Dissolution Rate Studies I: Design and Evaluation of a Continuous Flow Apparatus

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Abstract □ An apparatus for the study of dissolution rate under conditions of continuous flow is described. Typical data are presented; the effect of sample size, surfactant, and flow rate on the dissolution behavior of prednisone powder and prednisone tablets is shown. The requirements of an ideal standard method for studying dissolution rates are discussed, and the major advantages of this method over present methods are pointed out. The method: (*a*) is more flexible, (*b*) produces data in a differential form, (*c*) utilizes a small-volume system which assures greater homogeneity, (*d*) prevents excessive accumulation of solute in the system, and (*e*) provides agitation and solvent flow in a controlled, measurable, and physically meaningful manner.

Keyphrases □ Dissolution apparatus—design, evaluation □ Diagram—dissolution apparatus □ Prednisone—dissolution rate profile □ Surfactant concentration effect—prednisone dissolution □ Sample size effect—prednisone dissolution □ Flow rate effect—prednisone dissolution

There is little doubt that the determination of dissolution rates is an important tool in the design, evaluation, and control of solid dosage forms. Parrott *et al.* (1) has stated: "The release of a drug from the primary particle and its subsequent availability to the body is governed by the dissolution rate of the particle." Nelson (2–4) also pointed to the significance of dissolution rate in determining drug availability in his series of publications on the dissolution rates of weak acids and bases and their salts.

For obvious reasons, it would be ideal if one relatively simple and inexpensive apparatus and method could be used to determine the dissolution rates of most drugs and drug products. However, standing in the way of the one-method concept is the fact that a great variety of factors influence the results obtained from dissolution rate tests. These include factors intrinsic to the products, such as physical-chemical properties of the drug and the variations in the composition of the formulation, and factors extrinsic to the products, such as the type and volume of solvent, the degree, type, and uniformity of agitation, the geometry of the container, the state of homogeneity existing in the system, and adsorption or adherence of the drug to solid surfaces of the apparatus. In light of these factors, a single method is feasible only if it has adequate flexibility to allow sufficient controlled variation of experimental conditions to ensure, regardless of what drug is studied, that the results will reflect primarily the intrinsic variables rather than the extrinsic.

Flexibility is a necessary requirement for a standard dissolution rate method for another important reason. There is presently an acknowledged scarcity of data showing correlation between *in vitro* dissolution rates and *in vivo* absorption, but the great current interest and activity in this area indicate that more and more data will be forthcoming. As the knowledge in this area accumulates, problems and deficiencies in the *in vitro* methods will come to light, necessitating changes in equipment and procedures. The more flexible the standard method is, the more easily such changes can be made to accommodate the new findings.

In addition to flexibility, there are two other basic requirements that a standard dissolution rate method should meet. It should yield accurate, meaningful, and reproducible data that can be quantitatively related to theoretical dissolution rate equations, and it should be sensitive enough to detect small differences among various drugs and among different formulations of the same drug. Unfortunately, present dissolution rate methods lack the necessary flexibility, their basic design introduces far too many uncontrolled variables into the dissolution process, their method of agitation cannot be quantitatively related to dissolution rate equations except by including it in the constant, and they produce data in such a way that only gross differences in formulations can be detected.

The serious deficiencies in these methods can best be shown by first looking at the Noyes-Whitney equation (5) which, in theory, describes the dissolution process: $da/dt = KS(C_s - C)$, where da/dt is the dissolution rate expressed as amount dissolved per unit time, S is the surface area of undissolved solute presented to the solvent, C_s is the concentration of solute in a saturated solution, C is the solute concentration in the bulk of the medium at any time, and K is a constant dependent on a variety of factors including the temperature, viscosity, pH characteristics, degree of agitation of the medium, and the diffusion coefficient of the solute molecules. While numerous attempts have been made to expand this equation to include various additional factors (6–9), none of these has led to an expression which adequately takes into account all the variables involved.

