

*Review Article*

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## Dissolution Rates

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### DRUG AVAILABILITY

**I**N RECENT YEARS much attention has been focused on the problem of drug availability. The drug availability usually is determined by the rate of release from the physical system commonly referred to as the dosage form. The release of the drug from this system is in turn governed by such processes as the adsorption of the drug by other components of the system, the diffusion of the drug in the system, the dissolution rate of the drug, and other factors. As early as 1948 it was recognized that while the efficiency of a compressed tablet is to some degree related to the speed of disintegration, the dissolution of the drug particles is of prime importance (1). Parrott *et al.* (2) clearly indicated the importance of dissolution kinetics in determining the drug availability to the body. Subsequently, Nelson and others (3-7) reported that the dissolution rate does indeed control the rate of build up of certain drugs in the blood stream. In a review article dealing with drug absorption, Wagner (8) discussed the dissolution rate in some detail and indicated its importance in the absorption process. Thus, it is now well recognized that the dissolution rate of solid drugs can be the rate-limiting step in the absorption process when drugs in this physical state are introduced into the animal body. Because of the indicated im-

portance of the dissolution rate, the following discussion will deal only with this particular influence on drug availability.

### THEORY OF DISSOLUTION

The process of dissolution as well as the inverse process of crystallization can be considered as specific types of certain heterogeneous reactions in which a mass transfer is effected through the net result of escape and deposition of solute molecules at a solid surface. These reactions can be classified according to the following three general types. (a) The reaction or interaction at the interface occurs much faster than the rate of transport of reactants to and products from the interface. The rate, therefore, is determined by the transport process. In dissolution this would be the diffusion or convective transport of solute from the interfacial boundary to the body of the solution. (b) The rate of reaction at the interface is much slower than the transport processes and hence determines the rate. If this were to occur in dissolution, the actual processes of liberation and deposition of the solute molecules at the interface would determine the rate. (c) Both intrinsic rates or rate constants are of the same order of magnitude so that the over-all rate is a function of both processes.

Various procedures have been employed to delineate the primary process controlling a heterogeneous reaction. The usual procedure, of course, is to study the influence of a single specific factor while attempting to maintain all

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others constant. Therefore, this paper will be concerned mainly with those studies that treat factors that aid in determining the process by which the dissolution rate is controlled.

Noyes and Whitney (9) quantitatively studied dissolution by rotating cylinders of benzoic acid and lead chloride in water, then analyzing the solution at certain intervals. These workers derived the following equation:

$$\frac{dc}{dt} = k(C_s - C) \quad (\text{Eq. 1})$$

where  $C$  is the concentration at time  $t$ , and  $C_s$  is the equilibrium solubility of the solute at the experimental temperature. It thus was assumed that a thin layer of saturated solution formed at the interface and that the observed velocity was the rate at which molecules diffused from this layer to the bulk solution. In later experiments (10, 11) the surface area was incorporated into the equation to give

$$\frac{dc}{dt} = k_1 S(C_s - C) \quad (\text{Eq. 2})$$

Subsequently, Nernst (12) extended the concepts of Noyes and Whitney to include all heterogeneous reactions. Brunner (13) worked with Nernst and used Fick's law of diffusion to establish a relationship between the constant in the above equation and the diffusion coefficient of the solute,  $k_1 = DA/Vh$ , where  $D$  is the diffusion coefficient,  $A$  is the area of the dissolving surface or area of the diffusion layer,  $V$  is the solution volume, and  $h$  is the diffusion layer thickness. He also calculated the thickness of the postulated film layer existing at the surface of the dissolving solid.

Many workers have published data which tend to substantiate the film theory of Nernst and Brunner, while the other workers have found cases where the theory does not appear to hold. In formulating their theory, Nernst and Brunner assumed that the process at the surface proceeds much faster than the transport process and that a linear concentration gradient is confined to the layer of solution adhering to the solid surface. Obviously, if the intrinsic reaction rate at the interface were not faster than the rate of the transport process, deviations would occur. Roller (14) voiced his objections to the film theory concept and stated that an activation energy for the interfacial reaction should be required since all collisions of the solvent could not be expected to result in the release of molecules from the solid surface.

