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Mixing of Pharmaceutical Solids II: Evaluation of Multicomponent Mixing of Cohesive Powders in Cylindrical Shear Mixer

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Abstract □ The mixing of three organic carboxylic acids with micronized lactose, all cohesive in nature, was studied using a cylindrical shear mixer. Three mixing indexes (s/σ_A, s/σ_R, and the Ashton–Valentin mixing index) were used to evaluate mixing of the three drugs with lactose. The results suggested that maximum homogeneity was reached after 45 min of mixing. However, different mixing indexes showed different sensitivity to homogeneity of the individual components. The mixing index s/σ_A, which is based on setting standard specifications, appears to provide a better evaluation of homogeneity of individual components compared to the mixing indexes based on complete random mixing theory. The latter did not approach unity for any drug component used in this study. These results suggested that mixing of cohesive powders is a complex process and cannot be explained fully by simple theory based on complete random mixing.

Keyphrases □ Mixing—of multicomponent cohesive powders, evaluation of homogeneity using three mixing indexes based on statistical analysis □ Powders—multicomponent mixing of cohesive powders, evaluation of homogeneity using three mixing indexes based on statistical analysis □ Carboxylic acids—cohesive powders mixed with lactose for homogeneity evaluation, evaluation of three mixing indexes based on statistical analysis □ Dosage forms, design—multicomponent mixing of cohesive powders to determine homogeneity of individual components, three mixing indexes evaluated

The mixing of a cohesive drug with cohesive, noncohesive, and free-flowing excipients was studied previously (1) using two types of mixers, cylindrical shear and V-shaped tumbling. Most mixing studies use binary systems, and mixing indexes based on statistical analysis are used to evaluate homogeneity. However, many practical situations in dosage form design require mixing several powders. Although most multicomponent mixing has been studied theoretically (2–6), one practical multicomponent system used 10% phenobarbital, 1% secobarbital, 1% butobarbital, and 88% lactose (7–9).

The multicomponent mixing of cohesive powders is one of the most difficult and complex powder mixing systems. None of the reported mixing studies have dealt with this powder mixing system.

This paper reports the mixing of cohesive powders of three organic carboxylic acids and an excipient in a cylindrical shear mixer. The results were evaluated by the mixing indexes based on complete random mixing and on standard specifications described previously (10, 11).

EXPERIMENTAL

Materials—Three organic carboxylic acids, 7-methylsulfinyl-2-xanthone carboxylic acid (I), 7-methylthio-2-xanthone carboxylic acid (II), and 5-isopropoxy-7-methylthio-2-xanthone carboxylic acid (III), and mestranol were at least 99% pure[1]. USP grade lactose[2] was micronized[3]. Component I was micronized, and II and III were used as received. Methanol[4] was spectra grade, and polysorbate 80[5] was USP grade. All other chemicals were analytical grade unless specified otherwise.

Physical Properties—The particle-size distributions of I–III were determined[6] by electronic counting. The vehicle was a saturated solution of the compound in 0.6% HCl containing 0.018% polysorbate 80. The filtered vehicle was used to disperse the drug powder.

The particle-size distribution of the micronized lactose was determined[7] by automatic sedimentation, using photoextinction to measure the apparent projected area at decreasing sedimentation depths with increasing time.

The densities of the organic carboxylic acids were determined by the density matching method of Oster and Yamamoto (12). Mixtures of

[1] Institute of Organic Chemistry, Syntex Research, Palo Alto, CA 94304.
[2] Lactose regular, Foremost Food Co., San Francisco, CA 94104.
[3] Jet Pullverizer Co., Palmyra, N.J.
[4] Mallinckrodt Chemical Works, St. Louis, MO 63160.
[5] ICI America, Atlas Chemical Division, Wilmington, Del.
[6] Coulter counter model TA, Coulter Electronics, Hialeah, FL 33010.
[7] Sedigraph-L Micromeretics Instrument Corp., Norcross, Ga.

