Effect of Certain Tablet Formulation Factors on Dissolution Rate of the Active Ingredient I

Importance of Using Appropriate Agitation Intensities for *in Vitro* Dissolution Rate Measurements to Reflect *in Vivo* Conditions

By GERHARD LEVY

Evidence is presented to show that solid dosage forms are exposed to relatively low agitation intensities after oral administration, and that it is often mandatory to use similar mild agitation conditions for predictive *in vitro* dissolution tests. Based on considerations of the effect of stirring rate on boundary layer thickness, it is demonstrated that the effective surface area of heterogenous pellets (analogous in some respects to certain prolonged release dosage forms) may be different when such pellets are exposed to high and low agitation intensities, respectively. A proportionality between dissolution rate and the square root of stirring rate, demonstrated by others with rotating disks of inorganic salts, has been found to apply also to rotating disks of certain organic weak acids. It is shown that the ratio of dissolution rates of two or more drugs, when rates are determined by the rotating disk method, is independent of stirring rate, provided this proportionality or a similar more general relationship applies.

RECENT RECOGNITION that the availability for gastrointestinal absorption of drugs contained in compressed tablets is often reflected by *in vitro* dissolution rates and not by tablet disintegration times has stimulated the development and use of dissolution rate tests for compressed tablets (1–4). Ideally, the validity of a particular *in vitro* dissolution rate test for a given drug must be assured and proper interpretation of data made possible by demonstrating the correlation between *in vitro* and clinical data and by calibrating the former against the latter. The feasibility of such an approach has been demonstrated in a previous report from this laboratory (1). Based on physiologic considerations, we utilized a very low agitation intensity in our *in vitro* test (1, 5). In a study of the relation of *in vitro* dissolution rate to the rate of absorption of methylprednisolone implants in rats, Hamlin and co-workers have found that the *in vivo* results correlated only with those *in vitro* data that were obtained from dissolution tests utilizing very low agitation intensities (6). These workers were the first to point out the importance of stirring rate in dissolution rate studies of pharmaceuticals. The present communication deals with the development of meaningful dissolution rate tests for certain oral medication and includes the results of physiologic and physicochemical studies concerned with the effect of agitation intensity on the rate of dissolution of conventional compressed tablets and certain related dosage forms.

In this laboratory we have emphasized particularly the study of agitation conditions to which ingested tablets may be exposed in the stomach. One reason for this emphasis has been that solids may be retained in the stomach for a considerable length of time (7); therefore, the intestinal absorption of the ingested drug sometimes may be limited initially mainly to that portion which is dissolved in gastric fluids which flow into the intestine. Another reason for studying dissolution under conditions representative of gastric conditions has been the desirability (in many instances) that drugs reach intestinal absorption sites in absorbable (*i.e.*, dissolved) form, either because such drugs may be intrinsically slowly absorbed, or because they are absorbed only from the proximal region of the small intestine (26). Finally, part of our emphasis on gastric dissolution stems from our interest in the biopharmaceutics of salicylate drugs. Salicylates can be absorbed from the stomach, and their rapid dissolution and absorption is desirable in order to obtain a prompt analgesic effect. Perhaps more important is the prevention of serious mucosal erosion and bleeding because of aspirin solids that, on occasion, may lodge in the rugae of the gastric mucosa. Rapid dissolution of these solids will shorten the time of contact of the drug with the mucosa, and will tend to minimize the incidence and severity of mucosal damage (1, 8).

