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Review Article

Tablet Disintegration and Physiological Availability of Drugs

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THE CLINICAL effectiveness of tablets and other pharmaceutical dosage forms of drugs depends on at least two factors: the medication must not only be present in the labeled amount, but also must be available to the body. Until recently, however, manufacturers, regulatory agencies, and physicians have paid relatively little attention to the important effects which variations in dosage forms can have on clinical response. In most instances, clinical response is related directly to drug concentration in the tissues, which in turn is related to the amount of drug ingested. Determination of the potency of drugs has been, therefore, the most widely used procedure to ascertain that patients receive the amounts of drugs prescribed by physicians. However, considerable evidence exists which indicates that during production of various dosage forms, the absorbability of the active ingredient of drug preparations may be modified markedly, either intentionally or unintentionally. As a result, the amount of drug available to the body may be considerably less than the total amount of drug in the dosage form. It is apparent, therefore, that in addition to examination of oral dosage forms for amount, identity, and purity, there must be some evaluation of the physiological availability of the active ingredients thereof. Such information is absolutely necessary to insure clinical effectiveness; thus, it is of practical importance not only to regulatory agencies concerned with consumer protection, but also to the physician and pharmaceutical manufacturer.

It is the purpose of this paper to review the history of the relationship between tablet disintegration and physiological availability of drugs. The significance of more recent findings on dissolution rate of drugs also will be discussed. No attempt will be made to review all the literature on the subject, for several excellent reviews have appeared in the last few years on various aspects of these fields. These include absorption aspects by Wagner (1), kinetics of drug metabolism by Nelson (2), and prolonged-release preparations by Lazarus and Cooper (3) and Campbell and Morrison (4).

IN VITRO DISINTEGRATION TIME

Until recently, pharmaceutical manufacturers and regulatory bodies paid more attention to the development of *in vitro* tests than to procedures for evaluating physiological availability *in vivo*. Many *in vitro* procedures have been suggested for determining the disintegration time of tablets; in most of these, attempts were made, at least in part, to simulate *in vivo* conditions. For example, in examining *in vitro* disintegration times of enteric-coated tablets, Wruble (5) used simulated gastric and intestinal juices containing constituents the same as those proposed originally by Toplis (6). Test tubes containing the tablets were clamped to a revolving disk traveling at 12 r.p.m., and the whole apparatus was immersed

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in a water bath maintained at 36–37.5°. The first official method for tablet disintegration was that published in the Swiss pharmacopeia in 1934 (7). The method involved placing the tablet in a 100-ml. conical flask, adding 50 ml. of water at 37°, and shaking periodically. The maximum disintegration time permitted was 15 minutes. Five years later, Berry (8) investigated various methods for testing the disintegration time of tablets at the request of the British Pharmacopoeia Commission. He noted that many earlier *in vitro* procedures were inadequate because they failed to give a definite end point from which to judge when disintegration was complete. Accordingly, Berry suggested a procedure which depended upon a weighted wire cutting through the tablet after the latter had been softened in water kept at 18–20°. Maney and Kuever (9) devised an apparatus in which tubes containing enteric-coated tablets and simulated gastric and intestinal juices were fixed in a mechanically actuated swinging rack immersed in a water bath maintained at 37°. They concluded that an efficient enteric coating should be capable of withstanding artificial gastric fluid for at least 10 hours *in vitro*. When transferred to artificial intestinal fluid, disintegration should take place within 3 hours. Abbott and Allport (10) also tested enteric-coated tablets *in vitro* by using a complicated apparatus which provided for a continuous flow of warmed artificial digestive fluids over the tablets being tested.

In other studies, Bandelin (11) determined disintegration time of sugar or enteric-coated tablets by placing them on a screen immersed in simulated gastric or intestinal juice maintained at 37°. The solution was agitated at a slow constant rate of speed. Bandelin concluded that uncoated tablets should disintegrate within 30 minutes of immersion in simulated gastric juice and that enteric tablets should withstand simulated gastric juice for at least 2 hours, then disintegrate in simulated intestinal juice in not less than 1 hour or more than 3 hours. It is important to note that the time intervals reported by Bandelin and other early workers appeared to be purely empirical and were not related to quantitative *in vivo* measurements.

