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Homogeneity of Multicomponent Powder Mixtures

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Abstract □ A new concept of homogeneity enables a numerical value to be attributed to the homogeneity, or "mixedness," of a given system. This concept was used to calculate the homogeneity of single ingredients in multicomponent, or compound, tablets and to trace the degree of mixing in two multicomponent mixtures. The relationship between homogeneity and a mixing index is mathematically derived.

Keyphrases □ Homogeneity of multicomponent powder mixtures —numerical calculation of homogeneity and degree of mixing, particle-size considerations □ Powder mixtures, multicomponent—numerical calculation of homogeneity and degree of mixing, particle-size considerations □ Mixing and homogeneity of multicomponent powders—calculation of homogeneity and mixing indexes, particle-size considerations

The operation of powder mixing is common to the manufacture of many formulations in the pharmaceutical industry. While the problems involved with powder mixtures were elucidated previously (1), further investigations have been concerned with the relatively simple system of binary mixtures (2, 3). In practice, such binary mixtures are of academic importance only, since the mixing of either a single drug or a number of drugs with a number of excipients is a more frequent occurrence in pharmacy. Two such multicomponent powder mixing operations were recently investigated (4, 5).

DISCUSSION

The criteria for adequate mixing of binary systems were reviewed (6). Indexes of powder mixing were described utilizing the standard deviation of the theoretically randomized mixture (σ_R) originally described by Lacey (7); for simple binary mixtures of homosized particles:

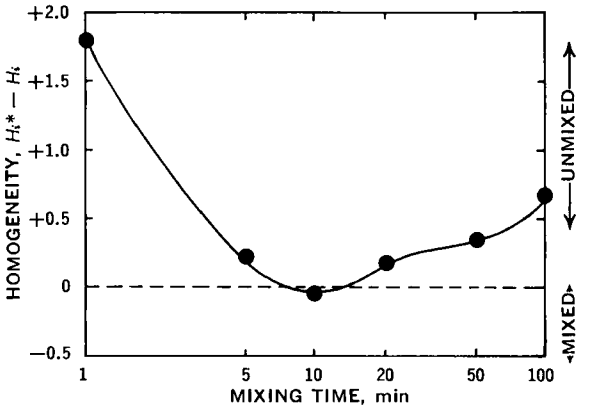

Figure 1—*Mixing of fenfluramine hydrochloride in Mixture A. Requirement for* H_i^* *is that 99.7% of the results (assuming a normal distribution) lie within 10% of the mean value.*

$$\sigma_R = (xy/N)^{1/2} \qquad \text{(Eq. 1)}$$

where x and y are the proportions of the two ingredients X and Y, and N is the number of particles per sample taken. Hersey (8–10) criticized such indexes for use in pharmacy since they are dependent upon the particle size and proportions of the components and are not related to the homogeneity of the systems under investigation. A more useful index for use in pharmacy was proposed, using as its criterion the desired degree of homogeneity as, for example, laid down by a pharmacopeial standard. An example of such a requirement would be that tablets containing 1% of an active ingredient should have contents within ±10% in 99.7% of the samples, assuming a normal distribution. The standard deviation (σ_A) corresponding to this requirement is given by:

$$\pm 3\sigma_A = \pm 10 \times 0.01 = (\text{tolerance} \times \text{mean}) \qquad \text{(Eq. 2)}$$

Such criteria can be used to assess the degree of powder mixing to a desired level [by plotting the standard deviation of an ingredient *(s)* for a number of samples taken from the mix] as a ratio of σ_A or to assess the homogeneity of a number of tablets taken after production from the batch.

Buslik (11) recently introduced a new concept of homogeneity of binary systems based on the weight of sample (W_1) necessary to give a fixed variation (*e.g.*, a standard deviation of 1%) between samples. The homogeneity *(H)* is then defined as the reciprocal of W_1:

$$H = \frac{1}{W_1} \qquad \text{(Eq. 3)}$$

The negative logarithm of W_1 is used to overcome the large range of values of homogeneity that could be found for H:

$$H_i = \log H = -\log W_1 \qquad \text{(Eq. 4)}$$

The percentage standard deviation (σ_B) of an ingredient *(G)* of particle weight w found from randomly mixed samples of weight W is given by (Eq. 1):

$$\sigma_B = [g(100 - g)w/W]^{1/2} \qquad \text{(Eq. 5)}$$

where g is the percentage weight of ingredient G, and w is the weight of all particles present in the mixture when σ_B = 1%; then $W = W_1$ and:

$$W_1 = g(100 - g)w \qquad \text{(Eq. 6)}$$

Substituting from Eq. 4:

