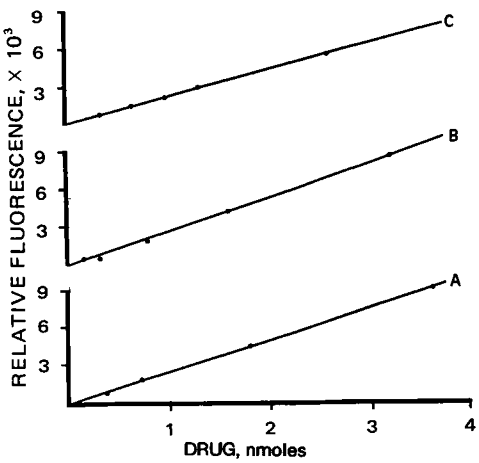

Figure 3—*Stoichiometric correlation of the direct reaction of imipramine (A), chlorprothixene (B), and amitriptyline (C) with 9-bromomethylacridine. Each point is the mean of three values.*

The described assay methodology has shown a specificity for tertiary amines, which precludes the possibility of interference due to the primary and secondary amine metabolites generally present in the blood of patients receiving drugs such as chlorpromazine (6, 7, 10) and amitriptyline (11, 12). However, the methodology does not presently discriminate between mixtures of tertiary amine drugs such as chlorpromazine and chlorprothixene. Nonetheless, it should be possible to differentiate the quaternary products of these drug mixtures by developing new TLC systems capable of such separations or by exploring electrophoresis prior to the photolytic step. These and other approaches are being attempted.

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ˣ To whom inquiries should be directed (at 625 Elm Avenue, Norman, OK 73069).

Effects of Various Hydrodynamic Conditions on Dissolution Rate Determinations

FRED L. UNDERWOOD * and DONALD E. CADWALLADER ˣ

Abstract □ An automated potentiometric procedure was used in dissolution rate studies to determine the effects of various hydrodynamic conditions on dissolution rate determinations. Changes in the hydrodynamics of the system resulted from using various sizes and shapes of dissolution vessels. Dissolution rate constants for benzoic acid prills in distilled water at pH-stat 6.2 were used as a measure of the agitation intensities present in the different shaped vessels. Great variations in the dissolution rates occurred in vessels with the same diameter and stirrer blade position when the shapes of the bottom of the vessel were varied. A similar order of dissolution rates was obtained at 100 and 150 rpm for the individual vessels at various propeller heights. The order differed from one vessel to another, depending on the shape of the bottom (concave, convex, or flat) of the vessel. In some cases, a change in the type of bottom resulted in the opposite order of rates for vessels with the same diameter.

Keyphrases □ Dissolution rate—benzoic acid, effect of varying hydrodynamic conditions by varying sizes and shapes of dissolution vessels □ Hydrodynamic conditions—effect on dissolution rate of benzoic acid by varying sizes and shapes of dissolution vessels □ Benzoic acid—dissolution rate, effect of varying hydrodynamic conditions by varying sizes and shapes of dissolution vessels

For several years, it has been recognized that the availability of a drug for GI absorption from solid dosage forms is often reflected by *in vitro* dissolution rates. This observation has stimulated research in dissolution rate studies. Many different variables, *e.g.*, particle size of dissolving substance, agitation intensity, temperature, and size and shape of the dissolution vessels can influence the dissolution rate of a substance.

Noyes and Whitney (1) made the first quantitative study of the dissolution process and derived an equation relating the dissolution rate to the surface area of the dissolving material. A relationship between dissolution rates and agitation intensity has been known to exist for some time, but relatively few studies have been carried out to show how various hydrodynamic conditions that can influence the agitation can affect the dissolution rate of a drug. The agita-

Table I—Sizes and Shapes of Dissolution Vessels

Outside Diameter, mm	Type of Bottom	500-ml Water Depth[a], mm
60	Flat	210
60	Concave	215
60	Convex	205
80	Flat	115
80	Concave	125
80	Convex	105
100	Flat	72
100	Concave	82
100	Convex	62

[a] This dimension is the height of the fluid surface from the bottom of the vessel when filled with 500 ml of distilled water at 37°.

tion effects on dissolution rates were studied using four vessels of different sizes and shapes (2). The effect of these different vessels on the dissolution rates was demonstrated; the vertical position of the agitator was varied in one vessel to study the effects of this variable on dissolution rates.