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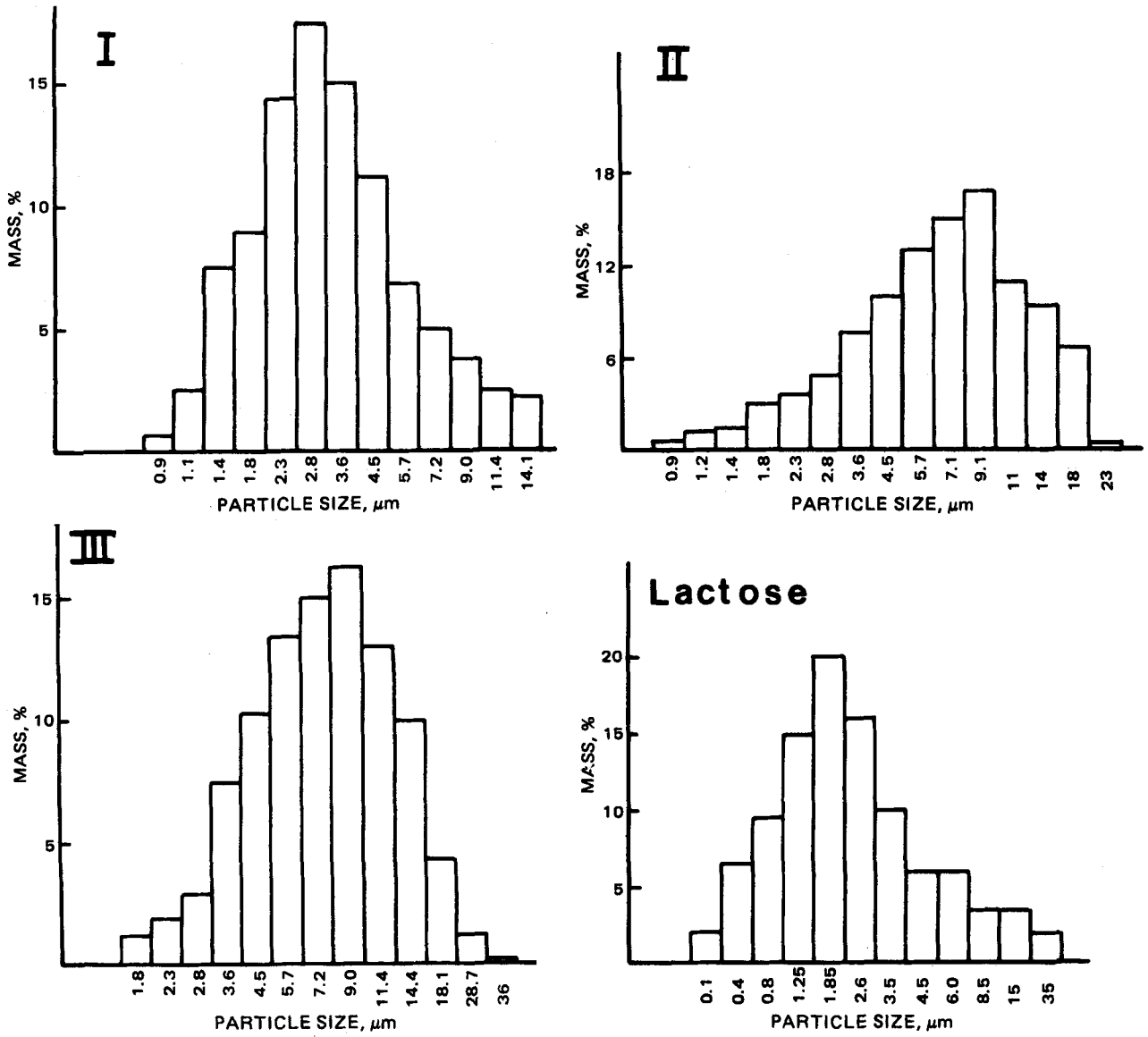

Figure 1—*Particle-size distribution of I, II, III, and lactose.*

hexane and carbon tetrachloride were prepared, and the powder was placed in the test tubes containing these solvent mixtures to pinpoint the density range. The powder density was determined by matching with the solvent mixture. The density of the final solvent was determined by weighing the solvent in a liquid pycnometer, which was calibrated with water at room temperature. The density of the lactose was obtained from the literature.