The dissolution process is particularly complicated when considering solid dosage forms. In the case of pure powdered drug, assuming immediate wetting, the surface area will continually decline as more and more particles dissolve. With capsules and tablets, however, the situation becomes more involved because, as they disintegrate or disperse in the medium, the amount of exposed surface area initially increases, going through a maximum and then decreasing in the conventional pattern.[1] How quickly a tablet disintegrates and the granules and drug particles disperse depends, among other factors, upon the composition of the formulation, the amount of pressure used in compression, the

[1] Wagner (10) has suggested an interesting statistical approach of the empirical linearization of the dissolution data using product or log product paper, which apparently takes into account the variation of dissolution surface area.

amount of entrapped air (which affects both the wetting and the bulk density of the particles), the volume of the liquid, the geometry of the container, and the degree and type of agitation.

Since these systems are so variable and complex, a dissolution rate method which seeks to meet the requirements listed for a universal method must help solve, not add to, the inherent problems involved in studying the dissolution process. Unfortunately, present methods are almost exclusively based on a static system involving solvent present in "bulk" form; the system is stirred by a motor-driven propeller or wire mesh basket or by a rocking device, and discrete samples are withdrawn and analyzed at various times (11). The basic disadvantages of these methods, inherent in the basic design, are: (*a*) a lack of flexibility, (*b*) a lack of homogeneity (caused by both the large volumes and agitation methods employed), (*c*) a variable concentration gradient, (*d*) a method of agitation that is semiquantitative at best and relates poorly to theoretical dissolution rate equations, and (*e*) the data produced tend to obscure the details of the dissolution process.

The inherent lack of homogeneity in these methods results from both the agitation methods and large volumes employed. Agitating the liquid by stirring with a wire mesh basket[2] or a propeller, or by a rocking motion, causes a variable shear rate of transfer over the surface of the particles, which results in excessive variations in their individual rates of dissolution. The movement of solvent over any particle will depend on the position of the particle in the vessel and the character of the stirring process at each position within the container.

The latter varies markedly with the geometry of the vessel, the volume of the liquid, and the speed and form of motion created by the agitator. While it is possible to standardize many of the geometric and mechanical factors, nevertheless the agitation varies at different positions in the container. In addition, various sized granules and particles disperse differently throughout the system. While a tablet is disintegrating, the granules tend to collect at the bottom of the container, the remainder of the tablet is in the basket in the center of the system, some of the granules are stuck in the screen, and the fine particles are dispersed throughout the medium. As a result, the apparatus introduces an inherent variability into the dissolution process, a variability that is extrinsic to the product under study, and one which cannot be eliminated merely by standardizing the procedure.

The lack of homogeneity caused by the agitation methods could be minimized by keeping the volume of the system small (*e.g.*, 50 ml. or less), but this is not feasible with present methods. As mentioned earlier, the basic equations describing the dissolution process include a term for concentration gradient ($C_s - C$), and since C_s remains constant, it is important that C (the solute concentration in the bulk of the system) be kept as low as possible. With the present static methods, and considering the low solubility of many drugs, using small volumes would result in a significant increase in C as the experiment progressed.

There is another reason why it is important to keep C as low as possible. The ultimate objective in dissolution rate studies is to discern dosage form effects that may later influence the absorption of the drug within the gastrointestinal tract. In the *in vivo* situation, the dissolution process most likely takes place from particles adhering to or very near the mucosal surface. Therefore, the diffusional pathway to the absorption site is very short, and the drug molecules are almost instantly absorbed into what is, for all practical purposes, a perfect sink—the body fluids. Consequently, the chances of achieving good *in vitro–in vivo* correlations in this area are better if the *in vitro* system more closely approaches these perfect sink conditions.

The need for such a perfect sink (*i.e.*, a relatively large volume of solvent) necessitates using a relatively high rate of agitation. But studies of Levy *et al.* (13) have shown that quite often the rate of agitation must be kept low in order to establish meaningful *in vitro–in vivo* correlations. In addition, it is often necessary to use low agitation in order to detect subtle differences between formulations. But low agitation of a relatively high-volume system results in poor homogeneity, and the sample withdrawn for analysis might not be representative of the whole system. Thus, an inherent disharmony exists in these systems between the requirements for homogeneity, large volumes, and low stirring rates.