Filleborn (12) pointed out that simple *in vitro* disintegration tests are valuable only if they are able to simulate *in vivo* conditions. He therefore developed an "artificial stomach" and attempted to simulate *in vivo* conditions of pH, presence of food, peristalsis, volume of gastric juice, and hydrostatic pressure. Depending on the conditions under which the tablet normally was taken, two different artificial gastric juices were used—one simulating the gastric contents of an empty stomach, the other a full stomach. Filleborn's procedure involved first immersing the tablet to be tested in simulated saliva, then placing it in a perforated plastic basket in simulated gastric juice. The time for disintegration was taken as the time necessary for the tablet to disintegrate into particles sufficiently small to pass through the holes of the plastic tablet basket. In general, disintegration times tended to be considerably longer by Filleborn's method than by those of the Swiss pharmacopeia (7) or the "British Pharmacopoeia" (13). For example, the disintegration time of a sulfapyridine tablet was 135 seconds by the Swiss method, 117 seconds by the B. P. method, and 588 seconds by the artificial stomach method.

Evanson and DeKay (14) introduced a rolling drum into their apparatus, which they claimed provided a rolling wavelike action on the tablet similar to that of stomach contractions. This method was found to give a decided advantage in reproducibility of results over the Gershberg and Stoll method (15), in which tubes with mesh bottoms were moved up and down in simulated juices. The latter method was modified and adopted by the U.S.P. (16) and is the basis for the official method of the Canadian Food and Drug Directorate (17). However, in the latter two methods no real attempt was made to reproduce physiological conditions.

A wide variety of simulated gastric and intestinal juices has been used in various *in vitro* methods (5, 6, 9–12). Most gastric juices contained HCl and pepsin, although a number also contained other ions, such as those of potassium and calcium. In most instances, the pH of simulated gastric juice ranged from 1.4 to 3.5. Perhaps the most elaborate attempt to simulate human gastric juice was that of Filleborn (12), who added mucin and actually developed two simulated gastric juices—one at pH 1.4, intended to simulate the gastric contents of an empty stomach—and the other at pH 4.0, intended to simulate a full stomach. The full stomach juice also contained mucilage gum acacia, and small pieces of sterilized sponge were added to the testing vessel to simulate the presence of food. Neutral, alkaline, or slightly acidic intestinal juices have been used by various workers. Few systematic attempts have been made, however, to compare critically various simulated digestive fluids. Chapman *et al.* (18) found that using simulated juices, prepared as recommended by Abbott and Allport (10),

was a definite advantage over the water in the U.S.P. XIV disintegration procedure. As pointed out by Chapman *et al.* (18), no available *in vitro* disintegration test can reproduce completely all physiological conditions. Thus, *in vitro* tests represent a more or less arbitrary or empirical approach which, to provide a valid estimate of *in vivo* availability, must be correlated with a quantitative measure of availability determined in humans.

IN VITRO DISSOLUTION RATES

Although the first quantitative study of the dissolution process was made by Noyes and Whitney in 1897 (19), most pharmaceutical studies on drug release from solid formulations have dealt mainly with disintegration time. There is evidence from theoretical studies (20) that drug concentration on both sides of the epithelial layer of the intestinal wall approaches equilibrium in a short time and that drugs are absorbed almost as rapidly as dissolved. Furthermore, Nelson (21) reported that dissolution rate was rate-determining in absorption of tetracycline, provided that the dosage form restricted the initial surface area and that absorption of benzylpenicillin and acetylsalicylic acid was rate-limited by the dissolution rate properties of the drugs (22). Therefore, it is apparent that the rate of dissolution of drug particles plays a fundamental role in determining drug availability. Rapid absorption is dependent on rapid dissolution of drug particles. Parott *et al.* (23) pointed out the fundamental importance of dissolution rate several years ago; but until recently relatively few workers have recognized the importance of dissolution rate in predicting physiological availability.