Mixing—The mixing was carried out in a cylindrical shear mixer equipped with a stainless steel blade. The cylindrical drum was rotated at a desired speed controlled by a speed regulator. The axis of rotation coincided with the axis of the cylindrical drum. The multicomponent system consisted of micronized lactose and the three carboxylic acids (I, 12%; II, 6%; and III, 2%). The loading was carried out through the same side of the mixer, and each component was dilated during loading.

The mixer was rotated at 60 rpm throughout the study. Twenty spot samples, 20 mg each, were withdrawn from six different locations of the powder bed at each time interval.

The samples were individually weighed, extracted with methanol, and assayed for I–III by high-performance liquid chromatography (HPLC) using mestranol as the internal standard.

Assay of I–III in Mixture—The samples of the powder mixtures were dissolved and extracted in methanol. Residual lactose was removed by filtration through a 0.8-μm pore diameter filter[8]. The first 15 ml of the filtered solution was discarded to account for any adsorption of the solute to the membrane filter. To an aliquot of the filtrate, an aliquot of mestranol in methanol was added and appropriately diluted before injection. The injection volume was 100 μl. The high-pressure liquid chromatograph was equipped with a fixed-wavelength UV detector at 280 nm. Separation was accomplished on a Spherisorb ODS, 10-μm, reversed-phase column (25 cm × 4.6 mm).

The mobile phase was 60% methanol and 1% acetic acid in distilled water. The eluent was filtered through a 2.0-μm filter[8] and degassed prior to use. The flow rate was adjusted to 1 ml/min (~1500 psi).

Calibration curves were prepared for solutions containing I–III and mestranol in the mobile phase. A linear relationship was obtained for I, II, and III over ranges of 1–7.0, I–4.0, and 0.1–1.2 μg/ml, respectively.

Method reproducibility was checked by injecting 20 samples from the same stock solution prepared from the accurately weighed amount of I–III and lactose in the same proportion as used in the mixing studies.

RESULTS AND DISCUSSION

The particle-size distributions of I–III and lactose are given in Fig. 1. Table I gives the mass median diameter, density, effective particle weight, and total number of particles in a sample of all components in the mixture. The classification of powders into cohesive and noncohesive powders was based largely on the particle-size distribution, because simple measurements such as the angle of repose did not differentiate between these

[8] Metricel membrane filter.

Table I—Particle Properties of Mixing Components

Property	I	II	III	Lactose
Mass median diameter, μm	3.06	7.23	6.40	2.10
Density, g/ml	1.53	1.50	1.40	1.53
Effective mean particle weight, μg	0.147×10^{-3}	0.799×10^{-3}	0.65×10^{-3}	0.821×10^{-3}
Total number of particles in sample	2.79×10^{8}	4.78×10^{7}	6.93×10^{6}	4.275×10^{11}
Cohesion	Cohesive	Cohesive	Cohesive	Cohesive

powders (1). Since the mass median diameter of all mixing components used was <10 μm, all powders were classified qualitatively as cohesive.

Figure 2 gives the chromatogram showing the separation of I–III and the internal standard. The observed retention times for I, II, mestranol, and III were 6, 10, 13, and 16 min, respectively. The error due to the method was determined, and the variance of the method was 0.0029, 0.00064, and 0.00031% for I, II, and III, respectively. This error was small and was considered negligible. Since the sampling error is difficult to determine and the error due to the impurities is very small, they were neglected also. The total error in powder mixing experiments is generally attributed to the error in the analytical method, sampling, impurities, and mixing:

$$S_t^2 = S_a^2 + S_s^2 + S_i^2 + S_m^2 \qquad \text{(Eq. 1)}$$

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 attributed to the error due to mixing.

The sample standard deviation s was obtained experimentally from the results of 20 samples. With the assumption of a normal distribution, the acceptable standard deviation σ_A with a 99.7% confidence level within ±10 and ±15% of the mean X was calculated from:

$$\pm 3\sigma_A = \pm 0.1X = (\text{tolerance} \times \text{mean}) \qquad \text{(Eq. 2a)}$$

$$\pm 3\sigma_A = \pm 0.15X = (\text{tolerance} \times \text{mean}) \qquad \text{(Eq. 2b)}$$

