Special Communication

DISSOLUTION OF DRUGS FROM SOLID DOSAGE FORMS II. IN VITRO AND IN VIVO DISSOLUTIONS

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Abstract

The biological effect shown by a drug in a given dosage form is not simply a function of the intrinsic pharmacological activity of the drug. The onset intensity and duration of therapeutic response produced by most drugs are subject to vide variation depending on many factors inherent to the biological system as well as the dosage form. Each of these factors play a role in bringing the drug to the site of biological effect in the body. Only when a drug molecule has reached its site of action, can the concept of inherent pharmacological activity be considered (Arayne and Najma, 1979).

The present attempt correlates IN VITRO and IN VIVO dissolutions vs biological availability of drugs from solid dosage forms.

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 labelled amount. but also must be available to the body. Until recently relatively little attention in our country has been paid 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 the drug 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 preparation may be modified markedly, either intentionally or unintentionally. As a result the amount of drug

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those of the Swiss pharmacopoeia (1934) or

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 of 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 drug controlling authorities to ensure consumer protection, but also to the physician and pharmaceutical manufacturer.

The purpose of this review is to study the *in vitro* and *in vivo* dissolutions, and their correlation and physiological availability of the drug. The significance of more recent findings on dissolution rates of drugs are also discussed.

IN VITRO DISSOLUTION

The process of dissolution or inverse process of crystallization can be considered as the specific types of certain heterogenous reactions in which a mass transfer is effected through the net result of escape and deposition of solute molecules at a solid surface. One of the most important as well as most difficult approaches in the biopharmaceutics evaluation of a drug is the quantitative correlation of absorption and *in vitro* dissolutions.

Although the first quantitative study of the dissolution process was made by Noyes and Whitney in 1897, most pharmaceutical studies on drug release from solid formulations have dealt mainly with disintegration time.

It is evident 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 artifical 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 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 (1934) or the British Pharmacopoeia (1945). 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 (1950 as cited by Morrison and Campbell, 1965) 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 an advantage in reproductibility of results over the Gershberg and Stoll method (1946, as cited by Morrison and Campbell, 1965), in which tubes with mesh bottoms were removed up and down in simulated juices. The latter method was modified and adopted by the U.S.P. (1960) and is the basis for the official method of the Canadian Food and Drug Directorate (1954). 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 (Morrison and Campbell, 1965). 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 the addition of mucin and actually the development to simulated gastric juices ——one at pH_4 1.4, intended to simulate the gastric contents of an empty stomach—— and the other at pH .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. Nutral, 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. (1954) found that using simulated juices, was a definite advantage over the water in the U.S.P. XIV disintegration procedure. However, as pointed out by Chapman et al. (1954), no available *in vitro* disintegration test can reproduce completely all physiological conditions. Thus, *in vitro* tests present 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. It is apparent that the rate of dissolution of drug particles play a fundamental role in determining drug availability. Rapid absorption is dependent on rapid dissolution of drug particles. There is evidence from theoretical studies (Edwards 1951) that drug concentration on both sides of epithelial layer of the intestinal wall approaches equilibrium in a short time and that drugs are absorbed almost as rapidly as dissolved. Further more Nelson (1959) 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 benzyl penicillin and acetyl salicylic acid was rate limited by the dissolution rate properties of the drug (Nelson and Schaldemose, 1959).

Dissolution rate, however is influenced by many factors. The dissolution rate of benzoic acid in agitated aqueous media was independent of tablet density, and was decreased when various concentrations of sodium chloride, sodium sulphate, and dextrose were added to the dissolving medium. Sodium sulphate 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 (1963) developed an automatic recording apparatus for use in dissolution rate studies and showed that the dissolotion rate of benzoic acid increased as the temperature of the dissolving medium was raised from 25 to 40°.

The design of an apparatus, suitable for the measurement of dissolution rates of solid dosage forms, is relatively straight forward. Hersey (1969) commented that: 'The number of dissolution rate methods described in the literature is almost equal to the number of workers in the field.' However, there is a paucity of data comparing dissolution data from the various dissolutions with quantitative *in vivo* availability results.

