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Review Article

Diffusional Models Useful in Biopharmaceutics

Drug Release Rate Processes

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THE EVOLUTION of a given body of knowledge from a catalog of apparently unrelated facts to an exact science at the molecular level generally follows a path in which somewhere along the way the consideration of quantifiable *physical* models becomes necessary. Such models, when they enter upon the scene, play many roles in the course of the development of the area of knowledge. Initially they serve to provide the primitive quantitative interrelationships among the variables that considered intuition alone had been unable to do. From these, suitable *in vitro, in situ,* or *in vivo* experiments are designed. With refinement of the models and with continued experimentation, knowledge is efficiently built up to a rather sophisticated level.

This review is intended to cover some of those stiuations in biopharmaceutics where physical models involving drug transport have materially helped or are helping in answering complex questions. Some situations are also discussed where such methods have not yet been applied but are indicated. Attention is given only to those problems in which physical models have been applied in contrast to those where empirical or arbitrary mathematical kinetic models have been employed.

DISSOLUTION RATES OF SOLIDS

General Considerations—Wurster and Taylor (1) have already presented a comprehensive review of this subject. Wagner (2), in an earlier review article, also discussed this subject and related it to biological availability. The readers are referred to both of these excellent reviews which serve to provide more than adequate background for the present discussion.

From the standpoint of rate mechanisms involving pure substances there are basically three processes that have been accessible to the physical model treatment. These have been employed alone or in combinations in setting up the models for describing dissolution rate mechanisms. Figure 1 schematically illustrates those cases when each of these alone is rate determining.

Case *A* represents the diffusion layer showing a crystal or a polycrystalline solid dissolving into pure solvent. This model in its earliest

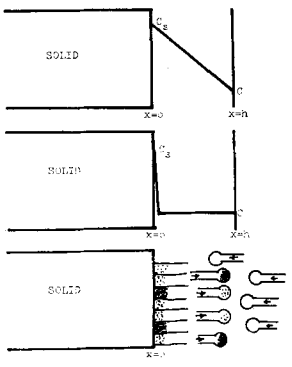

Fig. 1—Illustration of the situations for the three mechanisms of dissolution rate behavior of solids. Concentration profiles are shown for cases A *and* B, *and packet transport is depicted for case* C. *Case* A, *diffusion layer model (top); case* B, *interfacial barrier model (middle); case* C, *Danckwerts' model (bottom).*

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form was probably first discussed by Nernst (3). Here it is assumed that there is a liquid layer ("film") of thickness, h, in which there is a negligible velocity component in the x-direction (perpendicular to the surface). At $x > h$, it is assumed that rapid mixing is present. Therefore, no gradients of concentration may exist in this region. At $x = 0$ (the solid–liquid interface) it is assumed that solid–solution equilibrium exists. Then the rate of solute movement and therefore the dissolution rate is determined entirely by Brownian motion diffusion of the molecules in the liquid "film" ($x = 0$ to $x = h$).

Case B illustrates the interfacial barrier model where, because of a high activation free energy for the interfacial transport step, diffusion across the interface is much slower than diffusion across the "film" or transport by eddy packets to be discussed below. As a result, crystal–solution equilibrium at $x = 0$ may not be assumed, and this consideration must be included in the model.

Finally, we have case C representing the Danckwerts' model (4), where one imagines macroscopic packets of solvent reaching the solid–liquid interface by eddy diffusion in some random fashion. During its residence at the interface the packet is able to absorb solute according to the usual laws of diffusion. These surface elements are continuously replaced by new packets of solvent. This surface renewal process may then be related to the solute transport rate.

Rate Laws Predicted by the Different Mechanisms—Let us consider the situation where a one component, one phase, solid of macroscopic ($\gtrsim 1$ mm.) dimensions and of low to moderate ($\simeq 5\%$) solubility dissolves without disintegration and without chemical reaction into a solvent under mild to high agitation conditions. Then the dissolution rate per unit area, G, according to the diffusion layer model for this case will be

$$G = \frac{D}{h}(C_s - C) \qquad \text{(Eq. 1)}$$

where D is the solute molecule diffusion coefficient, C_s is the solubility, C is the solute concentration, and h as defined in Fig. 1 is the effective diffusion layer ("film") thickness.

