In view of the fact that the trituration prepared using spreading by frictional pressure gave the highest dissolution rate, it was concluded that this method of powder mixing was worthy of further study. Since frictional forces are used at various stages in the preparation of dosage forms in milling, blending, slugging, granulating, and tableting, an explanation of batch variations in the dissolution rates of tablets and capsules may be forthcoming from such a study.

Where a film of drug is spread over the surface of the diluent material, some degree of order is being introduced to the powder mixture. This is different from the random mixing of noncohesive powders, from which powder mixing theory has been developed. To distinguish between these two forms of powder mixing, the terms random mixing (for the mixing or shuffling of noncohesive particles) and ordered mixing (for the mixing, spreading, or coating by cohesive particles) have been used (2).

Random mixing has been more widely studied due to the ease of handling systems of noncohesive particles, whereas ordered mixing probably occurs widely in actual powder mixing practice, where cohesive particles usually have to be employed. This is particularly the case in pharmaceutical systems requiring a high degree of homogeneity and high dissolution rates, both of which can only be satisfied by the use of fine cohesive particles.

Just as the completely randomized system in random mixing is only approached in practice (3–5), in ordered mixing the completely ordered system would be difficult to attain. It would require homosized diluent particles with a layer of equal thickness (or an equal number of homosized particles) of drug. Ordered mixing requires the use of cohesive or spreadable material and, for most materials, is dependent upon particle size. For large noncohesive particles, mixing is predominantly random. As the particle size is reduced, the cohesiveness, as measured by angle of repose, flow through an orifice, shear cell, *etc.*, increases until the mixing is predominantly by the ordered mechanism. The transition occurs in the region of 100 μm, depending on the hardness and surface properties of the material.

The standard deviation of the theoretical, completely randomized binary mixture, σ_R, decreases with increasing sample size, M, according to:

$$\sigma_R = \left(\frac{xyw}{M}\right)^{0.5} \qquad \text{(Eq. 1)}$$

where x and y are the proportions of the two homosized ingredients of particle weight w. In contrast, the completely ordered mixture would have zero standard deviation until the sample weight, M, was reduced to such an extent as to contain less than one single particle of diluent and associated drug adhering or spread onto it.

Of the methods used for the formation of the digoxin–lactose and hydrocortisone–lactose triturations (1), the solvent deposition method may also be classified as an ordered process, since a thin film of drug should be deposited at the surface. The success or failure of this method to produce improved dissolution rates depends largely on the drying conditions and solution migration. Thus, a good dispersion may be obtained, such as aspirin deposited on a lactose–starch mixture, resulting in increased dissolution rates (6).

It is apparent that both decreased particle size and greater dispersion of the drug with the diluent are required for increased dissolution rates. Ordered mixing may give better results than random mixing, but only at the cost of the increased energy input required to bring about this degree of order. The use of frictional pressure to induce spreading of the drug over the diluent is one example of ordered mixing, where with extra energy input, more efficient dissolution rates have been obtained.

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Particle-Size Requirements Related to Content Uniformity of Solid Dosage Forms

Keyphrases □ Particle size—requirements related to content uniformity of solid dosage forms, particle-size limit compared to particle-size distribution □ Content uniformity, solid dosage forms—particle-size limit and particle-size distribution discussed

To the Editor:

In a recent publication (1), the particle-size requirements to achieve satisfactory content uniformity in a compound tablet were discussed. An example was given for a three-component system containing 50, 5, and 0.5% of the respective drugs with the requirement that these percentages be present in the final 100-mg tablet within ±10% of the nominal values at the 99.7% probability level. The resultant σ values related to the tolerance range of ±10% were

wrongly stated, and the subsequently evaluated particle-size requirements based on randomized mixtures are consequently in error.

Using the same notation (1), the system containing the three components P, Q, and R present in a 100-mg tablet at the 50, 5, and 0.5% levels is considered here. The tolerance of ±10% for a nominal value of 50% drug gives an acceptance range of 50 ± 5.0%. At the 99.7% probability level then:

$$3\sigma_{|A(P)|} = 5.0 \qquad \text{(Eq. 1}a\text{)}$$

Similarly, for Q and R the acceptance ranges equal 5 ± 0.5% and 0.5 ± 0.05%, respectively. Hence:

$$3\sigma_{|A(Q)|} = 0.5 \qquad \text{(Eq. 1}b\text{)}$$

$$3\sigma_{|A(R)|} = 0.05 \qquad \text{(Eq. 1}c\text{)}$$

The effective mean particle weight (w) in each case can be evaluated from the equation (1):