Other criticisms of the film theory have been directed toward the inordinately large calculated film thickness (20–50  $\mu$ ) which are considered to

be physically unacceptable. In calculating the film thickness, Nernst and Brunner proposed that diffusion was the only mode of transport, and the boundary film remained stationary. However, some studies have indicated fluid motion and turbulence extends to within a short distance from the solid surface. In this regard, the work of Van Name and Hill (15, 16) and also that of King (17) is most important. Their work led them to postulate that the fluid motion component perpendicular to the surface becomes small and thus does not affect the transport rate materially. This postulation is, in part, substantiated by Fage and Townend (18), who, in measuring velocity profiles, found essentially only laminar motion parallel to the interface existed in regions close to the interface. The above workers (15–17) thus believed that convection would aid solute transport only in the distant areas of the film.

In recent years the film theory has been considered acceptable with certain modifications. The similarity of calculated values for the film thickness has led investigators to refer to an "effective film thickness." This idealized film layer is not well defined, but it allows the correlation of experimental data with the physical properties of both the solute and solvent.

#### Factors Influencing the Dissolution Rate

It is evident that dissolution kinetics are subject to a large number of physical-chemical influences. These influences may deal with (a) influences applied directly to the total physical system, such as temperature and agitation; (b) influences resulting from changes in the characteristics of the solute particle; and (c) influences brought about by changes in the dissolution medium. While the information gained from studying these influences has aided materially in understanding dissolution theory, it is also of great practical value in showing the effects of both pharmaceutical and biological systems on the dissolution rate. Many of the following studies are, therefore, of much practical significance.

**Temperature and Agitation.**—Both temperature and agitation rate effects commonly are used to aid in distinguishing the process controlling the heterogeneous reaction rate. Some of the investigations involving agitation have led to the empirical relationship

$$K = a(N)^b$$

where  $N$  is the agitation or stirring rate,  $K$  the reaction rate, and  $a$  and  $b$  are constants. If the reaction is diffusion controlled, then the value of  $b$  should be 1 or near 1. This is in accord with

the Nernst-Brunner film theory (13), which stated that the thickness of the film was inversely proportional to the stirring speed. For the reactions controlled by the rate of the interfacial reaction, it would be expected that the agitation intensity would not influence the reaction rate, and  $b$  should approach zero. If both processes are influential in the control of the rate,  $b$  should vary between zero and 1 if a sufficiently wide range of agitation intensities are employed.

Inasmuch as the motion of the fluid changes from laminar to turbulent as the distance from the interface increases, the value of the exponent  $b$  also may vary with the type of agitation used. Hixon and Baum (19) observed this when they employed measurements obtained on the dissolution of benzoic acid pellets as criteria for agitation efficiency. By a dimensional analysis they assigned a Reynold's number to the point where the relationship between the variables changed. They attributed this change to turbulence and obtained separate relationships for high and low Reynold's number values. In a subsequent study (20), by changing only the type of stirring, they found that another empirical relationship must be assigned. More recently, a group of Japanese workers (21) in 1958 felt that Hixon and Baum's data were not randomly distributed about their empirical equation. Using these data with their own, they regrouped the assumed variables in different dimensionless groups and found a better correlation with the data. Thus, they also introduced additional variables upon which the rate of solution appeared to be dependent. The above studies and others have, therefore, indicated a rate dependency upon the degree of laminar and turbulent flow, the density of the solid phase, the size and characteristics of the solid, the stirrer, and the dissolution vessel, and the heat of solution of the solute in addition to those factors known to influence diffusion.

Garner and Hoffman (22) found that even in cases of free convection, turbulence existed in the boundary layer. They were able to demonstrate this vividly through photographs showing the light effects of the changing refractive index in this layer. It was the contention of Levich (23) that the variation in stirring rate-reaction rate relationships is due to the variable degree of turbulence in the solvent near the interface. In cases of forced convection, he felt this might be due, at least in part, to the different surface characteristics of the dissolving substance.