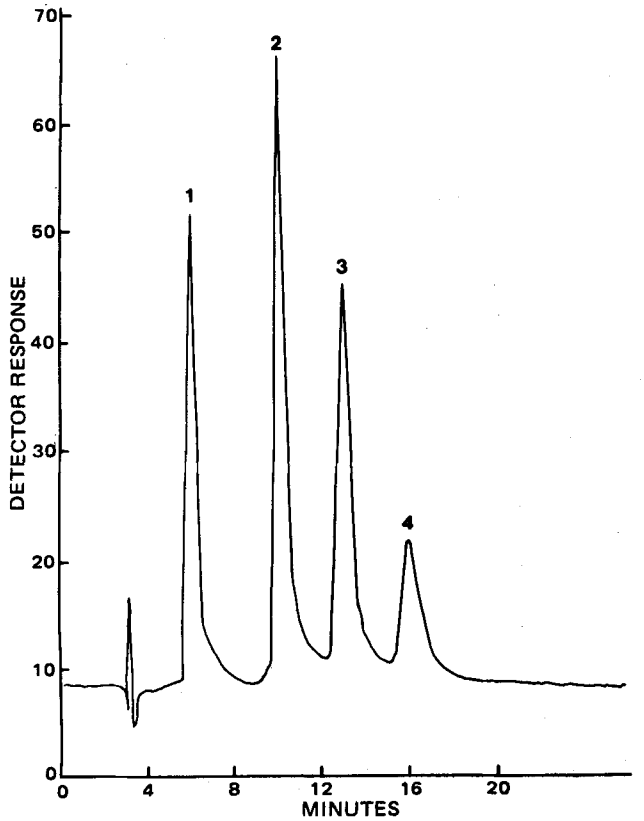

Figure 2—*Chromatogram of I–III from a mixture containing mestranol as the internal standard. Detector response was at 0.04 aufs. Key: 1, I; 2, II; 3, mestranol; and 4, III.*

The acceptable standard deviation σ_A may be fixed at any desired tolerance, for example, 15% within the mean. The sample standard deviation s is obtained from the mixing experiments. The mixing index s/σ_A approaches acceptability as the sample standard deviation approaches σ_A.

Figure 3 gives the results of s/σ_A as a function of the mixing time. As mixing approached acceptability, the ratio of the sample standard deviations and the acceptable standard deviation σ_A approached unity. The s/σ_A for I, which was at the highest concentration, approached unity after ~35 min of mixing. When mixing was continued, the s/σ_A remained below unity. The s/σ_A for II approached acceptable homogeneity after ~45 min of mixing. Component III, which was at the lowest concentration in the mixture, approached acceptability only after 75 min of mixing.

The results in Fig. 3 clearly indicate that homogeneity in a multicomponent cohesive system is very dependent on the concentration of the individual components[9]. The component at the highest concentration in the mixture appeared to approach the acceptability range at the fastest rate, and the component at the lowest concentration was slowest in approaching the acceptability range. Since the degree of mixedness in a multicomponent system is dependent on the concentration of individual components, it is important to monitor the homogeneity of individual