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EXPERIMENTAL

Radio-opaque Tablets.—The radio-opaque tablets

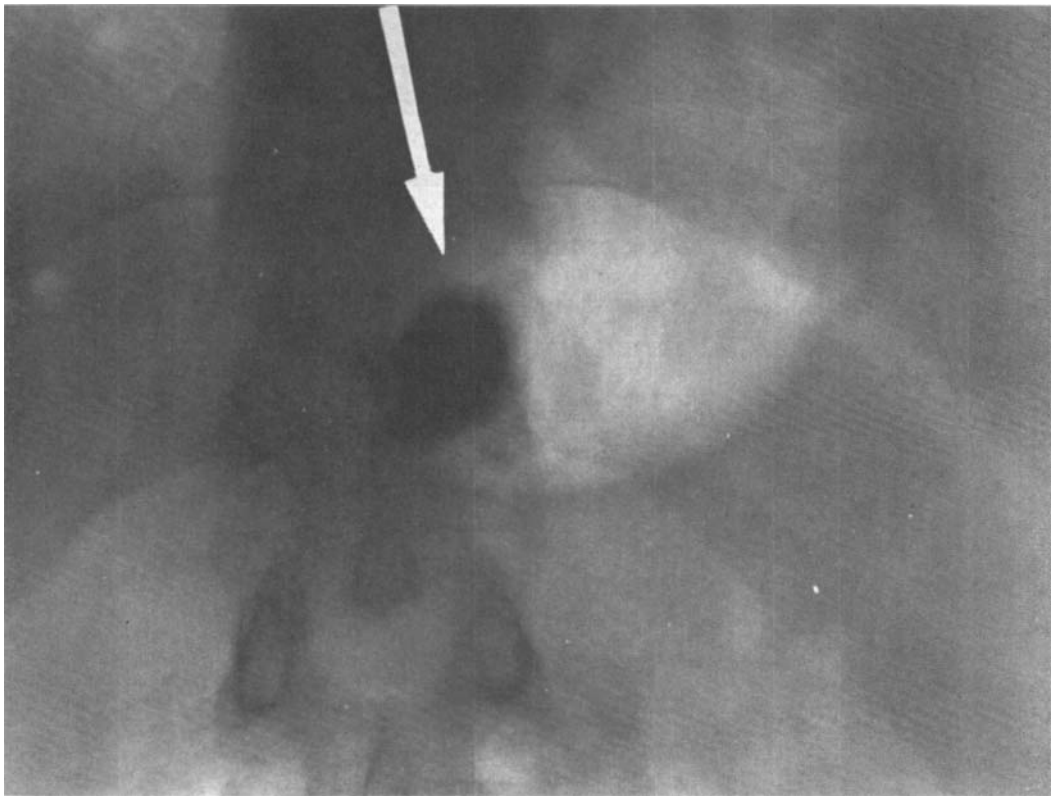
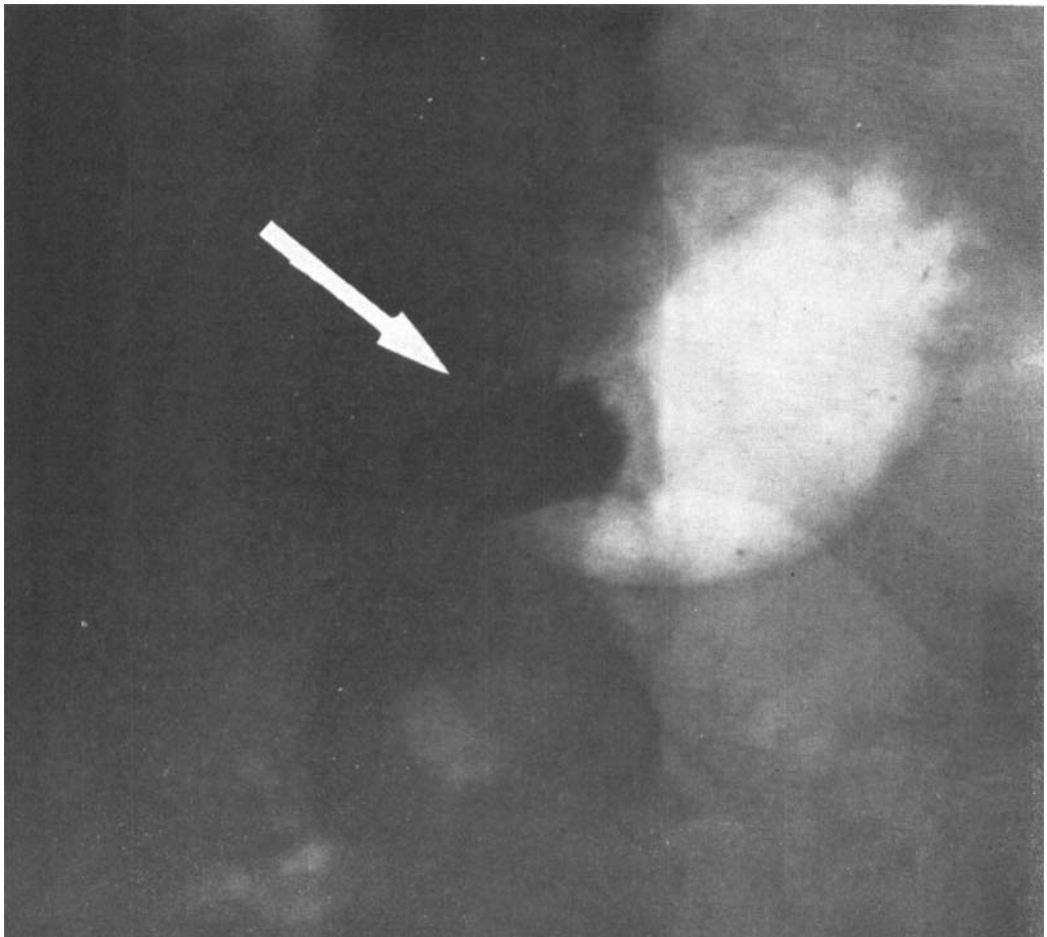


Fig. 1.—Radio-opaque tablet in human stomach 13 minutes after ingestion. Tablet is just beginning to disintegrate, as evidenced by the still noticeable tablet outline.

Fig. 2.—Radio-opaque tablet in human stomach 30 minutes after ingestion. Enlarged diameter of radio-opaque spot *vs.* Fig. 1 indicates that tablet has disintegrated.