$$H_i = -\log [g(100 - g)w] \qquad \text{(Eq. 7)}$$

By calculation of the required standard deviation according to Eq. 2 and assuming randomized mixing by analogy with Eq. 5:

$$\sigma_A = [g(100 - g)w/W]^{1/2} \qquad \text{(Eq. 8)}$$

Substituting in Eq. 7:

$$H_i^* = -\log [\sigma_A^2 W] \qquad \text{(Eq. 9)}$$

where H_i^* is the degree of homogeneity required by the pharmacopeial standard. By plotting the difference between H_i^* and H_t [the homogeneity during mixing found by evaluating the standard deviation *(s)* from a series of samples of weight W]:

$$H_i^* - H_i = -\log \sigma_A^2 W + \log s^2 W \qquad \text{(Eq. 10)}$$
$$= \log s^2 W/\sigma^2 W$$
$$= 2 \log (s/\sigma_A)$$

where s/σ_A is the same index of homogeneity previously proposed (8).

Equation 9 may also be used to calculate the desired degree of homogeneity of a number of pharmaceutical disperse systems and to calculate, using Eq. 8, the particle size *(w)* necessary to achieve that homogeneity.

The problem of dealing with real systems consisting of a particle distribution and of more than two ingredients complicates many of the previous findings. Work has been done to enable the calculation of the standard deviation of the completely randomized mixture for components having a distribution of particle sizes (12–14) and for multicomponent mixtures (15, 16), but the homogeneity of such systems has not been described.

Theory—The standard deviation (σ_P) of an ingredient *(P)* in a completely randomized mixture was calculated by Stange (15) to be given by:

$$\sigma_p^2 = \frac{p^2}{W}\left[\left(\frac{1-p}{p}\right)^2 p\sum(fw)_p + q\sum(fw)_q + r\sum(fw)_r \ldots\right] \qquad \text{(Eq. 11)}$$

where p, q, are r are the proportions of the ingredients P, Q, and R; $\Sigma(fw)$ is the effective mean particle weight of that ingredient denoted by the subscript and is calculated from the formula of Poole *et al.* (14); and W is the sample weight as before.

Assuming that the components must be reduced to the same particle-size level prior to mixing:

$$\sum(fw)_p = \sum(fw)_q = \sum(fw)_r = w \qquad \text{(Eq. 12)}$$

where w is the effective mean weight of all particles in the mixture.

Since $Q + R = 1 - P$ for the three-component systems, Eq. 11 reduces to:

$$\sigma_p^2 = wp(1 - p)/W \qquad \text{(Eq. 13)}$$

which is identical to Eq. 5 in percent terminology:

$$\sigma_{B_{(P)}} = [P(100 - P)w/W]^{1/2} \qquad \text{(Eq. 14)}$$

Similarly, for the other ingredients:

$$\sigma_{B_{(Q)}} = [Q(100 - Q)w/W]^{1/2} \qquad \text{(Eq. 15a)}$$

$$\sigma_{B_{(R)}} = [R(100 - R)w/W]^{1/2} \qquad \text{(Eq. 15b)}$$

When σ_B = 1%, then $W = W_1$ gives a different equation for the homogeneity of each of the four ingredients in the multicomponent mixture:

$$H_{i(p)} = -\log [P(100 - P)w] \qquad \text{(Eq. 16)}$$

etc. The equations can be used to follow the course of mixing of a single component in a mixing operation or to compare the various requirements of powders necessary for mixing to a desired degree of homogeneity in a multicomponent mixing operation.

Table I—Mixing of Fenfluramine Hydrochloride in Mixture A

Time (t), min	Standard Deviation of Fenfluramine Hydrochloride
1	0.0524
5	0.0086
10	0.0064
20	0.0089
50	0.0101
100	0.0147

Table II—Mixing of Barbiturates in Mixture B

Time (t), min	Standard Deviation		
	Phenobarbital	Butethal	Secobarbital
1	0.0310	0.0054	0.0042
2	0.0157	0.0017	0.0034
4	0.0060	0.0004	0.0002
8	0.0045	0.0006	0.0004
16	0.0044	0.0006	0.0008
32	0.0033	0.0005	0.0002
64	0.0058	0.0006	0.0004

Table III—Limiting Values of Homogeneity

Ingredient	Mixture	$H_{i\,\mathrm{lim}}$
Fenfluramine hydrochloride	A	2.53
Phenobarbital	B	3.00
Butethal	B	3.82
Secobarbital	B	3.84

