Design and Evaluation of a Rotating Filter–Stationary Basket *In Vitro* Dissolution Test Apparatus II: Continuous Fluid Flow System

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Abstract □ The rotating filter-stationary basket apparatus reported previously for the determination of dissolution rates in fixed fluid volumes was modified for use as a continuous fluid flow dissolution test system. The modified apparatus, consisting of a smaller size fluid container, provides a convenient means of maintaining sink conditions during the dissolution process by a continuous exchange of a portion of the dissolution medium with fresh solvent. Equations are developed to calculate the total amount of drug dissolved as a function of time from continuous-flow dissolution rate profiles. Dissolution rate results for several tablet samples of an antidiabetic drug evaluated under continuous fluid flow conditions are comparable with the results obtained under fixed fluid volume conditions, and they also correlate with *in vivo* blood sugar-lowering activity of the tablets.

Keyphrases □ Dissolution test apparatus—design and evaluation of a continuous fluid flow system, rotating filter-stationary basket □ Continuous fluid flow system—design and evaluation of rotating filter-stationary basket dissolution test apparatus □ Drug dissolution profiles—using continuous-flow system, design and evaluation of rotating filter-stationary basket apparatus, equations developed

In the design of a reliable *in vitro* dissolution test model that can positively characterize the role of the dissolution process in drug bioavailability, it is essential that the model is capable of simulating test conditions that are likely to prevail during the *in vivo* dissolution process. One such condition is the maintenance of nearly perfect sink conditions during *in vitro* dissolution rate determinations; *i.e.*, the drug concentration in the dissolution medium does not exceed 10–20% of solubility. This condition is required because in a dissolution rate-limited drug absorption process, there is no appreciable build-up of drug concentration in GI fluids—they act as an infinite sink. It has been suggested, therefore, that unless similar sink conditions are embodied in the *in vitro* dissolution test model, *in vitro* results will bear little relation to the *in vivo* observations (1, 2).

The types of systems employed for maintaining sink conditions during the dissolution process are: (*a*) fixed fluid volume, (*b*) multiple phase, and (*c*) continuous fluid flow. In the fixed fluid volume system, dissolution studies are performed in a finite volume of aqueous dissolution medium, a volume sufficient to maintain solution concentration below 10–20% of drug solubility. Simplicity in the design and operation of this system has probably favored its extensive use in a number of dissolution test methods (3–7), including those recognized by the official *compendia* (8, 9). However, the fixed fluid volume system is unsuitable for relatively insoluble and/or high dosage drugs because of the practical limits up to which large fluid volumes can be conveniently used in a dissolution test.

In the multiple-phase system, the drug upon dissolution into an aqueous medium is either partitioned into a water-immiscible organic phase or adsorbed by a solid adsorbent. Since both approaches provide sink conditions by constant removal of dissolved drug from the dissolution medium, they may be employed in the dissolution rate determinations of all drugs regardless of their solubility and strength per unit dose. Although the feasibility of these multiple-phase systems has been demonstrated (2, 10, 11), additional parameters involved in these systems, such as selection of proper organic phase or adsorbent, rate of partitioning and adsorption, and miscibility of organic and aqueous phases, will obviously complicate the dissolution test methodology. Niebergall *et al.* (12) stressed the importance of selecting the proper type of organic phase in a multiple-phase dissolution test method.

The continuous fluid flow system provides a relatively simple and convenient test system applicable for the determination of dissolution rates of all drugs under sink conditions, regardless of their solubility and dosage strength. As in the multiple-phase system, the sink conditions in this system are maintained by constant removal of the dissolved drug from the dissolution medium, but none of the above-mentioned partitioning and adsorption parameters are involved. The constant removal of the dissolved drug in this system is achieved by continuous elimination of the filtered dissolution medium from the dissolution chamber and simultaneous addition of fresh solvent into the chamber. Several continuous-flow dissolution test apparatus were reported in the literature (13–18). In all of these apparatus, continuous filtration of effluent dissolution medium is performed by wire mesh screen, sintered glass, membrane, or other similar static filter elements. As demonstrated in previous work (19), continuous filtration through such a static filter may not only create serious operational problems but may also introduce analytical errors in the dissolution rate results due to the occurrence of filter clogging, diminishing fluid flow rates, and escape of solid particles into the filtrate.

