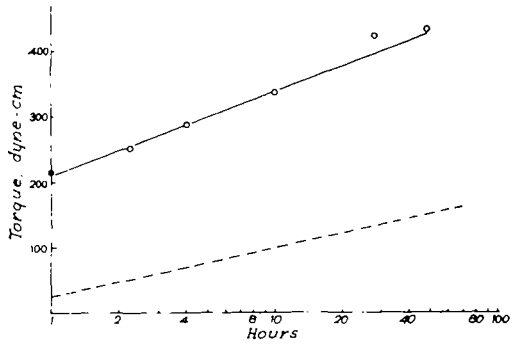

Fig. 7.—Effect of zinc oxide on static yield value and thixotropic recovery rate of 2.5% MAS dispersions. - - -, Plain suspension; O, with 10% zinc oxide.

ing zinc oxide in the aged MAS dispersions only 3 days prior to measurement. The results of this experiment may explain the lack of correlation between certain rheological properties of dispersions of two clays, bentonite and activated attapulgite, and their ability to suspend zinc oxide. Foernzler and co-workers indicate that the suspending ability of these dispersions, as reflected by the sedimentation velocity of zinc oxide, is directly related to the thixotropic area of the clay dispersion without zinc oxide (19). Wood could show subsequently, using the same data, that a similar or better correlation seems to exist between the sedimentation velocity and the reciprocal of yield value (20). Regardless of the treatment of the experimental data, however, the two clays yielded different proportionality constants and, thus, no absolute relationship of yield value or thixotropic area and suspending ability could be shown. While this may be due in part to differences in plastic viscosity as well as recovery rate of the two clays (a variable not considered in the experimental design), it is apparent from the present data that the static yield value of a pure clay dispersion differs greatly from the static yield value of a dispersion containing zinc oxide. Any attempt to correlate rheologic parameters with suspending ability should be based on the rheologic values of the final suspension, and not on those of the pure dispersion containing only the suspending agent.

REFERENCES

(1) Levy, G., This Journal, **51**, 947(1962).
(2) Hauser, E. A., *Kolloid Z.*, **48**, 57(1929).
(3) Broughton, G., and Squires, L., *J. Phys. Chem.*, **40**, 1041(1936).
(4) Heller, W., and Roeder, H. L., *Trans. Faraday Soc.*, **38**, 191(1942).
(5) Hauser, E. A., and Reed, C. E., *J. Phys. Chem.*, **41**, 911(1937).
(6) Freundlich, H., and Rawitzer, W., *Kolloidchem. Beihefte*, **25**, 231(1927).
(7) Houwink, R., "Elasticity, Plasticity and the Structure of Matter," 2nd ed., Dover Publications, New York, N. Y., 1958, p. 342.
(8) Braune, H., and Richter, I., *Kolloid Z.*, **113**, 20 (1949).
(9) Packter, A., *ibid.*, **150**, 60(1957).
(10) McVean, D. E., and Mattocks, A. M., This Journal, **50**, 785(1961).
(11) Chong, C. W., Eriksen, S. P., and Swintosky, J. V., *ibid.*, **49**, 547(1960).
(12) Voet, A., *Am. Ink Maker*, **35**, 34(1957).
(13) Samyn, J. C., This Journal, **50**, 517(1961).
(14) Wood, W. H., Granquist, W. T., and Krieger, I. M., *Proc. Fourth Natl. Conf. on Clays and Clay Minerals*, Publication **456**, 240(1956).
(15) Simon, T. H., DeKay, H. G., and Banker, G. S., This Journal, **50**, 880(1961).
(16) Vogt, H., *Pharm. Ind.*, **23**, 331(1961).
(17) Bradley, W. F., *J. Am. Chem. Soc.*, **67**, 975(1945).
(18) Utsugi, H., Gabrysh, A. F., Cutler, I. B., Ree, T., and Eyring, H., paper presented at the American Chemical Society meeting, Cleveland, April 5–14, 1960.
(19) Foernzler, E. C., Martin, A. N., and Banker, G. S., This Journal, **49**, 249(1960).
(20) Wood, J. H., *Am. Perfumer*, **76**, 37(1961).