Dissolution rate, however, is influenced by many factors. Parott *et al.* (23) found that the dissolution rate of benzoic acid in agitated aqueous media was independent of tablet density. The dissolution rate was decreased when various concentrations of sodium chloride, sodium sulfate, and dextrose were added to the dissolving medium. Sodium sulfate was most effective in decreasing the dissolution rate. When urea was used as an additive, an increase in the dissolution rate resulted. Niebergall and Goyan (24) developed an automatic recording apparatus for use in dissolution rate studies and showed that the dissolution rate of benzoic acid increased as the temperature of the dissolving medium was raised from 25 to 40°. Hamlin *et al.* (25) conducted extensive studies on the dissolution rates in deionized water of two polymorphic forms of methylprednisolone compressed into constant surface pellets. Four *in vitro* procedures were used: (*a*) a modification of the hanging pellet method of Nelson (26); (*b*) tablets held in polyethylene holders in the center of 4-oz. bottles containing 120 ml. of water and attached to the machine of Wruble (5), rotating at 6 r.p.m.; (*c*) a method similar to (*b*), except that the machine rotated at 12 r.p.m.; (*d*) a method similar to (*b*), except that the machine of Souder and Ellenbogen (27) was used, rotating at 40 r.p.m. The two polymorphic forms of methylprednisolone showed significant differences in *in vivo* dissolution rates, indicated by pellet implant studies in rats. *In vitro* procedures in which the intensity of agitation was low [methods (*a*) and (*b*) above] showed significantly different rates of dissolution between the two polymorphic forms. When the rate of agitation was increased, however [methods (*c*) and (*d*)], no significant differences in *in vitro* dissolution rates were observed between the two forms of the drug. Levy (28) has pointed out recently that dissolution rate of drugs in particulate form is determined by a large number of factors, including intrinsic dissolution rate, particle size distribution, speed and type of agitation, anisotropism, and presence of other solids. These results illustrate the importance of choosing *in vitro* test procedures which will differentiate between products producing different *in vivo* effects.

Levy and Hayes (29) described a procedure for determining *in vitro* dissolution rates of acetylsalicylic acid in several products. The method involved dissolution in an agitated solution of 0.1 *N* hydrochloric acid. Significant differences were observed in dissolution rates of nationally advertised brands and might account for some of the conflicting clinical reports (30, 31) concerning the relative advantages of plain and buffered tablets. In a subsequent study, Levy (28) found that the *in vivo* absorption rate of acetylsalicylic acid was proportional to *in vitro* dissolution rate, as determined by his previous procedure (29). This dependence of acetylsalicylic acid absorption on dissolution rate had been predicted previously on theoretical grounds (20). The slow and incomplete absorption of acetylsalicylic acid anhydride also can be explained on the basis of its low dissolution rate in aqueous media (32). Schroeter *et al.* (33) presented information on a procedure for determining dissolution rates of drugs in tablet or capsule form. The method involved the use of the U.S.P. tablet disintegration apparatus; aliquots of the dissolution medium (simulated gastric or intestinal juice) were withdrawn and

analyzed at various time intervals. This procedure also was used by Middleton *et al.* (34).

Despite the fact that several methods have been proposed for determining *in vitro* dissolution rates, few studies have been conducted to compare critically the various procedures available or to determine the specific effects of pH, enzymes, mucin, bile salts, electrolytes, etc. As with *in vitro* disintegration tests, it is unlikely that a dissolution test can furnish a clear indication of physiological conditions, which vary under the influence of a large number of factors, many of which have not yet been described in quantitative terms. Thus, *in vitro* dissolution tests can be considered valuable only if they give results which have been correlated at some stage with quantitative measures of physiological availability.

IN VIVO PROCEDURES

In vivo methods used to determine physiological availability of drugs have ranged from simple qualitative procedures to sophisticated quantitative measurements of drug concentration in blood or urine. One of the earliest attempts to demonstrate availability of drugs was carried out by Wruble (5), who administered enteric-coated tablets containing calcium sulfide and methylene blue to humans. If the tablet was coated inadequately and disintegrated in the stomach, the subject would eructate hydrogen sulfide; whereas if it disintegrated in the intestinal tract, a blue coloration would be observed in the urine. Early workers also attempted to use X-rays as an indication of *in vivo* availability of drugs. Maney and Kuever (9) found that generally *in vitro* results agreed with *in vivo* findings obtained with the X-ray. Abbott and Allport (10), on the other hand, concluded that X-rays were unsuitable for routine control of commercial production because of variability between humans and inability to detect many drugs in the gastrointestinal tract with X-rays. Use of X-rays to study disintegration of radiopaque tablets in the intestinal tract suffers from numerous faults. Evidence of disintegration in the intestinal tract is not proof of absorption (35). Furthermore, X-ray pictures often are difficult to interpret and are not amenable to quantitative treatment.

