

## Simulated ordered powder mixture

Felix K.Y. Lai <sup>1</sup> and John A. Hersey <sup>2,†</sup>

<sup>1</sup> Department of Pharmaceutics, Howard University, Washington, DC 20059 (U.S.A.) and <sup>2</sup> Victorian College of Pharmacy, Parkville, Vic. 3052 (Australia)

(Received 27 May 1986)

(Modified version received 7 November 1986)

(Accepted 17 November 1986)

**Key words:** Ordered mixture; Coarse-fine mixture; Adsorbent; Carrier; Computer simulation; Standard deviation; Sample size relationship; Size; Size distribution

### Summary

A computer simulation of ordered powder mixing has been carried out in order to ascertain the properties of ordered mixtures independently of errors associated with sampling and assay. The effect of sample size on the standard deviation of sample concentration has been ascertained for a variety of simulated mixes of various carrier particle sizes and particle size distributions. Excepting the case where the carrier particles are monosized, an inverse relationship between sample standard deviation and the square-root of sample size is found in all cases. This is identical to the situation when a random powder mix is formed. Thus distinguishing between ordered and random mixtures must be based on other factors, i.e. interparticulate interaction, degree of homogeneity and segregation tendencies. The standard deviation sample size relationship is not, as previously thought, a useful criterion for ordered mixtures. Only when the carrier is monosized is the theoretical independent relationship of standard deviation with sample size observed as demonstrated with ideal ordered mixtures. The results showed that for real ordered powder mixtures, the carrier particle size should be as large as possible within other technological constraints and of narrow size range in order to prepare homogeneous dose forms.

### Introduction

Powder mixing is one of the major unit operations in pharmaceutical manufacturing. Unfortunately pharmaceutical powder mixing is also one of the least investigated processes. Most of the available literature on powder mixing deals with mixing of non-pharmaceutical ingredients and in most cases, deals with random mixtures. Random

mixtures can be achieved only when the powders being mixed are free-flowing and non-interacting. However, most pharmaceutical powder mixtures do not fall into the criteria of random mixture and contain interacting and non-free-flowing ingredients. Hence, the concept of ordered mixing was proposed (Hersey, 1976) to explain powder mixing of cohesive or interacting fine powders.

The simplest ordered powder mixture is a coarse-fine particulate mixture in which the fine particles, the adsorbents, adhere to the coarser particles, the carriers. Several experimental methods have been developed to assess whether an ordered coarse-fine particulate mixture has been

<sup>†</sup> Deceased.

Correspondence: F.K.Y. Lai, Department of Pharmaceutics, Howard University, Washington, DC 20059, U.S.A.

formed. One of such methods is examining the powder mixture under an electron microscope to determine the degree of adhesion between the fine and coarse powders (Crooks and Ho, 1976). The electron microscopy method is tedious and requires expansive equipment; moreover, the preparation procedure of the sample for electron microscopy may introduce artifacts into the results. A simpler sieving method (Yip and Hersey, 1977a) was introduced in which the ordered mixture is sifted using a mesh size through which the fine powder but not the coarse powder can pass. The fine powders of a coarse-fine ordered mixture do not pass through the sieve because of their interaction with the coarse particles. So far the method of sifting has not been standardized and attrition of the powders during sifting may introduce erroneous results.

Another method of assessing ordered mixtures was proposed by Yeung and Hersey (1979). They suggested that an ordered mixture is formed if the standard deviation of samples of the mixture is a constant and independent of the sizes of the samples taken. The standard deviations of different samples of the microfine salicylic acid/coarse lactose powder mixtures they investigated seemed to confirm the independency of sample standard deviations and sample sizes for an ordered mixture. However, Orr (1979) suggested an alternate explanation to the independency relationship. He argued that the actual relationship between sample standard deviation and sample size was being masked by the large standard errors due to sampling and analytical procedures. However, Orr did not propose what the actual relationship is. The present investigation attempts to use computer simulation to determine the actual relationship between sample standard deviations and sample sizes for a coarse-fine ordered mixture. Computer simulation of ordered powder mixtures has the advantage of assessing the properties of a powder mixture without being affected by the dependent phenomena associated with real systems. The results generated by the computer simulation also give an insight to pharmaceutical powder mixing of what powder mixture properties will result if the size and size distribution of the carrier particle of ordered powder mixture are being altered.

