrease of particle size reduces to the increase of the increase of the number of particle involved in the mixing process and increased number of particles makes the mixing chance of individual particles average.

Furthermore, the relationship between the coefficient of variation at the equlibrium mixed state and the experimental parameters such as the dilution ratio and the particle sixe of active ingredient was generally expressed by a power law as follows:

$$s/C_\circ = k(1/C_\circ)^{0.35} \cdot D_p^{0.76} \qquad (7)$$

where k is the constant depending upon the properties of powders aud experimental equipment and its operating conditions. And the dilution ratio $1/C^\circ$ was varied oved over the range of 8~2,800 and the particle size D_p over that of 45~648μm.

Fig. 9 gives the plots of the ratio of coefficient of variance at any addition ratio of lubricant to CV at 1% addition ratio as a function of addition ratio of lubricant, magnesium stearate and talc. Both lubricants have similiar tendency but the effective range of addition ratio for talc

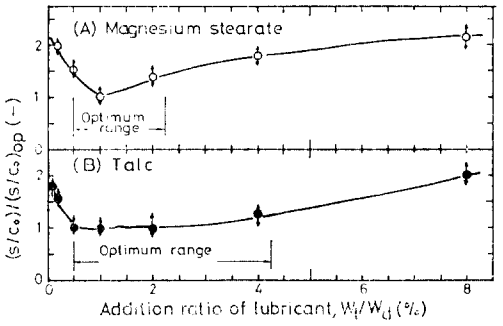

Fig. 9: Effect of dilution ratio of lubricants on the mixing.
Experimental conditions: dilution ratio 160, rotatory speed 50 r.p.m., charge ratio 30%, charge pattern I.

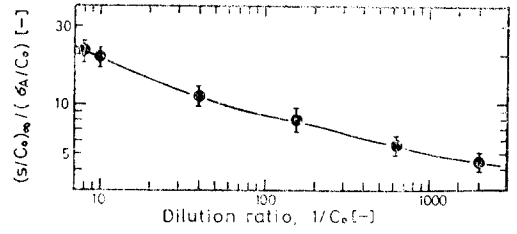

Fig. 10: Comparison of coefficient of variation under equlibrium mixed state $(s/C_0)_\infty$ and the estimated value $(\sigma A/C_0)$.

is wider than that for magnesium stearate, Even a small amount of lubricant in 1% addition ratio was added, the degree of mixedness is considerably improved. The addition ranges which have a noted effect on the goodness of mixedness are also shown as the optimum addition ranges of lubricants in Fig. 9.

Fig. 10 shows the comparison of coefficient of variation under equlibrium mixed state $(1/C_0)_\infty$ with the value estimated by Eq. (2) $(\sigma A/C_0)$. As the dilution ratio increases, the value of the $(s/C_0)_\infty/(\sigma A/C_0)$ approaches small value. This result shows that the mixing of multicomponents but it is suitable to estimate the experimental data to a certain extent. As the pharmaceutical powders dealt in this work are cohesive as

shown in Table I, the particles involved in the mixing are considered to be agglomerate particles rather than original particles. Moreover, it should be noted worthy that each particle in the multicomponent system is not in a completely randomnized state even after a sufficient mixing time. Therefore, it is considered that the analyses of multicomponent mixing based on the fundamental statistical concepts and the micrometric knowledge on powders involved in powder technology make the understanding of mixing clearly.

CONCLUSION

The followings were obtained from the experiments.

1) The optimum operation conditions of a V-type mixer were confirmed to be the rotatory speed of 50 r.p.m., the charge ratio of 30-40% in volume, and the charge pattern of filling the active ingredient at the bottom of mixer.

2) The relationship between the coefficient of variation at the equlibrium mixed state and the experimental parameters such as the dilution ratio and the particle size of active ingredient was generally expressed by a power law within the experimental ranges:

$$(s/C_0 = k(1/C_0)^{0.35} \cdot D_p^{0.76}$$

where $1/C_0$ was varied from 8 to 2800 and D_p from 45μm to 648μm.

3) It was found that the degree of mixedness in high dilution ratio could be considerably improved by diluting of multiple steps and adding of a small amount of lubricant.

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