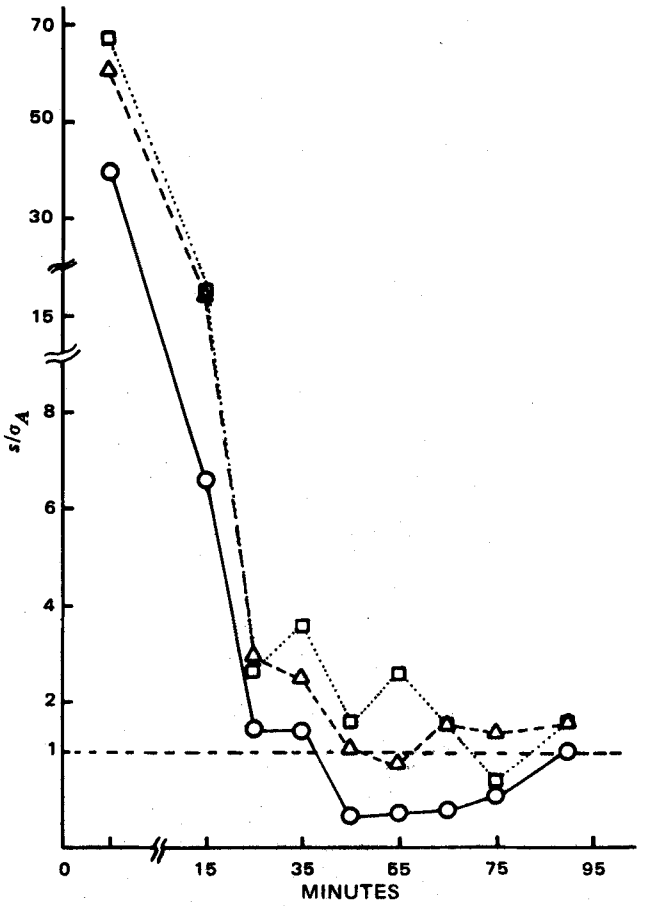

Figure 3—*Plots of* s/σ_A *versus mixing time, showing the mixing of I (○), II (△), and III (□). The* σ_A *was calculated at ±10% tolerance with a 99.7% confidence level.*

[9] Such a concentration effect has largely been ignored in the past except for one brief study (13). It has not been reported for multicomponent mixtures.

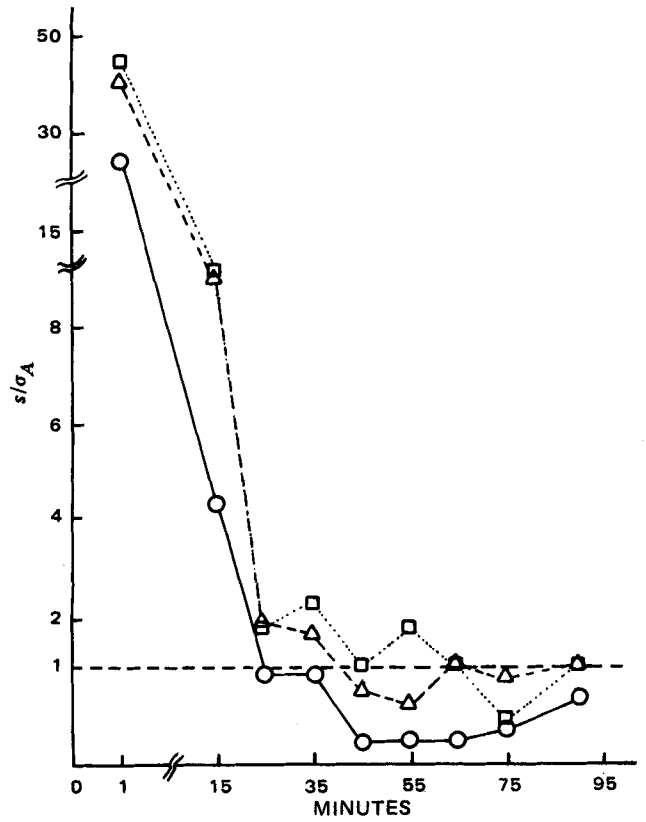

Figure 4—*Plots of* s/σ_A versus *mixing time, showing the mixing of I (○), II (△), and III (□). The* σ_A *was calculated at ±15% tolerance with a 99.7% confidence level.*

components to reach an acceptability range for all components in the mixture. It is obvious from the results in Fig. 3 that the mixture did not pass the 10% acceptable limit on standard deviation at any time point because the mixing index for at least one of the three components did not approach the acceptability range.

Figure 4 gives the results of the s/σ_A mixing index tested according to the USP criterion of ±15% for content uniformity at the 99.7% confidence level. All three components approached acceptable homogeneity