## Theory

The adsorbent particles were assumed to be much smaller than the carrier particles in size and there was no 'interbridge adhesion' of adsorbent particles with more than one carrier particle. Both theoretical and experimental particle size distributions in literature have been reported mostly to be log normal either by weight (Mehta et al., 1977) or by number (Carstensen and Patel, 1975; Carstensen and Rodriguez-Hornedo, 1985). In this study, the carrier particles were spherical particles, where  $(R_c)_i$  is the radius of the  $i^{\text{th}}$  carrier particle, whose sizes were assumed to be log-normally (by weight) distributed. The adsorbent particles were monosized spherical particles of radius,  $R_a$ . The respective densities of carrier and adsorbent components were  $\rho_c$  and  $\rho_a$ .

For a particular ordered system, 0.1% w/w microfine salicylic acid and crystalline sugar mixture, experiments have shown (Yip and Hersey, 1976) that the percentage coverage of the surface of carrier sugar particles by the salicylic acid particles is a constant and equal to approximately 2.5%. In the current work, this constancy in percentage coverage of the carrier particle surface by adsorbent particles was assumed, as a constant  $A$  (where  $A \leq 1$ ). Hence, the number of adsorbent particles  $(N_a)_i$  adhering to the  $i^{\text{th}}$  carrier particle is:

$$(N_a)_i = \frac{4A\pi(R_c)_i^2}{\pi R_a^2} \\ = \frac{4A(R_c)_i^2}{R_a^2} \quad (1)$$

The corresponding mass of adsorbent particles,  $(M_a)_i$  adhering to the  $i^{\text{th}}$  carrier particle is

$$(M_a)_i = (N_a)_i \frac{4}{3}\pi R_a^3 \rho_a \quad (2)$$

When a number of carrier particles is taken until their total weight equals approximately the nominal sample size,  $W$ , the sample concentration of the adsorbent component (in w/w unit) is calculated from the equation,

$$C_j = \frac{\sum_i (M_a)_i}{W_j} \quad (3)$$

$$W \cong W_j = \sum_i \frac{4}{3} \pi (R_c)_i^3 \rho_c \quad (3)$$

where  $W_j$  is the sample weight of the  $j^{\text{th}}$  sample and equals approximately the nominal sample size,  $W$ ;  $C_j$  is the concentration (in w/w unit) of the adsorbent component in the  $j^{\text{th}}$  sample. Eqn. 3 is simplified as:

$$C_j = \frac{K \sum_i (R_c)_i^2}{\sum_i (R_c)_i^3} \quad (4)$$

where  $K = 4A\rho_a R_a / \rho_c$  and is a constant for the current system which has constant percentage coverage of carrier particle surface,  $A$ , with monosized adsorbent particles,  $R_a$ .

## Experimental

The ideal ordered mixture was simulated according to the above theory. A Control Data Corporation CYBER 73 (96K) computer was used for the simulation. The computer program for the simulation which was written in Fortran language is shown schematically as a flow chart in Fig. 1.

The weight of the carrier particles, which had a log-normality of the size distribution was made possible by generating a set of Z-scores and using the logarithms of the mean carrier particle size,  $\mu$  and the standard deviation of the carrier particle size distribution,  $\sigma$ . Mathematically the random generation of particle weight, which has a log-normal size distribution, is described by the following Eqns. 5 and 6:

$$Z = \frac{x - \log \mu}{\log \sigma} \quad (5)$$

where  $Z$  is the randomly generated Z-score,  $x$  is the random number which is log normally distributed,  $\mu$  is the mean particle size of the carrier

particles, and  $\sigma$  is the standard deviation of the carrier particle size distribution. Hence, the weight of a carrier particle is:

$$W_c = 10^x \quad (6)$$

A number of carrier particles were taken until the total weight of carrier particles just exceeded the nominal sample weight. For each size distribution of carrier particles (which was characterized by  $\mu$  and  $\sigma$ ), 20 samples of 10 different nominal sample sizes were simulated.

The sample standard deviation at each sample size was calculated using  $C_j$  as defined by Eqn. 3. The percentage coverage,  $A$ , the densities of the carrier and the adsorbent components,  $\rho_c$  and  $\rho_a$  in Eqn. 3 were constants and assumed a value of unity to simplify the calculation.