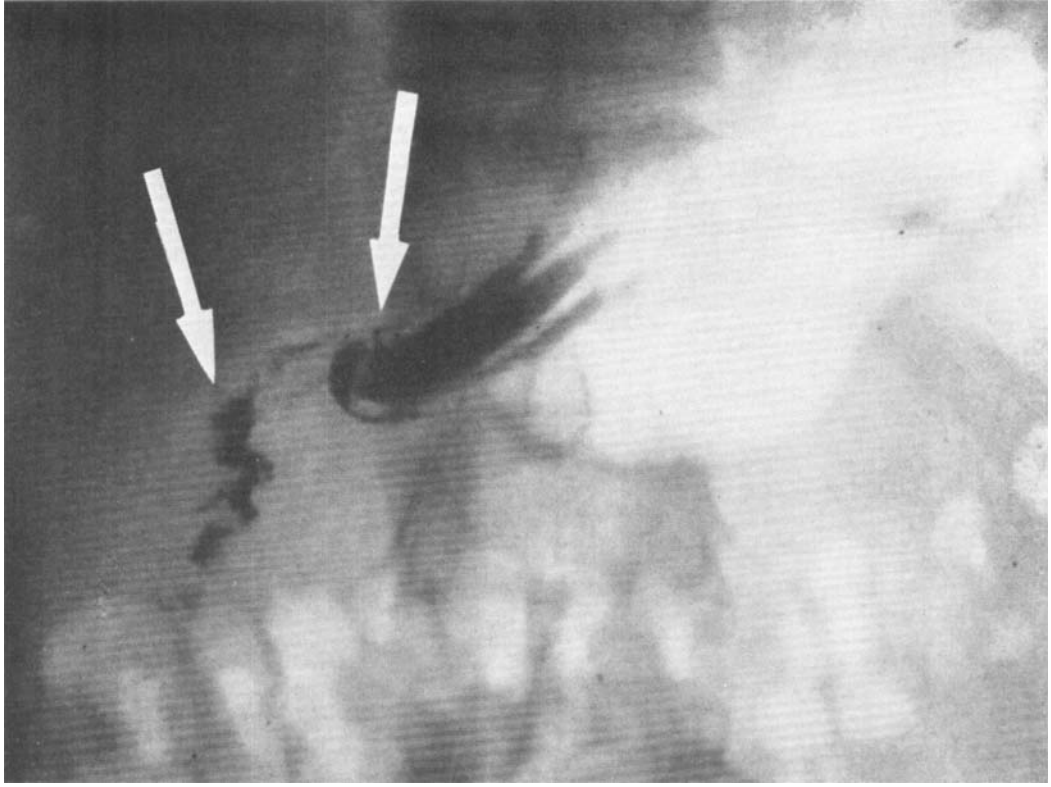
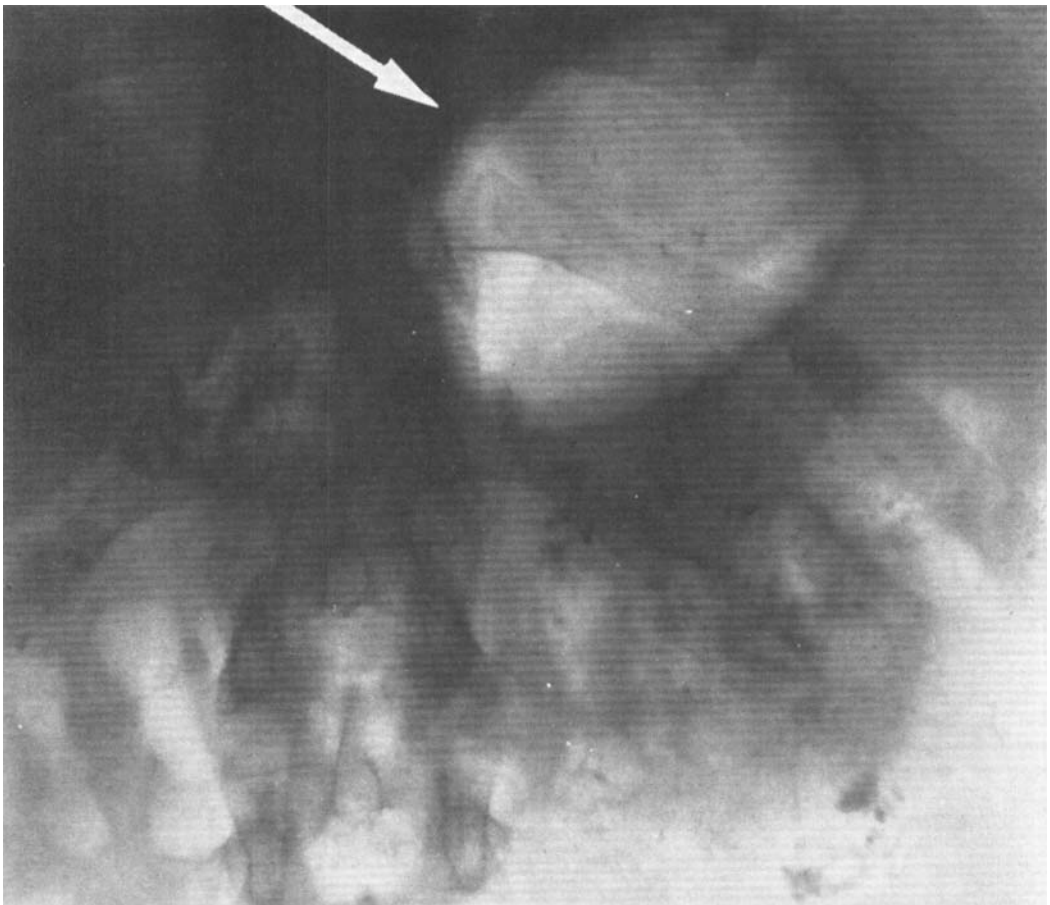


Fig. 3.—Radio-opaque tablet in human stomach 45 minutes after ingestion. Granules are passing through pylorus into small intestine. Note that granules are not dispersed throughout the stomach at any time.

