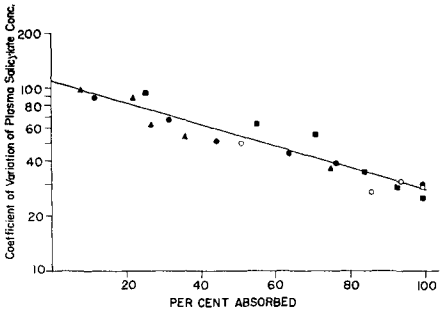

Fig. 6.—Coefficient of variation of plasma salicylate concentrations as a function of per cent of dose absorbed. Key: see Fig. 1.

absorption rate and variability of drug absorption. Rather, it is found that, under the conditions of the present study, the coefficient of variation of plasma salicylate concentrations decreased as the per cent of the dose absorbed increased.[5] The limiting value of the coefficient at 100% absorption reflects mainly the variation in plasma salicylate levels due to intersubject differences in relative and absolute apparent volumes of distribution. The coefficient at times prior to the completion of drug absorption reflects intersubject differences both in absorption rates and in volumes of distribution. When absorption is slow and elimination is rapid, the coefficient of variation is affected also by individual differences in drug elimination rate constants. After drug absorption is completed, intersubject variability of drug concentrations in the plasma may be expected to increase with time, due to intersubject differences in elimination kinetics.

[5] The same type of relationship is suggested by the data in Fig 3 of a recent paper by Lieberman *et al.* (24).

REFERENCES

(1) Levy, G., *Arch. Intern. Pharmacodyn.*, **152**, 59(1964).
(2) Levy, G., and Hollister, L. E., *J. Pharm. Sci.*, **53**, 1446(1964).
(3) Levy, G., and Hollister, L. E., *N. Y. State J. Med.*, **64**, 3002(1964).
(4) Levy, G., and Hollister, L. E., *J. Pharm. Sci.*, **54**, 1121(1965).
(5) Leonards, J. R., and Levy, G., *J. Am. Med. Assoc.*, **193**, 93(1965).
(6) Levy, G., unpublished data.
(7) Brodie, B. B., Udenfriend, S., and Coburn, A. F., *J. Pharmacol. Exptl. Therap.*, **87**, 237(1946).
(8) Wagner, J. G., and Nelson, E *J. Pharm. Sci.*, **52**, 610(1963).
(9) Levy, G., *ibid.*, **54**, 959(1965).
(10) Levy, G., and Hayes, B. A., *New Engl. J. Med.*, **262**, 1053(1960).
(11) Levy, G., and Tanski, W., Jr. *J. Pharm. Sci.*, **53** 679(1964).
(12) Levy, G., and Jusko, W. J., *ibid.*, **54**, 219(1965).
(13) Levy, G., *J. Am. Pharm. Assoc.*, **NS4**, 17(1964).
(14) Levy, G., *Anesthesia Analgesia, Current Res.*, to be published.
(15) Hollister, L. E., and Levy, G., *J. Pharm. Sci.*, **54**, 1126(1965).
(16) Hogben, C. A. M., *et al.*, *J. Pharmacol. Exptl. Therap.*, **120**, 540(1957).
(17) Levy, G., Gumtow, R. H., and Rutowski, J. M., *Can. Med. Assoc. J.*, **85**, 414(1961).
(18) Levy, G., *J. Pharm. Sci.*, **50**, 388(1961).
(19) Mattson, H. W., *Intern. Science Technol.*, **1965**, 66.
(20) Levy, G., *J. Pharm. Sci.*, **52**, 1039(1963).
(21) Hamlin, W. E., *et al.*, *ibid.*, **51**, 432(1962).
(22) Levy, G., and Procknal, J. A., *ibid.*, **53**, 656(1964).
(23) Nelson, E., O'Reilly, R. A., and Levy, G., unpublished data.
(24) Lieberman, S. V., *et al.*, *J. Pharm. Sci.*, **53**, 1486 (1964).