The standard deviation-sample size relationship of an ordered system was investigated in three different conditions which are of practical interest.

(A) *Varying the size range of the carrier particles.* The standard deviation-sample size relationship of an ideal ordered mixture was investigated, whose carrier particles had the following combination of mean particles size,  $\mu$  and standard deviation of carrier particle size distribution,  $\sigma$ .

- (1)  $\mu = 10, \sigma = 1.86$  (corresponding to a size range 1–100)
- (2)  $\mu = 31.48, \sigma = 1.34$  (corresponding to a size range 10–100)
- (3)  $\mu = 31.48, \sigma = 1.23$  (corresponding to a size range 14–70)
- (4)  $\mu = 31.48, \sigma = 0.00$  (corresponding to monosized carrier particle)

(B) *Varying the standard deviation of carrier particle size distribution,  $\sigma$ , while keeping the mean carrier particle size,  $\mu$ , constant.* The effects of the standard deviation-sample size relationship were investigated with various standard deviations of the carrier particle size distribution whose values ranged from  $10^{-4}$  to  $10^{-1}$  (in weight units). The mean particle sizes investigated were 31.48 and 314.8 (in weight units), respectively.

(C) *Varying the mean carrier particle size while keeping the standard deviation of the carrier particle*

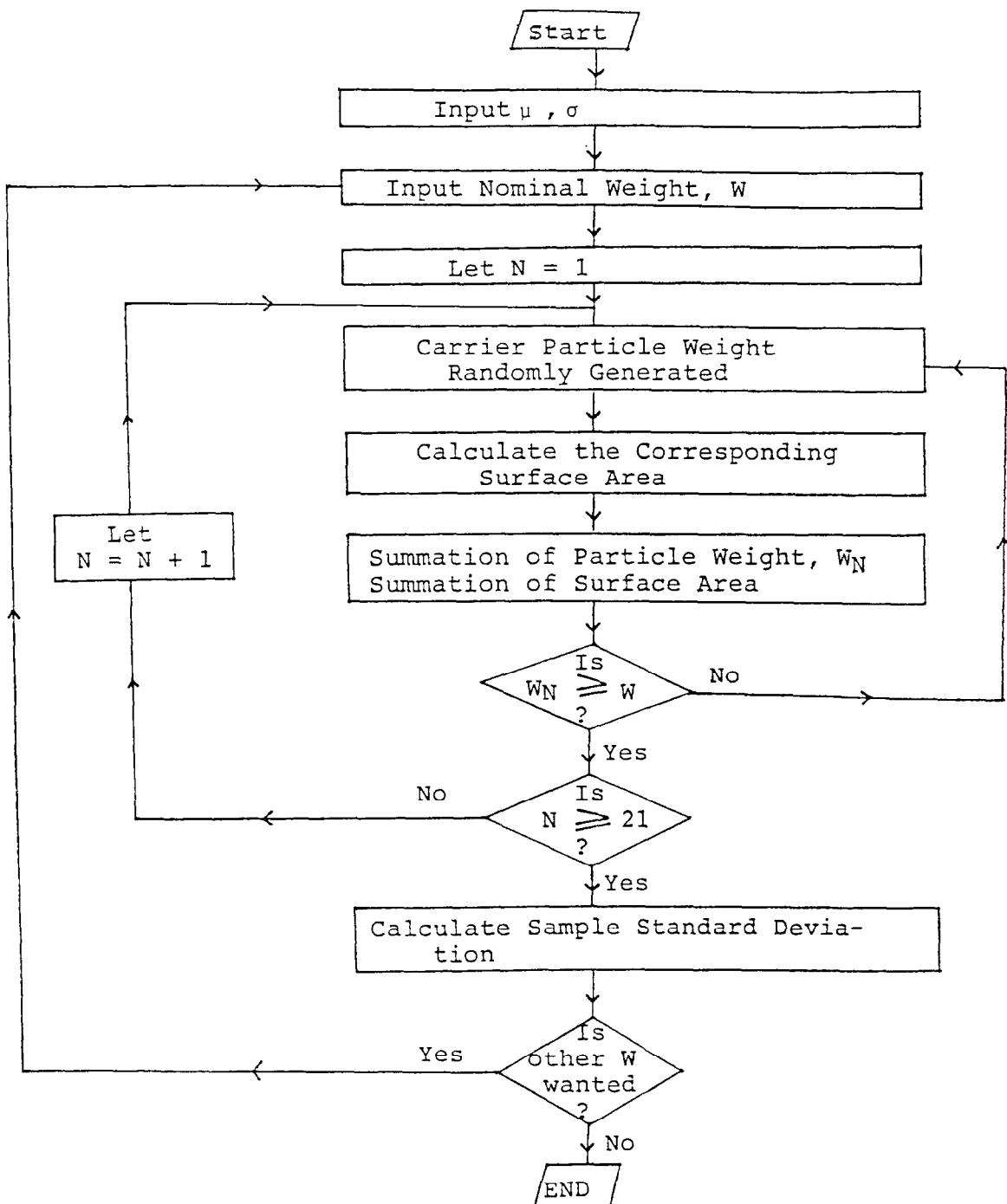


Fig. 1. Schematic representation of the computer simulation program.

size distribution constant at a value,  $10^{-4}$ . The effects on the standard deviation–sample size relationship were investigated with various mean carrier particle sizes whose values ranged from 10 to 1000. The nominal sample weight was changed proportionally with mean carrier particle. For example, when the mean carrier particle size was changed from 10 to 1000, the sample weight, 100 (in weight unit) was changed to 10,000 (in weight units). The changes in nominal sample weight with mean size were anticipated to allow a fair assessment of the effects of varying mean particle size, which eliminates the effects of changes in the number of particles per sample.