Fig. 4.—Radio-opaque tablet solids in human intestine 60 minutes after ingestion of tablet. Arrow points to empty stomach. Granules are well dispersed in intestine and are apparent as very small radio-opaque spots.



used in this study were prepared by wet granulation of barium sulfate with starch paste and subsequent compression of the dried granulation to which dry starch had been added as a disintegrant.

Dissolution Rate Determinations.—Dissolution rates of conventional tablets were determined by the beaker method and by the oscillating tube method. The *beaker method* involves the use of a double-wall, 400-ml. capacity beaker and a propeller-type stirrer attached to an electronic-controlled stirring motor. The method has been described elsewhere in detail (5). The *oscillating tube method* makes use of a plexiglass cylinder (2.5 × 19.5 cm.) with a 100-mesh stainless steel wire screen on the bottom. The cylinder is attached to the basic unit of the U.S.P. tablet disintegration apparatus (where it replaces the standard basket-rack assembly). The cylinder is immersed in a beaker (placed in a constant temperature bath) containing 800 ml. 0.1 *N* HCl at 37°, the apparatus is set in motion, a tablet is dropped into the cylinder, and the medium is sampled at intervals by a fritted-glass immersion filter tube.

Intrinsic dissolution rate determinations and certain other experiments were carried out by the *rotating disk method* which has been described elsewhere (18). The *static disk method* is a modification of the rotating disk method. The stem of the pellet holder is inserted in a one-hole rubber stopper which serves as a closure for 12-dram plastic vials containing 25 ml. of 0.1 *N* HCl at 37°. The end of the pellet holder, and therefore the exposed face of the pellet, is thus immersed in the solvent. The entire assembly is placed in an incubator set at 37°. The pellet holder is removed from the solution at appropriate intervals (usually 1 or 2 hours), the plastic parts are dried carefully with tissue (without touching the pellet surface), and the assembly is placed in another vial which contains fresh solvent. After removal of the pellet assembly, an aliquot of the solution contained in the vial is assayed and, by appropriate calculations based on concentration and volume, the total amount of dissolved drug is established. This procedure yields data which may either be expressed in terms of an average dissolution rate (amount/area/time) or be plotted cumulatively as amount dissolved *versus* time.

Analytical Methods.—Salicylic acid was determined spectrophotometrically with a Beckman DU spectrophotometer. Solutions were diluted appropriately with 0.1 *N* HCl. Aspirin solutions were hydrolyzed by heating with sodium hydroxide, then analyzed for salicylic acid.

Microenvironmental pH was estimated by immersing the miniature electrodes of a pH meter (Leeds and Northrup model 7664) into a paste prepared from crushed tablets and 0.1 *N* HCl.

RESULTS AND DISCUSSION

Agitation Intensities Encountered in the Human Stomach.—X-ray motion pictures of the human stomach (viewed by the author) show that the agitation of gastric content during normal contractions is mild. It appears a valid assumption, therefore, that the particles from a disintegrated tablet are not dispersed throughout the stomach but rather remain as an aggregate. In support of this assumption of minimum agitation, it has been observed in animals that different foods, when ingested successively, remain in the stomach as different "layers" which do not intermix (9). Similar observations have been made recently in the human stomach by means of the fiberscope (10). Other pertinent reports are those of Ivy, *et al.*, who have remarked on the lack of significant mixing of material held in the fundus of the stomach (11), and several that deal with the regional differences in gastric pH—for example, Tomenius and Williams (12). Accordingly, we developed a dissolution rate test in which the agitation intensity is just sufficient to assure homogeneity of the medium for proper sampling. In this test the solids of the disintegrated tablet remain as an aggregate or "mound" in the center of the bottom of the beaker (5).

The essential correctness of our assumptions has been borne out by the excellent correlation of our *in vitro* test with *in vivo* data (1). However, it has been felt that more direct evidence could be obtained by a serial X-ray study of the behavior of a radiopaque tablet in the human stomach. Such tablets were formulated from barium sulfate in a manner assuring their rapid disintegration (U.S.P. disintegration time was only 3.5 minutes). Figures 1–4 are X-ray photographs taken 13, 30, 45, and 60 minutes after ingestion of a whole tablet with approximately 50 ml. of water.[1] The outline of the tablet was still apparent 13 minutes after ingestion, indicating that the tablet was just beginning to disintegrate. (The longer *in vivo* disintegration time suggests that the U.S.P. test may be too vigorous, or it may reflect the retarding effect of gastric mucous observed by Abbott, *et al.* (13)). Thirty minutes after ingestion, the tablet was totally disintegrated, but the solids remained in an aggregate approximately 2–3 cm. diam. (Fig. 2). The next picture (Fig. 3) was taken at 45 minutes, just as fluoroscopic examination showed that the solids were entering the small intestine. It can be seen that no dispersion of the solid particles occurred while they resided in the stomach. In the final picture of the series (Fig. 4), it is apparent that thorough dispersion of the particles did occur in the small intestine.