Of all *in vivo* procedures, perhaps the one related most readily to dose is the urinary excretion of the drug and/or its metabolites after a test dose. Melnick *et al.* (36) used urinary excretion data in proposing the concept of physiological availability of vitamins in pharmaceutical products. They demonstrated clearly that within limits a direct relationship exists in normal subjects between the urinary excretion of water-soluble vitamins and the amount ingested. The concept of physiological availability was adopted and developed further by Chapman *et al.* (18) and Morrison *et al.* (37), who studied the relationship between *in vitro* disintegration time and physiological availability of riboflavin in sugar-coated tablets. The work of Chapman *et al.* (18) was one of the first attempts to correlate *in vitro* findings with quantitative *in vivo* results. The data of Morrison *et al.* (37) indicate clearly that sugar-coated riboflavin tablets, which did not disintegrate within 60 minutes when tested by an official method (17), were not fully available to the body. This relationship also holds for sodium *p*-aminosalicylate (38). The work of Chapman *et al.* (18) formed the basis for regulations promulgated in 1957 (17) requiring that in Canada ordinary sugar-coated tablets must disintegrate within 60 minutes *in vitro*. These regulations have been criticized on the basis that the time limit indicated may not apply to all drugs and that drugs which have *in vitro* disintegration times greater than 60 minutes may be fully available *in vivo*. Subsequent work showed, however, that time limits for disintegration of riboflavin tablets also were applicable to other water-soluble vitamins (39). The need for a disintegration time longer than 60 minutes for any drug has not been demonstrated.

Measurement of drug concentrations in the blood also has been used as an objective quantitative measure of physiological availability (40). For example, Juncher and Raaschov (41) found that two preparations of penicillin V tablets, which had different *in vitro* disintegration times, also gave significantly different blood levels when tested in humans. Chulski *et al.* (42) concluded that there was a direct proportionality between the urinary excretion rate and serum level of tetracycline in humans. Some drugs, such as certain antihistamines, have large volumes of distribution *in vivo* and hence are present in the blood in concentrations which are too low to measure readily. For many drugs, however, measurement of blood concentration provides a good indication of physiological availability.

The ultimate criterion of the usefulness of a drug obviously is objective evidence of clinical effectiveness in man. Unfortunately, many clinical trials reported in the literature are not acceptable scientifically since objective measurement of response and adequate controls were not used. The importance of placebo controls

and the double-blind procedure in conducting investigations have been emphasized by others (43, 44). Loranger *et al.* (45) concluded that less than 10% of published reports on tranquilizer and antidepressant drugs met minimum standards of scientific acceptability. They described studies in which physicians and patients were told that two products were a tranquilizer or an energizer when, in reality, both products were placebos. When uncontrolled subjective methods were used to evaluate the two products, 53 to 80% of patients supposedly benefited from them. On the other hand, the use of a critical objective approach yielded temporary improvement from the tranquilizer, but no effect from the energizer. Loranger *et al.* (45) concluded that studies of new psychopharmacological agents which do not involve double-blind and other controlled procedures are of dubious value. Obviously, any *in vivo* test used for the standardization of an *in vitro* one must in itself furnish results which can be assessed quantitatively and are reliable and reproducible.