Automated Dissolution Rate Studies of Capsules and Tablets

By LOUIS C. SCHROETER and JOHN G. WAGNER

Automation of dissolution studies of solid dosage forms has been achieved through the use of a timer-controlled sampling and dilution system which automatically removes filtered samples from the dissolution apparatus, makes reproducible dilutions, and records the absorption of the diluted sample as a function of time. The U.S.P. tablet disintegration apparatus was employed to provide constant, reproducible agitation. Versatility and reliability of the apparatus has been demonstrated by comparing automated dissolution rate results with values obtained by independent, manual analyses. Design requirements and specifications of individual components have been discussed in detail so that other functionally equivalent units may be employed to achieve comparable results with those reported in this study.

Dissolution characteristics of solid dosage forms such as tablets or capsules may be determined by agitating the dosage form in a suitable fluid and periodically assaying the solution for drug content. Reproducible agitation is essential to the test. Widespread availability of the standardized U.S.P. disintegration apparatus (1) makes it ideally suited for providing constant and reproducible agitation of the tablet or capsule since both design and operation of the apparatus are exactly prescribed. Periodic withdrawal of filtered, small aliquots of test fluid provides samples containing varying percentages of dissolved drug. Ultraviolet spectrophotometry serves as a rapid

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and versatile analytical method for determining drug content of most products. Assay of samples removed at various times provides the necessary data for preparing a plot of per cent drug in solution as a function of time.

Automation of the dissolution rate studies provide obvious savings in laboratory man-hours and would permit general use of this concept for designing and controlling superior solid dosage forms on a routine basis. Circulating a filtered sample of test fluid through a spectrophotometer flow cell and automatically recording the change in absorbance as drug goes into solution is the essential feature of this automated process; it provides a plot of per cent drug in solution as a function of time. The schematic diagram of such an arrangement is shown in Fig. 1. Component parts and the applications and limitations of the system will be described in detail. Emphasis will be placed on the functions performed by each component and the specifications necessary to achieve optimum versatility in operation. This permits substitution of different, but operationally equivalent, components which may be available in other laboratories.

DESCRIPTION OF THE AUTOMATED SYSTEM

Agitation of Dosage Form.—The U.S.P. disintegration apparatus and basket-rack assembly (1) provides reliable and reproducible agitation. It was used in all studies and a standard 1-L. beaker was employed as the dissolution vessel. The wire bottom of the basket was brought to within 2.3 ± 0.2 cm. of the bottom of the beaker on the downward stroke. Control of the lower limit appears to be critical since stirring action imparted to granules which have passed through the screen and rest on bottom of beaker is markedly affected by this factor. The test fluid was 37.5 ± 0.2° in all studies.

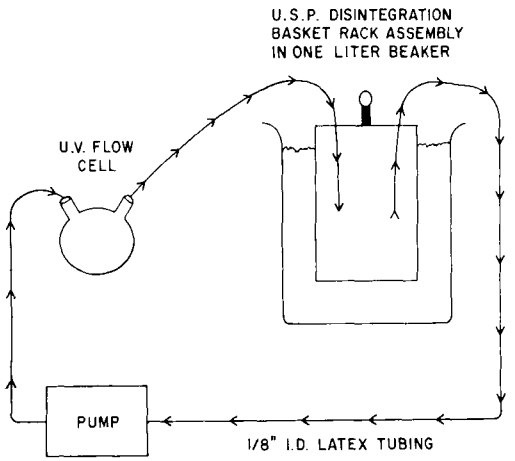

Fig. 1.—Flow pattern for continuous cycling of filtered dissolution fluid through spectrophotometer flow cell.