From the above studies it is apparent that a number of inherent variables can influence the relationship between the dissolution rate and the intensity of agitation and that this restricts the

application of a generalized relationship between them. The exponent,  $b$ , in the aforementioned equation thus will depend not only on the process controlling the dissolution rate but also on the characteristics of the fluid motion in the boundary layer.

From the investigations of several workers (24-26) it is shown that, if a heterogeneous reaction were diffusion controlled, the 10° temperature coefficient should be in the neighborhood of 1.3, while an interfacial controlled reaction possesses a coefficient of about 2.0. Abramson and King (24) studied the temperature coefficient of heterogeneous reactions at low and high agitation intensities. They obtained coefficients of 1.29-1.43 in the region where the agitation rate significantly influenced the reaction rate. In the region where the stirring speed did not influence the reaction rate, coefficients of 2.04-2.34 were obtained.

#### Changes in Dissolution Medium

**Viscosity.**—The influence of viscosity on heterogeneous reaction rate control also has been investigated (27, 28). The relationship between viscosity and the heterogeneous reaction rate is extremely complex and, as of now, only partially explained. Diffusion-controlled reactions therefore, should decrease in rate with an increase in viscosity, whereas viscosity should have little effect on interfacial controlled reactions.

Several equations have been derived which show the dissolution rate to be a function of viscosity raised to some power where the exponent varies from  $-0.25$  to  $-0.8$  (14, 29, 30). Other equations have been derived which express the diffusion coefficient as a function of viscosity. For example, the Stokes-Einstein equation (31) shows the diffusion coefficient to be inversely proportional to the viscosity. Sutherland (32) independently derived the same equation but found that it did not agree with existing data. Arnold (33) shows the diffusion coefficient as a function of viscosity raised to the  $-0.5$  power. In another study, where the dissolution rate of benzoic acid in methylcellulose solutions was determined over a range of 1 to 260 cps., the dissolution rate was found to be a function of viscosity raised to the  $-0.5$  power for 96% of the viscosity range studied (34).

**Solubilization and Surface Activity.**—Only a limited amount of information is available in the literature on the influence of solubilization and surface activity. Roller (35, 36) speculated that surface activity may play a part in the

dissolution process if spontaneous release from the crystal controls dissolution. His studies indicate this to be a distinct possibility since the increase in rate with a change in particle size was greater than that expected by the increase in surface area alone. He also believed that dissolution took place from active centers on the crystal; these were the edges and corners as well as points of crystal defects.

Ekwall and co-workers (37, 38) published solubilization curves for various steroids with sodium lauryl sulfate. Since their studies were conducted at high surfactant concentration, the effect of this surfactant on solubility in the region of the critical micelle concentration (CMC) cannot be distinguished. Wurster and Seitz (39) showed an increased solubility of benzoic acid at 0.2% concentration of sodium lauryl sulfate. It is possible, as shown in other studies (40-44), that with certain substances solubilization will occur at concentrations significantly below the CMC. It is felt by some that this can be attributed to penetration or incorporation of the solubilize within the micelle. If the solubilize is oriented between ionized surfactant molecules, the repulsive forces of the surface-active agent will be reduced, thus facilitating micelle formation at lower concentrations (40-42). Other investigators feel that limited association or aggregation between the solubilize and surfactant at concentrations considerably below the CMC is responsible for the increase in solubility (43, 44).

Working with certain crystal forms of prednisolone, Taylor (45) noted a solubilization effect with sodium lauryl sulfate at concentrations considerably below the CMC. Also, at a concentration of 0.1% of sodium lauryl sulfate, the release from supersaturation of a metastable anhydrous crystalline form was more rapid than in water solutions only. Substantial dissolution rate increases were observed in the surface-active media. It appeared that these increases could be accounted for by both the solubilization effect and an apparent increase in the interfacial reaction rate. Levy and Gumtow (46) reported that 3% sodium lauryl sulfate did not increase the dissolution rate of salicylic acid in water when these substances were incorporated into nondisintegrating disks.