The Danckwerts' model for this case gives

$$G = S^{1/2}D^{1/2}(C_s - C) \qquad \text{(Eq. 2)}$$

where S is the mean rate of production of fresh surface.

When an interfacial barrier is important, it is much more difficult to derive a relationship for G in physically significant terms. First of all, the true (or microscopic) surface area rather than the geometric external area (of a tablet) should be considered. Furthermore, the different faces of a crystal should have different interfacial barriers. However, one often writes for this case,

$$G = k_i(C_s - C) \qquad \text{(Eq. 3)}$$

where k_i is the effective interfacial transport rate constant. The first-order dependence on $(C_s - C)$ implies that the process is a unimolecular one. This is reasonable as one would expect that the step movement rate on a crystal surface would be usually unimolecular. However, perhaps at large undersaturations cooperative molecular effects may become important. More experimental studies are needed before the $(C_s - C)$ part of Eq. 3 can be regarded as the usually expected form in a surface controlled situation. For the present we shall take Eq. 3 as the best at the moment to represent this case.

When the interfacial barrier concept is combined with the diffusion layer case we have a double-barrier model

$$G = \frac{D(C_s - C)}{h\left[1 + \frac{D}{hk_i}\right]} \qquad \text{(Eq. 4)}$$

which reduces to Eqs. 1 or 3, respectively, in the limits, $k_i \gg D/h$ and $k_i \ll D/h$.

When the interfacial barrier idea is combined with Danckwerts' surface renewal mechanism we have

$$G = \frac{S^{1/2}D^{1/2}(C_s - C)}{\left[1 + \frac{S^{1/2}D^{1/2}}{k_i}\right]} \qquad \text{(Eq. 5)}$$

which reduces to Eqs. 2 or 3 in the limits.

The diffusion layer and the Danckwerts theories may also be combined (5, 6). Surface elements of a finite length, L, in the x-direction must be taken. This combination leads to expressions which reduce to Eqs. 1 and 2, respectively, in the limits, $L \to 0$ and $L \to \infty$.

Experimental Approach to an Examination of the Theories for One Component—One Phase Case—The reviewer believes[1] that there has been relatively convincing experimental work showing which theory is applicable and under what conditions. Part of this stems from the fact that the researchers frequently have been more interested in establishing other aspects than in differentiating the three basic models described above.

[1] Readers are referred to Wurster and Taylor's discussion (1). (See also *References 7* and *8*.)

The classical Noyes-Whitney law (9), which states that

$$G = \text{constant } x(C_s - C) \qquad \text{(Eq. 6)}$$

really, by itself, reveals very little mechanistically when a single substance dissolves in a pure solvent under constant hydrodynamic conditions. This is because all theories predict the same first-order dependence upon $\Delta C = C_s - C$.

When the dissolution behavior of many substances in the same solvent is compared under the same hydrodynamic conditions, it may be possible to separate those which follow Eqs. 1 or 2 from those following Eqs. 3, 4, or 5. If, furthermore, compounds with a sufficiently wide range of D values are included in the study while maintaining everything else but C_s constant, one should be able to distinguish data conforming to Eq. 1 from those following Eq. 2 or the diffusion layer–Danckwerts combination theory (6). The reviewer is not aware of work on this latter aspect that has led to unambiguous results. The work of Desai *et al.* (10), to be discussed later, probably provides a more promising approach to this problem.

Finally by varying the rate of agitation one should be able to distinguish between those following Eq. 3 from those following Eqs. 4 or 5, provided that sufficient data are available with other substances obeying Eqs. 1 or 2 under the same hydrodynamic conditions. Data obeying Eqs. 4 and 5 may then be distinguished by employing the method used for Eqs. 1 and 2.

Wurster and Taylor (11) in their studies of the dissolution rate behavior of prednisolone employed Eq. 4 and Eq. 1. These investigators suggested that the double-barrier mechanism (Eq. 4) better described their data on the influence of agitation upon the dissolution rates. Some recent single crystal studies by Tawashi (12) with cholesterol monohydrate and by Mehta (13) with methylprednisolone show that under certain conditions single crystals of these substances of about 100-μ dimensions dissolve by some interfacially controlled process in aqueous media.