A rotating filter–stationary basket dissolution test apparatus, described previously (19), incorporates a dynamic, nonclogging, microporous filter medium. This apparatus, with a relatively large-volume (1.5 liters) fluid container, was designed primarily as a fixed fluid volume dissolution test apparatus. While it can be employed as a continuous-flow system, replacement of a fraction of the large volume of dissolution medium requires excessively fast fluid flow

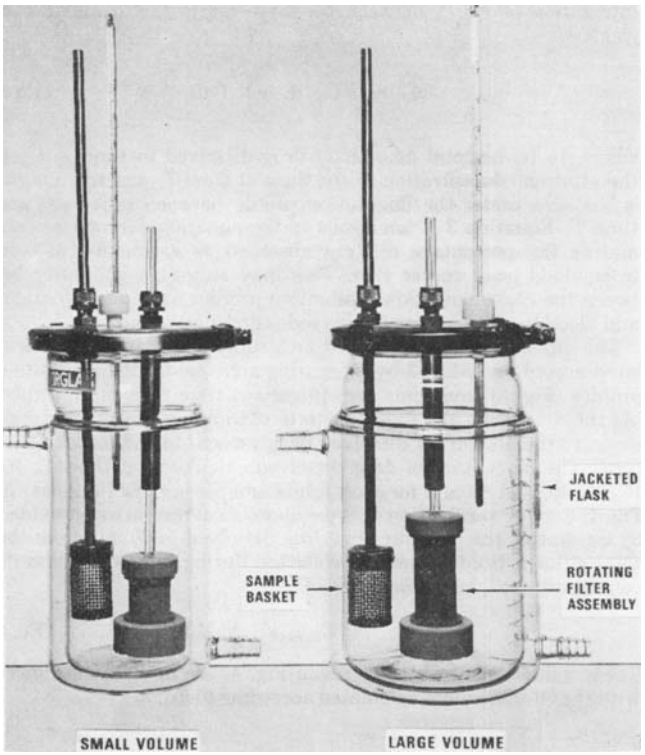

Figure 1—*Photograph of the small- and large-volume rotating filter–stationary basket apparatus.*

rates and consumption of appreciable quantities of solvent media. Fluid replacement at a rate of 20%/min for 1 liter of bulk dissolution medium, for instance, requires a flow rate of 200 ml/min; if the test is continued for 30 min, a total of 7 liters solvent media is consumed. These conditions are obviously not very convenient for routine dissolution experiments. This report describes the design of a small-volume rotating filter–stationary basket apparatus and its application as a continuous fluid flow dissolution test system.

EXPERIMENTAL

Test Samples—Samples from five different tablet lots of a highly insoluble antidiabetic drug were employed. The formulation of all five lots was identical, but each tablet lot was manufactured using a different particle-size bulk drug. The disintegration time of these tablet samples was less than 45 sec. These tablet samples were also employed in a previous study (19).

Apparatus—The basic design of the small-volume continuous-flow apparatus is similar to the large-volume rotating filter–stationary basket apparatus reported previously (19). Each consists of a rotating filter assembly, a stationary sample basket, and a closed jacketed flask (Fig. 1). A detailed description of these components was given previously (19). Modifications incorporated in the fabrication of the continuous-flow apparatus are a smaller diameter flask and a shorter size rotating filter assembly which suspends closer toward one side of the flask. The filter assembly was shortened by reducing the size of two of its parts: the filter head and the cylindrical filter element. Suspension of the assembly closer toward one side of the flask was necessary to accommodate both the filter assembly and the sample basket inside the small diameter flask. The small-volume apparatus can hold up to 700 ml of dissolution medium, and at least 300 ml is required to keep the filter assembly and the sample basket completely immersed in the liquid.

The broken lines in the schematic diagram of the continuous-flow apparatus (Fig. 2) represent the fluid flow system, with arrows pointing the direction of liquid flow. According to this arrangement, the dissolution medium is filtered continuously through the rotating filter assembly and withdrawn from the upper end of the pilot tube. Then it is circulated through a spectrophotometer flow cell by means of flexible tubing passing through a multichannel peristaltic pump[1] and finally discarded or collected in a separate container. Fresh solvent is simultaneously pumped into the flask at the same rate as the liquid elimination rate, so a portion of the dissolution medium in the flask is constantly being replaced with the fresh solvent without changing the volume of the fluid in the flask.

