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

central limit theorem leads to the univariate normal distribution; for several variables, the general limit theorem leads to the multivariate normal distribution. The suitable methods of analysis are based mainly on the standard operations of matrix algebra.

For a univariate normal distribution, variable Y was taken from the normal distribution N:

$$Y \sim N(\mu, \sigma^2) \qquad \text{(Eq. 1)}$$

where μ is the population mean and σ^2 is the population variance.

To test if the sample mean $\overline{X}$ is equal to the hypothetical population mean μ_0, t statistics is used:

$$t = (N)^{1/2} \frac{(\overline{X} - \mu_0)}{S} \qquad \text{(Eq. 2)}$$

where N is the number of observations in the sample and S is the sample standard deviation.

In the multivariate statistics, a vector random variable Y, which is a p-element vector, and T^2 statistics proposed by Hotelling are used:

$$T^2 = N(\overline{Y} - \mu_0)'S^{-1}(\overline{Y} - \mu_0) \qquad \text{(Eq. 3)}$$

where $\overline{Y}$ is the mean vector of a sample of N number, S is the sample variance–covariance matrix that is the unbiased estimation of the dispersion, and the prime is the transpose of the matrix.

Multivariate Test of Sampling Technique—In sampling a p-variate normal population, it is assumed that:

$$Y_i' \sim N_p(\mu, \Sigma) \qquad \text{(Eq. 4)}$$

$$
\begin{aligned}
Y_1' &= [y_{11} \quad y_{12} \quad \ldots \quad y_{1p}] \qquad \text{(Eq. 5)} \\
Y_2' &= [y_{21} \quad y_{22} \quad \ldots \quad y_{2p}] \\
&\quad \vdots \qquad \vdots \qquad \vdots \qquad \vdots\vdots \\
Y_N' &= [y_{N1} \quad y_{N2} \quad \ldots \quad y_{Np}]
\end{aligned}
\qquad \text{(Eq. 6)}
$$

or:

$$
Y' = \begin{bmatrix}
y_{11} & y_{12} & \ldots & y_{1p} \\
y_{21} & y_{22} & \ldots & y_{2p} \\
\vdots & \vdots & \vdots\vdots & \vdots \\
y_{N1} & y_{N2} & \ldots & y_{Np}
\end{bmatrix}
\qquad \text{(Eq. 7)}
$$

where μ is the sample mean vector, Σ is the variance–covariance matrix, and Y_i' is the p-vector random variable where $i = 1, 2, \ldots N$.

Next, the null hypothesis H_0 ($\mu = \mu_0$) is tested against the alternative hypothesis H_1 ($\mu \neq \mu_0$). The most likely estimator of the centroid is an unbiased estimator and is given by:

$$\overline{Y} = \frac{1}{N}\left(\sum_{i=1}^{N} Y_i\right) \qquad \text{(Eq. 8)}$$

The most likely estimator of the dispersion or variance–covariance matrix S is given by:

$$S = \frac{1}{N-1}\sum_{i=1}^{N}(Y_i - \overline{Y})(Y_i - \overline{Y})' \qquad \text{(Eq. 9)}$$

If the Hotelling statistics $T^2 > T^2_{\alpha(p,N-1)}$, the null hypothesis that the mean has not been significantly biased at level α is rejected. Thus, $T^2_{\alpha(p,N-1)}$ denotes the upper α percentage point of the T^2 distribution.

The rejection of the null hypothesis H_0, $\mu = \mu_0$, indicates that the sample mean is significantly different from the population mean. This result could be due to improper location and spacing of the spot samples, bias during sampling, or a peculiar segregation tendency that favored the concentration of one material in some small area.

Multivariate Test for Completely Random and Completely Segregated States—The criterion in multivariate analysis is to determine if the variance–covariance matrix of the mixture is significantly different from that of a completely random state. The test for a completely segregated state could be performed in a similar fashion.