Filtering and Circulating the Sample.—A filtered sample of test fluid must be rapidly circulated through a spectrophotometer flow cell,[1] such as shown in Fig. 2, and returned to the beaker. Residence time of the sample in the sampling lines must be very short compared to the time required for a significant amount of drug to dissolve. Rapid pumping of the sample at variable speeds may be accomplished with the Sigmamotor model T8 pump[2] which functions by pressing, in sequence, little "fingers" of metal into the tubing, thus effecting a rapidly pulsating flow. This has the particular advantage of avoiding contamination of the fluid by the pump and also avoids hold-up of a large volume of fluid in the pump since the fluid never comes in direct contact with working parts of the pump. Small centrifugal or gear pumps constructed of stainless steel or resistant plastics also may be used if provision is made for controlling pumping rate with a rheostat.

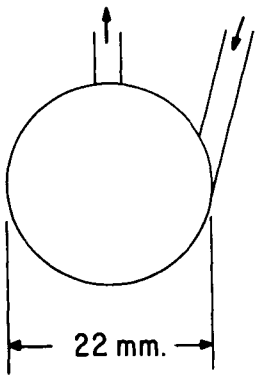

Fig. 2.—Spectrophotometer flow cell.

Filtering of the sample stream may be accomplished by placing a filter of design shown in Fig. 3 into one of the cylinders of the U.S.P. basket-rack assembly. The stainless steel filter tip is made from a 3 × 4 cm. sheet of #100 stainless steel wire cloth rolled into a cylinder with the end closed. This assembly provides reliable sampling of the solution and prevents clogging of the filter. The return stream of filtered solution should be discharged into a different cylinder, but not the cylinder containing the dosage form under test; it should not be discharged into the bottom of the dissolution beaker because this tends to magnify stirring action. Other filtering devices may be used but they should permit high flow rates so that sampling lag time is kept to a minimum. Also, it is desirable that the filter tube be weighted to prevent it from bouncing up in the cylinder and exposing the intake to air. Latex or Tygon tubing of internal diameter 1/8 inch or smaller and of shortest possible lengths should be used in the sampling line to keep sample lag time to a minimum.

[1] Ultracell Co., 22 Bland Ave., Emerson, N. J.
[2] Sigmamotor, Middleport, N. Y.

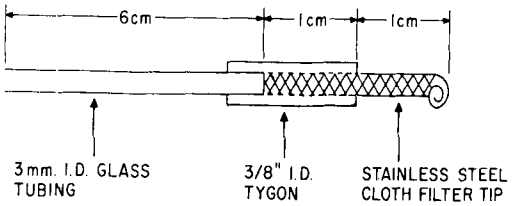

Fig. 3.—Sampling-filter device.

Spectrophotometry.—Automated measurement of the amount of drug in solution may be easily accomplished for those drugs which possess requisite chromophoric groups by automatically recording the change in absorbance of the solution flowing through the spectrophotometer flow cell. Many of the commercially available recording spectrophotometers, such as the Cary model 11, can be set to record absorption at a given wavelength (usually at a point where drug molecule exhibits maximum absorption) as a function of time. This requires no modification of the recording spectrophotometer other than arranging the cell compartment cover to permit entrance of tubing to the flow cell. The recording spectrophotometer may be converted to regular use in less than 30 seconds. However, as a permanent arrangement, the use of such a recording spectrophotometer would commit a versatile and expensive instrument to a specific job function. For this reason, a Beckman model DU spectrophotometer was converted for this specialized purpose.

Conversion of the Beckman DU spectrophotometer to an instrument which will record absorbance as a function of time may be accomplished with the Gilford model 200 optical density converter.[3] This attachment consists of two parts: a photodetector which is fastened to the spectrophotometer in place of the standard detector; and an electronic power supply and converter-amplifier. No modification of the spectrophotometer is necessary; the conversion can be made in minutes and does not impair use of the spectrophotometer for manual, conventional operation. The Beckman DU instrument was chosen for its excellent monochromator system; however, any spectrophotometer having a similar monochromator covering the ultraviolet and visible spectrum from 220 to 800 mμ and having a stabilized light source can be used. Recording can be done on any self-balancing potentiometer recorder with a 50 mv. full-scale sensitivity and a response time of one-half second.