## Results

Fig. 2 shows that an increase in carrier particle size range correspondingly increased the sample standard deviation. When monosized carrier particles (i.e.  $\sigma = 0$ ) were used, the sample standard deviation was independent of sample sizes and equated to a value of zero, i.e. a perfectly uniform mixture.

Tables 1 and 2 show that for a given sample size, the ratio of sample standard deviation to the logarithms of standard deviation of carrier particle size distribution,  $\sigma$ , is a constant at the 90% confidence level. The aforementioned observation suggests that the sample standard deviation and  $\log(\sigma)$  are proportionally related.

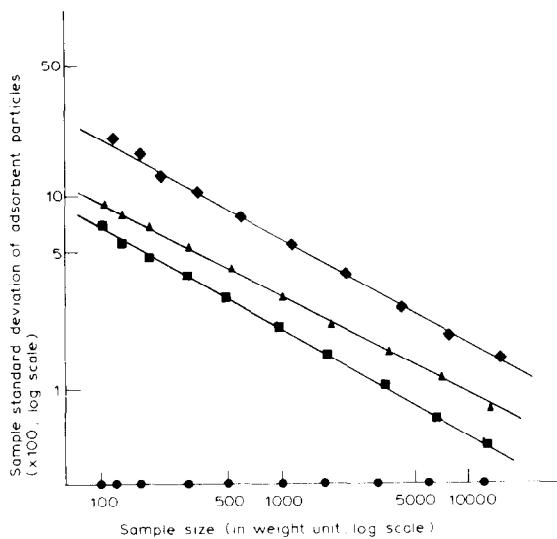
Table 3 demonstrates no simple relationship

TABLE 1

*The ratio of the sample standard deviation to the logarithm of standard deviation of carrier particle size distribution  $\sigma$ , with the corresponding lower and upper 90% confidence limits which are separated by a comma*

Mean carrier particle size = 31.48 (in weight unit).

Sample size	$\sigma$			
	0.1	0.01	0.001	0.0001
100	0.621	0.568	0.549	0.566
	0.483, 0.820	0.442, 0.750	0.427, 0.724	0.440, 0.747
150	0.475	0.500	0.573	0.500
	0.369, 0.627	0.389, 0.660	0.445, 0.757	0.389, 0.660
200	0.443	0.445	0.405	0.445
	0.345, 0.565	0.346, 0.588	0.315, 0.535	0.346, 0.588
300	0.390	0.349	0.394	0.348
	0.303, 0.515	0.271, 0.461	0.306, 0.520	0.271, 0.459
600	0.265	0.263	0.260	0.249
	0.206, 0.350	0.205, 0.347	0.202, 0.343	0.194, 0.329
1 000	0.226	0.205	0.189	0.216
	0.176, 0.298	0.159, 0.271	0.147, 0.250	0.168, 0.285
2 000	0.133	0.123	0.133	0.133
	0.103, 0.176	0.096, 0.162	0.103, 0.176	0.103, 0.176
4 000	0.113	0.102	0.102	0.103
	0.088, 0.149	0.079, 0.135	0.079, 0.135	0.080, 0.136
8 000	0.071	0.073	0.063	0.070
	0.055, 0.094	0.057, 0.096	0.049, 0.083	0.054, 0.092
15,000	0.052	0.049	0.051	0.048
	0.040, 0.069	0.038, 0.065	0.040, 0.067	0.037, 0.063