Content Uniformity of a Compound Tablet—This is a problem of required homogeneity in a multicomponent system. Consider the three components P, Q, and R present in a 100-mg tablet at the 50, 5, and 0.5% levels, respectively. It is required that these percentages be present to within ±10% at the 99.7% level, assuming a normal distribution. From Eq. 2 for ingredient P:

$$\pm 3\sigma[A_{(P)}] = \pm 10 \times 0.05 \qquad \text{(Eq. 17}a\text{)}$$

$$3\sigma[A_{(P)}] = 0.5 \qquad \text{(Eq. 17}b\text{)}$$

Similarly, $3\sigma[A_{(Q)}] = 0.05$ and $3\sigma[A_{(R)}] = 0.005$. Substituting these values in Eq. 8 allows calculation of the effective mean particle weight (w) and, assuming spherical particles of density 1.2 g cm^{-3}, the calculation of the particle diameter:

$$d_{(P)} = 120.9\ \mu m \qquad \text{(Eq. 18}a\text{)}$$

$$d_{(Q)} = 26.1\ \mu m \qquad \text{(Eq. 18}b\text{)}$$

$$d_{(R)} = 5.6\ \mu m \qquad \text{(Eq. 18}c\text{)}$$

To achieve the required homogeneity, it would be necessary to reduce the particle sizes of the components to these levels. In practice, it would be difficult to mix particles of differing particle size and an overall reduction to 5 μm would be necessary. This would bring the assumption implicit in Eq. 12 into order and would result in greater homogeneity than necessary for components P and Q in the resulting tablets, providing the particles were randomly dispersed and did not show a tendency toward segregation.

Multicomponent Powder Mixing—Two examples of multicomponent powder mixing were recently described (4, 5). In each case the particle size of each component was determined by sieving, the densities were determined, and the powders were mixed in a mixer[1]. Mixture A consisted of 20% fenfluramine hydrochloride in a 100-mg sample containing a number of tablet excipients. Samples were removed from the mixer at various intervals and assayed spectrophotometrically. Mixture B consisted of three barbiturates (10% phenobarbital, 1% secobarbital, and 1% butethal) blended with lactose as the diluent in a 100-mg tablet preblend. Samples were removed as previously described and assayed using GLC with hexobarbital as an internal standard. The standard deviations *(SD)* calculated for each drug in the two mixtures are given in Tables I and II.

From a consideration of the particle-size data and densities, the effective mean particle diameters for each component in the two mixtures were calculated. Since in these practical situations the powders for each mixture are reduced to similar dimensions, it is possible using Eq. 16 to calculate the value of H_i for each drug. Substituting the desired degree of homogeneity (σ_A) and the standard deviation *(SD)* found in practice, it is then possible to trace the homogeneity of each drug as it is mixed throughout the mixture using $H_i^* - H_i$. Figure 1 shows this relationship for fenfluramine hydrochloride in Mixture A. In this case, limits of ±10% for 99.7% (*i.e.*, at the 3σ level of a normal distribution) were used. Figure 2 shows this same relationship for each barbiturate in Mixture B, where limits of ±15% for 95% (*i.e.*, at the 1.96σ level of a normal distribution) were chosen. When $H_i = H_i^*$, the position of desired homogeneity is attained. When $H_i < H_i^*$, the term $H_i^* - H_i$ becomes negative and the drug is mixed within specification—a desirable state since further processing (*e.g.*, tableting) may cause some degree of segregation (loss of homogeneity).

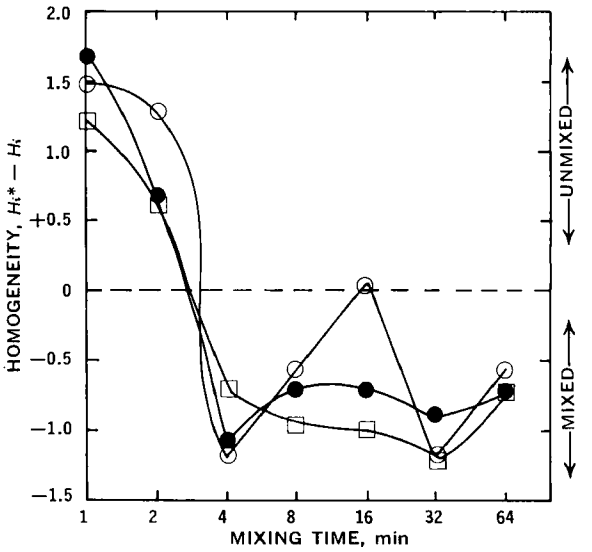

Figure 2—*Mixing of barbiturates in Mixture B. Requirement for* H_i^* *is that 95% of the results (assuming a normal distribution) lie within 15% of the mean. Key:* ●, *butethal;* ○, *secobarbital; and* □, *phenobarbital.*

According to the proportion of powder present in a mixture and its particle size, there will be a limiting homogeneity value which is possible to attain ($H_{i\,\mathrm{lim}}$), corresponding to the standard deviation of the randomized mixture (σ_R). It is essential if a powder is to be mixed within specification that $\sigma_A > \sigma_R$ or $H_i^* < H_{i\,\mathrm{lim}}$. Table III lists the $H_{i\,\mathrm{lim}}$ values for each active ingredient in the two mixtures. Figure 2 shows that the homogeneity of the different components does not follow the same pattern during the mixing process. Care should be taken when attempting to predict the homogeneity of a component from data on the homogeneity of another component in the same mixture.