Method for Determining Dissolution Rates of Multiparticulate Systems

By ARTHUR H. GOLDBERG*, MILO GIBALDI, JOSEPH L. KANIG, and JAI SHANKER

A method and apparatus are described for the measurement of dissolution rates of multiparticulate systems. Dissolution studies were conducted with benzoic acid and salicylamide in order to determine the applicability of the method. Replication between experiments was well within accepted limits. Furthermore, the results obtained demonstrated reasonable agreement with the extended Hixson-Crowell equation.

THE ABSORPTION of a large number of drugs is rate-limited by the dissolution process. Consequently, studies of dissolution rates can be useful in evaluating the prospective absorption rate and physiologic availability of these drugs. A number of methods for studying dissolution rates have been proposed. Levy (1, 2) has described a method involving the use of rotating nondisintegrating disks. Milosovich (3) employed a tablet mounted in a die which was subjected to solvent agitation. The use of disks or tablets of pure drug with either method permits the determination of intrinsic dissolution rates as a function of temperature and agitation.

Levy (4) has noted that a knowledge of intrinsic dissolution rate is not necessarily sufficient to determine the dissolution rate of a drug in particulate form. Frequently, certain complications arise that necessitate experimental measurement

Received July 26, 1965, from the College of Pharmacy, Columbia University, New York, N. Y.
Accepted for publication September 28, 1965.
* Present address: College of Pharmacy, University of Michigan, Ann Arbor.

of apparent dissolution rates. Levy (4) considers a number of such complications, including those situations where the functional surface area does not equal the apparent specific surface area of the drug solids, and where it is desired to determine the dissolution rate of a drug in the presence of other initially solid components. The former instance is usually the result of surface hydrophobicity and a tendency for particle aggregation.

Several methods have been developed to determine dissolution rates of drugs in multiparticulate systems. Niebergall and Goyan (5) studied the dissolution of small particles and described a continuous recording technique for following the rapid dissolution of the particles. This method employs a high rate of agitation in order to avoid the complications resulting from surface hydrophobicity. Unfortunately, the rapid agitation magnifies considerably the problem of interpreting such dissolution rates in terms of their biopharmaceutical significance. In addition, high stirring rates would tend to minimize or even obviate significant differences in the dissolution rate of a drug in the presence of other components.

Higuchi *et al.* (6) determined dissolution rates of finely divided powders by placing weighed quantities of the powdered drug in bottles containing the solvent, rotating the bottles at 6 r.p.m. in a constant-temperature bath, removing these periodically, and assaying the rapidly filtered solutions. The application of this method is limited to highly insoluble drugs which demonstrate little particle–particle interactions when dispersed in the solvent.

Certain studies presently being conducted in the authors' laboratories with solid solutions and eutectic mixtures created a need for a method of determining dissolution rates of multiparticulate systems. The requirements of these investigations precluded the use of the various methods proposed in the literature. It is the purpose of this communication to describe the development and evaluation of a technique for measuring the dissolution rate of moderately water-soluble drugs in multiparticulate form under conditions of low to moderate agitation.

EXPERIMENTAL

Apparatus.—The basic parts of the apparatus consist of (*a*) pressure-sensitive tape,[1] 3/4 in. wide, that holds the particles of the drug, (*b*) a frame for mounting the tape, (*c*) a beaker that has been modified to contain runners to position the frame in contact with the dissolution fluid, and (*d*) a stirrer and its controls.

The frame was constructed by reshaping a standard No. 2 paper clip into a rectangle with a short handle. Open joints were sealed with standard solder. Prior to each dissolution experiment, a strip of the tape was fastened to the frame (see Fig. 1). This presented a taut adhesive surface onto which a preweighed quantity of particles could be uniformly dusted as a monoparticulate layer. This was confirmed by carefully examining the particulate layer with a 10× lens.

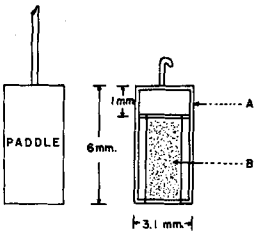

Fig. 1.—Detailed view of tape frame indicating its dimensions and positioning with respect to paddle. Key: A, tape frame structure; B, tape affixed to frame and containing particles.