**Unreactive and Reactive Additives.**—When neutral ionic ( $\text{NaCl}$ ,  $\text{Na}_2\text{SO}_4$ ) and nonionic organic compounds (dextrose) were employed as additives to the solvent phase, the dissolution rate of benzoic acid was linearly dependent upon the solubility of this acid in the particular solvent system (2). Increased dissolution rates for

benzoic acid were observed when certain bases and buffers were added to the aqueous solvent. From these experiments, it is apparent that for a solid weak acid, such as benzoic dissolving in a basic solution, the rate of dissolution becomes essentially independent of the strength of the base above certain values. In the region where the rate is independent of the base strength, the dissolution rate is a linear function of the product of the base concentration and the base diffusion coefficient (47). In a subsequent article, Higuchi (48) has shown that the simultaneous chemical reaction and diffusion method previously described for interpreting data on dissolution rates gives results similar to the total solubility method reported by Nelson (3, 49, 50) when the diffusion coefficients are set to the same value. The diffusion coefficients for most drugs of similar density would not be expected to vary greatly, since the diffusion coefficients vary approximately as the cube root of the molecular weight, according to the Stokes-Einstein equation.

The dissolution rates of several weak acids and their sodium salts in aqueous solutions having pH values corresponding to those of the gastrointestinal fluids were reported by Nelson (51). In all cases the dissolution rates of the salts were greater than those of the free acids.

**Adsorption.**—Experimental data on the influence of an adsorbent on the dissolution rate of a slightly soluble acidic solid indicated that an adsorbent was capable of increasing the dissolution rate in water under conditions of a decreased concentration gradient to the maximum rate obtained when a constant concentration gradient was maintained. The amount of adsorbent required to increase the slower dissolution rate to the maximum rate was calculated with the aid of adsorption isotherms obtained with the adsorbent and the particular solute (52).

**Chemical Reaction, Viscosity, and Adsorption.**—Using bentonite U.S.P., a montmorillonite clay, the simultaneous influence of several factors on the dissolution rate of compressed benzoic acid tablets was investigated (53). Thus, when the dissolution rate was determined in bentonite suspensions, the controlling factors were characterized as chemical reaction, adsorption, and viscosity. When the rate was determined in neutralized bentonite suspensions only adsorption and viscosity were the controlling factors. By comparing rates obtained in the latter system to those obtained in methylcellulose solutions of various viscosities, it was possible to separate the contribution of the adsorption and viscosity functions to the rate.

With this method the influence of the various factors on the rate were delineated clearly. The dissolution rate of a solid weak acid in bentonite suspension is greater than the rate indicated solely by the viscosity due to the superimposed influences of alkalinity and adsorption.

#### Changes in Solute Particle Characteristics

**Polymorphism.**—The influence of crystalline form on the dissolution rate was noted first by Wildermann (54) and then by Gross (55) when certain crystalline faces produced changes in the rate of solution. Most of the investigations to date in this area, however, have not been controlled to the extent where rigid quantitative comparisons can be made. The rate of solution and solubility of calcium sulfate in both the anhydrous and hydrate form have been measured by Roller (35, 36). The anhydrous form exhibited a solubility of 1.46 times that of the hydrate, yet, under certain conditions, the hydrate had a higher dissolution rate. Although it is possible that his results may have been distorted by entrapped air at the particle surface, he ascribed this variation to the relative rates of release at the interface of the crystalline forms.

The more recent work of Shefter (56) on the dissolution properties of certain polymorphic and solvate forms of various drugs also was carried out using a fine multiparticulate system. From the concentration *versus* time curves for these substances, definite differences in the dissolution rate of the crystal forms can be observed. However, it would be impossible to quantitate these differences because of the uncontrolled surface area and rapid dissolution rate of these materials.

Using a variety of methods to determine the dissolution rates, Hamlin and co-workers (57) studied the rate of dissolution of two polymorphic forms of methylprednisolone. They found that a loss of sensitivity in distinguishing between the rates occurred at higher agitation intensities. This change was ascribed to relative changes in the calculated diffusion layer thickness, assuming complete diffusion control of dissolution. In their study the ratio of the diffusion layer thicknesses of the two polymorphs varied from a value greater than 1 to less than 1. Even though this interpretation of the diffusion layer thickness does appear to be open to question, the study does point out, nevertheless, that relative dissolution rates will vary with agitation speed and conditions. Furthermore, as suggested by these authors, dissolution rate studies at high agitation intensities may not reflect necessarily the relative rates of different crystal forms under low agitation intensities.