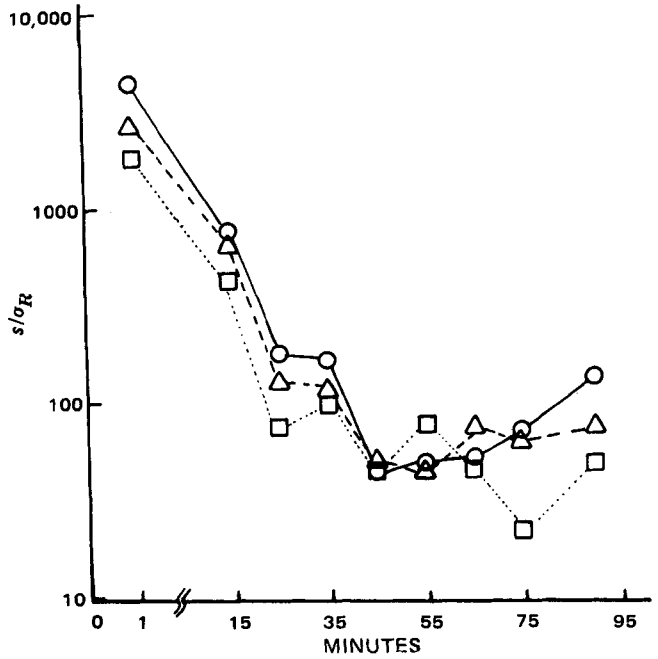

Figure 5—*Plots of* s/σ_R versus *mixing time, showing the mixing of I (○), II (△), and III (□).*

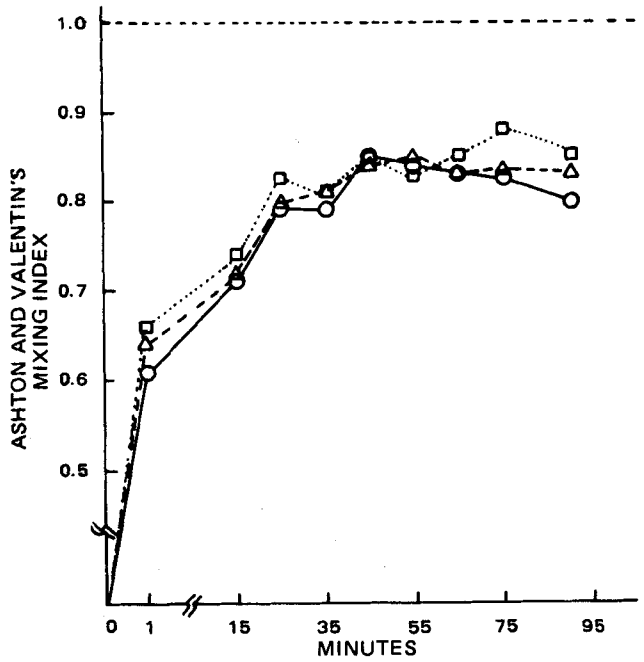

Figure 6—*Plots of* $(\log \sigma_0^2 - \log S^2)/(\log \sigma_0^2 - \log \sigma_R^2)$ versus *mixing time, showing the mixing of I (○), II (△), and III (□).*

after mixing for 45, 75, and 90 min.

Mixing processes are generally considered as random in nature. Over 30 different mixing indexes were reviewed by Fan *et al.* (14). For a fully randomized two-component system of identical densities and particle sizes, the standard deviation was given (11) by:

$$\sigma_R = \left(\frac{pq}{N}\right)^{1/2} \qquad \text{(Eq. 3)}$$

where p and q are the proportions of two components, N is the number of particles in the unit of scrutiny, and σ_R is in a unit of fraction of particles.

Poole *et al.* (15) modified an expression (16) to account for the particle-size distribution of a binary system:

$$\sigma_R = \left\{pq \Big/ \left[\frac{W}{q(\Sigma fw)_p + p(\Sigma fw)_q}\right]\right\}^{1/2} \qquad \text{(Eq. 4)}$$

where $\Sigma(fw)$ is the effective mean particle weight of that ingredient denoted by the subscript and W is the mass of the sample taken from a mix. Stange (5) extended this form to a multicomponent system:

$$\sigma_{R,p}^2 = \frac{p^2}{W}\left[\left(\frac{1-p}{p}\right)^2 p(\Sigma fw)_p + q(\Sigma fw)_q + r(\Sigma fw)_r + \cdots\right] \qquad \text{(Eq. 5)}$$

The ratio of the sample standard deviation and σ_R obtained from Eq. 5 is plotted *versus* mixing time in Fig. 5. As expected from the results of a binary system (1), this index was not suitable for evaluating mixing of multicomponents that are all cohesive.

Ashton and Valentin (17) proposed the following mixing index (Eq. 6), which is more sensitive to variations of mixedness in its entire span ranging from the completely segregated state to completely mixed state:

$$Mu^2 = \frac{\log \sigma_0^2 - \log S^2}{\log \sigma_0^2 - \log \sigma_R^2} \qquad \text{(Eq. 6)}$$

where σ_0^2, S^2, and σ_R^2 are the variances in the initial, intermediate, and ultimate random conditions, respectively. Figure 6 gives the plots of this mixing index as a function of the mixing time. All three components approached maximum homogeneity on mixing for ~45 min, after which some segregation tendency was noticeable with two components.

