Continuous Flow Apparatus for the Determination of the Dissolution Characteristics of Tablets and Capsules

By M. PERNAROWSKI, W. WOO, and R. O. SEARL

The apparatus described in this paper consists of a closed dissolution container, a basket-stirrer assembly, and a variable speed pump. It may be automated by connecting the pump to a flow cell in a suitable spectrophotometer. Two or more test fluids can be used interchangeably for the determination of dissolution characteristics.

THE DISSOLUTION characteristics of a tablet or capsule may be determined by using any one of the many methods described in the literature (1–4). Several different types of dissolution containers, agitation methods, test media, and sampling procedures have been used to determine dissolution profiles or values. However, most methodology is based on either the USP disintegration apparatus (5–7) or on the use of a beaker-stirrer assembly (8–10).

It is now generally accepted that *in vitro* results should be correlated to some physiological parameter. This can only be done if the dissolution method yields results which reflect the physiological differences between chemically similar drug products. This implies that the apparatus should be so designed that its operating characteristics can be easily changed. The apparatus described in this paper is a nodification of the beaker-stirrer method used by Levy (8) and others. A tablet-capsule container has been built into the assembly and provisions have been made for change of test fluids during a dissolution study.

Automated assemblies have been used by several investigators (11–14). The continuous flow apparatus used in this laboratory is easily automated but, at the same time, may be used as a simple flask-stirrer assembly with an auxiliary system for media transfer.

EXPERIMENTAL

Equipment—The continuous flow dissolution apparatus is illustrated in Fig. 1. A diagram of the stainless steel basket-stirrer assembly is shown in Fig. 2. The assembly is connected to a Fisher model 12 Stedi-Speed adjustable stirrer. Ten-mesh stainless steel wire cloth is used in the construction of the main part of the basket.

The dissolution container is a 1-l., three-neck flask. The main neck is 35 mm. in diameter; the secondary necks are 20 mm. in diameter. The total volume of the container is slightly more than 1l.

If fluid flow or changeover is necessary, the container is connected (*via* a suitable filtering device and short lengths of latex tubing) to a Cole-Palmer Series A-76910 pump. The dial readings on this pump are proportional to the pumping rate in ml./min. Flow rates of up to 70 ml./min. have been used in this laboratory. Test fluids may be pumped directly to a collection container. Alternatively, they may be circulated through a 1-cm. flow cell in a Spectronic 505 recording spectrophotometer to the collection flask. Tubing lengths are kept to a minimum.

Dissolution profiles are graphed externally on a previously calibrated Varicord model 43 recorder.

Procedure—Dissolution characteristics may be determined by using exactly 1 l. of fluid or by operating the apparatus as a continuous flow system. If the apparatus is operated continuously, the volume of fluid in the dissolution container is slightly more than 1 l. Dissolution characteristics are based, therefore, on the amount of fluid pumped through the dissolution container.

One of the procedures used in this laboratory for the determination of the dissolution characteristics of phenylbutazone tablets NF is given below and illustrates the continuous flow method of operation with fluid changeover.

Place one phenylbutazone tablet into the basket

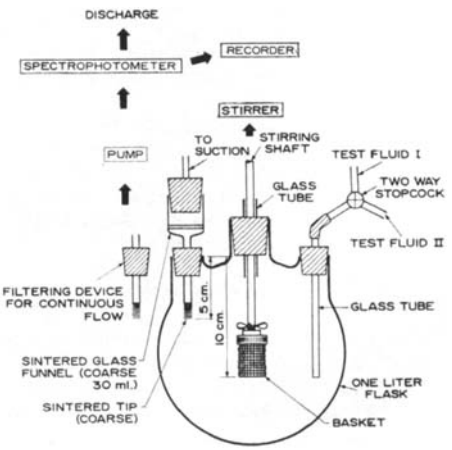

Fig. 1—Continuous flow dissolution apparatus.

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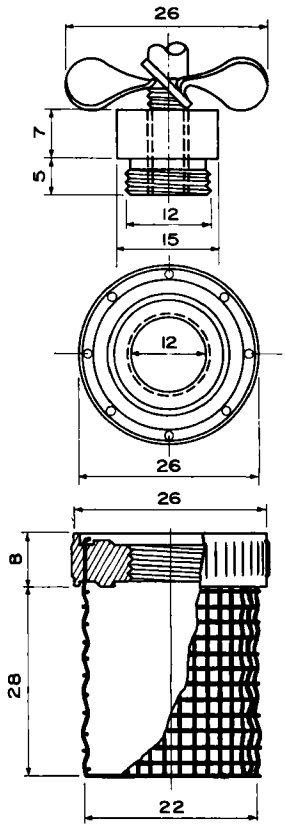

Fig. 2—Specifications (in mm.) for the basket-stirrer assembly used in the dissolution apparatus. The four impeller blades of the stirrer are set at an angle of 45°.

and attach the stirrer. Fill the dissolution container with 1 l. of simulated gastric fluid USP. (The fluid contains no enzyme and is preheated to 37°. Temperature is maintained by immersing the dissolution container in a water bath held at 37°.) Insert the basket-stirrer assembly into the dissolution container and rotate clockwise at 100 r.p.m. Set the pump to deliver 60 ml. of fluid per minute. Allow simulated gastric fluid USP to flow through the container for 30 min. Turn the stopcock connecting the media reservoirs to the dissolution container and allow simulated intestinal fluid USP (no enzyme) to flow through the system for the remainder of the test.