Given Y_1', Y_2', and Y_N' as observation vectors of the $p + 1$ component from $N_p(\mu, \Sigma)$, the most likely ratio criterion for testing the null hypothesis H_0:

$$\Sigma = \Sigma_0 \qquad \text{(Eq. 10)}$$

against the alternative hypothesis H_1 ($\Sigma \neq \Sigma_0$), where Σ_0 is the specified variance–covariance matrix as given by (12):

$$\lambda_1 = \left(\frac{e}{N}\right)^{1/2(pN)} |B\Sigma_0^{-1}|^{1/2(N)} e^{-1/2(tr)(B\Sigma_0^{-1})} \qquad \text{(Eq. 11)}$$

where $B = \sum_{i=1}^{N}(Y_i - \overline{Y})(Y_i - \overline{Y})'$.

It was shown (12) that:

$$\mathbf{X} = -2 \ln \lambda_1 \qquad \text{(Eq. 12a)}$$

$$\mathbf{X} = pN(\ln N - 1) - N \ln |B\Sigma_0^{-1}| + tr(B\Sigma_0^{-1}) \qquad \text{(Eq. 12b)}$$

is distributed approximately as a χ^2 random variable with $p(p + 1)/2$ degrees of freedom when H_0 is true. Thus, the null hypothesis is rejected at the significance level α if $\mathbf{X} > x_\alpha^2(p(p + 1)/2)$.

For the spot sample of size N taken from a completely random mixture, the particles in the mixture are expected to be randomly distributed. Assume the random variables $(\mathbf{X}_1, \mathbf{X}_2 \ldots \mathbf{X}_{p+1})$ for a mixture of $(p + 1)$ components, where $\mathbf{X}_j$ is the number of j components occurring among the n repetition of the event. Hence, $\mathbf{X}_j = n_j$, $n_j = 0, 1, \ldots, n$, and:

$$x_j = \frac{\mathbf{X}_j}{n} \qquad \text{(Eq. 13)}$$

where x_j denotes the number proportion of type j particles in the mixture. The probability of a spot sample to contain n_1 particles of type 1, n_2 particles of type 2, and $n_{(p+1)}$ particles of type $(p + 1)$ was given as the probability function:

$$
\begin{aligned}
P(\mathbf{X}_1 = n_1, & \mathbf{X}_2 = n_2 \ldots \mathbf{X}_{(p+1)} = n_{p+1}) \\
&= \frac{n!}{n_1! \, n_2! \ldots n_{p+1}!} c_1^{n_1} c_2^{n_2} \ldots c_{p+1}^{n(p+1)} \qquad \text{(Eq. 14)}
\end{aligned}
$$

where:

$$\sum_{i=1}^{p+1} n_i = n$$

$$\sum_{i=1}^{p+1} c_i = 1$$

and c_i is the fraction concentration of component i in the mixture. In a four-component system, $n_1 + n_2 + n_3 + n_4 = n$ and $c_1 + c_2 + c_3 + c_4 = 1$.

These random variables, $\mathbf{X}_1, \mathbf{X}_2, \ldots \mathbf{X}_{(p+1)}$, with the function given above have a multinomial probability distribution that is a generalization of the binomial distribution. The mean, variance, and covariance of the probability density (13), respectively, are:

$$E(\mathbf{X}_j) = nC_j \qquad \text{(Eq. 15)}$$

$$VAR(\mathbf{X}_j) = nC_j(1 - C_j) \qquad \text{(Eq. 16)}$$

$$COV(\mathbf{X}_i, \mathbf{X}_j) = -nC_iCj \qquad \text{(Eq. 17)}$$

Hence, for a completely random state, Σ_r may be expressed as:

$$
\Sigma_r = \frac{1}{n}\begin{bmatrix}
c_1(1 - c_1) & -c_1c_2 & \ldots & -c_1c_p \\
-c_1c_2 & c_2(1 - c_2) & \ldots & -c_2c_p \\
\vdots & \vdots & \vdots\vdots & \\
-c_1c_p & -c_2c_p & \ldots & c_p(1 - c_p)
\end{bmatrix}
\qquad \text{(Eq. 18)}
$$