Levy (1968) emphasized the need for *in vitro* tests that reflect faithfully dissolution rate-limited absorption of drugs from pharmaceutical dosage forms. A number of studies showed that dissolution characteristics of selected dosage forms of certain drugs (Nelson, 1962; Katchen and Symchowicz, 1967; Fincher, 1968; Martin et al., 1968; Cressman et al., 1969), obtained using specific dissolution conditions, parallel blood or urine levels of the drug. However, no dissolution apparatus has been evaluated which would predict physiological availabilities of a variety of formulations of different drugs.

The validity of a particular dissolution rate test for a given drug can only be assured by demonstrating the correlation between *in vitro* and clinical data. Levy (1965) developed an *in vitro* dissolution rate test quantitatively with the gastrointestinal absorption of aspirin in man for three different types of dosage forms. Significant differences were observed in dissolution rates of various brands and might account for some of the conflicting clinical reports (Truitt and Morgan, 1959; Batterman, 1958) concerning the relative advantages of plain and buffered tablets. In a subsequent study, Levy (1961) found that the *in vivo* absorption rate of acetyl salicylic acid was proportional to *in vitro* dissolution rate, as determined by his previous procedure (Levy and Hayes, 1960).

Recently (Ayub and Ali, 1979) studied the dissolution rate of various brands of commercially available acetylsalicylic acid tablets in Pakistan by U.S.P. XIX method. Although most of these brands showed a T 50 of less than 5 minutes, but exhibited different dissolution rates, which might account for different *in vivo* absorptions. This dependence of acetylsalicylic acid absorption on dissolution rate was predicted previously on theoretical grounds (Edwards 1951). The slow and incomplete absorption of acetylsalicylic acid anhydride can be explained on the basis of its low dissolution rate in aqueous media (Levy 1963a).

The term dissolution rate-limited absorption implies that there is no build up at drug concentration in the gastrointestinal fluids i.e., the fluids function as a perfect sink. Unless this condition is embodied in the design of the *in vitro* test, the results will bear little relationship to *in vivo* observations (Levy 1966).

Schoeter et al. (1962) presented information on a procedure for determining dissolution rates of drugs in tablets or capsule form. The method involved the use of the U.S.P. Tablet disintegration apparatus and aliquots of the dissolution medium were withdrawn and analyzed at various time intervals. This procedure was also used by Middleton et al. (1964).

A most significant contribution in methodology for handling the dissolution kinetics of finely divided powders was presented by Higuchi and Hiestand (1963). The long mathematical derivation given by these authors were applicable to those systems where the dissolution process was diffusion controlled, and the particle size distribution was known. In a subsequent paper Higuchi et al. (1963), reported reasonably good agreement between the calculated and experimental values obtained for micronized methylprednisolone.

Niebergall (1963) also studied the dissolution of small particles and described a continuous recording technique for following the rapid dissolution of the particles.

Another useful method for studying dissolution rates is the use of rotating non-disintegrating disks, as described by (Levy, 1963; Levy et al., 1963; Levy and Sahli, 1962). Milosovich (1964) employed a tablet mounted in a dye and subjected to solvent agitation produced by a baffle system. This system is similar, in some respects, to that reported by Nelson (1957 and 1962).

Schroeter (1962) devised an automated method for the dissolution rate of drugs in tablets and capsules. The method provides for automatic sampling, dilution and spectrophotometric analysis of the dissolution medium.

Recognition of the fact that the physiological availability of drugs from tablets is more realistically a function of dissolution rates than of disintegration times has stimulated the introduction of *in vitro* dissolution rate tests for compressed tablets (Levy & Jusko, 1966, 1966a). It has been suggested that the dissolution medium should be controlled and a series of pH conditions should be employed for adequate dissolution rate testing.

Furthermore, since the gastrointestinal fluids function as a 'sink' it is desirable that build up of drug concentration in the *in vitro* dissolution medium be followed only upto 10% of saturation. When working with poorly soluble drugs this condition is after exceedingly difficult. The use of an upper organic phase which can act as a reservoir for dissolved drug has been proposed to overcome the problem (Levy, 1966a; Gibaldi and Feldman, 1967).