Recording.—A Texas Instrument Servariter recorder model PWS[4] was used in all studies. This recorder has a chart speed selector which permits rapid selection of 10 different chart speeds. Normal range of chart speeds in most studies varied from $^1/_4$ to 2 in. per min.

Intermittent Sampling and Dilution.—Increased versatility of an automated dissolution device may be accomplished with the use of a sampling dilution arrangement shown schematically in Fig. 4. Introduction of a three-way magnetic valve[5] into the sample stream serves as a means of diverting a fixed, small volume of the sample stream into a diluent stream. The valve should have a minimum orifice of $^1/_{16}$ inch so that sample retention is reduced to a minimum. The valve is actuated by a signal from a timer which permits preselection of sampling time and duration of sample stream diversion. Thus, if the flow rate in the sample stream is 1 ml. sec.$^{-1}$, opening the valve for one-half second removes 0.5 ml. of sample. Withdrawal of 10 samples of 0.5-ml. volume from 1 L. of fluid during the course of a dissolution study introduces an overall error of only 0.5%.

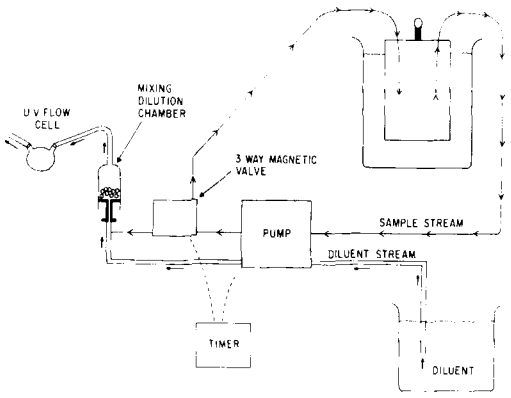

Fig. 4.—Flow pattern of filtered solution when intermittent sampling with dilution employed.

Transport of the diverted sample to the spectrophotometer flow cell may be accomplished by injecting it into a diluent stream flowing at a constant rate. However, streamline flow does not serve for effective mixing (2, 3). Mixing the sample and diluent stream may be accomplished by using a turbulent flow mixing chamber (Fig. 5). It is desirable to have a variable volume mixing chamber to provide requisite control of effective dilution necessary in adjusting absorbances of diluted sample stream between 0.1 and 3.0. It may be advan-

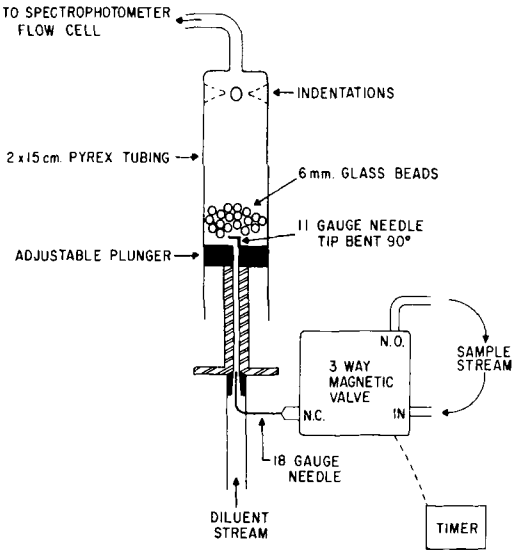

Fig. 5.—Three-way magnetic valve and turbulent flow dilution-mixing chamber for intermittent sampling and dilution of sample stream.