RELATIONSHIP BETWEEN *IN VIVO* AND *IN VITRO* METHODS

As pointed out previously, *in vitro* tests of any sort have no intrinsic value *per se* but are useful only to the extent that they correlate with quantitative *in vivo* results. It has been emphasized repeatedly (46, 47) that the length of time required for a tablet to disintegrate *in vitro* cannot be taken as a direct indication of the time required to dissolve *in vivo*. For example, it obviously is spurious to argue that since intestinal passage time may be 12 hours, tablets which require 9 hours to disintegrate *in vitro* will be fully available to the body. Furthermore, allowance must be made for certain drugs which are absorbed efficiently only from the upper portion of the intestinal tract. Despite the well-established nature of the relationship between *in vitro* and *in vivo* results, some authors still tend to equate *in vitro* disintegration times and *in vivo* availability.

It is apparent from the foregoing that quantitative aspects of the relationships between *in vivo* and *in vitro* results are of great importance. As indicated previously, Chapman *et al.* (18, 38) found that availability of riboflavin and *p*-aminosalicylate tablets to humans could be predicted from their *in vitro* disintegration time using a modified U.S.P. XIV disintegration test. Tablets disintegrating in more than 60 minutes were not fully available *in vivo*. Using disintegration test procedures different from those of Chapman *et al.* (18), Endicott and Kirchmeyer (48) reported that riboflavin and erythromycin tablets which took longer than 60 minutes to disintegrate *in vitro* were fully available *in vivo*. Nair and Bhatia (49) observed that merely altering the mesh of the screen in the U.S.P. disintegration apparatus could affect markedly the disintegration times of tablets. These studies indicate clearly the specificity of the relationship between *in vitro* disintegration time and *in vivo* availability.

Additional evidence that *in vitro* disintegration time may not give a clear indication of *in vivo* availability was obtained by Levy and Hayes (29), who conducted extensive studies with acetylsalicylic acid tablets. They found that tablets which showed short dissolution half-times (fast dissolution rates) had disintegration times longer than tablets which dissolved more slowly. They concluded that the *in vitro* disintegration time is "no criterion of availability" of acetylsalicylic acid tablets. In subsequent work, Levy (28) suggested that the U.S.P. tablet disintegration test be replaced by a dissolution test for compressed tablets. He concluded that absorption of acetylsalicylic acid was related to three factors: (*a*) the dissolution rate, (*b*) the gastric emptying time, and (*c*) the way in which the tablet was administered. Crushing or chewing the tablets or taking them with water reduced differences in absorption of various commercially available brands of tablets.

Schroeter *et al.* (33) determined *in vitro* dissolution rates and disintegration times of 76 lots of tablets, including a steroid, a sulfonamide, an oral antidiabetic agent, and an acetylsalicylic acid–phenacetin–caffeine combination. Disintegration tests were carried out with and without the use of plastic disks. There was a high degree of correlation between *in vitro* disintegration time and dissolution rate (T50%) for the steroid if the disintegration time was determined without the use of disks. Use of disks, however, masked the differences between the tablets. The slope of the regression line relating dissolution rate to disintegration time of the sulfonamide was influenced markedly by the presence of sodium chloride in one lot of tablets. There was a tendency for the more rapidly dissolving tablets of antidiabetic agent to disintegrate more rapidly, but no significant correlation could be observed. Significant correlation was absent between disintegration time of the acetylsalicylic acid–phenacetin–caffeine tablets and dissolution rates. Schroeter *et al.* (33) raised questions concerning the validity of uniform disintegration tests and disintegration time limits applied to large groups of drugs in compressed tablets. They suggested

the possibility that limits of dissolution rate or disintegration time should be based on *in vivo–in vitro* correlations specific for the drug in question and even the type of tablet.

Recently, Campagna *et al.* (50) presented the results of an interesting case history concerning prednisone tablets meeting U.S.P. XVI specifications which were clinically inactive *in vivo*. A female patient, suffering from familial Mediterranean fever with repeated episodes of peritonitis, used a brand of prednisone different from that which had been effective in controlling her symptoms; the new brand was without clinical effect. When subjected to the U.S.P. XVI procedure, the clinically inactive tablets disintegrated within 6 minutes, although they remained on the bottom of the test beaker in large particles. Production of large particles during the disintegration test was influenced by the presence of disks in the apparatus, which formed the large particles and subsequently forced them through the screen at the bottom of the apparatus. The inactive tablets had a dissolution half-time much longer than clinically effective lots of the drug. Furthermore, the inactive tablets showed extreme variability in dissolution rates. Omission of disks in the U.S.P. XVI disintegration time procedure gave values which agreed with *in vivo* results and dissolution rate values.