A 600-ml. beaker was modified to contain two stainless steel runners attached to its inner wall by means of epoxy cement (Fig. 2). The runners were placed just far enough apart to accommodate the width of the tape frame and functioned as tracks or guides for the rapid introduction of the frame into the dissolution medium. A constant speed motor (53.5 r.p.m.) was attached to a laboratory jack (Fig. 2) which was rigidly affixed to a frame at the top of the apparatus. By means of the jack, the motor may be lowered or raised. In this manner, the stir paddle (attached to the motor shaft) is positioned in the dissolution beaker. The depth to which the paddle is lowered into the dissolution medium may be regulated by adjusting the height-determining posts which were built into the apparatus frame.

Preliminary experiments conducted with the dissolution apparatus indicated several aspects which demanded critical consideration. It was determined that the length of the stir paddle must at least equal the length of the tape. Furthermore, the paddle must be vertically positioned so that no portion of the tape extends beyond the length of the paddle. If this precaution is observed, the effect of the position of the particles on the tape and the *particle density* (*i.e.*, the number of particles/unit area of tape) on the dissolution rate is greatly minimized.

A second critical consideration in the use of the *tape method* is the distance between the stir paddle

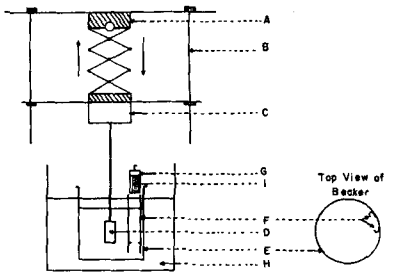

Fig. 2.—Dissolution apparatus. Key: A, laboratory jack; B, height-determining posts; C, constant speed motor; D, stir paddle; E, dissolution beaker; F, frame-positioning runners; G, tape frame, poised for introduction into the dissolution medium; H, constant-temperature water bath; I, tape, containing particles.

[1] Scotch Magic Tape, Minnesota Mining and Manufacturing Co., St. Paul, Minn.

TABLE I.—DISSOLUTION RATE OF BENZOIC ACID CRYSTALS USING THE TAPE METHOD

Time, min.	Concn., mg./400 ml. Run 1	Run 2	Run 3	Mean	S.D.
1	1.17	1.17	1.17	1.17	0.00 (0.0%)
3	3.82	3.82	4.11	3.92	0.17 (4.4%)
5	6.48	7.41	6.84	6.91	0.50 (7.3%)
7.5	9.32	10.45	9.63	9.80	0.58 (6.0%)
10	11.88	13.44	12.48	12.60	0.79 (6.3%)

TABLE II.—DISSOLUTION RATE OF SALICYLAMIDE CRYSTALS USING THE TAPE METHOD

Time, min.	Concn., mg./400 ml. Run 1	Run 2	Run 3	Mean	S.D.
1	1.00	0.85	1.04	0.97	0.10 (10.3%)
3	2.77	3.05	2.97	2.93	0.14 (1.6%)
5	4.47	4.68	4.70	4.61	0.12 (2.7%)
7.5	6.22	6.68	6.42	6.44	0.23 (3.6%)
10	7.86	8.28	8.15	8.09	0.21 (2.6%)

and the tape surface. The absolute distance is of no particular consequence for comparative studies. However, once the distance is established, it must be maintained constant for each subsequent experiment. Failure to comply with this precaution may result in a great deal of experimental variation.

Dissolution Tests

Benzoic Acid.—A sample of benzoic acid was fused in a stainless steel crucible immersed in a temperature-controlled silicone bath. The fused mass was poured onto ferrite plates and rapidly cooled at ambient temperature. The solidified mass was then carefully crushed in a mortar with a pestle. The resulting powder was screened using a Syntron shaker,[2] operated at 90 v. for 2 min. Only those particles that passed through a No. 50 but were retained on a No. 60 standard screen (250–300 μ) were used in the dissolution tests.

The dissolution fluid employed in these experiments was 400 ml. of water preheated to 37°, which was maintained by placing the beaker in a water bath at 37 ± 1°.