A further disadvantage of present methods has to do with the empirical nature of stirring or rocking as a device for ensuring homogeneity and moving solvent/solute molecules. Since these agitation methods are empirical, they cannot be related to fundamental dissolution rate equations except by including them in a catchall constant, which is a very superficial solution to the problem. This makes it critical that the various test systems be standardized as much as possible—one stirring rate, one type of container, one volume of solvent, *etc.* But this greatly reduces investigative flexibility, which is a prime requisite for a good standard method, as pointed out previously. Furthermore, the results obtained with such rigid standard procedures will be less and less quantitative and meaningful as drugs of lower and lower solubility are studied, because at fixed volumes the concentration gradient will vary more significantly. And yet it is precisely these drugs that are often most important to study from a drug availability standpoint.

There is one other disadvantage of present methods which should be mentioned. Because they are based on a concept of a static fixed volume, they produce data expressed as an integral function. That is, since the dissolved molecules are accumulating in the solution, the resultant data represent an integral function of the dissolution process rather than a differential function. Thus, these methods produce average dissolution rates at best, and this makes it difficult to detect subtle but possibly important differences in formulations. In other words, two formulations may differ significantly in their dissolution rate behavior; but with present methods these differences would be, in effect, hidden under the

[2] This refers to the proposed USP–NF Dissolution Test, Method I (12).

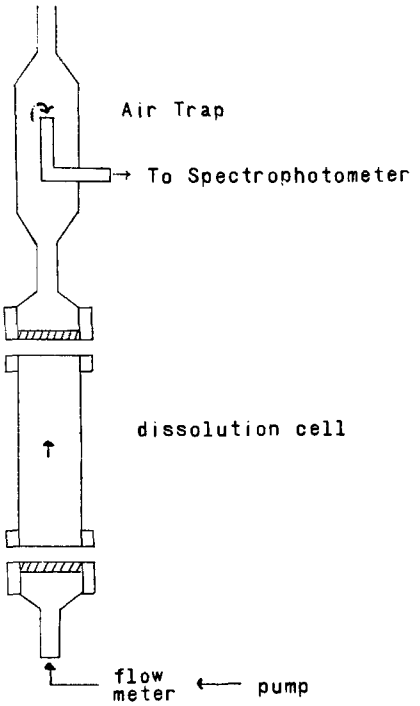

Figure 1—*Sketch of the dissolution rate apparatus. Arrows indicate direction of solvent flow.*

integral curve representing the accumulated drug dissolved up to that time. This will become more apparent in viewing the following experimental results.

In light of the serious deficiences in present methods, it is apparent that a new "standard" dissolution rate method is needed, one that: (*a*) has a much higher degree of flexibility, (*b*) yields data in a differential form which can then be converted to the integral form if desired, (*c*) utilizes a relatively homogeneous low-volume system, (*d*) prevents excessive accumulations of solute in the system, and (*e*) provides solvent flow in a controlled, precise, measurable manner which can be mathematically related to fundamental dissolution rate equations. This communication describes just such an apparatus and method, the basic idea for which was first suggested by Olson (14) and subsequently investigated by Hamlin and Rowe (15) and Langenbucher (16). The apparatus described herein is very similar to that used by these previous workers, with certain modifications.

EXPERIMENTAL

Description of Apparatus—The apparatus is described in Fig. 1. The dissolution cell is a glass cylinder 6.1 cm. long, 1.9 cm. in diameter, and has a volume of 17 ml. This cell was constructed from two small-volume glass filter funnels (Millipore catalog number XXLO-025.00), cut down in height and attached back to back. This allows use of filter membranes of sufficient retentive characteristics to limit the dissolution process to the dissolution cell and prevent solid particles from reaching the spectrophotometer. The dissolution chamber can be dismantled, cleaned, and dried for subsequent determinations with minimal effort. The pump is a centrifugal constant-capacity pump (Cole-Parmer) of low cost. The solvent flow to the system is controlled by external valves, with the excess capacity of the pump being recirculated to the reservoir from which the pump draws the solvent. The flowmeter is a Gilmont size 3 and the filters (shaded area) are standard coarse-porosity sintered glass. The spectrophotometer (Beckman model DB) has an attached recorder. The air trap prevents air bubbles from distorting the spectrophotometric reading.

