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## Prediction of Dissolution Rates of Drugs

**Keyphrases** □ Dissolution rates, slightly water-soluble powders—prediction from simple mathematics □ Powders, slightly water soluble—dissolution rates predicted from simple mathematics □ Powders, volume surface diameter—calculation of surface area

Sir:

Hussain (1) recently showed that, by making certain assumptions and using simple mathematics, it was possible to predict the dissolution rates of slightly water-soluble powders using the formula:

$$Q = \frac{A \cdot S \cdot D \cdot t}{h} \quad (\text{Eq. 1})$$

where:

$Q$  = amount of drug (in grams) dissolved in time,  $t$

$A$  = surface area occupied by the total weight of the sample

$S$  = solubility of the drug (in grams per milliliter) in the dissolution medium

$D$  = diffusion coefficient of the drug (in square centimeters per second)

$h$  = thickness of diffusional layer (in centimeters)

By assuming that the diffusion coefficient,  $D$ , and the thickness of the diffusional layer,  $h$ , are constant at  $9 \times 10^{-6}$  cm<sup>2</sup>/sec. and  $50 \times 10^{-4}$  cm., respectively, knowledge of only the surface area exposed,  $A$ , and the solubility,  $S$ , of the drug enables the dissolution rate  $Q/t$  to be calculated.

Despite the remarkable correlation between the experimental and calculated results for the dissolution rates of hydrocortisone, benzoic acid, levodopa, and

griseofulvin, there appears to be a considerable argument against the use of such predicted results as a routine measure.

Hussain's Eq. 3 is in error by a density factor ( $\rho$ ):

$$\text{number of particles in } W \text{ grams of powder} = \frac{W}{4/3\pi r^3 \rho} \quad (\text{Eq. 2})$$

assuming spherical particles:

$$V = 4/3\pi r^3 \quad (\text{Eq. 3})$$

Since the density for benzoic acid is 1.32 (2), the area would be overestimated without this correction by 32%, with a corresponding overestimation in the calculated dissolution rate.

Hussain also used the average particle size on an arithmetic basis, using the two extremes of the mesh fraction in his calculation of the surface area. While this may not lead to gross errors for the comparatively narrow size ranges considered by Hussain, for larger particle-size distributions a better mean size would be the volume-surface mean diameter,  $d_{vs}$  (3):

$$d_{vs} = \frac{\sum nd^3}{\sum nd^2} \quad (\text{Eq. 4})$$

and the surface area computed from:

$$A = \frac{W \times 6}{d_{vs} \rho} \quad (\text{Eq. 5})$$

Since the volume-surface mean diameter will also be larger than the arithmetic mean diameter, this will add further to the overestimation of the dissolution rate.

To explain Hussain's apparent correlation requires a compensating decrease in the value of the area used in Eq. 1. This may be due to assuming that the particles are spherical, while deviations from either spherical or cubical shape will lead to an increase in the constant value of 6 given in Eq. 5.

Due to the complexity of these compensating mechanisms, it would be rash to adopt Hussain's method for the prediction of the dissolution rate of sparingly soluble drugs without further evidence. Hussain's article dealt with particles in powder form only. However, for solid dose formulations, where it is known that the total area available may not come into contact with the dissolution medium due to failures of disintegration (4), or where the ingredients may invalidate the diffusion assumptions made by Hussain, we must be prepared to continue to determine experimentally the dissolution rate of the drug.

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