The stir paddle was positioned within the fluid and allowed to rotate for several minutes to establish normal flow patterns.

Forty milligrams of screened benzoic acid particles were uniformly spread onto the adhesive surface of the tape which had been affixed to the frame. The frame was then positioned between the runners in the beaker and held above the surface of the dissolution fluid within the beaker. At time zero, the tape frame was dropped down the runners below the surface of the stirred dissolution fluid. Ten-milliliter samples were withdrawn and immediately replaced with 10 ml. of water (preheated to 37°) at time intervals of 1, 3, 5, 7.5, and 10 min. These samples were then assayed spectrophotometrically at 270 mμ using a Beckman DB recording spectrophotometer. The observed concentrations were calculated in the usual manner and a cumulative correction was applied to account for the previously removed samples (7).

Salicylamide.—Salicylamide was prepared in a manner similar to that described under *Benzoic Acid*. The particle size range (250–300 μ), sample weight (40 mg.), volume of dissolution fluid (400 ml. of water), temperature (37°), stir rate, and sampling times were identical for both compounds. At each time interval a 2-ml. sample was withdrawn and diluted to a volume of 10 ml. with water. The diluted sample was assayed spectrophotometrically at 233 mμ. The same type of volume adjustment and cumulative correction was made as discussed previously.

In each dissolution study, consideration was given to the possibility that particles might be swept off the tape and thereby represent a source of error. Visual observation and filtration studies precluded this possibility. A number of samples were quickly placed in a Millipore filter assembly and the fluid rapidly aspirated. In no instance were crystals detected on the filter pad.

Control Experiments

Additional studies were conducted to insure that the components of the tape were in no way interfering with either the assay or the dissolution process. The possibility of leaching was examined by following the dissolution procedure discussed previously with the tape alone. Each sample of dissolution fluid was scanned in the ultraviolet and visible region. The effect of the tape on the equilibrium solubility of both salicylamide and benzoic acid was also evaluated. An excess of each compound was added to 15 ml. of water in a screw-top vial in the presence and absence of a 0.5-Gm. quantity of tape. The sealed vial was incubated in a gyratory shaker at 37° for 48 hr., and the solubility of each chemical was determined spectrophotometrically.

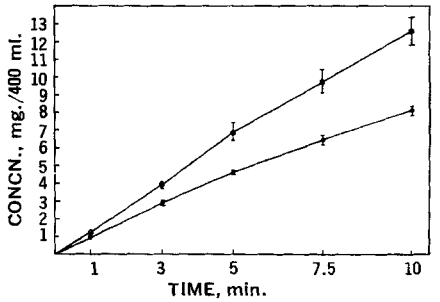

Fig. 3.—Mean cumulative dissolution of benzoic acid and salicylamide crystals as a function of time. Key: upper curve, benzoic acid; lower curve, salicylamide.

[2] Syntron TSS-25 test shaker, Syntron Co., Homer City, Pa.

RESULTS

Three dissolution experiments were conducted with each chemical. The results of each dissolution test are presented in Tables I and II with the standard deviation at each time interval. The mean cumulative amount of drug in solution *versus* time is plotted in Fig. 3.

The leaching studies indicated the absence of any materials capable of absorbing light in the ultraviolet or visible region within the first 30 min. In addition, equilibrium solubility experiments revealed that the solubility of each compound was unaffected by the presence of even a large amount of tape. In these studies a measurable degree of leaching was observed at 233 and 270 mμ and was accounted for in the calculation of solubility. The equilibrium solubility (in the presence or absence of tape) of benzoic acid was found to be 4.55 Gm./1000 Gm. as compared to 3.97 Gm./1000 Gm. for salicylamide.

DISCUSSION

To evaluate the dissolution process in a quantitative manner it is necessary to account for the constantly changing surface area of the material under study. Hixson and Crowell (8) derived an equation for the dissolution of a single particle in which the surface area changed with time. Niebergall and Goyan (5) extended the basic equation of Hixson and Crowell for use in multiparticulate systems by assuming a system of N equal-size particles. When the amount of solute needed to saturate a given volume of solvent is much greater than the amount in solution, the integrated form of the extended equation may be expressed as:

$$W_0^{1/3} - W^{1/3} = Kt \qquad \text{(Eq. 1)}$$

where W_0 is the initial weight of N particles, W is the total weight of the particles at time t, and K is the product of the intrinsic dissolution rate constant, solubility, density, and shape factors for the drug being tested.