The analyses of mixing data of multicomponent cohesive powders by the mixing indexes based on complete random mixing theory and on setting standard specifications suggested that the maximum attainable homogeneity was reached after 45 min of mixing. The two analyses show different sensitivity to the homogeneity of individual components. The mixing index s/σ_A, which is based on setting standard specifications, appears to provide a better evaluation of homogeneity of individual

components compared to the mixing index based on complete random mixing theory. The mixing indexes based on complete random mixing do not approach unity for any of the three drug components used in this study. These results suggest that mixing of cohesive powders is a complex process and cannot be fully explained by simple theory based on complete random mixing.

The analyses of multicomponent mixing were based on fundamental statistical concepts. The mixing index based on standard specifications provides satisfactory evaluation of mixing multicomponent cohesive powders. The mixing index of Ashton and Valentin (17) may be used to evaluate multicomponent mixing systems of the type described in this paper, although it has some disadvantages.

Recently, Wang *et al.* (2) applied multivariate statistical analysis to the mixing process and to a mixture of multicomponent solid particles. They used three types of lucite spherical particles which had identical properties except color. Since it is an interesting approach for evaluating multicomponent mixing, future work directed in this vein using a more practical multicomponent system would elucidate the understanding of mixing.

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Mixing of Pharmaceutical Solids III: Multivariate Statistical Analysis of Multicomponent Mixing

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Abstract □ The multicomponent mixing for cohesive powders was evaluated by multivariate statistical methods. Tests were carried out for the sampling technique, completely random state and completely segregated state. Hotelling's statistics were not helpful in testing the practical sampling technique. Comparisons of the mixing indexes based on univariate and multivariate statistics indicated excellent consistency in optimizing mixing time. Neither mixing index approached unity because cohesive powders do not reach a completely random state. The multivariate mixing index was smaller than the univariate indexes largely due to interparticular forces among small cohesive particles.

Keyphrases □ Mixing—of multicomponent cohesive powders, evaluation of homogeneity using multivariate statistical analysis □ Powders—multicomponent mixing of cohesive powders, evaluation of homogeneity using multivariate statistical analysis □ Dosage forms, design—multicomponent mixing of cohesive powders to determine homogeneity of mixture, comparison of univariate and multivariate statistical analyses

Theories concerning the state of mixedness of solids generally deal with univariate statistical analysis of the sample standard deviation and the theoretical standard deviation (1–6). However, almost all processes of experimentation, data collection, and observations are multivariate in nature. Multivariate analysis deals with summarization, representation, and interpretation of data sampled from populations where the variables yield measures of more than one characteristic (7–9). In pharmaceutical practice, the drug(s) and excipient(s) being mixed vary in their particle-size distribution, inter- and intraparticular forces, mixing composition, shape, *etc.* From a statistical viewpoint, analysis of heterogeneous solid mixtures using the univariate statistical approach does not account for the interactions and statistical dependency of individual components.

Recently, Wang *et al.* (10) applied multivariate statistical analysis to the mixing process and to a mixture of multicomponent solid particles. They used three types of spherical particles with identical properties except color.

The mixing of three organic carboxylic acids with micronized lactose, all cohesive in nature, was studied (11) using a cylindrical shear mixer. The results were evaluated by the mixing indexes based on univariate statistics. This paper analyzes the previous experimental results using multivariate statistical methods. Comparisons of the results of the mixing indexes based on univariate statistics (6) and multivariate statistics (10) indicate excellent consistency in optimizing mixing time for mixing multicomponent cohesive powders. Due to interparticular forces among small cohesive particles, the resulting multivariate mixing index was smaller than the univariate index of individual components. Neither mixing index approached unity, indicating that the mixing of cohesive powders is not completely random.

THEORETICAL

In the univariate normal distribution, measurement of the effect is evaluated through independent random events. The problems arising in the multivariate populations are mostly straightforward analogies of the problems arising in univariate populations. For a single variable, the

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