Special Communication

DISSOLUTION OF DRUGS FROM SOLID DOSAGE FORMS
I. GENERAL ASPECTS

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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 wide 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. The path of a drug must also be taken into account in getting from the dosage form to its site of action, where a basic understanding of drug absorption, distribution and elimination alongwith the potential of dosage form is required.

In this paper an attempt has been made to review the situation of the dissolution of drugs from solid dosage forms. The statistical data for the rate of dissolution of drugs and its theoretical concepts have been avoided, and will be dealt separately elsewhere, as those might be beyond the interest of readers of this journal.

Introduction

Almost forty years ago drug industry was unaware of the question of biological availability. The pharmacists were satisfied with a simple chemical assay plus a few additional tests, as an adequate form of quality control. But the fact that the formulation contained the correct quantity of active ingredient was no guarantee of the efficacy. Subsequently a disintegration test was introduced into the British Pharmacopoeia. This test has been an extremely useful indication of tablet properties but tells one almost nothing about the availability of the drug in solution. Thus one can easily formulate a product that will break up readily into its original granules and pass the BP test but will give an extremely slow release of the drug (Davies and Gloor, 1972).

Drug availability can be controlled largely by various pharmaceutical factors, which can be altered. In formulation the main contribution of the pharmaceutical scientist is to design a delivery system that gives the optimum quantity of drug in solution at the absorption site, at the correct time. Hence one must also consider the stability of the drug in solution and possible degradation by the fluid of the gastrointestinal tract. Drugs are known to be unstable at the low pH of the stomach as well as at the higher pH values of the intestine and blood (Garrett 1962).

Usually the most important process affecting drug availability in solid dosage forms is the rate of dissolution. When a drug is administered orally in solid form as a tablet, capsule or suspension or intramuscularly as a pellet or suspension, one frequently finds that the rate of absorption is controlled by how fast the drug dissolves in the fluids at the absorption site. Since the dissolution process proceeds the absorption process, any factor influencing the rate of solution must also influence the rate of absorption. Consequently, dissolution rate may affect the onset, intensity and duration of biological response. Absorption from the solution proceeds much more rapidly than from the tablets. Whenever a drug is more rapidly and far more completely absorbed from solution than from same solid, it is quite likely that absorption rate is limited by dissolution process.

Factors affecting dissolution rate:

There are a large number of biological and physico-chemical factors which may change dissolution rate, such as bulk solubility and solubility in the diffusion layer, effective surface area and crystals forms. Of the many physicochemical factors involved, the effects of agitation intensity, drug solubility and surface area on the dissolution rate must also be taken into account. The physicochemical factors that control the rate of dissolution include temperature, degree of agitation, pH, solubility and concentration gradient, composition and viscosity of dissolution medium and its potential for micellar solubilization. The presence of active or inactive additives and drug polymorphism.

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crystal mass and effective surface area must be taken into account when attempting to modify drug dissolution so as to enhance, delay or sustain biological availability, as reviewed in part by Levy (1966) and Tawashi (1969).

Wagner (1971) has summarised most of the important factors affecting rate of dissolution of drugs from tablets and capsules in vitro and in vivo. Most of these factors are the same as those which affect disintegration time of tablets and capsules.

Effect of different factors on dissolution rate of drugs:

As far back as 1942 differences in pharmacodynamic behaviour and therapeutic activity between microcrystalline and ordinary forms of sulfonamides administered orally were noted by a number of investigators. Simultaneously significantly higher serum sulfadiazine concentrations were obtained with microcrystalline sulfadiazine, which offered two possible explanations. The most plausible was that the absorption of the microcrystalline material in suspension was more rapid and more complete than would be the case with the larger particles. The other possibility was a difference in rate of solution between the two forms during contact with alkaline secretion in the intestine. Regardless of the validity of either postulate almost two decades passed before a particle size limit for a pharmacopoeial drug substance administered orally in dry form was included in a pharmacopoeia (Cooper 1971).

The gastrointestinal absorption rate of sulphaethylthiazole was increased when this drug was administered in smaller particle size. The degradation of slowly dissolving drugs such as erythromycin and its esters, in gastric fluids can be minimized by administering the drug in the form of relatively large particles. Dissolution rate was thereby reduced, less of the drug dissolved in the stomach and less was therefore destroyed by gastric fluid. However if the particles were too large they dissolved so slowly that they were not fully biologically available.