Hixson and Wilkens (3) conducted experiments in a series of geometrically similar cylindrical vessels, ranging in volume from 2.8 to 1338.7 liters (0.73 to 353 gallons), to study the performance of agitators in liquid–solid chemical systems. The same series of vessels was used to study the rate of dissolution of solids in liquids (4).

The flow patterns were compared in several geometrically dissimilar dissolution apparatus widely used in dissolution rate studies (5). Seven types of dissolution apparatus were tested to assess experimental reproducibility and apparatus variables and to examine the adherence of the kinetics of the dissolution process to theoretical rate laws (6). No attempt was made to examine the effect of changing variables such as agitation intensity, solvent volume, or geometry for a given apparatus. These studies appear to be the only reported experiments relating the effect of different geometrical shapes of dissolution vessels to dissolution rates.

Many types and shapes of containers are used in dissolution rate studies and testing procedures. Three commonly used ones are flat-bottom beakers (7), round-bottom vessels (8), and concave-bottom vessels (9). The purpose of this investigation was to show the effect of various hydrodynamic conditions, particularly the effect of different geometrically shaped dissolution vessels, on the dissolution rate of a model drug.

EXPERIMENTAL

Materials—Benzoic acid USP[1] was the model drug selected for these studies. Prills of benzoic acid were made by carefully melting benzoic acid powder (mp 122.4°) and spraying the melt into the air. The melt was aspirated into a preheated 1-ml tuberculin syringe fitted with a 1.27-cm (0.5-in.) 27-gauge stainless steel needle. The melt was sprayed into the air by pushing the plunger in rapidly. The droplets of benzoic acid formed spherical shapes while in the air, where they cooled and solidified. The prills were collected and separated into the desired size fraction (20–30 mesh) by sieving.

Equipment—A pH-stat instrumental setup[2] similar to that of Shah (10) was used. It consisted of an automated titrator with a pH meter, an autoburet unit, a titragraph recorder, and appropriate electrodes. The equipment recorded, as a function of time, the supply of correcting acid or base required to maintain a sample at a constant pH. A temperature compensator was used to compensate for slight pH variations at different temperatures.

[1] Fisher Scientific Co.
[2] Radiometer–Copenhagen, 72 E. M. Drupvej, Copenhagen NV, Denmark.

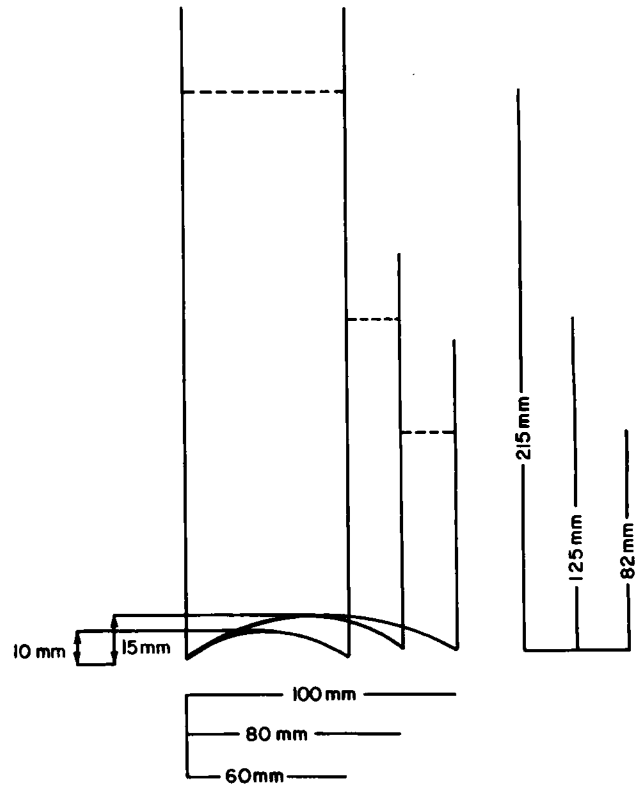

Figure 1—*Diagram of concave-bottom vessels. Broken lines (- - -) indicate water levels.*