Determine the amount of phenylbutazone in the collection flask at hourly intervals by diluting aliquots with simulated intestinal fluid USP (no enzyme) and reading the absorbance of the solution at 240 mμ (an isosbestic point). Record dissolution profiles on the external recorder.

DISCUSSION

A basket-stirrer assembly similar to that illustrated in Fig. 2 was used to determine the dissolution characteristics of phenylbutazone tablets (15). The apparatus diagrammed in Fig. 1 is currently being used to investigate phenylbutazone tablets using two test media and bishydroxycoumarin tablets using one test fluid.

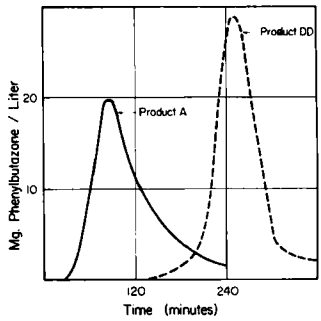

Fig. 3—Dissolution profiles for sugar-coated (Product A) and enteric-coated (Product DD) phenylbutazone tablets.

Dissolution profiles for sugar-coated (Product A) and enteric-coated (Product DD) phenylbutazone tablets are shown in Fig. 3. For the first 30 min., the pH of the fluid is 1.2. Simulated intestinal fluid USP (no enzyme) is then introduced into the flask. At a pumping rate of 60 ml./min., the pH of the fluid changes from that of simulated gastric fluid USP to that of simulated intestinal fluid USP (pH = 7.5) in 30 min.

The dissolution profiles show that both products release drug to a test fluid quickly. However, Product A released most of its phenylbutazone content in 3 hr. Product DD, which failed to comply with the disintegration specification for enteric-coated tablets, released, in 3 hr., only 4.9 (average of three determinations) of the 100 mg. claimed on the label. The apparatus does, therefore, differentiate between two different types of dosage forms. Moreover, these *in vitro* differences appear to be related to physiological availability. Product A was administered to three subjects. The area under the plasma concentration *versus* time curve for Product A was 20 sq. in. units or better. Under the same conditions of administration, the area value for Product DD varied from 4.6 to 11.2 in four subjects.

The basket-stirrer assembly has been used in this laboratory (both in the manner described in this paper and in conjunction with 1, 2, or 3-l. beakers) for approximately 2 years. It is a convenient assembly for tablets but is particularly useful when the dissolution characteristics of a capsule are being determined. Without such a container, capsules tend to float on the surface of the test media. Visual inspection during the test suggests that the tablets and capsules are subjected to much less abrasion than that observed in the USP disintegration test. A 10-mesh wire cloth is used in the construction of the basket and it is possible, therefore, to measure "disintegration" times. Although such values are routinely recorded, no relationship between this time and dissolution characteristics has been established.

This apparatus can be easily adapted to the routine control of tablets and capsules. Although dissolution profiles may be required in certain instances, total amount of drug eluted in a certain period of time would be a satisfactory criterion for many products. For example, the specification for phenylbutazone tablets NF would state that the total quantity of drug eluted from the tablet under specified conditions shall be not less than $x\%$ of that claimed on the label.

Slight changes in pumping rate do not materially change dissolution characteristics. With Product A, the amount of drug in solution at the end of 3 hr. was approximately the same (85 to 90 of the 100 mg. claimed on the label) even though the pumping rate was varied from 50 to 70 ml./min.

The operating characteristics of this apparatus can be easily altered. However, when conditions are fixed, similar dissolution profiles are obtained when drug or tablets from a uniform lot are subjected to the procedure. Repeated tests with Product A[1] produced dissolution profiles similar to that shown in Fig. 3. Moreover, the basket-stirrer assembly positions the tablet in the same way from run to run and helps, therefore, to produce results which are characteristic of the product rather than the apparatus.

[1] Butazolidin tablets, Geigy, Ardsley, N. Y.

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Keyphrases

Continuous flow apparatus—tablet, capsule dissolution
Dissolution profile determination—apparatus
Diagram—continuous flow dissolution apparatus

Some Measurements of Friction in Simple Powder Beds

By EVERETT N. HIESTAND and CHARLES J. WILCOX

An apparatus and procedure for measuring the static friction coefficient of powders in simple beds are described. The relative merits of three variations of the shear cell are considered. A sandwich of powder between two surfaces covered with sandpaper is satisfactory under most experimental conditions. Examples of the effect of relative humidity, time under load, mechanical vibration of the powder bed, and variations in the experimental procedure are presented. Reproducible values of the friction coefficient can be obtained readily if the experimental and environmental conditions are standardized. The results of the experiments suggest that a single value of the friction coefficient applies only to a specific powder bed. In practical applications the entire range of values that may be encountered must be within acceptable limits.

FRICTION COEFFICIENTS and cohesion values have been used to characterize the flow properties of powders. In a recent review (1), the methods used and the problems encountered have been discussed. In the opinion of the authors, there are limitations on the usefulness of such data because neither the friction coefficient nor the cohesion is a single valued property of the powder. As stated in the review article, "The properties of a powder bed depend on the cumulative effect of the previous history of all the portions of the bulk being considered. Isolated regions of shear, vibration, or compaction may have produced high bulk density regions. These may remain intact in subsequent flow of the powder or may fragment into macroscopic regions mixed throughout the less dense bed. The forces acting on the top of the bed may be quite different from those at the bottom of the bed." In the studies reported here, considerable data have been collected that reveal the large number of factors that cause changes in the properties of powder beds as well as indicating the magnitude of these effects.

The basic measurements of friction coefficient and cohesion may be obtained from a simple shear cell described by Nash *et al.* (2). Though

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