Procedure—Dissolution characteristics of antidiabetic tablet samples were evaluated by continuous fluid flow and fixed fluid volume test systems using the small- and large-volume rotating filter–stationary basket apparatus, respectively.

In continuous-flow experiments, 300 ml of simulated intestinal fluid USP (without pancreatin) was equilibrated at 37° and 400 rpm stirring speed in the small-volume apparatus. Approximately 3 liters of the fluid was maintained at 37° in a separate thermostated reservoir. The peristaltic pump was set to regulate continuous addition of fresh solvent from the reservoir into the dissolution flask at the rate of 38 ml/min and liquid removal from the flask at the same rate through the filter assembly. During the dissolution experiment, minor adjustments in fluid flow rates were required to maintain a constant liquid level corresponding to 300 ml bulk fluid volume in the flask. The dissolution experiment was started by lowering the sample basket containing two 2.5-mg tablets through the opening in the Plexiglas cover. A Plexiglas disk attached to the basket-holding rod fits inside the cover opening (Fig. 2) to hold the sample basket stationary at a precise level inside the flask. Dissolution rate profiles were obtained by continuous automated recording of the absorbance upon circulation of the dissolution medium through the spectrophotometer flow cell. To calculate the amount of drug dissolved as a function of time, areas under the dissolution profile from zero to various time intervals were measured using a planimeter. The total amount of drug dissolved in 60 min was also determined from the total volume of the effluent fluid collected during this period and the overall concentration of the total effluent.

The procedure employed in the fixed fluid volume dissolution test experiments was similar to the previous studies (19). One

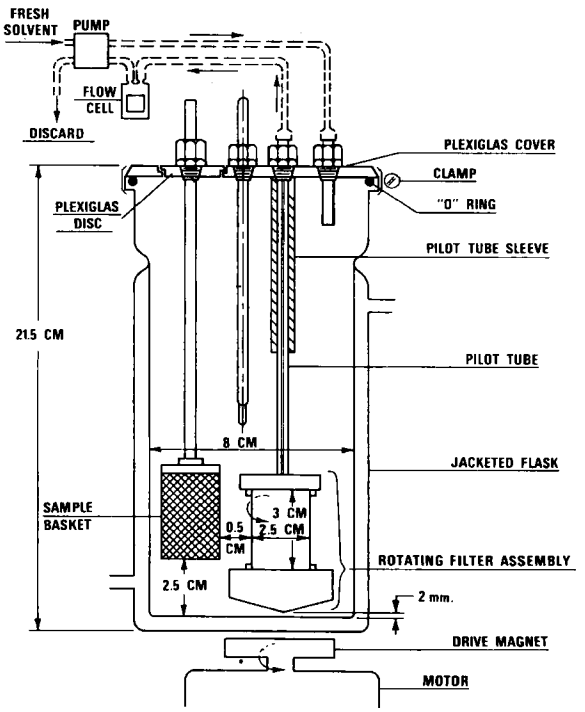

Figure 2—*Schematic diagram of the small-volume rotating filter–stationary basket apparatus.*