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

where W is the sample weight (100 mg), and g is the percentage weight of the active ingredient. The results give:

$$w_P = 0.1111 \text{ mg} \qquad \text{(Eq. 3}a\text{)}$$

$$w_Q = 0.005847 \text{ mg} \qquad \text{(Eq. 3}b\text{)}$$

$$w_R = 0.0005584 \text{ mg} \qquad \text{(Eq. 3}c\text{)}$$

When assuming spherical particles of density 1.2 g/cm^3, the effective mean particle diameters become:

$$d_{(P)} = 561\ \mu\text{m} \qquad \text{(Eq. 4}a\text{)}$$

$$d_{(Q)} = 210\ \mu\text{m} \qquad \text{(Eq. 4}b\text{)}$$

$$d_{(R)} = 96\ \mu\text{m} \qquad \text{(Eq. 4}c\text{)}$$

The results can be confirmed using Eq. 9 of Ref. 2, which is an expression for the coefficient of variation of drug content in a two-component mixture:

$$C_v = 100\left(\frac{\pi\rho}{6G}\right)^{1/2}\left(\sum fd^3\right)^{1/2} \qquad \text{(Eq. 5)}$$

where ρ = drug density (grams per cubic centimeter), G = weight of drug per sample (grams), d = diameter of spherical drug particle (centimeters), and f = weight fraction of drug existing with mean particle diameter d.

Equation 5 is based on a simplification of Stange's (3) equations and holds for two-component mixtures containing up to 1% by weight of drug. For calculation purposes, the three components P, Q, and R can be dealt with separately, thus reducing the problem to consideration of a mixture containing one active ingredient with excipient. Hence, in the case of R (0.5%), Eq. 5 may be used to calculate $d_{(R)}$. In this case, where mean particle diameters are being considered, Σfd^3 becomes d^3 and:

$$C_v = 100\left(\frac{\pi\rho d^3}{6G}\right)^{1/2} \qquad \text{(Eq. 6)}$$

For a tolerance of ±10%, the coefficient of variation, C_v, will be 3.333%. With 100-mg tablets, the weight of drug per sample, G, in case R will be 0.0005 g. When the density is taken as 1.2 g/cm^3, the calculated value for $d_{(R)}$ from Eq. 6 is 96 μm, the same result as Eq. 4c, using the correct σ value.

Table I—Data for Determining Equivalent Particle-Size Distribution

Diameter, μm	Percent by Weight Greater than Stated Diameter	Mean Fraction Particle Diameter, d_i, μm	Weight Fraction, f_i
250	0		
		225	0.03
200	3		
		175	0.04
150	7		
		135	0.02
120	9		
		105	0.11
90	20		
		75	0.3
60	50		
		50	0.2
40	70		
		30	0.2
20	90		
		10	0.1
0	100		

In the cases of components P and Q, Eq. 5 does not give the correct solution since the drug concentrations are too high. With the assumption that the drug and excipient have similar particle-size distributions, that is the effective mean particle weights are equal, Stange's equation for a two-component mixture (see Eq. 13 of Ref. 2) reduces to:

$$C_v = 100\left(\frac{Y\pi\rho d^3}{6G}\right)^{1/2} \qquad \text{(Eq. 7)}$$

where Y = weight fraction of excipient in mixture, and d = effective mean particle diameter of drug.

Equation 7 holds for all drug concentrations and may be used to calculate $d_{(P)}$ and $d_{(Q)}$. For 100-mg tablets containing only component Q (5%) and excipient, Y = 0.95 and the weight of drug, G, per tablet will be 0.005 g. Assuming a density of 1.2 g/cm^3, the value of $d_{(Q)}$ obtained from Eq. 7 equals 210 μm. Similarly, in the case of component P, Y = 0.5 and G will be 0.05 g, giving a value of $d_{(P)}$ from Eq. 7 equal to 561 μm. The results confirm the corrected values given in Eqs. 4a and 4b and also demonstrate the equivalence of the two methods for calculating the effective mean particle diameters necessary to produce a product of specified content uniformity.

According to these results, this would necessitate an overall reduction in particle size to 96 μm and not 5 μm as stated in Ref. 1.

Practically speaking, components of a mixture are very rarely, if ever, homogeneous with respect to particle size, so it would be more instructive to consider the problem in terms of the particle-size distribution desirable for the component instead of a single particle-size limit.