Subsequent to our study, Weiss, *et al.* (14), have reported the results of their gastroscopic observations of aspirin tablets in the human stomach; the results tend to confirm our findings. They noted during a period of 10 to 40 or 50 minutes after the ingestion of whole aspirin tablets that "frequently (the aspirin) appeared as a white gelatinous mass of granules adherent to the mucosa" and "in the more marked cases of bleeding, the pulverized mass of aspirin, coagulated blood, and mucus formed an adherent gelatinous layer of 10 to 15 mm. in diameter."

Differences in Comparative Dissolution Rates That May be Encountered When Using Different Agitation Conditions for Compressed Tablets.—The increase in dissolution rate of drugs contained in compressed tablets, when they are subjected to increasing agitation intensities, does not follow a simple mathematical relationship. A variety of effects, characteristic of each formulation, come into play and account for the need to use appropriate

[1] The author acknowledges gratefully the cooperation of Dr. Julian Ambrus, Roswell Park Memorial Institute, who took the X-ray photographs shown in this paper.

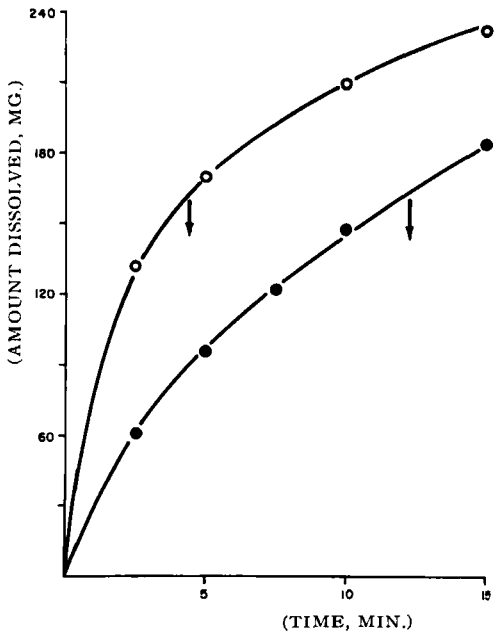


Fig. 5.—Dissolution of aspirin tablets (●) and "buffered" aspirin tablets (○) determined by the beaker method. Vertical arrows point to half-dissolution times.

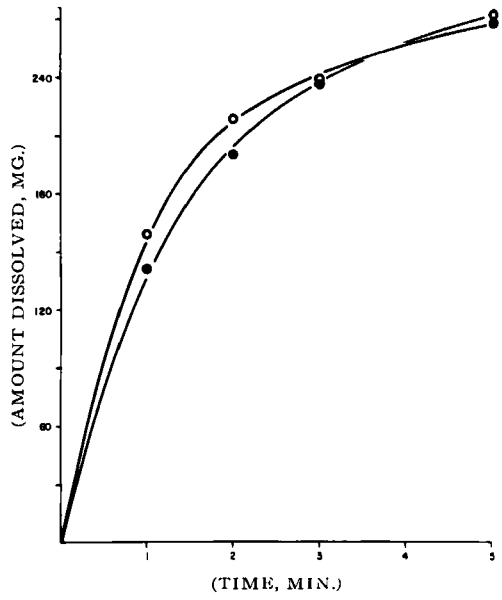


Fig. 6.—Dissolution of aspirin tablets (●) and "buffered" aspirin tablets (○) determined by the oscillating tube method.

agitation conditions for meaningful *in vitro* tests. When the solids of a disintegrated tablet form an aggregate or "mound," the effective surface area with respect to dissolution is primarily the surface of the mound, depending to some extent upon the porosity of the aggregate and the viscosity of the fluids in the interstices, among other factors. Under these conditions, the effect of particle size (specific surface area) on dissolution rate is considerably less than when the particles are dispersed throughout the medium by intensive agitation. This is evident from data presented in a following communication (15). The effect of other tablet components upon the dissolution rate of the active ingredient is also reduced under conditions of intensive agitation because of the greater physical separation of these components and the drug. On the other hand, such effects can be considerable in the microenvironment of a solid aggregate. They may result from high viscosity due to hydrocolloids and gums, lowering of interfacial tension by surfactants, other adsorption phenomena, changes in zeta potential associated with the presence of ionic species, chemical reactions because of high concentrations of potential reactants in the microenvironment, and particularly, changes in the pH of the microenvironment. These effects can directly or indirectly affect the primary drug particles and modify their rate of dissolution.

The importance of these considerations becomes evident from the following experiment. The dissolution rate of aspirin contained in (*a*) a proprietary product of plain aspirin in compressed tablets and (*b*) a proprietary product of aspirin and alkaline additives in compressed tablets was determined by two different methods. One was our previously described beaker method (5) which utilizes a very low agitation rate and permits the solid particles to remain on the bottom of the beaker as an aggregate. The other test was by the oscillating tube method which involves relatively high agitation intensities and causes the solid particles of the disintegrated tablets to be dispersed in the dissolution medium. The results of dissolution rate tests of the two tablet products, using the two different test methods, are shown in Figs. 5 and 6. Each point in the figures represents an average value obtained from four tablets.