[1] Model 1210, Harvard Apparatus Co., Millis, MA 02054

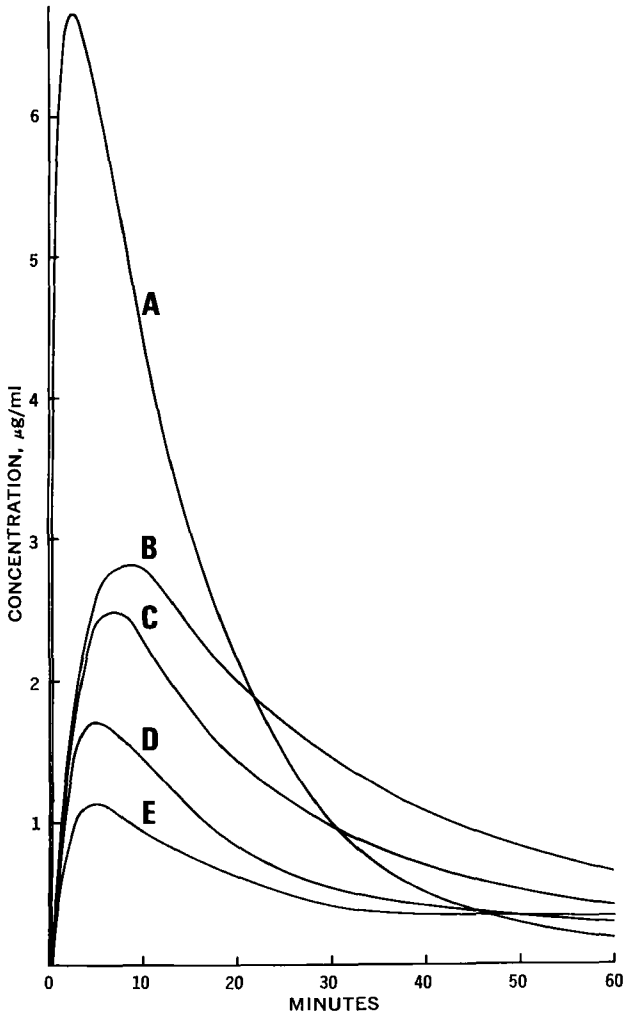

Figure 3—*Spectrophotometric recordings of the continuous-flow dissolution profiles for five antidiabetic tablet samples.*

liter of simulated intestinal fluid USP (without pancreatin) was equilibrated at 37° and 400 rpm stirring in the large-volume apparatus. The sample basket containing one 2.5-mg tablet was introduced into the apparatus. The dissolution rates were monitored by automated spectrophotometric analysis of the dissolution fluid samples.

RESULTS AND DISCUSSION

Dissolution profiles for the five tablet samples determined by the continuous fluid flow system are shown in Fig. 3. The initial rise followed by a decline in solution concentrations indicates occurrence of drug dissolution initially at a faster rate and later at a slower rate than the rate of elimination of the dissolved drug. For these continuous-flow dissolution profiles, the rate of dissolution as a function of time may be expressed as:

$$\frac{dA}{dt} = V\left(\frac{dC}{dt} + KC\right) \qquad \text{(Eq. 1)}$$

where dA/dt is the rate of dissolution, V is the fluid volume in the dissolution flask, K is the first-order rate constant for elimination of the dissolved drug from the flask, dC/dt is the slope of the dissolution profile at time t, and C is the concentration of drug in the dissolution medium at time t. Since the elimination rate constant equals the ratio of fluid flow rate ν, to the fluid volume V, substitution of ν/V for K in Eq. 1 yields:

$$\frac{dA}{dt} = V\frac{dC}{dt} + \nu C \qquad \text{(Eq. 2)}$$

Integration of Eq. 2 between the time limits $t = 0$ and $t = T$ yields:

$$A_T = VC_T + \nu\int_0^T C\,dt \qquad \text{(Eq. 3)}$$

where A_T is the total amount of drug dissolved in time T, C_T is the solution concentration in the flask at time T, and the integral is the area under the dissolution profile between time zero and time T. Equation 3 is analogous to the equation derived for estimating the percentage of drug absorbed as a function of time from blood level curves (20). This may suggest a similarity between the continuous-flow dissolution profiles as an *in vitro* index and blood level data as an *in vivo* index of drug availability.

The amount of drug dissolved as a function of time was calculated according to Eq. 3 by measuring areas under the dissolution profiles (Fig. 3) from time zero to various time periods, multiplying these areas by the fluid flow rate (38 ml/min), and then adding it to the amount of dissolved drug present in the flask at that time. The percentage of drug dissolved calculated at times 5, 10, 15, 20, 40, and 60 min for each tablet sample is shown (circles) in Fig. 4. Further verification of these dissolution results was provided by estimating the percentage of drug dissolved in 60 min from the total effluent fluid volume V_e collected during this period and its concentration C_e according to Eq. 4:

$$A_{60\,\text{min}} = C_{60\,\text{min}}V + C_eV_e \qquad \text{(Eq. 4)}$$

These values, shown by squares in Fig. 4, are in close agreement with the 60-min values calculated according to Eq. 3.