In the completely segregated state, particles of the same kind aggregate together. The variance–covariance matrix for the completely segregated state is:

$$VAR(x_i) = c_i(1 - c_i) \qquad \text{(Eq. 19)}$$

$$COV(x_i, x_j) = -c_ic_j \qquad \text{(Eq. 20)}$$

For a completely segregated state, Σ_s can be expressed as:

$$
\Sigma_s = \begin{bmatrix}
c_1(1 - c_1) & -c_1c_2 & \ldots & -c_1c_p \\
-c_1c_2 & c_2(1 - c_2) & \ldots & -c_2c_p \\
\vdots & \vdots & \vdots\vdots & \\
-c_pc_1 & -c_pc_2 & \ldots & c_p(1 - c_p)
\end{bmatrix}
\qquad \text{(Eq. 21)}
$$

Multivariate Mixing Index for Multicomponent Mixture—Wang et al. (10) proposed a mixing index for a multicomponent mixture that can range between 0 and 1, based on the value of the determinant of the variance–covariance matrix at the completely segregated state and that at the completely random state:

$$Mm = \frac{(\ln |\Sigma_s| - \ln |S|)^{1/2}}{(\ln |\Sigma_s| - \ln |\Sigma_r|)^{1/2}} \qquad \text{(Eq. 22)}$$

where:

$|S|$ = determinant of sample variance–covariance matrix
$|\Sigma_s|$ = determinant of variance–covariance matrix at completely segregated state

Table I—Sample Mean and Standard Deviation

Number	Mixing Time, min		Mean Recovery ± SD
1	1	I	0.1535 ± 0.1583
		II	0.0926 ± 0.1233
		III	0.0320 ± 0.04507
2	15	I	0.1237 ± 0.0266
		II	0.0640 ± 0.0305
		III	0.0224 ± 0.0104
3	25	I	0.1182 ± 0.0058
		II	0.0594 ± 0.0060
		III	0.0199 ± 0.0018
4	35	I	0.1210 ± 0.0058
		II	0.0602 ± 0.0051
		III	0.0203 ± 0.0024
5	45	I	0.1208 ± 0.0015
		II	0.0607 ± 0.0023
		III	0.0205 ± 0.0011
6	55	I	0.1192 ± 0.0016
		II	0.0601 ± 0.0019
		III	0.0202 ± 0.0018
7	65	I	0.1205 ± 0.0017
		II	0.0601 ± 0.0033
		III	0.0201 ± 0.0011
8	75	I	0.1178 ± 0.0023
		II	0.0596 ± 0.0029
		III	0.0196 ± 0.00048
9	90	I	0.1179 ± 0.0043
		II	0.0606 ± 0.0033
		III	0.0200 ± 0.0011

$|\Sigma_r|$ = determinant of variance–covariance matrix at completely random state

RESULTS AND DISCUSSION

The experimental results of the multicomponent mixing (11) are summarized in Table I. As the mixing time increased, the mean composition of the individual components became closer to the theoretical values until plateau values were reached. The standard deviations decreased up to 45 min of mixing time, after which the standard deviation increased or decreased depending on the individual components.

To test for the sampling technique, the null hypothesis H_0:

$$\begin{bmatrix} \mu_1 \\ \mu_2 \\ \mu_3 \end{bmatrix} = \begin{bmatrix} 0.12 \\ 0.06 \\ 0.02 \end{bmatrix} \qquad \text{(Eq. 23)}$$

was tested against the alternative hypothesis H_1:

$$\begin{bmatrix} \mu_1 \\ \mu_2 \\ \mu_3 \end{bmatrix} \neq \begin{bmatrix} 0.12 \\ 0.06 \\ 0.02 \end{bmatrix} \qquad \text{(Eq. 24)}$$

For the first time point:

$$Y_1 = \begin{bmatrix} 0.408 \\ 0.1062 \\ 0.0272 \end{bmatrix} \qquad \text{(Eq. 25a)}$$

$$Y_2 = \begin{bmatrix} 0.2832 \\ 0.2916 \\ 0.0332 \end{bmatrix} \qquad \text{(Eq. 25b)}$$

.
.
.