Sekiguchi and Obi (1961) developed a new technique to achieve particle size reduction of a drug and thereby permit sparingly soluble drugs to become dispersed finely in the fluids of the gastrointestinal tract. The method involves the formation of a eutectic mixture of the drug (solid at room temperature) and a pharmaceutically inert, readily soluble carrier. Sulphathiazole in a eutectic mixture with urea exhibited higher absorption and urinary excretion in man than ordinary sulfathiazole after oral administration. Later, Sekiguchi et al. (1964) studied the chloramphenicol — urea system. Still later, Goldberg et al. (1965) and (1965) summarized literature on eutectic mixture and solid solutions and studied the acetaminophen — urea system (Goldberg et al., 1966), the griseofulvin-succinic acid system (Goldberg et al., 1966) and the chloramphenicol-urea system (Goldberg et al., 1966).

Hamlin et al. (1962) showed that increasing the intensity of agitation in dissolution rate studies on two polymorphic forms of methylprednisolone resulted in a loss of sensitivity and a failure to distinguish between the polymorphs with respect to dissolution rate. This study emphasized the need for low intensities of agitation in many in vitro dissolution rate tests. Levy and Procknal (1964) studied the same polymorphs by the rotating disk method and confirmed that the observation of Hamlin et al. (1962) were due to the intrinsic properties of the drugs and not to the particular apparatus employed. The observations of Hamlin et al. (1962) were explained on the basis of the Danckwert's model by Goyan (1965) and on the basis of a double barrier model by Wurster and Taylor (1965) and (1965). However, the most plausible explanation of the observations of Hamlin et al. (1962) was given by Higuchi (1967).

Schroeter and Wagner (1962) reported that with some tablets there was a quantitative relationship between rate of dissolution (as reflected by 50% values) and disintegration time but with other tablets there was no such relationship; where a quantitative relationship existed, the slopes of the lines relating the variables varied widely and depended upon the particular drug involved and, in one case upon the presence and absence of sodium chloride as an ingredient in the tablets. These authors questioned the use of plastic disks in the official tablet disintegration test. They also re-evaluated the early data and showed that physiological availability of p-aminosalicylate was correlated with dissolution rate as well as with disintegration time.

Middleton et al. (1964) conducted studies on the relationship between dissolution rate, disintegration time and physiological availability of several sugar coated multivitamin tablets. A close relationship was found between in vitro disintegration time and the dissolution rate (T50%) of riboflavin for the various products.

Levy (1963, 1963 , 1963) studied the effect of certain tablet formulation factors such as the granule size, binders, lubricants and compression force on the dissolution rate of the active ingredient from model tablets. These studies yielded a great deal of basic information relevant to formulation procedures required to optimize availability. The influence of the granule size used to prepare compressed tablets of salicylic acid was found to be significant. Dissolution from tablets made with smaller granules (40-60 mesh) was about 50% faster than from tablets containing 16-20 mesh granules. Inclusion of starch in the granules also resulted in a large increase in dissolution rate, probably because of more efficient disintegration of the granules to primary particles and increased surface area. Concerning the effect of tablet lubricants on dissolution, it was found that hydrophobic materials such as magnesium stearate and stearic acid, reduce significantly the rate of dissolution of salicylic acid from model tablets. These agents appear to decrease the effective drug-solvent interfacial area and thereby decrease dissolution rate. Conversely the surface active, water soluble lubricant sodium lauryl sulphate enhanced dissolution by permitting better penetration of solvent into the tablet and granules.

The force of compression is an important factor which may be critical in drug availability. Disintegration time of tablets has been found to be directly proportional to compression force and tablet hardness (Higuchi et al., 1954). High compression forces also may increase the strength of the internal structure of the granules and retard the dissolution rate of the drug from the disintegrated tablet. It has been suggested that some advantages resulting from particles size reduction may be negated by compression.

Shefter and Higuchi (1963) showed that the anhydrous and organic solvate forms of several drugs dissolved more rapidly than the corresponding hydrated forms. They derived equations relating the solubility products and diffusional constants to rate of solution of organic solvent. They pointed out that the formation of organic solvates of many highly insoluble drugs is a very useful method for effecting rapid dissolution of such drugs.

