Modified Automated Apparatus for Determination of Dissolution Rates of Capsules and Tablets

By LOUIS C. SCHROETER and WILLIAM E. HAMLIN

Intermittent filtration and sampling of the dissolution fluid permits the routine use of short light path (1 mm.) spectrophotometer flow cells in the monitoring of the *in vitro* dissolution process of tablets and capsules by an automated method.

CONTINUOUS MONITORING of the dissolution process of a tablet or capsule may be accomplished most easily by cycling a sample of dissolution fluid through a spectrophotometer flow cell and recording the change in absorbance as a function of time (1). Spectrophotometer flow cells of minimum volume ($\leq$ 5 ml.) with light paths from 10–100 mm. may be used to extend the useful range of the continuous cycling method to those dosage forms which contain small amounts of drug(s) with low molar absorptivities. Determination of the dissolution characteristics of tablets containing large amounts of drug(s) with high molar absorptivities through the use of short light path ($\leq$ 5 mm.) flow cells has in the past involved many operational difficulties: particles of insoluble tablet additives tend to collect in the flow cells and continuous filtration of the sample stream results in rapid and progressive diminution of flow rate as filters become clogged with insoluble materials.

This brief report describes a modification of the continuous cycling procedure for automated dissolution rate studies (1) which greatly extends the utility of the method by employing a 1-mm. light-path flow cell. A three-way solenoid valve is used to shunt the circulating sample stream away from the filter, except during the time actual recording of the dissolution process is underway.

EXPERIMENTAL

Equipment.—The arrangement of components for modified continuous cycling with intermittent filtration and sampling is shown in Fig. 1. The U.S.P. disintegration apparatus and basket rack assembly (2) were used to provide reproducible agitation; disks were *not* used. Sampling lines were of shortest possible length and of minimum internal diameter consistent with sampling-line flow rates of 1 to 1.5 ml. per second. Typical lengths of connecting tubing and volumes of components shown in Fig. 1 were as follows: *A*, 70 cm.; *B*, 50 cm.; *C*, 20 cm.; *D*, 10 cm.; *E*, 30 cm.; *F*, 85 cm.; valve (sample port open), 1 ml.; filter, 4.6 ml.; 1 mm. flow cell,[1] 1.0 ml. Configuration of the glass filtering device and the solenoid valve is shown in Fig. 2. An electronic repeat cycle timer[2] was used to actuate the solenoid valve to divert the rapidly circulating sample fluid through the filtering device and flow cell every 1 or 2 minutes for a period of 15–20 seconds. A more detailed description of the automated dissolution rate apparatus and its design requirements has been reported (1).

Procedure.—Operationally, the dissolution rate determination of tablets or capsules by the intermittent filtration-sampling method is the same as that used with the previously reported continuous monitoring process (1). Recorder response was adjusted to read 100 units or 100% drug in solution when a filtered sample stream from the beaker containing drug from one tablet wholly dissolved (100% drug in solution) was pumped through the flow cell. The sampling system was flushed with fresh buffer and connected with a new beaker containing 750 ml. of fresh buffer maintained at 37°. One tablet was placed into the U.S.P. disintegration basket assembly (no disks), immersed into the buffer solution, and agitated at the prescribed rate of 30 cycles per minute. Introduction of the tablet into the buffer marked zero time for the process. The timer was adjusted to divert the sample stream through the filter and flow cell every minute for a period of 15 seconds.

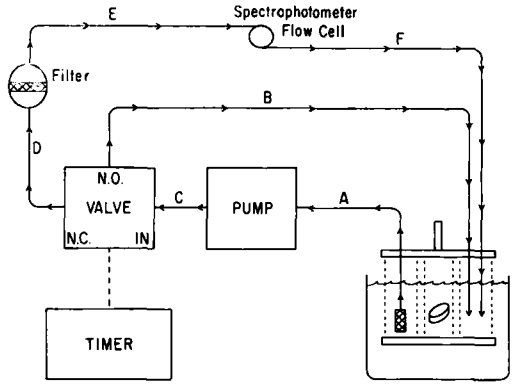

Fig. 1.—Arrangement of components for modified continuous cycling with intermittent filtration and sampling.

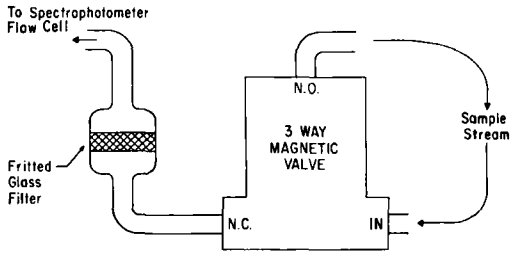

Fig. 2.—Configuration of filter and three-way solenoid valve for intermittent filtration and sampling. The abbreviations "N.O." and "N.C." designate the normally open and normally closed valve parts.

Received November 23, 1962, from the Pharmacy Research Section, Product Research and Development, The Upjohn Co., Kalamazoo, Mich.

Accepted for publication December 20, 1962.