Small Particle Problems—Goyan (14) derived a relationship for the dissolution rate of a small spherical particle involving the surface renewal mechanism. In one form it may be written

$$G = \left[\frac{D}{a} + S^{1/2}D^{1/2}\right](C_s - C) \qquad \text{(Eq. 7)}$$

where a is the particle radius (equivalent volume sphere) and the other symbols have been defined. Goyan has suggested that Eq. 7 rather than Eq. 1 better describes the data (15) on the dissolution rate of salicylamide particles in water at high agitation rates.

Equation 7 nicely reduces to the purely diffusion controlled case when $S \to 0$ or when $a \to 0$, *viz.*,

$$G = \frac{D}{a}(C_s - C) \qquad \text{(Eq. 8)}$$

It is noteworthy (compare Eq. 8 with Eq. 1) that, for small particles, $h \simeq a$ even with *no* agitation.

For micron size particles at low to moderate agitation rates, Eq. 8 should be applicable if interfacial barrier effects are absent. The dissolution rate behavior of dibutyl phthalate droplets in water agreed very well with this theory (16).

If interfacial barrier effects are not negligible, a double-barrier relation may be written,

$$G = \frac{D}{a}\left[\frac{C_s - C}{1 + \frac{D}{ak_i}}\right] \qquad \text{(Eq. 9)}$$

which is identical to Eq. 4 when $a = h$.

Particle size distribution effects may be taken into account by selecting a particle size distribution function (17, 18) that is time dependent and by combining it with the appropriate Eqs. 7, 8, or 9. For example, if the particle size distribution may be expressed by the function $f(a)$, where a is a function of time and where $f(a)da$ is the number of particles between the sizes a and $a + da$, we may write for the total dissolution rate, J, of the suspension,

$$J(t) = \int_{a_s}^{a_e} f(a)G(a)da \qquad \text{(Eq. 10)}$$

where a_s and a_e are, respectively, the smallest and the largest particles in the distribution. If $f(a)$ is known by a particle size distribution measurement, then Eqs. 7, 8, or 9 may be employed for G to provide an equation for J explicit in time. This procedure was used employing Eq. 8 to analyze data on the dissolution rate of a steroid suspension in water (18).

Dissolution Rates with Simultaneous Solution Interactions Involving Additives in the Solvent—In many practical situations the dissolving drug may become involved in an acid–base reaction, in complex formation, or in some other kind of solubilization interaction. In these instances the three basic models (Fig. 1) still apply in a qualitative sense. However, detailed consideration of the move-

ment of all solution species becomes necessary, resulting in equations that are generally different from those for the one component problem.

As an illustrative example, let us choose the case where the dissolving molecule, A, reacts with an additive molecule, B, present in the solvent to form a complex, AB, according to $A + B = A \cdot B$, with

$$K = \frac{(A \cdot B)}{(A)(B)} \qquad \text{(Eq. 11)}$$

Assume that equilibrium is rapid compared to diffusion over distances of importance ("film" thickness, packet dimensions, etc.). This is a reasonable assumption for most acid–base reactions and for most interactions leading to complex formation. Assume also that no new phases may precipitate. Then the diffusion layer theory gives for this situation (19–21)

$$G = \frac{D_A}{h}\left[1 + \frac{D_B B_h}{D_A\left(A_0 + \frac{D_B}{D_{AB}K}\right)}\right](A_0 - A_h) \qquad \text{(Eq. 12)}$$

D_A, D_B, and D_{AB} are the diffusion coefficients for A, B, and AB. A_0 and A_h are the concentrations of A at $x = 0$ and $x = h$. B_h is the concentration of B in the solvent ($x \geq h$).

Physically the situation regarding the species leading to Eq. 12 may be described as follows. Species A is diffusing from $x = 0$, where A_0 = solubility of A, to $x = h$, where $A = A_h$. Species B diffuses in the opposite direction from $x = h$, where $B = B_h$, to $x = 0$. Along the way B complexes with A according to Eq. 11 and the complex $A \cdot B$ diffuses out along with free A in the same direction as A. The net effect is a "facilitation" of the transport of A into solution, resulting in the factor

$$\left[1 + \frac{D_B B_h}{D_A\left(A_0 + \frac{D_B}{D_{AB}K}\right)}\right]$$

multiplying the rate given by Eq. 1.