Hamlin et al. (1962), using compressed pellets in a standard apparatus, showed that the intestinal rate of dissolution (sink condition) was directly proportional to the solubility of the drug in the dissolution medium, in conformity with the Noyes-Whitney law for a large number of drugs of widely varying structures. This supported the conclusion of Higuchi et al. (1965). Exceptions to such a relationship are self-coating pellets such as described by Levy and Procknall (1964) and Higuchi et al. (1963).

In addition to increasing the specific surface area of poorly soluble drugs by microionization, other attempts have been made to modify the dissolution kinetics of such substances. Following the work of Sekiguchi et al. (1964), Goldberg et al. (1965, 1965 , 1966, 1966 , 1966) investigated the dissolution rate characteristics of a eutectic mixture of urea acetaminophen and solid state dispersions (solid solution) of griseofulvinsuccinic acid and chloramphenicol-urea.

On the basis of the acquired data the authors suggest that such methods of physical modification might prove to be more important than micronization in enhancing the absorption and therapeutic effect of many water insoluble drugs. Along similar lines, a solid state dispersion of griseofulvin in polyvinylpyrrolidone (Mayersohn and Gibaldi, 1966) resulted in a five to ten fold increase in the dissolution rate of the drug.

Among the techniques that can potentially enhance the dissolution rates and, hence the extent of absorption of hydrophobic drugs in the formation of coprecipitates with pharmacologically inert, polymeric materials such as PVP, several investigations (Stone, 1963; Mayersohn and Gibaldi, 1966; Bates, 1969; Simonelli et al., 1969; Svoboda et al., 1971; Stupak and Bates, 1972) have demonstrated in vitro, that the solubility and dissolution rates of drugs can be increased in this manner. Little information is available in the literature related to the in vivo absorption pattern of drugs orally administered as polyvinylpyrrolidone co-precipitates. Recently Stupak and Bates (1972) demonstrated that both the rate and extent of absorption of water insoluble drugs could be markedly enhanced in the form of 1:5 (w/w) co-precipitate with PVP.

PVP has also been employed in a number of tablets as a complementary product to overcome the dissolution problem as co-precipitates (Najma et al., 1979), despite its inherent toxicity (Najma et al., 1978, 1979).

Higuchi (1967) and Higuchi et al. (1965, 1965) elucidated the role of a number of factors controlling the rate of drug release from a variety of plastic and wax matrices and deve-

loped and applied theoretical approaches to these areas. Higuchi (1967) reported a correlation between the rates of reversion of the metastable form to the stable forms during dissolution and the crystal growth rates of the stable form for two polymorphic forms of both sulphathiazole and methylprednisolone. Thus the usefulness of a polymorphic form of a drug to increase the rate of dissolution may be gauged.

Finholt et al. (1966) and Solvang and Finholt (1969) investigated the effect of different factors on dissolution rate of drugs from powders, granules and tablets. Their studies included the effect of formulation factors e.g. particle size, binders, lubricants, diluent, surfactants method of granulation and tablet processing on various drugs as model substances. Various factors were shown to exert the influence on the dissolution rate to different extent.

Finholt and Solvang (1968) compared the kinetics of in vitro dissolution of phenacetin and phenobarbital in powdered form in human gastric juice with those in dilute hydrochloric acid containing varying amounts of polysorbate 80. The effect of polysorbate 80 on the rate of dissolution of phenacetin was shown to be due only to a small extent to its solubilizing power, but the principal tension being between the drug particles and the dissolution medium. They showed that the surface tension of the dissolution medium has an appreciable effect on the dissolution kinetics of the two drugs studied.

The extent to which certain processing variables influence the dissolution rate of active ingredients from tablets was also investigated. The addition of sodium chloride to the tablet mixture made it possible to measure dissolution rate by the relatively simple conductivity technique. The dissolution time and relative density become constant at the same compression force. The authors recommended that in comparing the dissolution time of tablets, the relationship with compression force used in their preparation should be ascertained.

Aguiar et al. (1968) demonstrated that de-aggregation of powder in capsules after disintegration of the capsule shell may be a most important factor in drug availability and rate of dissolution. Such de-aggregation kinetics may explain, in large part, the marked differences in physiological availability of various brands of chloramphenicol capsules.