It is possible to interpret the calculated value of $d_{(R)}$ in terms of an equivalent particle-size distribution as shown in Table I. From Table I:

$$\sum f_i d_i^3 = 889{,}702.5\ \mu\text{m}^3 \qquad \text{(Eq. 8)}$$

In a distribution the effective mean particle weight can be written:

$$w = (f_1 w_1 + f_2 w_2 + \ldots f_n w_n) \quad \text{(Eq. 9)}$$

where f_1 is the weight fraction of particles of weight, w_1, *etc.* For spherical particles:

$$w = \frac{\pi\rho}{6} \sum_1^n f_i d_i^3 \quad \text{(Eq. 10)}$$

In the case where particles are the same size, Eq. 10 becomes:

$$w = \frac{\pi\rho d^3}{6} \quad \text{(Eq. 11)}$$

For Eqs. 10 and 11 to be equivalent:

$$d^3 = \sum_1^n f_i d_i^3 \quad \text{(Eq. 12)}$$

Substituting the result from Eq. 8 into Eq. 12 gives $d = 96.2$ μm. Hence, the particle-size distribution given in the example, which was determined by trial and error, is equivalent to the calculated value of $d_{(R)}$ of 96 μm. This distribution is typical of the kind of result encountered in practice. Use of such a particle-size distribution for all active ingredients would allow a safety margin for ingredients *P* and *Q* but, in the case of *R*, would necessitate achieving a truly random mixture to fulfill the desired tolerance range of ±10%.

In practice, a random mix is not always achieved and it may be desirable to introduce an additional safety margin for the lowest concentration drug, *R*. Hersey *et al.* (1) did this in effect by setting the calculated effective mean particle-size limit for *R* as the maximum particle-size limit for the mixture. Alternatively, the coefficient of variation used in Eq. 7 could be set at a lower value than that corresponding to the specified tolerance range of ±10%. For example, instead of 3.333%, a C_v value of 2.5% could be used which would give $d_{(R)}$ from Eq. 7 equal to 79 μm. An equivalent particle-size distribution corresponding to this value of $d_{(R)}$ would contain a considerable fraction above the proposed maximum limit of 96 μm (1) while still incorporating a safety margin to allow for the occurrence of nonrandomized mixing.

In conclusion, converting the particle-size limit into an equivalent particle-size distribution increases the utility of the calculations and provides a more convenient guideline in the practical situation. Additionally, a particle-size distribution of a drug obtained on recrystallization or precipitation or after milling can be tested for its suitability with regard to content uniformity by evaluating $\Sigma f_i d_i^3$ and comparing this value with the value of d^3 derived from Eq. 2 or 7.

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Definitive GLC Method of Identifying Cocaine

Keyphrases □ Cocaine—definitive GLC identification □ Trimethylanilinium hydroxide—on-column methylation of cocaine, GLC identification □ GLC—identification, cocaine

To the Editor:

The identification of underivatized cocaine by GLC can be misinterpreted and erroneously reported as pentazocine, levorphanol, or methaqualone when using programmed or isothermal temperatures on 7% OV-17[1]. TLC can also pose problems and lead to the report of a false positive for methadone instead of cocaine (1). Many laboratories are combining mass spectrometry with GLC to provide a more definitive instrumental method for identifying drugs such as cocaine (2); however, many laboratories cannot afford a mass spectrometer and, therefore, more definitive GLC methods of analysis are desirable.

In view of these problems encountered when employing GLC or TLC as a means of identifying cocaine, we wish to report a novel, definitive GLC method of identifying cocaine *via* an on-column GLC reaction under methylation reaction conditions that is applicable to confirming the presence of cocaine in various legitimate and illegitimate dosage forms. In our laboratory we have routinely used trimethylanilinium hydroxide in methanol as a methylating reagent for GLC analysis of anticonvulsant drugs in body fluids (3, 4). We anticipated that this methylating reagent would have an interesting on-column

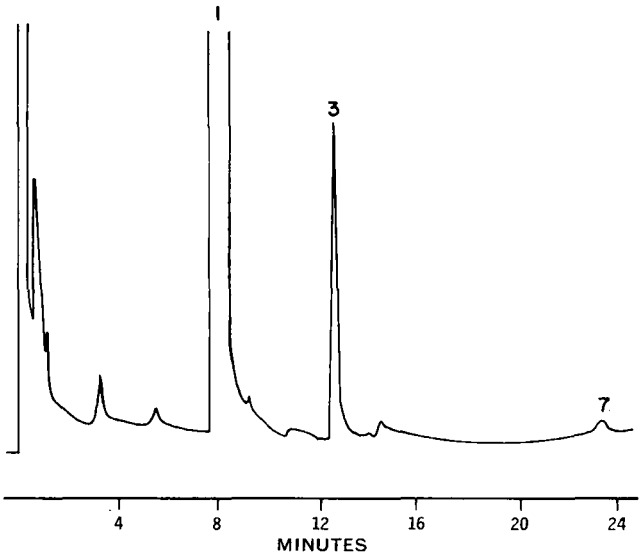

Figure 1—*Characteristic chromatogram representing an on-column reaction of cocaine (1.5 μg) and trimethylanilinium hydroxide (no time lapse after adding the methylating reagent to cocaine). See Table I for identification of the peaks.*

[1] In our laboratory, these drugs have retention times similar to cocaine under programmed and isothermal conditions and are extracted concurrently with cocaine at basic pH.