$$Y_{20} = \begin{bmatrix} 0.0468 \\ 0.0042 \\ 0.0028 \end{bmatrix} \qquad \text{(Eq. 25c)}$$

$$Y' = \begin{bmatrix} 0.408 & 0.1062 & 0.0272 \\ 0.2832 & 0.2916 & 0.0332 \\ 0.2664 & 0.2346 & 0.0510 \\ 0.4044 & 0.3576 & 0.0910 \\ 0.4836 & 0.3690 & 0.1474 \\ 0.1392 & 0.1440 & 0.1446 \\ 0.1596 & 0.0702 & 0.0134 \\ 0.1752 & 0.0852 & 0.0212 \\ 0.144 & 0.0828 & 0.0154 \\ 0.0408 & 0.0696 & 0.0156 \\ 0.0204 & 0.0036 & 0.0009 \\ 0.0186 & 0.0066 & 0.0019 \\ 0.0138 & 0.0027 & 0.0482 \\ 0.0216 & 0.0036 & 0.0009 \\ 0.0126 & 0.0027 & 0.0001 \\ 0.0264 & 0.0057 & 0.0010 \\ 0.0198 & 0.0045 & 0.0128 \\ 0.0270 & 0.0033 & 0.0113 \\ 0.3855 & 0.0039 & 0.0003 \\ 0.0468 & 0.0042 & 0.0028 \end{bmatrix} \qquad \text{(Eq. 25d)}$$

with a sample mean of:

$$\bar{Y} = \frac{1}{N}\left(\sum_{i=1}^{N} Y_i\right) = \frac{1}{20}\left(\begin{bmatrix} 0.408 \\ 0.1062 \\ 0.0272 \end{bmatrix}\right.$$

$$\left. + \begin{bmatrix} 0.2832 \\ 0.2916 \\ 0.0332 \end{bmatrix} + \cdots + \begin{bmatrix} 0.0468 \\ 0.0042 \\ 0.0028 \end{bmatrix}\right) = \begin{bmatrix} 0.1535 \\ 0.0926 \\ 0.0320 \end{bmatrix} \quad \text{(Eq. 26)}$$

The sample variance–covariance matrix is:

$$S = \frac{1}{N-1}\sum_{i=1}^{N} (Y_i - \bar{Y})(Y_i - \bar{Y})' \qquad \text{(Eq. 27a)}$$

$$S = \frac{1}{19}\sum_{i=1}^{20} (Y_i - \bar{Y})(Y_i - \bar{Y})' \qquad \text{(Eq. 27b)}$$

$$S = \begin{bmatrix} 0.2505 \times 10^{-1} & 0.1529 \times 10^{-1} & 0.3910 \times 10^{-2} \\ 0.1529 \times 10^{-1} & 0.1520 \times 10^{-1} & 0.4126 \times 10^{-2} \\ 0.3910 \times 10^{-2} & 0.4126 \times 10^{-1} & 0.2032 \times 10^{-2} \end{bmatrix}$$

$$\text{(Eq. 27c)}$$

$$S^{-1} = \begin{bmatrix} 0.1040 \times 10^3 & -0.112 \times 10^3 & 0.2733 \times 10^2 \\ -0.1120 \times 10^3 & 0.2673 \times 10^3 & -0.3271 \times 10^2 \\ 0.2733 \times 10^2 & -0.3271 \times 10^3 & 0.1104 \times 10^4 \end{bmatrix}$$

$$\text{(Eq. 28)}$$

$$T^2 = N(\bar{Y} - \mu_0)'S^{-1}(\bar{Y} - \mu_0) \qquad \text{(Eq. 29a)}$$

$$T^2 = 20 \times \left(\begin{bmatrix} 0.1535 \\ 0.0926 \\ 0.0320 \end{bmatrix} - \begin{bmatrix} 0.12 \\ 0.06 \\ 0.02 \end{bmatrix}\right)' S^{-1} \left(\begin{bmatrix} 0.1535 \\ 0.0926 \\ 0.0320 \end{bmatrix} - \begin{bmatrix} 0.12 \\ 0.06 \\ 0.02 \end{bmatrix}\right)$$