The excellent technical assistance of N. K. Hine is gratefully acknowledged.

[1] Suprasil flow cell, No. L134FT, 1-mm. light path, Lux Scientific Instrument Corp., New York 13, N. Y.

[2] Repeat cycle timer, model 1, G. C. Wilson and Co., Huntington, W. Va.

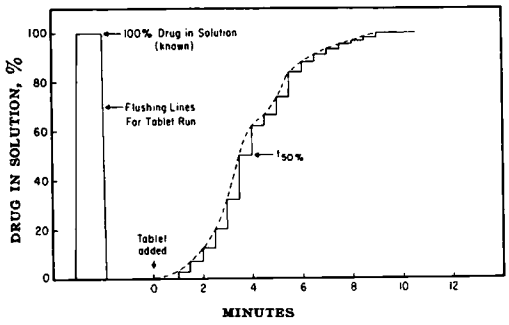

Fig. 3.—Idealized recorder curve obtained with modified continuous cycling method. Actual curves recorded at sufficiently fast chart speeds will show the vertical lines to be more nearly sigmoidal, due to the time lag involved in the establishment of optical density equilibrium. Dashed line indicates dissolution profile; vertical line indicates flow cell open; horizontal line indicates flow cell closed.

RESULTS AND DISCUSSION

Vertical lines shown in the idealized recorder tracing in Fig. 3 represent the rapid change in recorder response which occurs when the sample stream is diverted through the flow cell at 1-minute intervals. Shortly after establishment of equilibrium in the lines, the rapidly flowing sample stream is once again shunted away from the filter and flow cell. During this time no sample flows through the cell; hence a horizontal trace is made by the pen until the valve once again opens to divert the sample stream through the filter and flow cell. Intersection of the horizontal and vertical lines represents a concentration of drug in solution at that time; the dissolution profile of the dosage form is shown by a dashed line joining these intersections or concentration-time values.

Accuracy and reliability of the modified continuous cycling method has been determined by simultaneous independent assays of the dissolution fluid during the dissolution process of various tablets. The dissolution profile of a sulfonylurea tablet in pH 7.2 buffer at 37° was determined in a series of studies conducted on different days by different investigators using the modified method described above and by simultaneous independent spectrophotometric assays of the dissolution fluid. Figure 4 is typical of the excellent agreement which exists between the automated and manual methods.

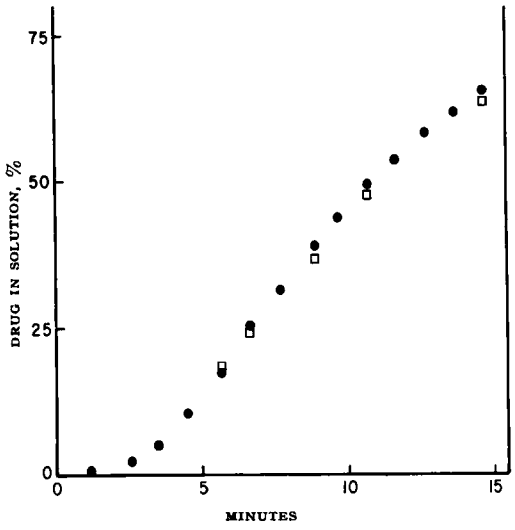

Fig. 4.—Dissolution profile of a sulfonylurea tablet obtained by the automated procedure and by simultaneous independent assay: ●, automated; □, independent assay.

REFERENCES

(1) Schroeter, L. C., and Wagner, J. G., THIS JOURNAL, 51, 957(1962).
(2) "United States Pharmacopeia," 16th rev., Mack Publishing Co., Easton, Pa., 1960, p. 934.

Ferguson Principle and the Critical Micelle Concentration

By BERNARD ECANOW and FREDERICK P. SIEGEL

The thermodynamic activity values of a series of quaternary ammonium salts were calculated through the use of critical micelle concentrations. The correlation of these thermodynamic activities to the published values of their bactericidal activities is shown through application of the Ferguson principle. The value of the Ferguson principle in helping to point out the possible presence of different mechanisms of activity within a series of similar compounds has been suggested.

FERGUSON (1) has suggested that the toxicities of physically toxic substances should not be compared by the values of the toxic concentrations in the external solution but by the chemical potentials in this phase, which must be identical with the chemical potential at the site of activity. Ferguson used the activity function of G.N. Lewis as the chemical potential. From a review of published data, he showed that "though diverse chemical compounds exert the same toxic effect on a given organism at widely different concentrations, the activities corresponding to these concentrations lie within a relatively narrow range. The differences in activity within this range are ascribed to the effect of chemical constitution."

It has been shown (1, 2) that when the toxic agent is applied as a vapor, the activity is given with "useful" accuracy by the ratio of the partial pressure of the agent over that of the saturated vapor pressure of the substance at the temperature

Received November 29, 1962, from the College of Pharmacy, University of Illinois at the Medical Center, Chicago. Accepted for publication December 19, 1962.