[3] Gilford Instrument Laboratories, Inc., Oberlin, Ohio.
[4] Texas Instruments, Inc., Houston, Tex.
[5] Skinner Electric Valve Div., New Britain, Conn.

tageous to employ fixed volume mixing chambers for studying a series of tablets containing the same amount of drug, *i.e.*, in cases where dilution of sample stream remains constant. Fixed volume mixing chambers can be constructed from ordinary volumetric pipets by cutting off the tubing to within 1 cm. of the body and filling the body with 3- or 4-mm. glass beads. Most reproducible mixing occurs when these are employed in a vertical position with sample and diluent entering the bottom and emerging mixed from the top.

Controlled flow of diluent may be accomplished with a hydrostatic device constructed from a 500-ml. separator modified with a side arm tube (about 5 cm. from top) for overflow. Adjusting height of liquid level permits accurate control of diluent flow. The Sigmamotor pump described above can also be used to pump both the sample stream and the diluent stream simultaneously since it will accommodate tubing on both sides of the "fingers." Different tension adjustments on either side of the pump and the use of larger diameter tubing for the diluent stream permits variable pumping rate selections for both streams. It is not necessary to know the exact dilution factor since all measurements during a dissolution study are relative. However, effective dilution must be reproducible during the course of the study and for comparative studies. Flow rate control may be achieved by periodically checking both the sample and diluent stream with a flow meter.[6]

Timing sequence may be provided by any timer or series of timers which will, at predetermined intervals of from $^1/_2$ to 5 minutes, open for a period from $^1/_2$ to 5 seconds, and then close the three-way solenoid valve. The timer should then automatically reset (recycle) and repeat the sequence. A sequential timer[7] was used to control the operation since it contained six circuits; however, other, less sophisticated timers would be equally satisfactory if they fulfilled the timing requirements. If a Sigmamotor pump is used for pumping both sample and diluent stream, it may be advisable to conserve the diluent, especially when buffers or other color-developing solutions are employed.

Conservation of diluent fluid may be accomplished by intermittent timer-controlled operation of the pumping system. A multiple circuit timer should control the following sequence: (*a*) pump on, 15–20 sec.; (*b*) valve open, $^1/_2$–5 sec.; (*c*) valve shut, 15–30 sec.; (*d*) pump off, 60–300 sec.; (*e*) repeat cycle. Operating the pump for a period of at least five residence times (15 sec.) permits flushing of lines and taking a representative sample from the dissolution vessel. The pump must run a minimum of 15 to 30 sec. after sampling to flush dilution-mixing chamber and spectrophotometer flow cell.

RESULTS AND DISCUSSION

Continuous Monitoring of Dissolution Process.—The schematic arrangement of equipment shown in Fig. 1 was used to follow the dissolution process of a 4-mg. steroid tablet. Complete dissolution of one tablet in 750 ml. of pH 1.35 buffer yielded a solution with an absorbance of 0.21. This low absorbance of the dissolution fluid provided a good test of the sensitivity of the automated procedure for determining dissolution characteristics of dosage forms containing small amounts of drug or drugs with low molar absorptivities. Total volume of sampling lines, filter device, and flow cell was 7.3 ml.; the sample flow rate was 1.34 ml. sec.$^{-1}$. Residence time in the sampling system was 5.4 sec. This can be reduced further by decreasing the volume of the sampling system or increasing flow rate, or both; however, these are upper limits on permissible flow rates. If the flow rate is greater than 2 ml. sec.$^{-1}$, this tends to contribute to the stirring action in the dissolution beaker and results in faster dissolution of the tablet or capsule. A filtered sample stream from the beaker containing drug from one tablet wholly dissolved (100% drug in solution) was pumped through the flow cell and the recorded response adjusted to read 100 units or 100% drug in solution. Sample lines were flushed with pH 1.35 buffer and the test repeated by placing one tablet in the U.S.P. basket-rack assembly immersed in a new beaker containing 750 ml. of pH 1.35 (μ = 0.1) buffer at 37.5°. The dissolution curve produced by the automated procedure is shown in Fig. 6 along with 2 independent individual dissolution rate determinations of other tablets from the same lot.