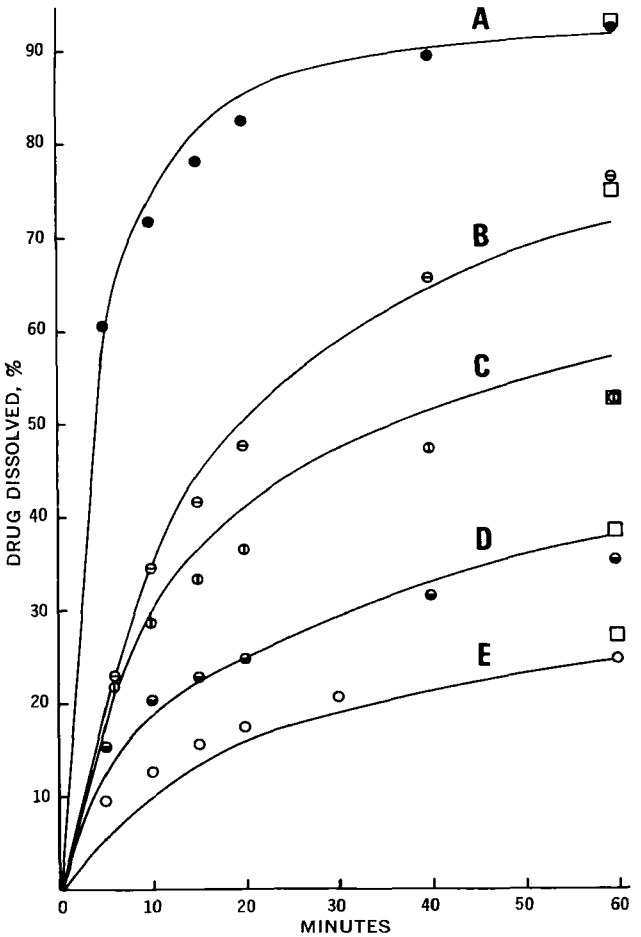

Figure 4—*Comparison of dissolution rate results for tablet samples obtained by continuous-flow and fixed fluid volume systems. Lines represent the results obtained by fixed fluid volume experiments and points are the values calculated from continuous-flow experiments.*

Table I—Correlation between Continuous-Flow Dissolution Rates of Antidiabetic Tablets and Their Blood Sugar-Lowering Response in Dogs

Sample	Percent Dissolved in 60 min	Total Blood Sugar-Lowering Response in 24 hr, mg %
A	92.3	293
B	76.2	256
C	52.5	250
D	35.3	225
E	24.7	167

Dissolution profiles for the tablet samples determined by the fixed fluid volume process are represented by lines in Fig. 4. These results also seem to be in reasonable agreement with the continuous-flow dissolution test results. However, although the stirring speed of 400 rpm was employed in both the continuous-flow and fixed fluid volume experiments, because of the different size apparatus and liquid volumes employed in these two experiments the actual intensity of liquid agitation may not be the same. Nevertheless, for the tablet samples examined, it seems that the rate of dissolution is not significantly influenced by minor differences in the intensity of liquid agitation.

The dissolution rate results for the antidiabetic tablet samples obtained by the continuous fluid flow test system are listed in Table I along with the previously reported results for the blood sugar-lowering activity of these tablets (19). Comparison of these two sets of data indicates a rank-order correlation between the *in vitro* dissolution rates of the tablets and their *in vivo* activity ($\gamma = 0.9191$).

In the continuous-flow dissolution experiments, the test sample consisted of two 2.5-mg tablets; in the fixed fluid volume experiments, one 2.5-mg tablet was employed. Selection of the sample size was based on the consideration of maintaining sink conditions in the fixed fluid volume system while simulating conditions that may arise in testing relatively insoluble high dosage drugs by the continuous-flow system. Since the solubility of this drug is 20 μg/ml, dissolution of 2.5 mg drug in 1 liter fixed fluid volume will yield solution concentrations up to 12.5% of saturation. Similarly, it is evident from the continuous-flow dissolution profiles (Fig. 3) that except for the fast dissolving Sample A, solution concentration never exceeded more than 14% of saturation. For the fast dissolving Sample A, the peak solution concentration reached was about 34% of saturation. In this case, the sink conditions were maintained by repeating the test at a faster fluid flow rate of 90 ml/min, which lowered the peak solution concentration to about 19% of saturation.

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