Under the low agitation conditions of the beaker method, the tablets containing aspirin and alkaline additives dissolved much more rapidly than plain aspirin tablets. This is in accord with results of human absorption tests of these products conducted previously in our laboratory (1). The vertical arrows in Fig. 5 denote half-dissolution times—one comparative measure of dissolution rates. These times differed approximately threefold. At no time did the extreme values of the two types of tablets overlap. On the other hand, there was practically no difference in dissolution rates of the two tablet formulations when tested by the oscillating tube method (Fig. 6). The ranges of the respective values overlapped at all times, and half-dissolution times were essentially the same.

The difference in the results obtained by the two methods can be explained readily. In an aggregate of disintegrated tablet solids, the alkaline components of the "buffered" aspirin tablet caused an increase in the pH of the microenvironment from approximately pH 1 (0.1 *N* HCl) to about pH 5.6. This increase in pH results in a more rapid dissolution of aspirin particles (8).[2] The dissolution rate enhancing effect is absent when aspirin and alkaline components are physically separated by intensive

[2] A similar formulation approach can be used to increase the dissolution rate of other weak acids.

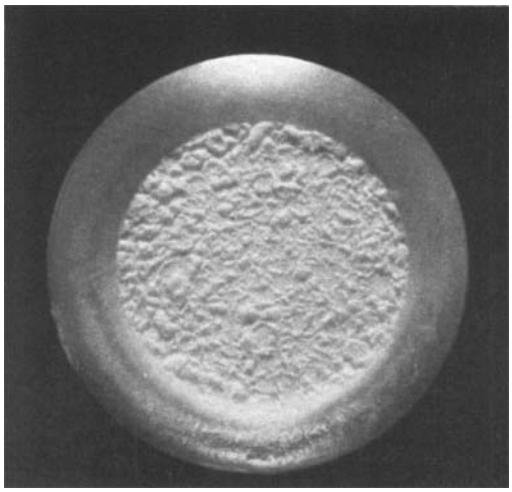


Fig. 7.—Pitted surface of a pellet made from pure salicylic acid granules and 3% magnesium stearate. Picture was taken after dissolution of 10 mg. salicylic acid from the pellet surface. (Pellet diameter, 1.27 cm.)

agitation, since the amount of alkaline components is insufficient to alter significantly the bulk pH of the medium. Thus it is evident that dissolution tests using agitation intensities sufficient to cause dispersion of particles would yield misleading results when used in the evaluation of the described type of pharmaceutical product.[3]

In this connection it is appropriate to comment upon the findings of Rubin, *et al.* (16), and Davison, *et al.* (17). These workers determined the pH of gastric fluids in humans after administration of a commercial "buffered" aspirin tablet product. They found no significant change in pH compared with control values. This should not be surprising on the basis of the quantities of alkaline components involved and the usual acidity and volume of gastric fluids. However, the significance of the cited observations can be misinterpreted easily. It must be recognized that the dissolution rate enhancing function of the alkaline components is because of their ability to raise the pH of the microenvironment, and that the absence of any change in bulk pH is of little pertinence in this respect.

In the course of studies of the effect of tablet formulation factors upon the dissolution rate of the active ingredient, we have also encountered differences in comparative dissolution rates as a function of agitation intensity in formulations that differed in starch content, granule size, and type of lubricant. These studies will be reported in subsequent communications.

Effect of Stirring Rate on the Rate of Dissolution from Irregular Surfaces of Heterogeneous Solids.—A phenomenon encountered in determinations of dissolution rate by the rotating disk method (18) may be pertinent to dissolution rate studies of nondisintegrating tablets containing several components, such as certain sustained-release pellets that consist of drug particles dispersed in a more slowly dissolving matrix. Pellets which were prepared by compressing a mixture of pure 20–40-mesh granules of salicylic acid and 3% magnesium stearate powder developed a rough pitted surface during dissolution. This effect became evident after dissolution of approximately 5 mg. of drug from the pellet, which had an exposed surface area of 1.27 cm.^{2} The surface pitting, which is clearly evident in a photograph of a representative pellet (Fig. 7), is because of the relatively rapid dissolution of salicylic acid granules, and the slower erosion of the hydrophobic magnesium stearate in the interstices between granules. In a dissolution rate determination where the pellets were rotated at 555 r.p.m. in 0.1 *N* HCl at 37°, an initial dissolution rate of 22.8 mg./hour/cm.^{2} was found. After 5 mg. of salicylic acid had dissolved and pits had formed on the pellet surface, the slope of the amount dissolved *versus* time plot increased until it yielded an apparent dissolution rate value of 34.6 mg./hour/cm.^{2} (19). This apparent 52% increase in dissolution rate can be attributed to the increase in surface area of the pellet as a result of pitting. When a similar test was conducted under static conditions (*i.e.*, the pellet was immersed in 0.1 *N* HCl but was not rotated), the dissolution rate was of course considerably lower (1.97 mg./hour/cm.^{2}), but the characteristic formation of surface pits did occur. However, pitting was not accompanied by an increase in apparent dissolution rate.