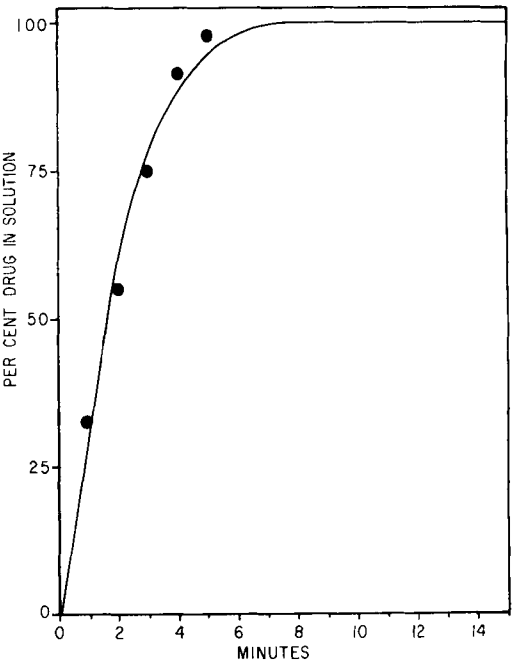

Fig. 6.—Dissolution characteristics of a steroid tablet in 750 ml. buffer (μ 0.1) at 37.5° using U.S.P. disintegration apparatus without disks. Solid line redrawn from curve obtained using automated procedure. Solid circles represent independent assays of tablets from same lot.

The schematic arrangement shown in Fig. 1 serves very well for the accurate monitoring of the dissolution process of this particular steroid tablet. However, it must be emphasized that not all dosage forms contain just the right amount of drug which, when dissolved in about 1 L. of fluid, will yield solutions having absorbance values between 0.1

[6] Flowrator, Fischer and Porter Co., Hatboro, Pa.
[7] Multiflex, Eagle Timer Corp., Moline, Ill.

and 3.0. Many dosage forms contain drugs with high molar absorptivities so that resultant solutions from complete dissolution of the drug have absorbance values of 10 or higher. Thus, with the total volume of fluid set at about 1 L. and the limit of spectrophotometric sensitivity fixed at 0.1 to 3.0 absorbance units, the need for dilution of sample stream becomes evident. The sample stream, once it is diluted, cannot be returned to the test beaker because this would increase the total volume of fluid present. Likewise, the dissolution beaker cannot be constantly sampled nor can the combined withdrawn samples constitute a large volume because this would deplete the fluid in the beaker.

Sampling with Dilution.—A typical "combination of ingredients" tablet containing aspirin, phenacetin, and caffeine was selected to demonstrate automated sampling with dilution. One tablet was dissolved completely in 750 ml. of pH 1.35 buffer (μ = 0.1) by equilibrating at 37.5° for 1 hour. Absorbance of the undiluted solution was 23.6 at the wavelength of maximum absorption which was a composite of the 3 chromophores. This indicated the need for an effective dilution of 20× to give a measurable absorbance. Sample flow rate was regulated to 1 ml. sec.$^{-1}$ and the timer adjusted to send a $^1/_2$ sec. signal (0.5 ml. sample) to the three-way solenoid valve every 1.7 min. Volume of the sampling line and valve was 4.1 ml.; sample lag time was 4.1 sec. The wavelength of the absorption maximum (230 mμ) of the dissolved mixture in pH 1.35 buffer was selected on the monochromator. The recorder was then balanced to give a maximum response to 100 units (100% drug in solution) by manipulating the flow rate of pH 1.35 diluent and adjusting the turbulent flow mixing chamber volume. The sampling system was flushed with pH 1.35 buffer and connected with a new beaker containing 750 ml. of pH 1.35 (μ = 0.1) maintained at 37.5°. One tablet was placed into the U.S.P. disintegration basket assembly and immersed into the buffer solution and agitated at the prescribed rate of 30 cycles per min. Introduction of the tablet into the buffer marked zero time for the process. Reproduction of the curve produced by the recorder is shown in Fig. 7. The heights of the solid vertical lines represent instrumental response or per cent drug in solution. Absorbance of the solution flowing through the cell rapidly returns to zero as the diluted sample is flushed from the cell. The one flow cell serves as a sample cell and as a blank cell since the diluent stream constantly flushes the cell; this assures instrumental reliability of measurements made over long periods. The inherent reliability of the automated system is shown by the close fit of peak heights obtained with the automated procedure to the individual points obtained by an independent method on tablets from the same lot.