As pointed out by Levy (1966), these drugs, which represent the greatest dissolution problem are also those which are least soluble and give the greatest difficulty with respect to maintainence of perfect sink conditions. Frequently, it is necessary to use exceedingly large volumes of solvent for this purpose and to adopt very sensitive analytical procedures. At times, it may be very difficult to follow the dissolution of more than a small fraction of the drug contained in the dosage form. Under these conditions one may assume a uniform pattern of release rate. A definite need exists for the development of methodology to maintain sink conditions during dissolution rate determination of poorly soluble drugs. Levy (1966) suggested two possibilities: the use of an upper organic phase which can act as a reservoir for the dissolved drug or the addition of adsorbents to the aqueous medium. The ability of adsorbents to maintain 'sink' conditions have been demonstrated by Wurster and Polli (1961). Both approaches involve the same principle i.e., removal of dissolved drug from the dissolution medium and prevention of accumulation. The removal of drug from the dissolution fluid is analogous to removal of drug from the gastrointestinal fluids by the absorption process in dissolution rate-limited absorption.

Hersey (1969) attempted to classify dissolution models on the basis of not only the type of agitation but also whether the dissolution process occurs under sink or non-sink conditions.

The importance of dissolution rate determination in the examination of drug transport systems has been recognized by numerous investigators whose work has been reviewed by Wagner (1961, 1971), Wagner and Metzler (1969) and Wurster and Taylor (1965). However, unwarranted comparison with the tablet disintegration test and efforts to develop a uniform general dissolution rate test for regulatory purposes have tended to cloud the merits and limitations of dissolution rate testing.

Despite the fact that several methods have been proposed for determining *in vitro* dissolution rates, few studies have been conducted to compare critically 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. This, *in vitro* dissolution tests can be considered valuable only if they give results which have been correlated at some stage with quantitative measurement of physiological availability.

In vivo Dissolution:

It is now well recognized that the *in vivo* dissolution characteristics of drug formulations may have a pronounced effect on their bioavailability. Because *in vivo* dissolution rates are difficult to measure directly, attempts to assess this aspect of drug quality are commonly made from *in vitro* dissolution rate data. Dissolution specifications *in vitro* have been promulgated for a number of drugs (The United States Pharmacopoeia, 1970; The National Formulary, 1970) and attempts to correlate these with bioavailability have met with varying degrees of success (Wagner 1971; Mattok et al., 1971; Mattok et al., 1972) reduces the concentration of free drug (Lovering and Black, 1973). Substances having an adverse effect on absorption rates may be endogenous to the GI tract or may be introduced as nutrient or tablet excipients. *In vitro* assessment of the latter can be made by comparing the permeation rate of unformulated drug to that of drug released from formulations dissolved, or dispersed, in an appropriate buffer. Drug excipient interactions may account for the low bioavailabilities observed in some formulations.

Various methods used to determine physiological availability of drugs have ranged from simple qualitative procedures to sophisticated quantitative measurements of drug concentrations in blood or urine. One of the earliest attempts to demonstrate availability of drugs was carried out by Wruble (1930, as cited by Lowering and McRae 1973) who administered enteric coated tablets containing calcium sulphide and methylene blue to humans. If the tablet was coated inadequately and disintegrated in the stomach, the subject would eructate hydrogen sulphide; whereas if it is disintegrated in the intestinal tract, a blue coloration would be observed in the urine. Early workers also attempted to X-rays as an indication of *vivo* availability of drugs. Generally *in vitro* results agreed with *in vivo* findings obtained with the X-ray, but X-rays were unsuitable for routine control of commercial production because of variability drugs in the intestinal tract suffers from numerous faults. Evidence of disintegration in the intestinal tract is no proof of absorption (Melnick et al., 1945). Further more X-ray pictures are often 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. (1945a) 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. (1954) and Morrison et al. (1959), who studied the relationship between *in vitro* disintegration time and physiological availability of riboflavin in sugar coated tablets. The work of Chapman et al. (1954) was one of the first attempts to correlate *in vitro* findings with quantitative *in vivo* results. The data of Morrison et al. (1959) indicates clearly that sugar-coated riboflavin tablets which did not disintegrate within 60 minutes when tested by an official method (1954) were not fully available to the body.

