Table I—pKa Values of Some Aniline Derivatives

Substance	Substituent	Position	pKa[a]
Aniline	—	—	4.60[b]
Aniline	Benzoyl	4	2.2[c]
Aniline	Chloro	4	3.98[b]
N-Methylaniline	—	—	4.85[b]
N-Methylaniline	Chloro	4	3.9[c]

[a] At 25°. [b] References 10 and 11. [c] Reference 11.

absorbance, both in relation to the increasing sample acidity. The I pKa was calculated from Eq. 1 (9) to be 1.45 ± 0.04[3]:

$$\text{pKa} = \text{pH} + \log (A_b - A/A - A_i) \qquad \text{(Eq. 1)}$$

where A_b, A_i, and A = the absorbances of the nonionized base, the conjugate acid, and the various samples, respectively.

The pKa values of substituted anilines such as I are lowered more by an *ortho*- than by a *meta*- or *para*-electron-withdrawing substituent (10, 11). Thus, the inductive effect of 2-benzoyl and 4-chloro groups on *N*-methylaniline (*i.e.*, I) as regards the pKa of the anilino nitrogen atom would be predicted to exceed that of the sum of these substituents at the 4-position. From Table I, the pKa differences among anilines substituted with *N*-methyl, 4-benzoyl, and 4-chloro groups are 0.25, −2.4, and −0.62 units, respectively. The arithmetic sum of these differences is −2.77 units, thereby predicting a pKa of ~1.8 (*i.e.*, 4.6 − 2.8) for I. However, the pKa lowering caused by a 4-chloro substituent is 0.1 unit greater for *N*-methylaniline than for aniline. Therefore, the observed anilino pKa decrements (Table I), augmented by the expected superior electron-inducing capability of a 2-benzoyl (*ortho*) over that of a 4-benzoyl *N*-methylaniline substituent, appear to be in reasonable agreement with the pKa estimate of 1.4–1.5 for I.

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[3] Average of five values in the pH range of pKa ± 1 unit.

Drug Dissolution within a Cascade Barrier Bed

Keyphrases □ Dissolution—test apparatus, cascade barrier bed □ Pharmacokinetics—drug dissolution tests, apparatus, cascade barrier bed □ Cascade barrier bed—for testing drug dissolution

To the Editor:

When dissolution limits the rate of drug absorption, *in vitro* dissolution tests are useful for quality control or in formulation development only if they correlate well with *in vivo* drug levels. Where satisfactory correlations have not been found, differences in solubility behavior among the polydisperse particles produced during dosage unit disintegration may be a factor. Where the relative intrinsic solubilities of particles are size dependent and sensitive to formulation variables, a single dissolution test method cannot be relied upon. Depending on the desired degree of resolution among formulations, at least two procedures are needed that produce linearly independent functional relationships between particle size and dissolution hydrodynamics. To accomplish this result, they must control the dissolution fluid mechanics as a function of particle size.

This communication discusses a cascade barrier bed test method, which complements existing procedures by providing distinctly different dissolution conditions. It differs from the USP–NF (1, 2), stationary basket–rotating filter (3), and flowthrough cell (4, 5) methods by favoring the dissolution of small particles over large.

The device consists of a vertical cylindrical cell (Fig. 1). It is partially filled with discrete layers, B, of uniformly sized, silanized glass balls. The ball size of each layer is successively increased from the bottom to the top of the bed. The prototype tested contained five layers, each 6.25 cm in height and composed of 0.25-, 0.56-, 1-, 2-, and 4-mm balls. The cell was 50 cm in height × 1.9 cm i.d.

In preparation for a run, solvent was introduced through the efflux chamber, C, to the top of the previously loaded bed so as to preclude air entrapment. The powder was then placed on top of the bed; the solvent receiving chamber, A, was filled with solvent; and flow was initiated. Flow was controlled and maintained by hydrostatic pressure; solvent flowed from an elevated reservoir through Tygon tubing to the receiving chamber, A. Samples of effluent were collected through tubing attached to chamber C and assayed. A sintered-glass frit, D, retained and supported the bed within the cell.

In operation, drug particles are carried into the bed by viscous drag forces and by gravity to a level where they are trapped. Their location is determined by drug particle size and the pore size characteristic of each layer in the bed. Particles from polydispersed systems are thus separated into various size fractions within the bed.