The importance of *in vitro* tests in reflecting clinical response of tolbutamide has been the subject of considerable interest. Carter (51) pointed out the great difference in response of a patient to two brands of the drug. A patient who had been under adequate control for 11 months inexplicably went out of control, with a rapid rise in blood sugar values when given a second brand of tolbutamide. Tablets of the second brand failed to disintegrate when subjected to simulated gastric juice for 45 minutes and simulated intestinal juice for a subsequent 63 minutes. Caminetsky (52) reported a similar case and also found that the ineffective tablet was slow to disintegrate *in vitro*. Levy (53) studied both tablets used by Carter and found marked differences in their *in vitro* dissolution rates. The clinically ineffective tablet had a slow rate of dissolution *in vitro*. In this instance, disintegration time and dissolution rate appeared to give similar results.

As a result of the above reports, McKendry *et al.* (54) and Lu *et al.* (55) investigated 26 lots of tolbutamide produced by 21 manufacturers by *in vitro* tests and five of these by several clinical tests. They found that, of the five products tested in controlled clinical trials, there was no significant difference in response, except for one criterion; *i.e.*, fasting blood sugar was slightly better controlled by one brand.

To obtain further information on the problem of clinically ineffective samples of tolbutamide, Brudney and Stewart (56) made *in vitro* studies of 18 commercially available brands. All those examined met the standards for disintegration time set out in the Canadian Food and Drug Regulations (32) but varied in dissolution rate. The latter finding was interpreted to indicate a need for a study of *in vivo* effects of tolbutamide and a dissolution test in addition to the disintegration test presently required. No *in vivo* data were presented, however, to show that tablets with different dissolution rates varied in clinical effectiveness.

The results of Campagna *et al.* (50) indicate unequivocally that *in vitro* disintegration tests may not distinguish between fast and slow dissolving drug particles. Levy (28) has pointed out that disintegration tests also may not distinguish between tablets with dissolution rates which differ because of the presence of different crystalline structures of polymorphic compounds.

Despite their weaknesses, however, disintegration time tests still can provide valuable information on the *in vivo* availability of some drugs. Middleton *et al.* (34) recently examined relationships between *in vitro* dissolution rate, disintegration time, and physiological availability of riboflavin in sugar-coated tablets. They found a close relationship between disintegration time and dissolution rate, and both *in vitro* procedures correlated reasonably well with physiological availability, measured by urinary riboflavin excretion. Middleton *et al.* concluded that either *in vitro* procedure used can provide a useful estimate of the availability to the body of riboflavin in sugar-coated tablets. It would appear that the results of disintegration times in this instance were a useful indication of *in vivo* availability.

It is apparent from the foregoing that *in vitro* disintegration tests, as presently used, have certain inherent faults and eventually must be modified or replaced by more critical tests of physiological availability. Various other workers (28, 33) have suggested that disintegration tests should be replaced by dissolution tests. Except for a few drugs, however, little is known of quantitative relationships between rate of solution and *in vivo* availability. Such information is essential for the development of meaningful *in vitro* dissolution time limits. Replacement of present *in vitro* disintegration tests raises many problems for a regulatory agency responsible for control of hundreds of drugs produced by many manu-

facturers in a number of oral dosage forms. An examination of the evolution in Canada of *in vitro* tests for drug availability illustrates some of the problems involved.

When originally made mandatory in 1957, the present *in vitro* disintegration time limits (17) for sugar-coated tablets were based on work carried out by Chapman *et al.* (18, 38) on riboflavin and *p*-aminosalicylate, two drugs which differ widely in solubility. It was realized then that limits based on these two drugs might not apply to others. No additional data on quantitative relationships between *in vitro* and *in vivo* results were available at that time; but it was obvious that many products on the market had excessively long disintegration times, and the need for better control of drugs was urgent. Furthermore, it was felt that a single relatively short time limit would insure the availability of a large number of drugs, particularly those more soluble than riboflavin. Experience has shown that most manufacturers were able to meet the required time limits without undue difficulty and produce products with greatly improved availability. Manufacturers were encouraged to submit data for drugs which exhibited *in vivo–in vitro* relationships different from those shown by riboflavin and *p*-aminosalicylate. When time limits were placed on the *in vitro* disintegration of enteric tablets (17), exemption was made for preparations which had been shown by objective tests to be fully available to the body, even though they exceeded the designated *in vitro* disintegration time limit.