Intermittent Circulation with Sampling and Dilution.—A sulfonylurea tablet formulation was used to evaluate the applicability of intermittent fluid circulation followed by sampling with dilution. Two tablets of the sulfonylurea product were dissolved in 750 ml. of pH 7.2 THAM[8] buffer by equilibrating with stirring at 37.5° for 1 hour. Complete solution of the drug content of the tablets corresponds to 100% drug in solution or 1000 mg. of drug dissolved in 750 ml. of buffer. Absorbance of the undiluted solution was 65 at the wavelength of maximum absorption, thus indicating the need for an effective dilution of from 30 to 50×. The sample flow rate was regulated at 1.0 ml. sec.$^{-1}$ and the timer adjusted to start the pump 15 sec. before sending a signal to the valve and to continue pumping 15 sec. after the event. The timer was adjusted to send a 0.5-sec. (0.5-ml. sample) signal to the three-way magnetic valve every 60 sec. Volume of sampling lines and valve was 3.5 ml.; the time required for a sample to complete the circuit from beaker and return was 3.5 sec. Monochromator was adjusted to provide monochromatic radiation at the absorption maximum of the sulfonylurea in pH 7.2 THAM buffer (228 mμ). The recorder was balanced to give a maximum response of 100 units (arbitrarily marked as 1000 mg.) by manipulating the flow rate of diluent and adjusting volume of the mixing chamber. The sampling system was flushed with fresh pH 7.2 THAM buffer and connected with a new beaker containing 750 ml. of pH 7.2 THAM buffer maintained at 37.5°. Two tablets were placed into the U.S.P. disintegration basket-rack assembly and immersed into the buffer solution; this marked zero time on the recorder. Reproduction of the curve obtained from the recorder is shown in Fig. 8. The heights of the solid vertical lines represent instrumental response or per cent drug in solution. Absorbance of the solution rapidly returns to zero as the diluent sample passes through the cell; this serves as a further in-process instrumental check. Analyses of solution composition at various times during the dissolution test by an independent spectrophotometric method served to validate the method.

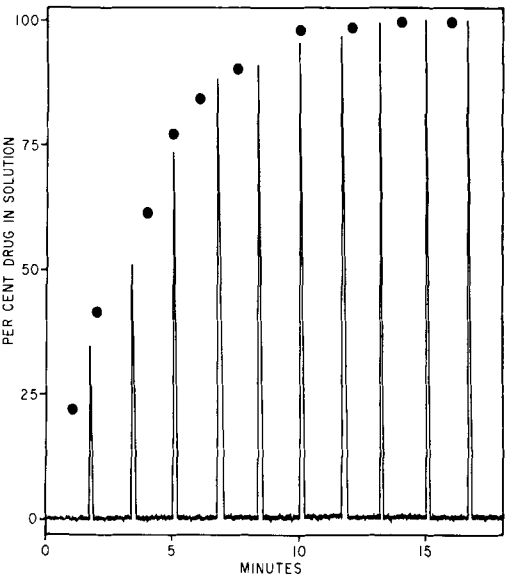

Fig. 7.—Dissolution profile of acetophenetidin-acetylsalicylic acid-caffeine tablet in 750 ml. pH 1.35 buffer (μ 0.1) using U.S.P. disintegration apparatus without disks. Vertical solid lines redrawn from curve obtained using automated procedure with dilution device. Solid circles represent independent assays of tablets from the same lot.