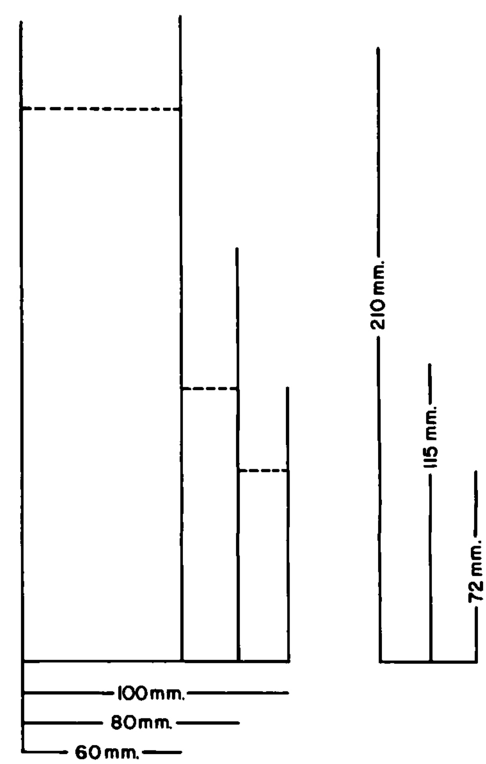

Figure 2—*Diagram of flat-bottom vessels. Broken lines (- - -) indicate water levels.*

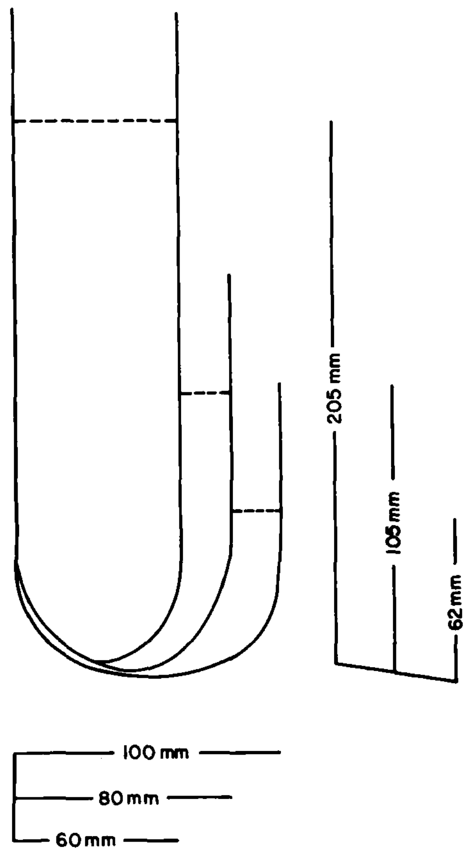

Figure 3—*Diagram of convex-bottom vessels. Broken lines (- - -) indicate water levels.*

The dissolution assembly used for the dissolution rate studies consisted of a double-walled glass-jacketed container and a constant-temperature circulating water bath[3]. This container could accommodate different types and sizes of dissolution vessels. Agitation was produced using a stainless steel marine-type propeller attached to a stainless steel shaft 8 mm in diameter. The propeller consisted of three round blades, 18 mm in diameter, set at 45° angles to the shaft. The propeller had a stirring diameter of 5 cm, and its speed was maintained at a constant rate by a constant-speed torque-controlled unit[4].

Nine glass dissolution vessels with different shaped bottoms were used. Their dimensions are presented in Table I, and diagrams are shown in Figs. 1–3.

Dissolution Studies—A volume of 500 ml of distilled water was placed in the dissolution vessel and brought to 37 ± 0.1° in the constant-temperature bath. A pH-stat of 6.2 was used in all experiments. The propeller was centered at a preselected distance from the bottom of the dissolution vessel, and an accurately weighed sample (0.50 g) of the drug was added to the dissolution medium while the stirrer was rotating at the desired speed. A dissolution rate profile of the drug was obtained directly from the chart recorder.

RESULTS AND DISCUSSION

Figures 4–6 and Table II summarize the data concerning the effect of various hydrodynamic conditions, associated with different shapes of vessels and propeller positions, on the dissolution rate of benzoic acid. Dissolution rate constants for the dissolution of benzoic acid prills under various conditions were calculated using the Hixson–Crowell cube root equation (11).