General Procedure—The dissolution cell and the filters are thoroughly cleaned of residue from the previous run and the apparatus is assembled. The pump is then turned on and the entire system flushed with solvent until the spectrophotometric reading recedes to zero (a few minutes). Then the dissolution cell and the filters are disassembled and dried, and the sample (in these experiments, a tablet or weighed quantity of powder) is placed on the lower filter. The dissolution cell is then clamped into place and the upper filterpiece/air trap attached with a similar clamp. The apparatus is then submerged in a constant-temperature bath, including the flowmeter, lower filter, dissolution cell, and the lower part of the upper filterpiece/air trap. The solvent reservoir and as much connecting tubing as possible are also in the bath. As soon as the cell has reached the bath temperature, the pump is turned on and the flow regulated to the desired flow rate, which is then held constant. At lower flow rates, the flow remained constant; at higher flow rates, occasional adjustments in the valve system were necessary to maintain a constant flow rate. The air outlet, open when the pump is turned on, is closed as soon as the liquid level in the air trap is above the outlet tube to the spectrophotometer. The absorbance is continuously recorded on the strip chart, and the "waste" solution is either discarded or saved in an appropriate receptacle.

For these experiments, prednisone USP[3] (screened 80 mesh) and prednisone tablets USP, 5 mg.,[4] were studied using as solvents either distilled water or various aqueous solutions of sodium lauryl sulfate USP. The bath temperature was 25.0 ± 0.1°. The absorbance was read at 239 mμ using a 1-cm. cell and a molar absorptivity of 15,500. In the concentration ranges studied, the Beer-Lambert law was found to be valid. All determinations were in duplicate. The following experiments were performed primarily to test the usefulness of this apparatus and method. More complete and detailed studies, where the emphasis is on investigating the dissolution process rather than evaluating the method, are in progress.

Effect of Surfactant Concentration—The dissolution behavior of a 5-mg. sample of prednisone powder was studied using various concentrations of sodium lauryl sulfate in distilled water as the solvent. The flow rate was 20.2 ml./min.

Effect of Sample Size—The dissolution behavior of various sized samples of prednisone powder (5, 10, 15, and 20 mg.) was studied using 0.02% w/v sodium lauryl sulfate as the solvent. The flow rate was 20.2 ml./min.

Effect of Flow Rate—The dissolution behavior of 5-mg. prednisone tablets was studied using distilled water as the solvent and varying the flow rate between 10 and 54 ml./min.

RESULTS AND DISCUSSION

Typical dissolution curves for prednisone powder (upper plot) and prednisone tablets (lower plot) as recorded on the strip chart are reproduced in Fig. 2. The tracings are presented for illustrative purposes. No quantitative comparison of the two should be made, since different experimental conditions were used (tablet: 5 mg. prednisone and water as the solvent; powder: 10 mg. prednisone and 0.02% sodium lauryl sulfate as the solvent; in both cases, the flow rate was 20.2 ml./min.). The curves record absorbance, but this is easily converted to dissolution rate (mg./min.) by converting absorbance to concentration (mg./ml.) and multiplying by flow rate (ml./min.).

The roughness of the tablet curve, contrasted with the smooth curve for the powder, is not surprising, since the granules in the tablet do not release the drug at an even rate. Figure 2 shows that a very meaningful and revealing quantitative "dissolution rate profile" (a continuous tracing of the differential function) can be directly obtained with this method. Such a profile has obvious advantages in the development, evaluation, and control of solid dosage forms. The profile gives the formulator and the control analyst a good closeup view of how the tablet or capsule is performing in the dissolution system.

[3] Supplied by The Upjohn Co.
[4] Supplied by the Pharmaceutical Technology Laboratory, School of Pharmacy, University of California, San Francisco Medical Center.