[8] Tris(hydroxymethyl)aminomethane 0.1 *N* in water brought to pH 7.2 by addition of hydrochloric acid.

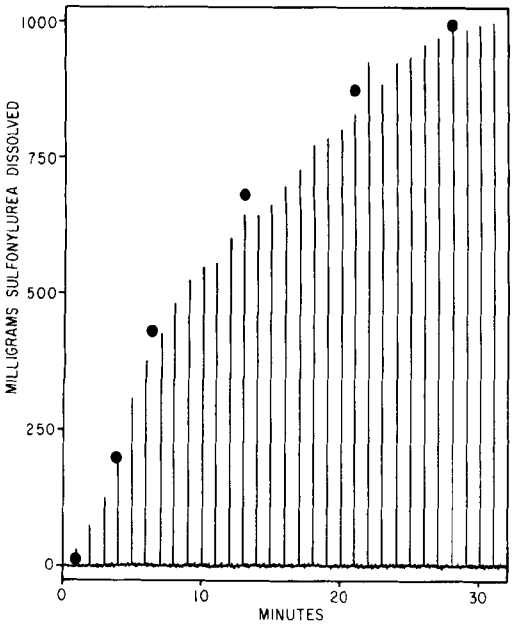

Fig. 8.—Dissolution profile of two sulfonylurea tablets in 750 ml. pH 7.2 THAM buffer at 37.5° using U.S.P. disintegration apparatus without disks. Vertical solid lines redrawn from curve obtained using automated procedure with dilution device. Theoretical drug content of two test tablets taken as 1000 mg. Solid circles represent values obtained by simultaneous, independent assays of dissolution fluid.

CONCLUSIONS

Automated dissolution rate studies of solid dosage forms serve as an extremely useful method for controlling the quality of these products. The method is applicable to the evaluation of virtually all tablets, capsules, and granules containing drugs soluble in about 1 L. of dissolution fluid. The total dissolution profile expressed as per cent drug in solution as a function of time may be obtained for these products. However, dosage forms containing drugs not wholly soluble in the dissolution medium may also be evaluated; results are expressed in terms of absolute initial rate of dissolution.

Savings in laboratory man-hours can be enormous if the automated procedure is used regularly to control the quality of solid dosage forms. One investigator working with the automated device can perform the same number of dissolution studies as four technicians working with conventional, manual procedures. Also, the automated procedure uses a modified Beckman DU spectrophotometer in place of a Cary recording spectrophotometer for measuring absorption changes in the solution. This frees the more expensive recording spectrophotometer for other more versatile analytical jobs. The automated device also serves as a useful and versatile analytical tool for automatically re-recording the progress of chemical kinetic reactions which involve changes in absorption of monochromatic light.

REFERENCES

(1) "United States Pharmacopeia," 16th rev., Mack Publishing Co., Easton, Pa., 1960, p. 934.
(2) Dryden, H. L., *Ind. Eng. Chem.*, **31**, 416(1939).
(3) Levenspiel, O., *ibid.*, **50**, 343(1958).

Synthesis and Antifungal Evaluation of Some Derivatives of Dialkoxybenzoic and Dialkoxycinnamic Acids

By A. K. KAPADIA† and GAIL A. WIESE

A number of dialkylaminoalkyl esters of dialkoxybenzoic and dialkoxycinnamic acids and their halogenated analogs were prepared. The compounds, in the form of their hydrochloride salts, together with the parent acids were tested *in vitro* against three pathogenic fungi using undecylenic acid and griseofulvin as controls. In general, the results of the tests indicated that most of the compounds had little or no antifungal activity *in vitro*.

IT HAS BEEN shown that fungal diseases in man are a growing health hazard (1). The search for antifungal agents has been in progress for several decades. In reviewing the literature it was noted that there have been few investigations directed toward the study of antifungal activity of the derivatives of dialkoxybenzoic and dialkoxycinnamic acids and their halogenated analogs.

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