critical when it exceeds a certain range, *i.e.*, 45–74 μm. The statistical analysis of the area under the curve (Table II) yielded the following sequence: $AUC_{F45} > AUC_{F160} > AUC_{F500}$. Figure 1 shows that for these preparations, there was a nearly linear relationship between the logarithm of the area under the curve and the logarithm of the mean particle size in the particle-size range investigated. Therefore, the dissolution of the drug in the intestines appears to constitute the rate-limiting step for the whole process of intestinal absorption; *i.e.*, $k_1 < k_2$.

Figure 2 shows a clear linear relationship between the logarithm of the area under the curve and log τ_D. The statistically significant difference between the area under the curve and τ_D for the preparations suggests that there is a genuine correlation between the *AUC* and the *in vitro* dissolution rate.

These results indicate that it may be possible, in principle, to estimate the *AUC* from the *in vitro* dissolution rate. The same correlation probably is obtained for any drug where dissolution is the rate-limiting step in absorption.

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COMMUNICATIONS

Correlation between Porosity and Dissolution Rate Constants for Disintegrating Tablets

Keyphrases □ Correlation coefficients—disintegrating tablets, relationship between porosity and dissolution rate □ Disintegration—tablets, correlation between porosity and dissolution rate □ Dissolution rate—correlation with porosity for disintegrating tablets □ Tablet disintegration—correlation between porosity and dissolution rate

To the Editor:

The importance of tablet porosity from a mechanical point of view has been discussed extensively (1, 2). Porosity also has been linked to the release characteristics of drugs from dosage forms and enters directly into the Higuchi square root law for dissolution (3). In the latter case, both penetration and diffusion characteristics are important.

There are cases in which tablets disintegrate and where the dissolution is relatively rapid so that the dissolution is a function of the disintegration (4, 5). However, there are cases in which tablets disintegrate fairly rapidly and where the dissolution is dictated by the rapid penetration of water into the granule. If the dissolution of the active ingredient and its diffusion out through the granule are rapid in relation to the penetration, then the dissolution is given by the amount of water that penetrates, *i.e.*, by an equation of the type described by Jost (6, 7):

$$\ln (m/m_0) = -k(t - t_i) \qquad \text{(Eq. 1)}$$

where m is the undissolved mass at time t, t_i is the disintegration time, and k is the dissolution constant (in reciprocal time units). Since the penetration rate is expected to be a function of the porosity, ϵ, of the tablet, then k also should be a function of ϵ. This argument assumes that the granules after disintegration have the same porosity as did the tablet before disintegration (8).

In a recent study in these laboratories, tablets were formed from granulations made by several processes: (*a*) fluid bed granulation[1], (*b*) chopper–ribbon blender[2], (*c*) chopper–ribbon blender followed by an oscillating granulator, and (*d*) chopper–ribbon blender followed by a rotating granulator[3]. The formula used was equal parts of dibasic calcium phosphate (anhydrous) and sulfanilamide granulated with 0.7 parts of 5% cornstarch paste. Drying was carried out to 1% loss on drying. Several differences were observed among these processes, and the phenomena related to dissolution and porosity will be discussed.

The granulations were screened and separated into four size fractions (<315, 315–400, 400–630, and >630 μm). Each fraction was compressed at three machine pressures (1200, 2400, and 3600 kg), and the resulting 12 batches of tablets from the four manufacturing procedures were subjected to dissolution tests by the beaker method (9). The porosities were measured using a mercury porosimeter.

The dissolution tests followed the relationship expressed in Eq. 1, and the prepared tablets had dissolution rate constants described by:

$$k = a_i + b_i\epsilon \qquad \text{(Eq. 2)}$$

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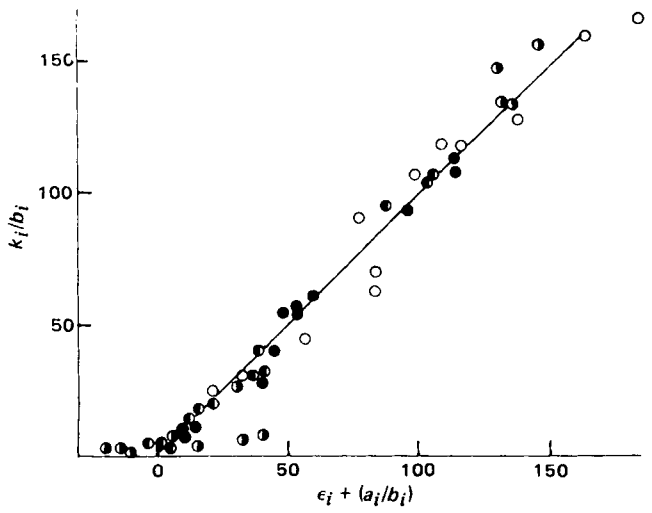