In a more recent investigation (58) by Wurster and Taylor, the activity, dissolution rate, and crystal behavior of three crystalline forms of prednisolone were studied. By determining the relative dissolution rates of these crystal forms under different agitation conditions, it was found that the dissolution process could be described by consecutive processes involving a reaction at the interface and transport away from the interface. Thus, under the experimental conditions employed, the data suggest that these two processes pose a double barrier to dissolution. Milosovich employed dissolution rate measurements to determine the solubility of a metastable sulfathiazole polymorph (59).

**Isotropic Crystalline Mass.**—It was found that an isotropic crystalline mass prepared by compression underwent dissolution in a manner similar to a single crystal. The dissolution rate of a nondisintegrating compressed benzoic acid particle was independent of the particle density over a measured density range of 1.054 to 1.304 (2).

**Effective Surface.**—In a dissolution study (39) conducted in which the surface area-weight ratio was not maintained constant, cylindrical compressed tablets containing large pores were employed to follow the dissolution process. Studies in distilled water indicated that the surface area of the pore was exposed incompletely to the solvent due to occlusion by air. Solutions with a lower surface tension than water were capable of wetting the entire surface, and a corresponding increase in the dissolution rate was obtained. When the air was evacuated from the pores, the solvent again was able to contact the entire surface, and the dissolution rate again increased. Dissolution from the pore surface occurred at a slower rate than from the exterior surface of the particle due to the longer diffusional pathway of the solute molecules (39). Similar effects would be expected in lyophilized and other porous particles.

Schroeter and co-workers (60) studied the dissolution rates and disintegration times of a large number of tablets prepared from a variety of drugs. Their results emphasize the difficulty to be expected in obtaining a quantitative relationship between the two rates as a result of the many variables involved.

Levy (61–63) studied the effect of certain tablet formulation factors on the dissolution rate of the active ingredient. Included in the factors studied were the agitation intensity, granule size, starch concentration, compression pressure, and lubricants. Using rotating disks, it could be

shown that for a single component in the disk the dissolution rate varied as the square root of the stirring rate in the same manner as shown by Cooper and Kingery (64). Levy and Procknal (65) also have shown the inhibition of the dissolution rate of aluminum acetylsalicylate due to the formation of a basic water-insoluble aluminum compound on the surface of the dissolving solid.

Morozowich (4) and Higuchi (66) both have reported on the inhibition of benzphetamine release in acid medium due to the deposition of pamoic acid on the surface of the dissolving particle, according to the reaction: benzphetamine pamoate (pellet)  $\xrightarrow{H^+}$  benzphetamine (solution) + pamoic acid (pellet surface).

### METHODS OF STUDY

To study dissolution in a quantitative manner, it is necessary to alter the Noyes-Whitney equation to account for the variable surface. Hixon and Crowell (67) derived a general expression for the reaction rate in terms of variable surface area and concentration. The derivation of their well-known "cube root law" was based on the following assumptions: (a) dissolution takes place normal to the surface of the dissolving solid, (b) the same effect of agitation is observed on all areas of the surface, (c) no stagnation of the liquid takes place in any region, and (d) the solid particle remains intact throughout dissolution.

The Noyes-Whitney equation can be written

$$\frac{dw}{dt} = -K_2 S (C_s - C) \quad (\text{Eq. 3})$$

with the notation the same as in Eqs. 1 and 2. Letting  $W_0$  represent the initial weight of the particle,  $W$  the weight at time  $t$ ,  $W_s$  the weight of solute needed to saturate the liquid,  $S$  the effective surface area,  $V$  the solution volume, and  $d$  the crystal density, the following relationship can be set up:  $(W_0 - W) / V = C$ , and  $W_s / V = C_s$ . Substitution into Eq. 3 gives

$$V \left( \frac{dw}{dt} \right) = -K_2 S (W_s - W_0 + W) \quad (\text{Eq. 4})$$

If there is no change in the shape of the solid during dissolution, the surface can be related to the weight by means of shape-volume factors:  $S \propto V^{2/3}$  (for a sphere  $S = 4.85 V^{2/3}$ ). With the consideration of density,  $S = a W^{2/3}$ , where  $a$  includes the density and a shape-volume constant (for a sphere  $a = 4.85/d^{2/3}$ ).