The observations described above can be explained on the basis of the changes in the thickness of the boundary layer as a function of stirring rate. The effective boundary layer thickness δ can be determined by (20)

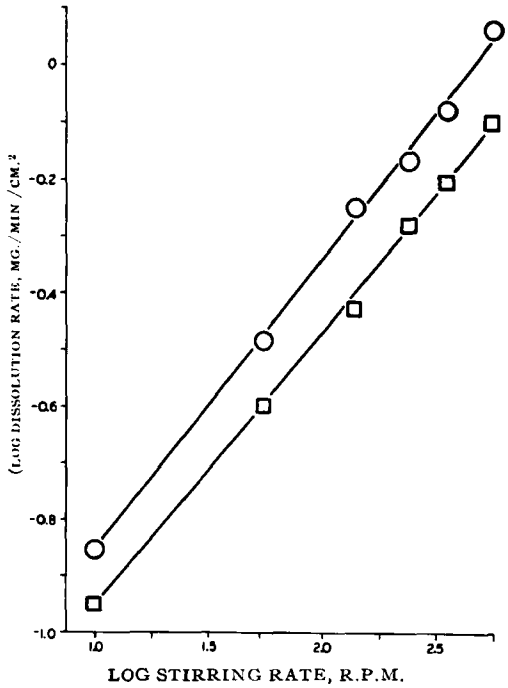


Fig. 8.—Plot of logarithm of dissolution rate *vs.* logarithm of stirring rate (spinning disk method). Key: (○) aspirin, (□) salicylic acid. (Dissolution rates of aspirin are expressed in terms of salicylic acid.)

[3] This should not detract from the usefulness of the oscillating tube method and similar methods to reflect the relative dissolution rates (particularly in the intestine) of many other types of drugs.

$$\delta = \frac{DSC_s}{R} \qquad \text{(Eq. 1)}$$

where D is the coefficient of diffusion, S is the surface area, C_s is the solubility, and R is the intrinsic dissolution rate. The diffusion coefficient of salicylic acid at 37°, calculated from Edwards' data (21), is 11.3×10^{-6} cm.²/second. This value is only slightly affected by concentration and may therefore be used as such. The solubility of salicylic acid in 0.1 N HCl at 37°, as determined in our laboratory, is 2.66 mg./ml. Thus, the boundary layer thickness for the pellets used in this study could be calculated by

$$\delta = \frac{(11.3 \times 10^{-6})(1.27)(2.66)}{R} \qquad \text{(Eq. 2)}$$

or

$$\delta = \frac{3.82 \times 10^{-5}}{R} \qquad \text{(Eq. 3)}$$

where δ is expressed in cm. and R is expressed in mg./second.[4]

The thickness of the boundary layer covering a pellet rotated at 555 r.p.m. is therefore

$$\frac{3.82 \times 10^{-5}}{6.34 \times 10^{-3}} = 0.0060 \text{ cm.}$$

while under static conditions, the boundary layer thickness is

$$\frac{3.82 \times 10^{-5}}{5.47 \times 10^{-4}} = 0.070 \text{ cm.}$$

The depth of the surface pits may be approximated in the following manner. The granules used to prepare the pellets were those which passed a 20-mesh screen but not a 40-mesh screen. This is equivalent to a granule diameter range of 0.042 to 0.084 cm. The maximum average depth of a surface pit may be considered to be equivalent to the average diameter of the granules and probably more realistically to one-half or two-thirds of this value. Since the pellets were compressed at very high pressure (20,000 lb.), it is likely that the granules were distorted in a manner which caused their elongation in a direction parallel to the pellet face and a decrease in diameter normal to the pellet face (22). Such a flattening would cause the depth of the pits on the pellet surface to be even smaller than indicated above. On the basis of all these considerations, the depth of the pits should, in all probability, be somewhat less than 0.04 cm. It is thus apparent that under static conditions (as contrasted with rapid agitation conditions) the surface irregularities would be effectively covered by the boundary layer, and the effective surface area of the pellet would not be increased by pitting. For this reason, there is no increase in the apparent rate of dissolution of the pellet during a static dissolution test. On the other hand, the thickness of the boundary layer covering the surface of a pellet rotating at 555 r.p.m. is insufficient to cover the pits which are formed during the dissolution process. Therefore, the effective surface area of the pellet increases as the smooth surface of the pellet becomes pitted; this results in an increase in apparent dissolution rate.

Although this may not be recognized readily upon initial consideration, the above can be pertinent to the evaluation of dissolution characteristics of certain nondisintegrating pellet-like dosage forms, such as some sustained-release tablets composed of a drug dispersed in a relatively hydrophobic matrix. These dosage forms are exposed to relatively mild agitation *in vivo*, and their effective surface area under these conditions may differ considerably from the effective surface area that is functional at higher stirring rates that may be used in an *in vitro* test. However, stirring rate should not be important if the rate of dissolution is limited by the rate of diffusion through a nondissolving coating or matrix, or if the boundary layer is not on the surface but within the tablet—as is the case with certain prolonged release tablets containing drug in a permanent plastic matrix.

