Letters to the Editor

Comments on "Particle Size and Content Uniformity," by Yalkowsky and Bolton

In a recent report (1), Yalkowsky and Bolton presented an approach to estimate the mean particle size and particle size distribution of low-dose drugs required to ensure a high probability of passing the USP Content Uniformity Test. However, the authors seem to have missed the previous work of Johnson (2) and Egermann and co-workers (3,4), which is in considerable contrast to their results. These differences may be reduced to the different types of mean particle diameters $\bar{d}$ (m in their notation) used to define the particle size. Although Yalkowsky and Bolton did not specify the mean they did apply, it is obvious from the data in their Table II that it was not the type representative of mixing homogeneity and content uniformity. This resulted in erroneous conclusions as to the particle size specifications required.

For unambiguous definition of mean particle diameters, the general Eq. (1) given by Edmundson (5) may be used:

$$\bar{d} = \left(\frac{\Sigma n d^{p+f}}{\Sigma n d^{f}}\right)^{1/p} \quad (1)$$

where n is the number of particles in a size range the midpoint of which is d. The index p is the diameter power function, with a value of 1, 2, or 3, corresponding to the length, surface, or volume of the particles; f is the frequency index, which may be 0, 1, 2, or 3, depending on whether the size frequency distribution is expressed in terms of the total number, length, surface, or volume of the particles.

Previously (6) it has been shown that the mean representative of mixing homogeneity is the "volume-weighted/volume-number mean diameter" $\bar{d}_v$, with the indices p and f both equal to 3. $\bar{d}_v$ may be derived from the particle size distribution according to (2)

$$\bar{d}_v = \sqrt[3]{\Sigma(f \cdot d^3)} \quad (2)$$

where f is the particle size fraction by mass of the powder and d is the particle size of the fraction.

For low-dose drugs, the limiting effect of $\bar{d}_v$ on the homogeneity of the random mixture may be defined by the Poisson equation derived in Ref. 7 and applied earlier (4). With the spherical particles of density 1 assumed in (1), this equation may be written as

$$C_R = \sqrt{\frac{\bar{d}_v^3 \cdot \pi}{G \cdot 6}} \quad (3)$$

where C_R is the coefficient of variation of the mean drug content G per sample of the random mixture. Experimentally, the validity of this simple equation has been broadly confirmed by several authors (3,4,8,9) with a variety of drug constituents showing significant differences in particle size, size distribution, and dose level.

$\bar{d}_v$ is representative of the effects of both particle size and size distribution on mixing homogeneity; e.g., provided that C_R does not exceed a value of 5.5%, conforming to the assumptions of (1), and G equals 1 mg, the limiting value of $\bar{d}_v$ is derived from Eq. (3) as 180 μm, irrespective of the particle size distribution of the drug powder.

In contrast, the unspecified mean diameter of (1) is dependent on the size distribution. It complies to $\bar{d}_v$ only if the particles are monodisperse (particle diameter coefficient of variation C equals 0), and it becomes significantly smaller with a size distribution. On increasing C from 0 to 100%, Yalkowsky and Bolton (1) calculated their $\bar{d}$ to decrease from 180 to 11.3 μm at the 1-mg dose level.

This dependency does not conform to the established methods of particle size characterization. A powder of log-normal distribution as provided in Ref. 1 is defined by two independent variables: by the mean particle diameter as a measure of the particle size and by the geometric standard deviation s_g (less common, the coefficient of variation C) as a measure of the size distribution (5). In case of log-normality, the mean is identical to the median 50% diameter which divides the log-normal curve into two equal parts. Its value is dependent on the type of the mean, i.e., on the indices p and f in Eq. (1), but is independent of s_g.

The use of an unspecified mean which is neither representative of mixing homogeneity nor independent of the size distribution did in fact produce basic misunderstandings as to the particle size specifications required. Since the limiting value of Yalkowsky and Bolton's $\bar{d}$ decreased on increasing particle size distribution, the authors concluded that in order to comply with the USP content uniformity standards, the particle size must be reduced strongly if the size distribution is broad. They further recommended that the mean particle size does not provide enough information, and therefore particle size specifications for low-dose drugs should include a requirement to a limit size distribution. These suggestions are in striking contrast to the theory of Eq. (3) and to the experimental evidence available (3,4,8,9).

It is an additional limitation of this approach that the drug powder must adhere to the log-normal distribution. The quantities of the representative diameter $\bar{d}_v$ and, in turn, of C_R are governed almost exclusively by the coarsest particle size fractions, which may amount to less than 10% of the total drug (10). With real powders, just these fractions show significant deviations from log-normality, and this assumption therefore produces further increased errors. In contrast, the representative mean $\bar{d}_v$ may easily be calculated from the actual particle size data by means of Eq. (2) without providing statistical prerequisites.

In conclusion, the approach of Ref. 1 is inaccurate and misleading. It cannot be recommended as a suitable alternative to $\bar{d}_v$ in order to specify the particle size requirements for content uniformity.

H. Egermann
Institute of Pharmaceutical Technology
University of Innsbruck
A-6020 Innsbruck
Innrain 52, Austria

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Reply to the Comments by Ergemann

Ergemann suggests that the results presented in our article (*Pharm. Res.* 7:962–966, 1990) are incorrect (see the above Letter to the Editor). His criticism is based largely upon the fact that we did not make the same assumptions about particle size distribution as he did in his published work. He states that we did not define our system and the distribution of particles, yet we clearly stated that our derivation was based on spherical particles with the diameters having a log-normal distribution. He also states that it is obvious from results in our Table II that our definition is not representative of mixing homogeneity and content uniformity. However, our mean particle size is defined by his Eq. (1) with $p = 1$ and $f = 0$.

We have derived a general result based on simple assumptions of spherical particles, a log-normal particle size distribution, and random mixing. We feel that this derivation is accurate based on the assumptions. In the one example that Ergemann gives (180 μm), our results agree well with his; we obtain an answer between 170 and 180 μm. It is not obvious which method, if any, gives the best results. It may be that both methods have usefulness, depending on the circumstances.

Sanford Bolton
Samuel Yalkowsky
College of Pharmacy
University of Arizona
Tucson, Arizona 85721