Oxytetracycline serum concentration were also performed in 16 two-way crossover studies in 20 subjects. A single lot of Pfizer Oxytetracycline capsules was the control treatment in each of the studies. Sixteen lots of oxytetracycline from 13 different suppliers constituted the other treatments. In each study the Pfizer Oxytetracycline capsules produced superior serum levels. Seven of the 16 lots from other suppliers produced serum levels which were generally below the usually accepted minimum therapeutic level of 0.6 mg/ml. In an attempt to explain the differences these authors performed various disintegration and dissolution tests. They found that, in general, lots which gave poor serum levels also had slower rate of dissolution in vitro. They stated, "However, it is apparent that prediction of therapeutic availability cannot be made with precision from in vitro experiments in this case."

Wagner and Metzler (1969) discussed the interpretation of per cent dissolved-time data derived from conventional testing of tablets and capsules from which drug dissolves reasonably rapidly. It was shown why, when surface area decreases exponentially with time, after some log time, one would expect the data to obey first order kinetics. A distribution function, such as the logarithimic-normal distribution or the logisticlogarithimic distribution, may better be utilized to linearize per cent dissolved time data.

Chiou and Niazi (1971) determined the phase diagram of the sulphathiazole-urea binary system through DTA and X-ray diffraction method. These dissolution rates of sulphathiazole in solid solutions of urea were found to be extremely fast over 700 times higher than the pure compound. The intrinsic dissolution properties of active drug substances can be altered by additive or processing conditions which adversely affect therapeutic efficiency. While generally accepted as useful in production control, the value of the tablet disintegration test also lies in the evidence it provides of the significant increase in surface area which accompanies separation of the granules from the intact tablet. However the rate limiting step in the absorption process for most drugs in tablet form, is the dissolution rate from granules and basic drug particles. Properly designed and implemented, a dissolution-rate test can isolate the contributions which additives or processing variables make the inherent solution rate of the active drug substance. The selection of a definite formation and process must, however, be based upon due consideration of other factors besides maximum or ragulated bioavailability. The proper-

ties of a granulation or powder mixture must be such that following compression inter-tablet potency variations fall within acceptable limits and all other regulatory requirements including adequate stability are met. The biopharmaceutic "revolution" has added an additional dimension to the complex problems in the development of tablet dosage form. Probably to a greater extent than with other radical changes in the past, the net result will be a further reduction in the empiricism which has for a century characterized much of the research and development in this important field (Wagner and Metzler, 1969).

Sustained Release Preparations

The general aim of a sustained action formulation is to delay the time during which the drug is available, by obscuring the attack of the absorption pool menstruum, by using the limited amount of some agent required to free the drug from the dosage form or by so reducing the solubility that this factor becomes the controlling characteristic. There are four general physical procedures (i.e. coating, matrix imbedding, ion exchange and insoluble forms) by which control over the delivery of such drug to the absorption pool can be obtained (Eriksen 1970).

In 1953 Smith Kline and French Laboratories marketed the first "sustained release" spansule product. Subsequently, a host of prolonged action and sustained released products have been marketed. The results achieved with these products are directly related to slower absorption of the contained drugs relative to conventional dosage form. Indirectly, the slower absorption is attributable to slower dissolution of the drug from the dosage form in the gastrointestinal tract of man (Wagner 1971).

The interest of investigators in sustained-release preparations continues in the direction of quantitation of drug release rates. For sustained release preparations consisting of slowly and immediately available portions, Kruger-Thiemer and Erikson (1966) found a useful pharmacokinetic model involving first order processes for drug release, absorption and elimination. Mathematical and analogue computer simulation showed the shift in the rate-determining step as the relative rates of absorption and release were changed. These authors were able to interpret data from experiments with 2-sulfanilamide — 5-methylpyrimidine, compressed tablets, which possess sustained-release properties. Robinson and Eriksen (1966) concluded that only the vagaries of the human gastrointestinal tract interfered with the development of preparations with the capability of achieving the most constant blood level of a drug over a desired interval of time.