The mean data obtained with benzoic acid and salicylamide were recalculated in terms of the parameters expressed in Eq. 1, and a plot of $W_0^{1/3} - W^{1/3}$ *versus* time is presented in Fig. 4. Reasonable agreement with Eq. 1 was obtained over the entire experimental period with benzoic acid. The salicylamide data demonstrated linearity for the first 5 min. but thereafter showed significant curvature.

The deviation obtained in the salicylamide studies is explained in part by a consideration of the shape factor contained in the rate constant, K. The constancy of the shape factor demanded by Eq. 1 can only be satisfied by spherical particles. The greater the departure from a hypothetical spherical shape, the greater the change in the shape factor during the course of the dissolution process. Microscopic examination of each sample indicated that benzoic acid crystals had a height (h) to diameter (d) ratio of close to unity (about 1.4). The salicylamide crystals, on the other hand, showed an h/d ratio considerably greater than unity (about 5). This may be observed in Fig. 5. Thus, a change in the h/d ratio would be expected when a significant change in the total weight of the salicylamide sample had occurred. Therefore, the extended Hixson-Crowell equation would theoretically not be applicable beyond a certain weight change during the dissolution process.

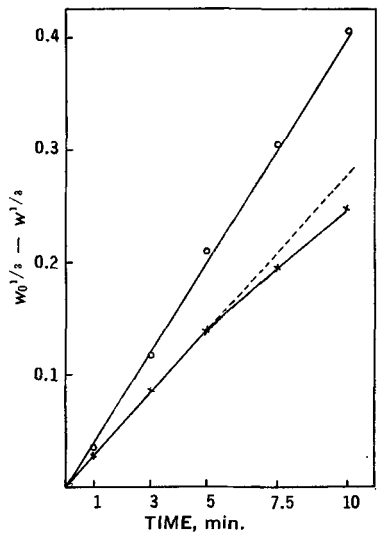

Fig. 4.—Dissolution data fitted to the extended Hixson-Crowell equation. Key: O, benzoic acid; X, salicylamide.

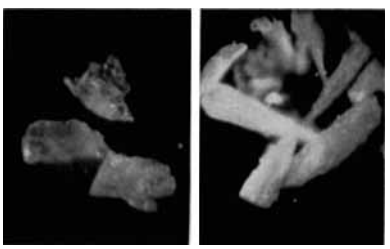

Fig. 5.—Photomicrographs of benzoic acid (A) and salicylamide (B) crystals (both 50–60 mesh).

CONCLUSIONS

The tape method described herein appears to be a promising research tool in the measurement of dissolution rates of multiparticulate systems. Replication between experiments is well within accepted limits and may be further improved by more stringent adherence to the precautions noted. Furthermore, the results obtained with the tape method demonstrated reasonable agreement with the extended Hixson-Crowell equation which theoretically describes the dissolution process of a multiparticulate system consisting of either granules or powder.

REFERENCES

(1) Levy, G., *J. Pharm. Sci.*, **52**, 1039(1963).
(2) Levy, G., *et al.*, *ibid.*, **52**, 1047(1963).
(3) Milosovich, G., *ibid.*, **53**, 484(1964).
(4) Levy, G., *Am. J. Pharm.*, **135**, 78(1963).
(5) Niebergall, P. J., and Goyan, J. E., *J. Pharm. Sci.*, **52**, 29(1963).
(6) Higuchi, W. I., Rowe, E. L., and Hiestand, E. N., *ibid.*, **52**, 162(1963).
(7) Wurster, D. E., and Taylor, P. W., Jr., *ibid.*, **54**, 670 (1965).
(8) Hixson, A., and Crowell, J., *Ind. Eng. Chem.*, **23**, 923 (1931).