Significance of Intrinsic Dissolution Rate Values Determined at Relatively High Stirring Rates.—For practical purposes, *intrinsic* dissolution rate determinations are frequently made at rather high stirring rates. In view of the emphasis placed in the present communication on the importance of using low stirring rates for dissolution rate tests of pharmaceutical dosage forms, the validity of biopharmaceutical interpretations based on intrinsic dissolution rate values obtained at high stirring rates (8, 23, 25) may be questioned. When the intrinsic dissolution rates of two substances differ by two or three orders of magnitude at high stirring rates, there should be little doubt that similar differences, at least qualitatively, should obtain at low stirring rates and under appropriate *in vivo* conditions. But what about differences in dissolution rates at high stirring rates that are only 50% or so in magnitude?

Cooper and Kingery (24) have recently presented the following equation which relates the diffusion-controlled dissolution rate from the surface of a rotating disk to the velocity of rotation (stirring rate),

$$j = 0.621\, D_o\, (V^*/D^*)^{1/3}\, (\omega/V_\infty)^{1/2}\, \Delta C \qquad \text{(Eq. 4)}$$

where j is the flux density of solute entering the solvent (dissolution rate per unit area), D_o is the diffusion coefficient of the solute in saturated solution, V^* is the effective viscosity in the immediate vicinity of the solid-liquid interface, D^* is the weighted average diffusion coefficient of the solute in the solvent (assuming that D varies with concentration), ω is the angular velocity (in radians per second) of the rotating disk, V_∞ is the bulk viscosity, and ΔC is the concentration differential, representing the difference between interface and bulk concentration. Under our usual experimental conditions, ΔC is maintained essentially constant and is equal to the solubility C_s of the solute in the solvent. In such cases,

$$j = K\omega^{1/2} \qquad \text{(Eq. 5)}$$

where

$$K = 0.621 D_o\, (V^*/D^*)^{1/3}\, (1/V_\infty)^{1/2} C_s$$

Equation 5 may also be written as

$$j = K_1\, (\text{r.p.m.})^{1/2} \qquad \text{(Eq. 6)}$$

[4] Certain complications associated with the application of Eq. 3 to heterogeneous pellets may cause the calculated δ values to be slightly too high (19). However, this will not affect the validity of the subsequent comments.

where

$$K_1 = 0.3236\ K$$

Expressed logarithmically, Eq. 6 yields

$$\log j = 0.5 \log (\text{r.p.m.}) + \log K_1 \quad \text{(Eq. 7)}$$

According to Eq. 7, a plot of the logarithm of dissolution rate (expressed here in mg./minute/cm.^{2}) *versus* the logarithm of stirring rate (expressed in r.p.m.) should yield a straight line with a slope of 0.5. This has been found by others to be the case with inorganic salts (20, 24).

We now present data to show (*a*) that the described relationship between dissolution rate and stirring rate holds for the apparatus used in our studies, and (*b*) that this relationship applies to compounds other than inorganic salts.

Using the rotating disk procedure (18), which is a modification and adaptation of the technique of Nelson (25), we determined intrinsic dissolution rates of aspirin and salicylic acid in 0.1 *N* HCl and 37° at stirring speeds ranging from 10 to 555 r.p.m. The data, appropriately plotted, are shown in Fig. 8. Each of the points in the figure represents from two to ten separate determinations. These points yield satisfactory straight lines which were fitted by the method of least squares. The slope of the line for salicylic acid is 0.492 and that for aspirin is 0.515. As is evident, the experimental slope values are very close to the theoretical value.[5]

It can be shown that the ratio of dissolution rates of two compounds is independent of stirring rate, provided the Cooper-Kingery equation or a similar, more general equation applies. Equation 7 may be rearranged to

$$\log (\text{r.p.m.}) = 2 \log j + K_2 \quad \text{(Eq. 8)}$$

where

$$K_2 = -2 \log K_1$$

On the basis of Eq. 8, at any given stirring rate

$$2 \log j_a + K_{2a} = 2 \log j_b + K_{2b} \quad \text{(Eq. 9)}$$

where the letter subscripts denote j and K_2 values for compounds *a* and *b*, respectively. Then

$$\log \frac{j_a}{j_b} = 1/2(K_{2b} - K_{2a}) \quad \text{(Eq. 10)}$$

and

$$\frac{j_a}{j_b} = 10^{1/2\,(K_{2b} - K_{2a})} = \text{constant} \quad \text{(Eq. 11)}$$

[5] This has also been found true for the dissolution of these weak acids in pH 8.0 Sorensen buffer solution.

In general, the ratio of the dissolution rates of two or more compounds will be independent of stirring rate as long as the respective dissolution rates increase with stirring rate according to the general equation

$$\text{dissolution rate} = (\text{constant})\,(\text{stirring rate})^a \quad \text{(Eq. 12)}$$

and the value of *a* is the same for each compound.

When these conditions are met, comparative dissolution rate data obtained at high stirring rates reflect properly the relative dissolution rates encountered at lower stirring rates. However, the observations by Hamlin and co-workers (6), and work currently in progress in this laboratory indicate that, in certain instances, the effect of stirring rate on dissolution rate cannot be described by either the Cooper-Kingery equation or by the general Eq. 12. In such cases it is often imperative to use appropriately low stirring intensities in intrinsic dissolution rate determinations for biopharmaceutical purposes.

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