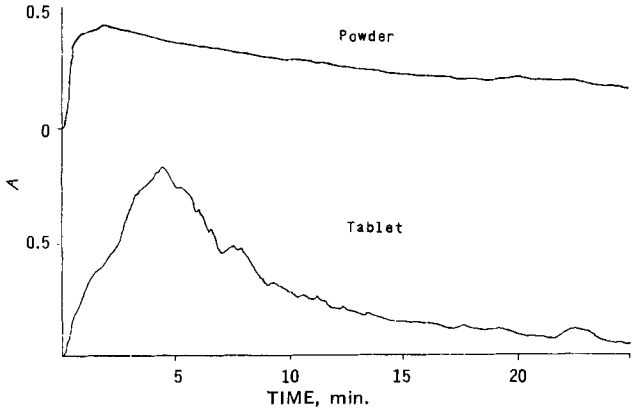

Figure 2—*Typical dissolution rate curves for prednisone powder (upper plot) and prednisone tablets (lower plot) as recorded on the spectrophotometer strip chart.*

The tablet curve in Fig. 2 shows that a definite maximum dissolution rate is reached. In these experiments the peak dissolution rate correlates reasonably well with the total amount of drug dissolved at the end of 5, 10, and 15 min. The total amount of drug dissolved (the integral of da/dt) was obtained by cutting out and weighing the area under each curve. Figure 3 shows the correlation between peak dissolution rate and amount dissolved in the first 15 min. in the tablet experiments. Since (as expected) the values for the integral were more reproducible than the peak dissolution rate, the area under the curve for various time periods was used in subsequent plots.

Effect of Surfactant Concentration—When first working with prednisone powder using water as the solvent, it was observed that the powder agglomerated into one mass in which a considerable amount of air was entrapped. The problem was greatly reduced by including a surfactant in the solvent, but concentrations had to be kept low because of excessive foaming. Wetting was not complete at the highest (0.05%) concentration employed. The influence of surfactant (Fig. 4) emphasizes that the dissolution processes (as commonly considered) is really a combination of two distinct processes: wetting of the solid and subsequent dissolution. As long as the powder is not completely wet, the effective surface area can be considerably less than the total surface area, because a significant amount of the solid is involved in solid–air and solid–solid interfaces rather than in a solid–liquid interface. In such cases, attempts should be made to wet the sample first before trying to perform highly definitive quantitative dissolution rate studies. The desirability of considering the wetting process in dissolution rate studies has been emphasized by Finholt (17).

Since the amount of sodium lauryl sulfate used in the system is well below the critical micelle concentration (~0.2%), it is likely that the surfactant used in these experiments had negligible effect on the saturation solubility of the prednisone. While surfactant solutions were used in studying the dissolution behavior of prednisone powder, water proved to be satisfactory for the tablets.

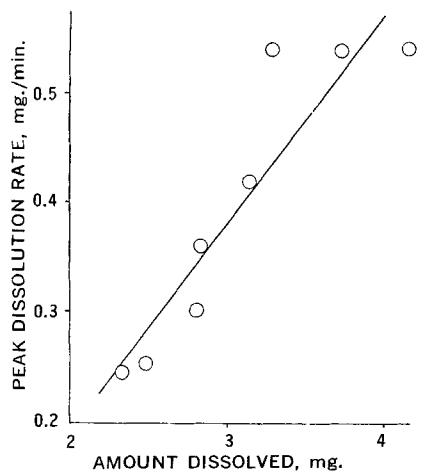

Figure 3—*Plot illustrating the correlation between peak dissolution rate and amount dissolved in the first 15 min. for prednisone tablets.*