Then by substituting for  $S$  in Eq. 4 and setting  $W_s - W_0 = g$ , the following equation is obtained:

$$V \left( \frac{dw}{dt} \right) = -K_1 W^{2/3} (g + W) \quad (\text{Eq. 5})$$

Rearrangement and integration gives

$$V \int \frac{dw}{g W^{2/3} + W^{5/3}} = -K_1 \int dt + C \quad (\text{Eq. 6})$$

where  $C$  is the constant of integration.

By imposing  $t = 0$ ,  $W = W_0$ , and  $C = 0$  as a limit of integration and letting  $g^{1/3} = b$ ,  $W_0^{1/3} = c$ , and  $W^{1/3} = x$  the integrated equation for the general case is obtained.

$$K_1 t = \frac{V}{b^2} \left[ \sqrt{3} \tan^{-1} \frac{2\sqrt{3}(bc - x)}{3b^2 + (2c - b)(2x - b)} + 1.1513 \log \frac{(b + c)^2 (b^2 - bx + x^2)}{(b + x)^2 (b^2 - bc + c^2)} \right] \quad (\text{Eq. 7})$$

Niebergall *et al.* (68), working with various particle size powders stated that the Hixon-Crowell cube root law did not describe their data. They reported results which adhered to a rate expression in which it was assumed that the thickness of the diffusion layer was proportional to the square root of the mean volume diameter.

If certain conditions are invoked by imposing certain experimental restrictions, this equation can be simplified greatly. These conditions are (a)  $W_0 = W_s$ , (b)  $C_s - C$  is constant, and (c) the surface remains constant. Thus, if the concentration gradient,  $(C_s - C)$ , is maintained essentially constant by keeping the dissolution medium sufficiently dilute, the dissolution rate then is proportional to the surface only or

$$- \frac{dw}{dt} = 3KS = 3Ka W^{2/3} \quad (\text{Eq. 8})$$

Integration between the limits  $W_0$  and  $W$  yields

$$Kat = W_0^{1/3} - W^{1/3} \quad (\text{Eq. 9})$$

With the aid of the above mathematical model and large particles, an easy method for determining dissolution rates can be devised (2). The large particles of known geometry and effective surface area are allowed to rotate freely in a medium which is being agitated at a constant rate. Then by analyzing the solution and/or the particle, the dissolution rate in terms of Gm. cm.<sup>-2</sup> hr.<sup>-1</sup> is determined easily. The method is particularly useful for studying various influences on the dissolution rate as other complicating factors, such as surface area, etc., are minimized.

A most significant contribution in methodology for handling the dissolution kinetics of finely divided powders has been presented by Higuchi and Hiestand (69). The long mathematical derivation given by these authors is beyond the scope of this paper but is applicable to those systems where the dissolution process is diffusion controlled, and the particle size distribution is known. In a subsequent paper (70), these

authors report reasonably good agreement between the calculated and experimental values obtained for micronized methylprednisolone.

Niebergall (68, 71) 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 nondisintegrating disks, as described by Levy (61-62, 72). Milosovich (59) employed a tablet mounted in a die and subjected to solvent agitation produced by a baffle system. This system is similar, in some respects, to that reported by Nelson (3, 73).

Schroeter (74) devised an automated method for following the dissolution rate of drugs in tablets and capsules. The method provides for automatic sampling, dilution, and spectrophotometric analysis of the dissolution medium.

It is not possible in a single review article to include all of the important work in a field as broad as dissolution kinetics. Particular attention, however, has been paid to the pharmaceutical literature and those investigations of apparent importance to pharmaceutical research and development. It is hoped that the information presented will serve as a starting point for those intending to initiate investigational work on or to study dissolution rates.

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