exists between the sample standard deviation and mean carrier particle size. But in general, an increase in mean particle size,  $\mu$ , decreases the sample standard deviation.

Fig. 2 shows that the logarithm of sample size and the logarithm of the sample standard deviation are linearly related with a slope of an ap-

Fig. 2. The variance-sample size relationship of ideal ordered mixtures which have the following combination of mean particle size,  $\mu$ , and standard deviation of carrier particle size distribution,  $\sigma$ .

- ◆:  $\mu = 10.00$ ;  $\sigma = 1.86$  (slope  $-0.532$ ; correlation coefficient  $-0.997$ )
- ▲:  $\mu = 31.48$ ;  $\sigma = 1.34$  (slope  $-0.509$ ; correlation coefficient  $-0.998$ )
- :  $\mu = 31.48$ ;  $\sigma = 1.23$  (slope  $-0.510$ ; correlation coefficient  $-0.999$ )
- :  $\mu = 31.48$ ;  $\sigma = 0.00$  (slope  $0$ ; coefficient  $1.000$ )

TABLE 2

*The ratio of the sample standard deviation to the logarithm of standard deviation of carrier particle size distribution  $\sigma$ , with the corresponding lower and upper 90% confidence limits which are separated by a comma*

Mean carrier particle size = 314.8 (in weight unit).

Sample size	$\sigma$			
	0.1	0.01	0.001	0.0001
1 000	0.269	0.264	0.263	0.278
	0.224, 0.380	0.205, 0.349	0.205, 0.347	0.216, 0.327
1 500	0.221	0.232	0.232	0.259
	0.172, 0.292	0.180, 0.306	0.180, 0.306	0.201, 0.342
2 000	0.206	0.207	0.207	0.230
	0.160, 0.272	0.161, 0.273	0.161, 0.273	0.179, 0.303
3 000	0.181	0.162	0.162	0.161
	0.141, 0.239	0.126, 0.214	0.126, 0.214	0.125, 0.213
6 000	0.123	0.122	0.116	0.117
	0.096, 0.162	0.094, 0.161	0.090, 0.153	0.091, 0.154
10,000	0.105	0.095	0.100	0.096
	0.082, 0.139	0.074, 0.125	0.078, 0.132	0.075, 0.127
20,000	0.062	0.057	0.062	0.062
	0.048, 0.082	0.044, 0.075	0.048, 0.082	0.048, 0.082
40,000	0.052	0.047	0.048	0.046
	0.040, 0.069	0.037, 0.062	0.037, 0.063	0.063, 0.061
80,000	0.033	0.034	0.032	0.033
	0.026, 0.045	0.026, 0.045	0.025, 0.042	0.026, 0.044
150,000	0.024	0.023	0.022	0.024
	0.019, 0.032	0.018, 0.030	0.017, 0.029	0.019, 0.032

TABLE 3

*The sample standard deviation ( $\times 10^5$ ) at different sample sizes of an ideal mixture with different mean carrier size distribution, but with a constant standard deviation of carrier size distribution,  $10^{-4}$*

Nominal sample size <sup>a</sup>	Mean carrier particle size (in weight units)			
	10	100	1000	10,000
100	5.379	2.497	1.159	0.438
150	3.763	1.747	0.883	0.387
200	3.708	1.721	0.833	0.439
300	3.032	1.408	0.653	0.315
600	2.018	0.937	0.435	0.202
1000	1.796	0.834	0.387	0.180
2000	1.331	0.618	0.287	0.133
4000	0.831	0.386	0.179	0.083
8000	0.583	0.271	0.126	0.058
15,000	0.443	0.206	0.096	0.044

<sup>a</sup> The nominal sample size is the sample size for the ideal ordered mixture with mean carrier particle size, 10, the sample size for mixture with different mean carrier particle size is changed proportionally (see text).

proximated value,  $-0.5$ , with the exception of sample standard deviation at value zero when the logarithm of sample standard deviation is mathematically undefined. In linear terms, there is an inverse linear relationship between sample standard deviation and the square-root of sample size.