$$\text{(Eq. 29b)}$$

$$T^2 = 20 \times [0.0335 \quad 0.0326 \quad 0.0120]\, S^{-1} \begin{bmatrix} 0.0335 \\ 0.0326 \\ 0.0120 \end{bmatrix} \qquad \text{(Eq. 29c)}$$

$$T^2 = 20 \times 0.0811 \qquad \text{(Eq. 29d)}$$

$$T^2 = 1.6217 \qquad \text{(Eq. 29e)}$$

$$T^2_{0.05(3,19)} = 10.729 > 1.6217 \qquad \text{(Eq. 30)}$$

Thus, H_0 was accepted.

Table II gives the results of the sampling technique test. Comparison of the data in Tables I and II indicates that the smaller the difference in the mean vector from the initial composition, the larger the Hotelling statistic value is. As the mixing time increased, the Hotelling statistic

Table II—Test of the Sampling Technique

Mixing Time, min	Hotelling's T^2	Acceptance of H_0	Variance–Covariance			Determinant
1	1.6217	Yes	0.2505×10^{-1}	0.1529×10^{-1}	0.3910×10^{-2}	0.1333×10^{-6}
			0.1529×10^{-1}	0.1520×10^{-1}	0.4126×10^{-2}	
			0.3910×10^{-2}	0.4126×10^{-2}	0.2032×10^{-2}	
15	1.1159	Yes	0.7064×10^{-3}	0.7618×10^{-3}	0.1843×10^{-3}	0.455×10^{-11}
			0.7618×10^{-3}	0.9299×10^{-3}	0.2036×10^{-3}	
			0.1843×10^{-3}	0.2036×10^{-3}	0.1078×10^{-3}	
25	3.0466	Yes	0.3323×10^{-4}	0.2648×10^{-4}	0.5387×10^{-5}	0.111×10^{-14}
			0.2648×10^{-4}	0.3584×10^{-4}	0.4664×10^{-5}	
			0.5387×10^{-4}	0.4664×10^{-5}	0.3148×10^{-5}	
35	0.8262	Yes	0.3397×10^{-4}	0.2159×10^{-4}	0.7391×10^{-5}	0.1496×10^{-14}
			0.2159×10^{-4}	0.2563×10^{-4}	0.1849×10^{-5}	
			0.7391×10^{-5}	0.1849×10^{-5}	0.599×10^{-5}	
45	8.4767	Yes	0.2319×10^{-5}	-0.4899×10^{-7}	0.5543×10^{-6}	0.1263×10^{-16}
			-0.4899×10^{-7}	0.5282×10^{-5}	0.8504×10^{-6}	
			0.5543×10^{-6}	0.8504×10^{-6}	0.1304×10^{-5}	
55	5.2375	Yes	0.2608×10^{-5}	-0.3062×10^{-6}	0.6129×10^{-6}	0.3022×10^{-16}
			-0.3062×10^{-6}	0.3571×10^{-5}	-0.7514×10^{-6}	
			0.6129×10^{-6}	-0.7514×10^{-6}	0.3552×10^{-6}	
65	1.8884	Yes	0.2750×10^{-5}	0.3027×10^{-6}	-0.8375×10^{-7}	0.3558×10^{-16}
			0.3027×10^{-6}	0.1077×10^{-4}	-0.2977×10^{-6}	
			-0.8375×10^{-7}	-0.2977×10^{-6}	0.1215×10^{-5}	
75	31.2681	No	0.5323×10^{-5}	0.4861×10^{-5}	0.9437×10^{-6}	0.1343×10^{-17}
			0.4861×10^{-5}	0.8507×10^{-5}	0.8758×10^{-6}	
			0.9437×10^{-6}	0.8758×10^{-6}	0.2293×10^{-6}	
90	7.5040	Yes	0.1832×10^{-4}	0.4772×10^{-5}	0.1489×10^{-5}	0.1295×10^{-15}
			0.4772×10^{-5}	0.1092×10^{-4}	0.2353×10^{-5}	
			0.1489×10^{-5}	0.2353×10^{-5}	0.1251×10^{-5}	