Many sustained release preparations are based upon the principle of retarding the release of a solid drug dispersed in a matrix composed of pharmacologically inert material. Efforts to demonstrate a quantitative relationship between theoretical and experimental data have attracted the attention of a number of investigators. Desai et al. (1965, 1966, 1966) and Wai et al. (1966) attempted to elucidate the factors influencing the release rate of solid drugs dispersed in polyethylene or polyvinylchloride matrices. Refinements in experimental procedures enabled these investigators to quantitatively determine matrix tortuosity and to differentiate between matrix porosities for available and inaccessible pores. The unusual behaviour of polyvinyl chloride (PVC) matrices when compared to polyethylene matrices in drug release rates, it was interpreted to be the result of the relatively slow release of air from the (PVC) tablets.

Singh et al. (1967) studied the simultaneous release of a mixture of two non-interacting drugs from a plastic matrix, and quantitative relationship based on a physical model which expresses the diffusion controlled rates of release of both drugs as function of their concentrations, solubilities and diffusional coefficients as well as the porosities and tortuosities of the tablet. The experimental data for salicylic acid-benzoic acid mixture were in close agreement with the theoretical values. A similar agreement was demonstrated for admixture of benzocaine and caffeine, two mutually interacting drugs (Singh et al., 1967).

Lazarus et al. (1964) reported the factor controlling the rate of release of a very soluble drug, tripelennamine hydrochloride, from a compressed grannular wax matrix. They found that drug particle size and concentration exerted the greatest influence on the release rate while the size of the granules before compression was less significant. At the same concentration of drug, a more rapid release occurred with the larger particles. In view of the greater complexity of the wax system as compared to plastic system, Schwartz et al. (1968) endeavoured to quantitate the mechanism of drug release from wax matrices by use of the diffusion model. The diffusion controlled mechanism proved to be operative when adequate time intervals for measurement were employed but

additional experiments with a sulfanilamide-wax system showed a change in mechanism from aqueous, diffusion controlled for low drug concentration to a more rapid process for higher concentration which does not appear to be aqueous diffusion controlled.

Another type of sustained release preparation which has been subjected to release rate studies is based upon a compressed mixture of hydrophilic polmer and drugs.

Christenson and Date (1960) and Huber et al. (1966) proposed that drug release was controlled by drug diffusion, through the gel sheath around the tablet and by the degree of attribution of the sheath. Lapidus and Lordi (1966, 1968) ascribed the sustained drug release properties of the hydrophilic polymer, hydroxypropyl methylcellulose, as the result of the formation of a hydration layer at the tablet surface. As long as the integrity of the hydrated polymer was maintained, drug release was diffusion-controlled.

Asker and Becker (1966) studied spray dried dissolution retarding materials, together with sulfaethylthiazole, in the development of sustained-release preparation. Only Glycowax S-932 formulation containing one part of drug to two parts of wax yielded a significant retardation of drug release when tested in both 0.1N hydrochloric acid and alkaline, pancreatin solution. There has also been reports that surfactants, waxes and various modifiers influence the dissolution behaviour of sulfaethylthiazole. Rankin (1967) described a new drug application for sustained-release products to demonstrate that it is properly made and controlled to release the active compounds at a safe rate and at a rate at which the drug will have its intended effect.

The introduction of timed-release tablets as a dosage form required the development of in vitro test procedures capable of reflecting the rate at which the active drug substance is released to simulated physiologic fluids. Lazarus and Cooper (1959) reviewed the in vitro test methods proposed by various investigators. In spite of regulatory pressure for the prompt establishment of a single-test method, difficulties were encountered due to the utilization of different principles in the formulation of such preparation. Eventually the National Formulary XII selected the rotating bottle method, useful in establishing suitable test criteria to assure product uniformity of most timed-release tablets or capsules. In order to eliminate interference by the test fluid in the assay procedure and better sampling, the residues rather than drug in solution are assayed. The procedure can be varied with respect to speed of rotation, time interval for assay, pH, composition and volume of extracting fluids, size and position of the bottles and other conditions in order to achieve the desired correlation with the in vivo studies and clinical results. Under such circumstances it is obvious that even though included in an official compendium this procedure is advisory rather than regulatory.

Anderson and Sakr (1967) have described an apparatus specifically designed to study the release rates of drugs included in coatings on compressed tablets. These investigators obtained random movement of a coated tablet in a fixed volume of extracting fluid at a standard temperature. The inclusion of a trip bar within a perforated drum minimized contact of the tablet with the sides of drums and prevented sliding. These timed-release in vitro tests have been described by Cooper (1971).

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