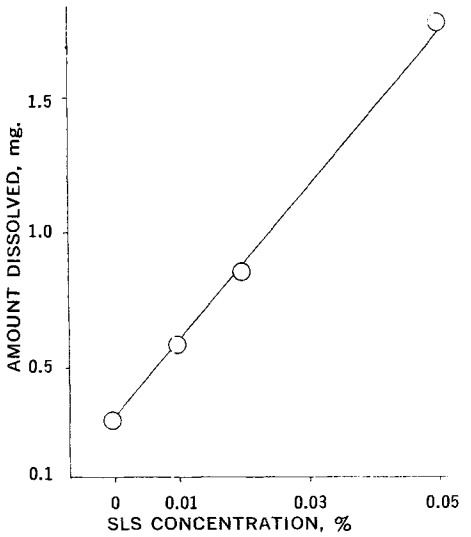

Figure 4—*Plot showing the effect of the sodium lauryl sulfate (SLS) concentration on the dissolution behavior of prednisone powder. The amount dissolved represents the area under the curve for the first 5 min.*

Effect of Sample Size—As mentioned earlier, it is important to keep the concentration of dissolved drug well below saturation. This will depend upon the dissolution rate, the solubility of the drug, and the flow rate. To get some indication of the degree of saturation in these systems, the sample size was varied in the prednisone powder studies and its effect on dissolution rate observed. If the system was close to saturation, increasing the sample size would have only a small effect on the dissolution rate because the concentration gradient ($C_s - C$) would rapidly disappear.[5] Figure 5 shows this effect on the total amount dissolved in 5 min., using sample weight to the two-thirds power as the abscissa. While this coordinate is not entirely accurate (it assumes that the solid is composed of uniform spheres), it does suffice to show that added surface area does significantly increase the dissolution rate, a clear indica-

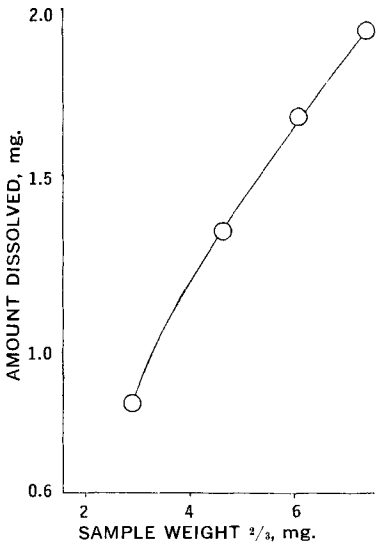

Figure 5—*Plot illustrating the effect of sample size on the dissolution behavior of prednisone powder. The amount dissolved represents the area under the curve for the first 5 min.*

[5] With this flow method, ($C_s - C$) would remain essentially constant using a constant surface pellet. With tablets, powders, *etc.*, the concentration gradient does not remain constant, but the continuous flow of fresh solvent into the system will help keep the concentration gradient at a high level.

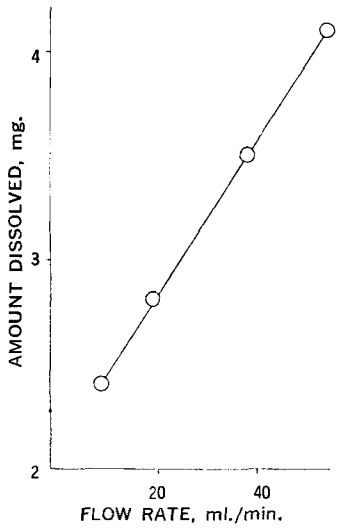

Figure 6—*Plot showing the effect of flow rate on the dissolution behavior of prednisone tablets. The amount dissolved represents the area under the curve for the first 15 min.*

tion that the system is not close to saturation. This was confirmed by determining, in a separate experiment, that these systems were about one-tenth saturated. It should be pointed out that the flow rate in these studies was 20.2 ml./min. It is desirable to repeat this study at lower flow rates for various systems, since the lower the flow rate, the more critical the problem with saturation. However, these experiments have been deferred until more modifications have been made in the equipment.

This emphasizes the flexibility inherent in this method as compared to present methods. If two drugs had widely different solubilities, present methods would dictate changing the volume of the system (*i.e.*, the "dissolution chamber") and the stirring rate (to retain some measure of homogeneity), which would very likely result in a major change in many undefinable variables. With the authors' flow method, drugs of different solubilities can easily be accommodated simply by changing the flow rate (a clearly defined and easily measured parameter) and the amount of solvent used; the size of the dissolution cell would remain the same. While it is true that such changes would produce some undefinable changes in the flow system, it is also true that such changes are very likely to be much less than with present systems.