value increased so that a value of 31.268 was obtained at 75 min. This finding resulted in the rejection of the null hypothesis, indicating that the sample mean is not equal to the theoretical composition. However, the data at 75 min of mixing indicated that the sample mean was very close to the theoretical mean. If it is assumed that:

$$y_1 = y_2 = y_3 \ldots y_{20} \qquad \text{(Eq. 31)}$$

then:

$$Y_i = \overline{Y} \qquad \text{(Eq. 32)}$$

This leads to a variance–covariance of zero. Hence, T^2 is infinitely large and the Hotelling statistic T^2 would be $>>> T^2_{\alpha(p,n-1)}$. Hence, the null hypothesis ($\mu = \mu_0$) would be rejected at any given μ_0 except when $\mu_0 = \mu$.

This procedure leads to the conclusion that when there is small variance between 20 samples, the small differences between the sample mean vector and the theoretical mean (μ_0) would tend to reject the null hypothesis when it should accept it. This result also could be due to the interactions between the mix components and the mixer, which were not accounted for in this analysis.

Thus, the Hotelling statistics is sensitive to small errors introduced in the theoretical composition of the three components during weighing, which could lead to false rejection of the best time points in evaluating powder homogeneity.

At early time points, the significant differences between the sample mean and theoretical mean were offset by the large value of the determinant of the variance–covariance matrix, leading to acceptance of the null hypothesis.

Table III—Test of Completely Segregated and Completely Random State

Mixing Time, min	Statistic X		Statistic X	
	Random State	Rejection of H_0	Segregated State	Rejection of H_0
1	0.548×10^{13}	Yes	0.9114×10^2	Yes
15	0.2585×10^{12}	Yes	0.2846×10^3	Yes
25	0.9852×10^{10}	Yes	0.4504×10^3	Yes
35	0.9493×10^{10}	Yes	0.4444×10^3	Yes
45	0.1520×10^{10}	Yes	0.5399×10^3	Yes
55	0.2194×10^{10}	Yes	0.5225×10^3	Yes
65	0.2286×10^{10}	Yes	0.5192×10^3	Yes
75	0.1883×10^{10}	Yes	0.5847×10^3	Yes
90	0.3710×10^{10}	Yes	0.4934×10^3	Yes

To test for the completely random state after 1 min of mixing, Eq. 18 gives:

$$\Sigma_r = \frac{1}{4.275 \times 10^{11}} \begin{bmatrix} 0.12 \times 0.88 & -0.12 \times 0.06 & -0.12 \times 0.02 \\ -0.06 \times 0.12 & 0.06 \times 0.94 & -0.06 \times 0.02 \\ -0.02 \times 0.12 & -0.06 \times 0.02 & 0.02 \times 0.98 \end{bmatrix}$$

$$\text{(Eq. 33a)}$$

$$\Sigma_r = \begin{bmatrix} 2.47 \times 10^{-13} & -1.68 \times 10^{-14} & -5.61 \times 10^{-15} \\ -1.68 \times 10^{-14} & 1.32 \times 10^{-13} & -2.81 \times 10^{-15} \\ -5.61 \times 10^{-15} & -2.81 \times 10^{-15} & 4.58 \times 10^{-14} \end{bmatrix} \quad \text{(Eq. 33b)}$$

To investigate if a completely random state was reached after 1 min of mixing at 60 rpm, the null hypothesis H_0 is tested:

$$\Sigma = \Sigma_r = \begin{bmatrix} 2.47 \times 10^{-13} & -1.68 \times 10^{-14} & -5.61 \times 10^{-15} \\ -1.68 \times 10^{-14} & 1.32 \times 10^{-13} & -2.81 \times 10^{-15} \\ -5.61 \times 10^{-15} & -2.81 \times 10^{-15} & 4.58 \times 10^{-14} \end{bmatrix} \quad \text{(Eq. 34)}$$

against the alternative hypothesis H_1 ($\Sigma \neq \Sigma_r$).
From Eq. 12b:

$$X = 3 \times 20 \times (\ln 20 - 1) - 20 \times \ln |B\Sigma_0^{-1}| + tr(B\Sigma_0^{-1}) \quad \text{(Eq. 35)}$$

and:

$$x^2_{0.05} \left(\frac{3(3+1)}{2} \right) = 12.6 \quad \text{(Eq. 36)}$$

since:

$$X = 0.548 \times 10^{13} > 12.6 \quad \text{(Eq. 37)}$$

the null hypothesis is rejected, and the mixture did not attain a completely random state after 1 min of mixing at a significance level of 0.05.