In the 60-mm convex-bottom vessel, the dissolution rates increased as the distance of the stirrer blade from the bottom of the vessel increased. The opposite results were obtained in the 60-mm concave-bottom vessel, where the dissolution rate decreased as the distance from the bottom of the vessel and the stirrer blade increased. In the 60-mm flat-bottom vessel, the dissolution rates decreased with increasing distances between the stirrer blade and vessel bottom up to 90 mm and then increased with increasing distances between the stirrer blade and vessel bottom. The same general pattern was observed at both 100 and 150 rpm (Figs. 4 and 5).

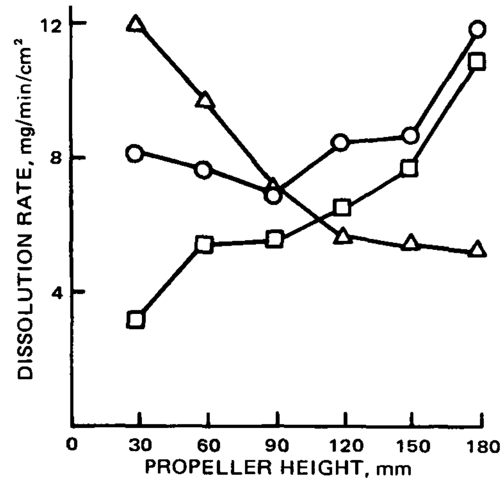

Figure 4—*Effect of propeller position and vessel shape on the dissolution rate of benzoic acid prills in 60-mm o.d. vessels at 100 rpm. Key:* ○, *flat bottom;* □, *convex bottom; and* △, *concave bottom.*

A comparison of the dissolution rates in the 80-mm vessels (Fig. 6) showed the same pattern for 100 and 150 rpm, but the pattern differed from the one shown in the 60-mm vessels. The dissolution rates decreased with increasing distances between the stirrer blade and vessel bottom in the 80-mm concave-bottom vessel and increased in the 80-mm flat-bottom vessel. In the 80-mm round-bottom vessel, the dissolution rate decreased when the distance be-

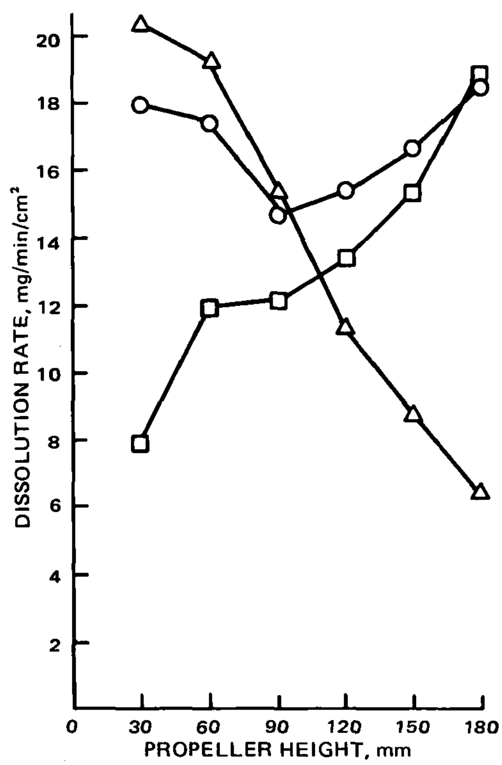

Figure 5—*Effect of propeller position and vessel shape on the dissolution rate of benzoic acid prills in 60-mm o.d. vessels at 150 rpm. Key:* ○, *flat bottom;* □, *convex bottom; and* △, *concave bottom.*

[3] Haake, Yellow Spring Instrument Co.,
[4] Master Servodyne System No. 4425, Cole-Palmer Instrument and Equipment Co., Chicago, Ill.