Although fluid flow fields in this type of packed bed are complicated, the hydrodynamics within the various layers are simply related. With column and ball diameters in a practical range for dissolution testing, random packing fractions of uniform spheres are size independent. For a constant column cross-sectional area, the average linear velocity of the solvent also will be constant throughout the bed for incompressible fluids. Voids and pores are geo-

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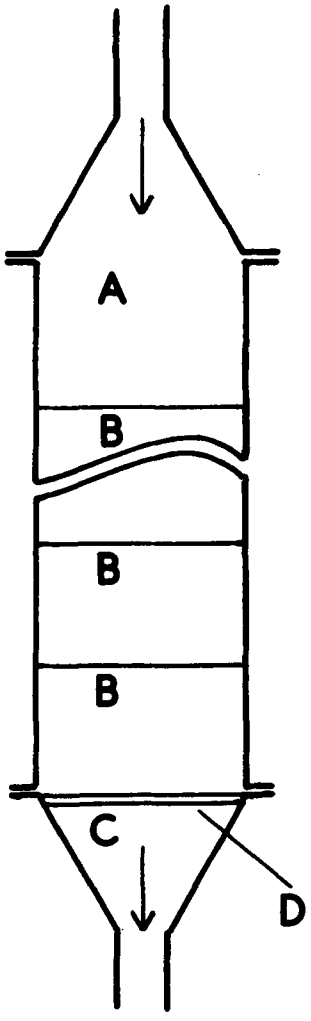

Figure 1—*Cascade barrier bed cell. Key: A, solvent receiving chamber; B, layers of monodisperse silanized glass balls; C, solvent efflux chamber; and D, sintered-glass frit for bed support.*

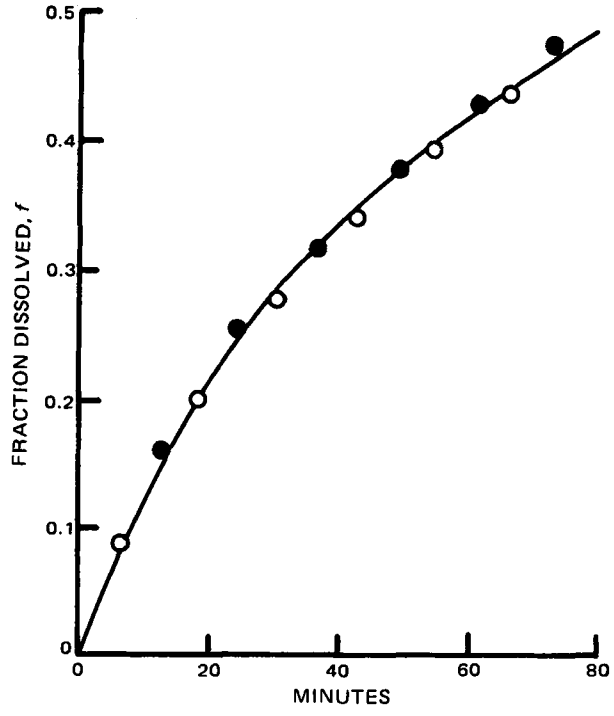

Figure 2—*Sulfadiazine dissolution data from cascade barrier bed method. Key: ○, 10-mg mixture of equal weights of fine and coarse powders; and ●, sum of fraction dissolved from separate runs of 5 mg of the individual, unmixed fine and coarse powders.*

metrically similar among the various bed layers and have dimensions in direct proportion to ball size. Therefore, solvent laminar flow shear rates are inversely proportional to ball size at equivalent locations within the voids and pores of various layers. This result is a direct consequence of the principle of geometric similarity from dimensional analysis of fluid mechanics (6). Under these conditions, shear rate gradients are inversely proportional to the square of ball dimension. No loss of solubility rate dependency on particle size will occur in going from sink to nonsink conditions, provided significant saturation does not occur in a single pass of solvent through the cell.

Table I—Regression Coefficients for Sulfadiazine Dissolution by Cascade Barrier Bed (CBB) and USP Basket Methods

Method	Sulfadiazine, mg	Particle Size, mesh	Linear Coefficient, $b \times 10^3$, min^{-1}	Quadric Coefficient, $c \times 10^5$, min^{-2}
CBB	10	100/200[a]	21.0	31.4
	10	30/50[a]	2.7	1.6
	5, 5	100/200[b], 30/50	14.5	19.7
USP	10	100/200[a]	11.1	9.1
	10	30/50[a]	2.5	2.6
	5, 5	100/200[b], 30/50	7.1	5.4

[a] Average of duplicate runs. [b] Average of triplicate runs.