Because of the great volume of control work carried out by a regulatory agency, there are obvious advantages to an official *in vitro* test with a single time limit applicable to all drugs in the same oral dosage form. However, it would appear from present evidence that a single time limit for dissolution rate, based on the results of an *in vitro* test, cannot be applied validly to all drugs. The possibility that a single *in vitro* dissolution test, based on some minimum time limit, may be applied to drugs having similar dissolution characteristics remains to be established. Because the formulation used can influence dissolution rate markedly (57), it is possible that the relationship between *in vitro* dissolution rate and *in vivo* availability will have to be worked out for each individual preparation, and that even for the same drug, time limits which apply to one manufacturer's product may not apply to another. There is evidence for spironolactone that no available *in vitro* test will differentiate between preparations which are fully available to the body and those which are not. At present, a biological test is required for this purpose (58). If the views stated above are correct, one is led to the conclusion that, to insure clinical effectiveness, a quantitative, objective, *in vivo* measurement of availability may be required for each drug in each formulation and that *in vitro* tests may serve primarily for purposes of pharmaceutical control by manufacturers. *In vivo* procedures should be based on a comparison of the response to the drug in the oral dosage form being tested to that of the drug in its most readily available form. Such a requirement would be similar to that embodied in regulations presently in effect in Canada for oral prolonged-action products. These regulations require that manufacturers of drugs in prolonged-action form present evidence from quantitative, objective, *in vivo* tests that the drug is available as claimed (17). These criteria were chosen because no single *in vitro* test was applicable to the variety of preparations on the market. It would appear that the same attention must be paid to factors affecting the availability of drugs in compressed tablets as that given to drugs in prolonged action form, where the rate of solution has been modified intentionally.

SUMMARY

Tablet disintegration tests have served a useful purpose and resulted in improvements in the availability of drugs in oral dosage forms. Recent evidence indicates, however, that they have certain inherent faults which limit their usefulness as measures of physiological availability of drugs. Therefore, they must be replaced eventually by more critical tests. Despite the fundamental relationship between *in vivo* availability and dissolution rate, present evidence suggests that no single dissolution rate test can be applied to all drugs. The possibility that a single test may be applied to drugs having similar physicochemical properties remains to be established. If such is not possible, it may be necessary to obtain direct evidence of availability of each drug in each formulation by quantitative objective measurements carried out *in vivo*. Properly designed *in vitro* tests would then be required primarily to insure that products were manufactured under proper pharmaceutical control.

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Research Articles

Dissolution Kinetics of a Weak Acid, 1,1-Hexamethylene *p*-Tolylsulfonylsemicarbazide, and Its Sodium Salt

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The dissolution behavior of the acid and the sodium salt of this drug in phosphate buffers has been investigated. Data have been analyzed by relationships derived from the diffusion controlled model for dissolution of solids in reactive media. The results of this study show that surface conversion of the sodium salt to the acid occurs in the lower pH range of these studies. Calculations suggest that appreciable conversion takes place only after initial surface supersaturation ratios of about 20 or greater are achieved. Under conditions of much greater initial surface supersaturation ratios, a relatively impermeable acid surface coating is formed, and the dissolution rate is governed by this acid phase.

IN MOST CASES the diffusion-controlled dissolution behavior of monophase solids in reactive media may be predicted by knowledge of the appropriate solubility equilibria and the effective diffusion coefficients of the species in solution (1–4). However, in those situations involving more than one phase, the problem is more difficult to describe. Cases in point are the recent studies (5, 6) on dissolving disks that exhibit simultaneous surface deposition of new phases and the experiments with prior mixed phases (7, 8).

In this report an analysis of the incongruent

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