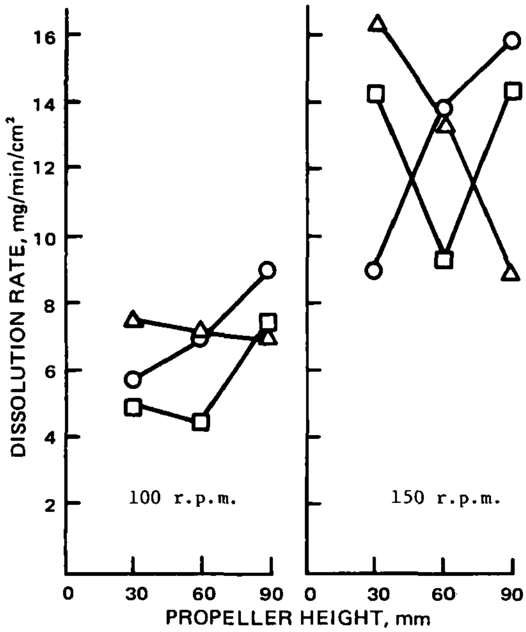

Figure 6—*Effect of propeller position and vessel shape on the dissolution rate of benzoic acid prills in 80-mm o.d. vessels. Key:* O, *flat bottom;* □, *convex bottom; and* Δ, *concave bottom.*

tween the stirrer blade and vessel bottom was increased from 30 to 60 mm, and it increased when the distance was increased from 60 to 90 mm at 100 and 150 rpm.

The dissolution rates increased in all 100-mm vessels when the distances between the stirrer blade and the bottoms of the vessels were increased (Table II). However, variations in dissolution rates occurred between vessels having different shaped bottoms.

As seen in Figs. 4 and 5, the dissolution rates were relatively close together when the distance between the bottom of the vessels and stirrer blade was 90 mm. This finding indicated that approximately the same hydrodynamic conditions were present in the various shaped vessels when the propeller was positioned about midway in the dissolution vessels.

The results of this study emphasize the need for carefully scrutinizing *in vitro* dissolution rate data. This need is illustrated dramatically by the opposite order of dissolution rates obtained from experiments carried out in the 60-mm concave- and convex-bottom vessels. The results of this study indicate that the rate of solution of a drug formulation from a dosage form could pass the dissolution requirement using a vessel with one type of bottom and fail using another.

The wide range of dissolution rates obtained in the same vessels at various propeller heights and from different vessels at the same propeller height stresses the importance of propeller positions and vessel shapes in dissolution studies. The need for using the same size and shape vessels, identical stirrer blades, and the same stirrer blade positions for obtaining reproducible dissolution data in quality control or for reproducing results between laboratories is evident from the results obtained in this study.

There appears to be general agreement among those engaged in dissolution rate studies that a correlation between *in vitro* dissolution data and *in vivo* absorption data is of utmost importance. Levy *et al.* (12) pointed out the pronounced sensitivity of the dissolution rate of a drug in tablet form to small changes in agitation intensity. They also showed that small changes in agitation intensity as obtained by a change in stirring rate can yield results contrary to those obtained *in vivo* or with much greater differences from those observed in the clinical data. Results of this present study indicate that maintaining a constant shaped vessel and stirrer blade position in *in vitro* dissolution tests could be just as important as using a constant stirrer speed to maintain a constant agitation intensity.

Table II—Dissolution Rate Constant (Milligrams per Minute per Square Centimeter) for Dissolution of Benzoic Acid Prills (20–30 Mesh) in Different Vessels at Various Propeller Heights at 100 and 150 rpm

Type[a] and Diameter of Vessel, mm	100 rpm		150 rpm	
	30 mm	60 mm	30 mm	60 mm
A-100	11.36	14.85	17.25	19.28
B-100	7.28	12.64	15.68	18.86
C-100	7.13	—	19.01	—

[a] A = flat-bottom vessel, B = convex-bottom vessel, and C = concave-bottom vessel.

Hixon and Crowell (2, 11, 13) thoroughly investigated the dependence of reaction velocity upon surface and agitation. In describing the nature of agitation on a liquid medium in a qualitative way, they concluded that it would be impossible to calculate the agitation of the total volume of the liquid as a continuous medium, since it varied from point to point. They also pointed out that the shape of the container was important, since it served in general to modify the motion generated in the fluid medium by the agitator. The results of this study tend to bear out their statements.

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* Present address: School of Pharmacy, University of Arkansas, Little Rock, AR 72201

ˣ To whom inquiries should be directed.