Figure 1—*Plot of* k_i/b_i versus $\epsilon_i + (a_i/b_i)$ *according to Eq. 3. Key:* ○, *chopper–ribbon blender;* ●, *chopper–ribbon blender followed by an oscillating granulator;* ◐, *chopper–ribbon blender followed by a rotating granulator; and* ◑, *fluid bed granulation.*

where a_i and b_i are constants and the subscript i refers to the ith condition (sieve fraction, manufacturing method, or compression pressure). The constants a and b are functions of these variables. Therefore, there are 48 lines corresponding to Eq. 1. The correlation coefficients generally were >0.94, and it is possible to tabulate all 48 values or draw 48 regression lines on one graph. For graphical presentation, a method (10) was used for which the data for each condition were recast in the following form:

$$k/b_i = \epsilon + (a_i/b_i) \qquad \text{(Eq. 3)}$$

where k/b_i and $\epsilon + (a_i/b_i)$ are dimensionless parameters. When one parameter is plotted as a function of the other, a straight line with a unity slope and a zero intercept should result. The 48 data points are plotted in Fig. 1 (the origin is offset), which shows visual agreement with the statements. The treatment is not statistical since the two variables (the left- and right-hand expressions in Eq. 3) are not independent. If a least-squares fit is drawn, the following relationship is obtained:

$$k/b_i = (0.98 \pm 0.05)[\epsilon + (a_i/b_i)] + (0.22 \pm 0.30) \qquad \text{(Eq. 4)}$$

in accordance with a unity slope and a zero intercept.

Equation 3 includes all of the data points, but Fig. 1 shows that the relationship fails at very low porosity values (high compression pressures). The four cases where $-a_i/b_i > \epsilon_i$ [*i.e.*, where values of $\epsilon_i + (a_i/b_i)$ are negative] do not seem to be part of the line. In these four cases, the adherence to Eq. 1 also was marginal (the correlation coefficients for these four points were 0.85–0.91), whereas the agreement was good to excellent in all of the other cases (*i.e.*, correlation coefficients of >0.94).

The data and the treatment show that there is a correlation between the dissolution constants, k, and the porosity, ϵ, in the case where a tablet disintegrates into porous granules and the limiting process is the penetration of water into the dislodged granule.

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Identification of Subvisible Barium Sulfate Crystals in Parenteral Solutions

Keyphrases □ Barium sulfate—crystal formation in commercial parenteral solutions, identification by polarizing microscopy, scanning electron microscopy, micro X-ray powder diffraction, and micro Raman spectroscopy □ Parenteral solutions, commercial—barium sulfate crystal formation, identification by polarizing microscopy, scanning electron microscopy, micro X-ray powder diffraction, and micro Raman spectroscopy □ Crystals—barium sulfate formation in commercial parenteral solutions, characterization by polarizing microscopy, scanning electron microscopy, micro X-ray powder diffraction, and micro Raman spectroscopy

To the Editor:

Concern about the presence of particulate matter in parenteral products is increasing, and certain harmful effects when such contamination is introduced into the body during intravenous therapy have been described (1–4). Additionally, studies in our laboratory implicated particulate contamination in infusion fluids as a cause of phlebitis (5–7).

To gain insight into the nature and clinical significance of particulate matter in intravenous solutions, an extensive research program has been undertaken in cooperation with the Food and Drug Administration, which includes the identification of particulate matter in parenteral products. During this investigation, barium sulfate crystals were isolated and identified in six parenteral solutions packaged both in sealed glass ampuls and in glass vials with rubber stoppers. The conclusive identification of barium sulfate crystals was achieved through the correlation of analytical data from polarizing microscopy, scanning electron microscopy with energy-dispersive X-ray analysis capability, micro X-ray powder diffraction, and micro Raman spectroscopy.

With the polarizing microscope, barium sulfate crystals isolated from the parenteral solutions appeared as single or agglomerated, well-formed, birefringent crystals, 8–30

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