To test for the completely segregated state from Eqs. 19 and 20:

$$\Sigma_s = \begin{bmatrix} 0.1056 & -0.0072 & -0.0024 \\ -0.0072 & 0.0564 & -0.0012 \\ -0.0024 & -0.0012 & 0.0196 \end{bmatrix} \quad \text{(Eq. 38)}$$

To investigate if the mixture remained completely segregated after

Table IV—Comparisons between Univariate and Multivariate Mixing Indexes

Mixing Time, min	Univariate (Eq. 42)	Multivariate (Eq. 22)
1	0.61	0.2901
	0.64	
	0.66	
15	0.71	0.4606
	0.72	
	0.74	
25	0.79	0.5619
	0.80	
	0.83	
35	0.79	0.5586
	0.81	
	0.81	
45	0.85	0.6094
	0.84	
	0.85	
55	0.845	0.6005
	0.85	
	0.83	
65	0.84	0.5988
	0.83	
	0.85	
75	0.83	0.6319
	0.83	
	0.88	
90	0.80	0.5852
	0.83	
	0.85	

1 min of mixing, the null hypothesis H_0 is tested:

$$\Sigma = \Sigma_s = \begin{bmatrix} 0.1056 & -0.0072 & -0.0024 \\ -0.0072 & 0.0564 & -0.0012 \\ -0.0024 & -0.0012 & 0.0196 \end{bmatrix} \quad \text{(Eq. 39)}$$

against the alternative hypothesis H_1 ($\Sigma \neq \Sigma_s$).
    Equation 12b gives:

$$X = 0.9114 \times 10^2 \quad \text{(Eq. 40)}$$

since:

$$X = 0.914 \times 10^2 > 12.6 \quad \text{(Eq. 41)}$$

The null hypothesis H_0 is rejected.
    Table III gives the results of these two states as a function of mixing time. At early mixing times, the value of the X statistics for testing complete randomness decreased. At later mixing times, a major change in X statistics did not occur, indicating that the powder system used in this study was unable to reach a completely random state. This finding confirms earlier (11, 14) results that cohesive powders do not reach a state of complete randomness.

For testing the segregation state, the X statistics also increased at the initial mixing times. After 1 min of mixing, segregation tendency was not observable (Table III). Wang et al. (10) showed that large spherical particles segregated after 2 min of mixing. Thus, the segregation tendency is largely dependent on the physical properties of the system.
    The results of the mixing index of Ashton and Valentin (6) were reported previously (11). This mixing index based on univariate statistical analysis (Eq. 42) is similar to that proposed by Wang et al. (10), which is based on multivariate analysis (Eq. 22):

$$M_u^2 = \frac{\ln \sigma_0^2 - \ln S^2}{\ln \sigma_0^2 - \ln \sigma_r^2} \quad \text{(Eq. 42)}$$

where σ_0^2, S^2, and σ_r^2 are the variances in the initial, intermediate, and ultimate random conditions, respectively.
    Comparisons of the mixing indexes based on univariate and multivariate analyses are given in Table IV. The powders in the multicomponent heterogeneous system interact with each other and are affected by other components before an optimized mixed state is reached. The interparticular dependency among the particles of each component was considered through the variance–covariance matrix, and the results were a scalar quantity instead of the three individual quantities. Due to the interparticular forces among the small cohesive particles, the resulting multivariate mixing index is expected to be smaller than the univariate mixing indexes of individual components. The values of both mixing indexes increased with mixing time until there was a very small change. The results suggest that an optimized mixing time was ~45–55 min, which is consistent using both approaches.

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