It is apparent that the size and quantity of balls comprising the layers, B, the desirable number of such layers, and the solvent selected will depend on the size distribution, the amount of multiparticulate material, excipients, and drug solubility. The preliminary experiments reported were designed to test the operation of the fluid mechanical principle, which is the basis of the method.

The prototype cell was tested using deaerated 0.01 N H_2SO_4 at a flow rate of 30 ml/min under sink conditions. For comparison, the USP–NF rotating-basket method was run at 120 rpm using the same solvent, essentially under sink conditions due to low saturation levels. Sulfadiazine USP powder was compressed into tablets, coarsely ground in a mortar, and screened through U.S. standard sieves. Two size fractions were used as test materials: those passing a 30-mesh and retained on a 50-mesh sieve and those passing a 100-mesh and retained on a 200-mesh sieve.

The nondisintegrating powders were placed either on top of the bed or in the basket[1], depending on the apparatus, at the start of each run. All experiments were conducted at 25 ± 0.1°, and samples withdrawn at 3–5-min intervals were assayed by UV absorption at 243 nm. The cumulative fraction dissolved, f, was fitted to the equation $f = bt - ct^2$ by the method of least squares. Results are shown in Table I. Equally satisfactory cleaning of the cell following a run was obtained by simply continuing solvent flow or by disassembly and washing with solvent.

The ratio of the initial dissolution rate of the small particles to that of the large particles can be taken as the

[1] Hanson Research Corp., Northridge, CA 91324.

ratio of the corresponding b values. These ratios are 7.7 and 4.4 for the cascade barrier bed and USP methods, respectively. If a uniform size distribution for each powder fraction is assumed, the finer powder should have approximately four times the specific surface area of the coarse powder. Thus, the initial dissolution rate per unit surface area of the fine powder is nearly twice that of the coarse powder for the cascade barrier bed method and is comparable to the coarse powder for the USP method. These observations conform to expectations based on apparatus design and fluid mechanical theory.

Figure 2 shows the cascade barrier bed dissolution behavior of a mixture of 5 mg each of the fine and coarse sulfadiazine powders. For comparison, results of separate cascade barrier bed runs of 5 mg of the individual powder grades were added and the sum was plotted. The two plots closely correspond and indicate independent dissolution behavior of the two powder fractions within the bed.

These findings do not indicate the superiority of one *in vitro* dissolution apparatus over another. Instead, they suggest that, where particle-size effects prevent useful correlations with *in vivo* drug levels, parallel use of two such contrasting methods is necessary.

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BOOKS

REVIEWS

Analytical Profiles of Drug Substances, Volume 7. Edited by KLAUS FLOREY. Academic, 111 Fifth Ave., New York, NY 10003. 1978. ix + 504 pp. 15 × 23 cm.

Volume 7 of this series includes individual drug monographs dealing with supplementary information that is not listed in the official compendia. The entire series of volumes was undertaken as a cooperative venture by the Pharmaceutical Analysis and Control Section, Academy of Pharmaceutical Sciences. The profiles of drug substances in each volume are submitted by contributors and checked by selected reviewers. A typical profile includes such topics as a description of the compound (name, formula, molecular weight, color, odor, and salts), physical properties (IR, NMR, UV, and mass spectra, melting or boiling point, solubility, partition coefficient, and dissociation constant), syntheses, stability, analysis methods, and metabolism and pharmacokinetic data.

The monographs include up-to-date references, and many contributors state that their references are complete through a certain year, a worthwhile piece of information for the reader. Among the drugs covered in Volume 7 are allopurinol, amoxicillin, chlorpheniramine maleate, dihydroergotoxine methanesulfonate, diphenoxylate hydrochloride, droperidol, epinephrine, ethambutol hydrochloride, fluoxymesterone, hexetidine, hydroflumethiazide, hydroxyzine dihydrochloride, 6-mercaptopurine, phenobarbital, sulfamethazine, thiostrepton, trimethoprim, and tubocurarine chloride.

The entire series should be included in school of pharmacy library reading rooms and in university science libraries. They contain important drug data that have not been available previously in one single reference source. The series is not meant to be used as a textbook but can be employed effectively as reference material for any pharmaceutical or medicinal chemistry course.

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NOTICES

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