## Discussion

The above results suggest that there is an inverse relationship between sample standard deviation and the square-root of sample size, excepting when the sample standard deviation is zero, when it is independent of sample size. Also sample standard deviation increases with larger size range of carrier particles, and sample standard deviation decreases with larger mean carrier particle size. Thus the empirical relationship of the coarse-fine ordered mixture investigated is similar to the standard deviation-sample size relationship of a random mixture (Lacey, 1953). The present results seem to confirm Orr's (1979) belief that the sample standard deviation is not independent of the sample size for an ordered mixture. The empirical relationship between sample size and standard

deviation can be used for extrapolating the standard deviation-sample size relationship to the required sample size. This extrapolation is possible only when the trend of the standard deviation-sample size is not masked by large experimental errors.

A wide size range of carrier particles has been suggested to cause 'ordered unit segregation' which subsequently leads to a less homogeneous ordered mixture (Yip and Hersey, 1977b). The above relationship suggests that even in the absence of 'ordered unit segregation', the homogeneity of an ordered mixture can be decreased by simply using a large size range of carrier particles. A narrow size range of carrier particles has dual advantages of both increasing the homogeneity and maintaining that homogeneity by avoiding 'ordered unit segregation', while monosized carrier particles will produce a perfectly uniform mixture.

For an ideal ordered mixture, Eqn. 4 shows that the sample concentration, from which the sample standard deviation is calculated, is a measure of the ratio of the total surface area in a sample to the sample weight. For a given size (with respect to the number of carrier particles), the total surface area of carrier particles is smaller with larger mean carrier particle size. Hence, the standard deviation is anticipated to decrease with larger mean carrier particle size, which is consistent with the observed empirical relationship.

In summary an inverse linear relationship between sample standard deviation and the square-root of sample size was observed in the computer simulation of a coarse-fine ordered mixture. The results also suggest that a more homogeneous mixture is formed if the carrier particles have either a narrower size range or a larger mean size. These results may assist a pharmaceutical scientist to formulate an ordered mixture of high degree of homogeneity by paying attention to the effect of carrier particle size and size distribution on the final homogeneity of the mixture.

## Acknowledgement

The present work was completed as a partial fulfillment of the requirements of the Master of

Pharmacy degree (Victoria Institute of Colleges, Australia) of F.K.Y.L.

## References

Carstensen, J.T. and Patel, M., Dissolution patterns of polydisperse powders: oxalic acid dihydrate. *J. Pharm. Sci.*, 64 (1975) 1770-1776.

Carstensen, J.T. and Rodriguez-Hornedo, N., Expected particle size distributions of crystals produced from nonisothermal recrystallization. *J. Pharm. Sci.*, 74 (1985) 1322-1326.

Crooks, M.J. and Ho, R., Ordered mixing in direct compression of tablets. *Powder Technol.*, 14 (1976) 161-167.

Hersey, J.A., Ordered mixing: A new concept in powder mixing practice. *Powder Technol.*, 11 (1975) 41-44.

Lacey, P.M.C., The mixing of solid particles. *Trans. Inst. Chem. Eng.*, 21 (1943) 53-59.

Metha, A., Adams, K., Zoglio, M.A. and Carstensen, J.T., Influence of granulation liquid flow rate on particle-size distribution in spray-granulated products. *J. Pharm. Sci.*, 66 (1977) 1462-1464.

Orr, N., Assessment of an ordered mix. *Powder Technol.*, 24 (1979) 105-107.

Yeung, C.C. and Hersey, J.A., Ordered powder mixing of coarse and fine particulate systems. *Powder Technol.*, 22 (1979) 127-131.

Yip, C.W. and Hersey, J.A., Ordered powder mixing. *Nature (London)*, 262 (1976) 202-203.

Yip, C.W. and Hersey, J.A., Powder mixing in a revolvo-cube mixer. *Aust. J. Pharm. Sci.*, 6 (1977a) 49-51.

Yip, C.W. and Hersey, J.A., Segregation in ordered powder mixtures. *Powder Technol.*, 16 (1977b) 149-150.