The work of Chapman et al. (1954) formed the basis for regulations promulgated in 1957 (an Official Method, 1954) requiring that in Canada ordinary sugar-coated tablets must disintegrate within minutes *in vitro*. These regulations have been criticized on the basis that the time limit 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*. 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 (Swintosky and Hough, 1957). For example, Juncher and Raaschov (1957 as cited by Morrison and Campbell, 1965) found that 2 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 (1963) 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,

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 (Model and Houde, 1958). Loranger et al. (1961) 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. (1961) 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.

In vitro test of any sort have no intrinsic value per se but are useful only to the extent that they correlate with quantitative *in vivo* results. The length of time required for tablet to disintegrate *in vitro* cannot be taken as a direct indication of the time required to dissolve *in vivo*. 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 discussion that quantitative aspects of the relationships between *in vivo* and *in vitro* results are of great importance. As indicated by ability of riboflavin and p-amino salicylate 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. (1954), it was reported that riboflavin and erythromycin tablets which took longer than 60 minutes to disintegrate *in vitro* were fully available *in vivo*. 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 (1960) who conducted extensive studies with acetyl salicylic 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' for acetyl salicylic acid tablets. In subsequent work, Levy (1961) suggested that the U.S.P. tablet disintegration test be replaced by a dissolution test for compressed tablets. He concluded that absorption of acetyl salicylic acid was related to three factors: a) the dissolution rate, b) the gastric emptying times, and c) the way in which the tablet was administered.

Schroeter et al. (1962) determined *in vitro* dissolution rates and disintegration times of 76 lots of tablets, including a steroid, a sulfonamide, an oral anti-diabetic agent, and an acetyl salicylic acid-phenacetin caffeine combination. There was a high degree of correlation between *in vitro* disintegration time and dissolution rate (T50%) for the steroid.

There was a tendency for the more rapidly dissolving tablets of anti-diabetic agent to disintegrate more rapidly but no significant correlation could be observed. Significant correlation was absent between disintegration time of acetyl salicylic acid-phenacetin-caffeine tablets and dissolution rates. The results of Campagna et al. (1963) indicate unequivocally that *in vitro* disintegration tests may not distinguish between fast and slow dissolving of drug particles. Levy (1961) has pointed out that disintegration tests also may not distinguish between tablets with dissolution rate which differ because of

of polymorphic compounds.

Despite their weakness, however disintegration time test still can provide valuable information on the *in vivo* availability of some drugs. Middleton et al. (1964) 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., (1964) 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.

The present *in vitro* disintegration time limits for sugar-coated tablets were based on the work carried out by Chapman et al. (1954, 1956) on riboflavin and p-aminosalicylate, two drugs which differ in solubility. It was realized that limits based on these two drugs might not apply to others. No additional data on quantitative relationship between *in vitro* and *in vivo* results were available at that time but it was obvious that many products in 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 ensure the availability of a large number of drugs, particularly those more soluble than riboflavin. 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 of the formulation used can influence dissolution rate markedly (Levy et al., 1963), 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. If the views stated above are correct, one is led to the conclusion that, to ensure 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. It would appear that the same attention must be paid to factors affecting the availability of drugs in compressed tablets as that given in prolonged action form (Arayne and Najma, 1979) where the rate of solution has been modified intentionally.

While one has been completely successful in correlating *in vitro* with *in vivo* dissolution vs biological availability, nevertheless, there seems to be agreement by all that dissolution tests are more discriminating than disintegration tests in lot to lot variability control. The USP, NF, dissolution tests are not completely satisfactory, they have served as a vehicle of introducing the dissolution test and provide an objective means of determining the dissolution characteristics of a solid dosage form.

It is apparent from the foregoing discussion that *in vitro* disintegration test, have certain inherent faults and eventually must be modified or replaced by more critical test of physiological availability. Various other workers (Levy, 1961; Schroeter et al., 1962) 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. Although replacement of present *in vitro* disintegration tests may raise many problems for a regulatory agency responsible for control of hundreds of drugs produced by many manufacturers in a number of oral dosage forms, a critical evaluation of *in vitro* tests for drug availability illustrates some of the problems involved. Therefore they must be replaced eventually by more critical tests. Despite the fundamental relationship between *in vivo* availability and dissolution rate, pre-

sent 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 ensure that products were manufactured under proper pharmaceutical control.

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