CONCLUSION

The concept of homogeneity is useful for following the mixing of a drug or drugs in a multicomponent mixture. It also allows calculation of the particle size necessary to produce the desired degree of homogeneity (*i.e.*, within tolerance specifications) for powders in multicomponent mixtures.

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Evidence for Variable Digoxin Absorption as Estimated by Pharmacological Response Intensities

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Abstract □ A dose–effect curve constructed from ventricular rate slowing and oral maintenance doses for digoxin provided evidence for assuming that occupation theory correctly describes drug–receptor site interaction. From the tenets of occupation theory, response intensities were linearly related to biophasic drug levels and provided the input for bi- and triexponential least-squares fits for an intravenously administered 1.2-mg dose of digoxin to patients hospitalized with auricular fibrillation. A biexponential fit best described biophasic drug levels when the biophase was represented by a peripheral compartment. Intravenous biexponential equation parameters were utilized to perform an absorption analysis following oral dosing of 1.2 mg of digoxin to the same patients. From calculations of fractional amounts unabsorbed with time, significant absorption of digoxin was found to be occurring through 24 hr at progressively decreasing but noticeably variable rates; absorption was calculated to be 98.7% complete by 120 hr. Absorption rates were most rapid over the first 5 hr but quite variable thereafter. Oscillations in the intravenous and oral response–time curves, observed between 3 and 12 hr following dosing, likewise produced fluctuations in mathematically derived biophasic drug levels, fractional amounts unabsorbed, and absorption rates for the oral dose, suggesting enterohepatic cycling of digoxin to be more significant than previously thought.

Keyphrases □ Digoxin, variable absorption—estimated by pharmacological response intensities, dose–effect curves, ventricular rate slowing, response–time curves □ Absorption, digoxin—evidence for variability estimated by ventricular rate slowing, dose–effect and response–time curves constructed □ Ventricular rate slowing—used as pharmacological response intensity parameter for studying variable digoxin absorption □ Enterohepatic cycling, digoxin—evidence suggesting new significance

Recent reports (1–3) focused on the variation in bioavailability of digoxin following oral dosing. Blood level curves representing dosing of different brands as well as different lots of the same brand have shown variations in the values[1] of C_{max}, t_{max}, and areas under plasma curves, encouraging authors to conclude that various tablets of digoxin are not uniform. Formulation defects in the drug products administered were cited as probable causes for the differences in bioavailability. From computer simulations of central and peripheral compartment digoxin levels, Sorby and Tozer (4) concluded that bioavailability differences reported for commercial tablets of digoxin could additionally be a consequence of a variable absorption rate. Although variations in tablet formulation and/or method of manufacture are quite often responsible for the observed differences in drug blood level patterns, a variation in absorption rate must also be considered. The purposes of this report are to illustrate the variability in apparent absorption rates of digoxin following oral dosing and to demonstrate the sensitivity of pharmacological response intensities in obtaining this information.

[1] The C_{max} is defined as the maximum concentration of digoxin in plasma corresponding to the time t_{max}.

THEORETICAL

Experimental results often suggest that dose–effect relationships can be mathematically expressed according to drug–receptor (biophasic) occupation theory assuming a single type of receptor:

$$F_I = \frac{I}{I_{max}} = \frac{Q_B}{K_d + Q_B} \qquad \text{(Eq. 1)}$$

where F_I is the fraction of the maximum intensity attainable, Q_B is the quantity of drug in the biophase responsible for eliciting the response, and K_d is a constant which, under the conditions of one-half maximum intensity, equals the quantity of drug in the biophase. Although the relationship is not linear, it is possible to rearrange Eq. 1 to produce Eq. 2 so that dose is directly proportional to the transformed response intensities, f (5):

$$Q_B = K_d f \qquad \text{(Eq. 2)}$$

where:

$$f = \frac{F_I}{1 - F_I} \qquad \text{(Eq. 3)}$$

If pharmacological response is a direct consequence of biophasic drug levels and if drug disposition adheres to first-order kinetics, then it follows that Q_B can be described by Eq. 4:

$$Q_B = K_d f = D\sum_{i=1}^{n} A_i e^{-m_i t} \qquad \text{(Eq. 4)}$$