Effect of Flow Rate—As mentioned, one of the major advantages of this method is that solvent flow around the solid can be carefully and quantitatively controlled. Solvent flow affects the dissolution process by: (*a*) physical abrasion of the solid, (*b*) affecting the solution concentration in the effluent, and (*c*) probably reducing the diffusion layer thickness around each particle. Thus, flow rate, a physically relatable parameter, affects dissolution rate in a quantitative, definable way. Precisely what that effect is must await further studies, but Fig. 6 illustrates that flow rate does, in fact, have the expected significant effect on dissolution rate.

While the development of this apparatus is in its initial stages, it is apparent that the basic design offers many advantages over present methods, many of which have already been discussed. The vertical alignment of the dissolution cell helps ensure that the liquid flow through the cell will be reasonably homogeneous, even when flow rates are very low or comparatively high. Of course, some inherent variation still exists in the flow method because: (*a*) at times it may be necessary to increase flow rate to the point where the flow becomes turbulent, and (*b*) the flow of solvent will not be exactly the same past each and every particle. However, it is obvious that such problems of deviations from ideal will be much less with a smaller, more homogeneous system such as the authors' flow system. The small (17 ml.) volume of the system also ensures homogeneity. If a change of solvent pH is desired in the same experiment (simulating the *in vivo* change from stomach to duodenum), this can quickly and easily be done by switching from one reservoir to another. In contrast, this would be a major problem with present methods.

The number of definitive studies on the apparatus has been minimal, but even with the limited data gathered to date, several postulates arise:

1. The ascending curve for a tablet represents the disintegration and dispersal processes, although they still continue after the peak dissolution rate is reached.
2. At a fixed flow rate, the maximum dissolution rate and/or the time needed to achieve maximum dissolution rate may be useful parameters for comparison of tablet additives relative to the pure (wetted) powder.
3. The descending curve appears to be exponential in shape and, therefore, it may be possible to express the slope in terms of a rate constant or a half-life.

It should be emphasized that the described apparatus is a prototype, and numerous improvements are both possible and probable as more experience is gained. For example, as Langenbucher (16) points out, the cross-sectional area of solvent flow is a variable that must be taken into account. It is also probable that the volume of the dissolution cell should be reduced to a minimum to optimize homogeneity of the system. Fortunately, with this method, reducing system volume is no problem; cell size is limited only by the physical size of the sample and the need to keep the filters of sufficient cross-sectional area to avoid excessive clogging. In addition, the size and shape of the air trap should probably be altered toward a minimum size and optimum shape, because any mixing and pooling of solution beyond the dissolution cell tend to distort the spectrophotometric tracing. An inexpensive integrater can easily be attached to the spectrophotometer to obtain the integral curve as well as the differential tracing.[6] It would be better if the solvent flow was electronically controlled to keep flow rate constant automatically. Finally, the system should lend itself easily to automation.

But despite the preliminary nature of this work, there is little doubt that, based on theoretical considerations, and the results of these experiments, this method is far superior to present methods both for fundamental and practical studies. It is by far the best candidate for a "standard" method among the presently available procedures. Not only is it superior to present methods, but it possibly has the inherent flexibility that may allow it to meet, with appropriate modifications, most or all of the requirements listed for the ideal dissolution rate method.

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ACKNOWLEDGMENTS AND ADDRESSES

Received June 4, 1969, from the *University of California School of Pharmacy, San Francisco Medical Center, San Francisco, CA 94122*
Accepted for publication October 31, 1969.

[6] With present dissolution rate methods, the integral curves obtained can be differentiated by appropriate means, but these would be only average figures unless measurements were made on a continuous basis—and this requires a flow system. But for continuous measurement, the homogeneity of the system becomes even more critical for assay purposes, and it is likely that stirring rates would have to be increased.