The Danckwerts theory does not give differential equations that can be solved analytically for the situation (19) involving this equilibrium between A, B, and $A \cdot B$. However, Olander has solved the special case, when $D_A = D_B = D_{A \cdot B} = D$, in which

$$G = S^{1/2}D^{1/2}\left[1 + \frac{B_h}{A_0 + \frac{1}{K}}\right](A_0 - A_h) \qquad \text{(Eq. 13)}$$

It is noteworthy that, when $D_A = D_B = D_{A \cdot B} = D$, the diffusion layer theory (Eq. 12) reduces to

$$G = \frac{D}{h}\left[1 + \frac{B_h}{A_0 + \frac{1}{K}}\right](A_0 - A_h) \qquad \text{(Eq. 14)}$$

As Olander points out (20), Eqs. 13 and 14 are identical except for the dependence on D and the hydrodynamics. It is further noteworthy that both Eqs. 13 and 14 reduce to Eqs. 1 and 2, respectively, if one notes that

$$(C_s - C) = (A_0 - A_h)\left[1 + \frac{B_h}{A_0 + \frac{1}{K}}\right] \qquad \text{(Eq. 15)}$$

where $C_s - C$ is the "total" concentration differential for A between the solid–solvent interface and the bulk solvent.

It follows from the above that, when all the diffusion coefficients are equal, the Noyes-Whitney law should apply regardless of whether the diffusion layer theory or the Danckwerts theory is appropriate. These conclusions are not restricted to the reaction, $A + B = A \cdot B$. Situations involving other kinds of equilibria have also been worked out (19–21). Because the diffusion coefficients of molecules and ions vary approximately as the cube root of the molecular weight, the Noyes-Whitney law should be frequently applicable as long as interfacial barrier effects or the precipitation of new phases are absent. Extensive experimental studies by Nelson (22, 23) and by Hamlin *et al.* (24) substantiate this.

Situations where significant deviations from the Noyes-Whitney law should occur, except when phase changes take place, are those involving either very small or very large diffusion coefficients. A case in point is the dissolution rate behavior of a basic amine drug in HCl solutions (25). Here the large diffusion coefficient of the HCl apparently caused the dissolution rate to be as much as 3 times greater than the Noyes-Whitney law predictions.

The studies by Desai *et al.* (10) on the initial dissolution rate behavior of benzocaine in aqueous polysorbate 80[2] solutions are particularly noteworthy. Their experiments carried out under constant hydrodynamic conditions provided data that could be used to simultaneously test the diffusion layer theory, the Danckwerts theory, and the Noyes-Whitney law. For this situation the diffusion layer theory gives the following equation (10, 26)

$$G = \frac{D}{h}C_s + \frac{D^1}{h}C^1_s \qquad \text{(Eq. 16)}$$

where D^1 is the diffusion coefficient of the micelle-

[2] Marketed as Tween 80 by Atlas Chemical Industries, Wilmington, Del.

solubilized drug and C_s^1 is the solubility increase due to solubilization. All other terms are the same as in Eq. 1.

In contrast to Eq. 16, Danckwerts theory (10) leads to the following equation for the dissolution rate of benzocaine in polysorbate solutions.

$$G = S^{1/2} \times \sqrt{(C_s + C^1_s)(DC_s + D^1C^1_s)} \quad \text{(Eq. 17)}$$

The symbols have the same meanings as before.

Finally, according to the Noyes-Whitney law, we have for this situation

$$G = \text{constant } x(C_s + C^1_s) \quad \text{(Eq. 18)}$$

The comparison of the experimental data with Eqs. 16, 17, and 18 is shown in Fig. 2. Clearly, in this example, the diffusion layer theory agrees best with the experimental data. Both Eqs. 17 and 18 show discrepancies with data that are far greater than the scatter of the data.

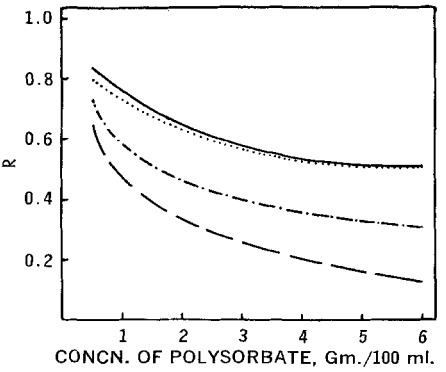

Fig. 2—Data and theory on the influence of polysorbate 80 solubilization on the dissolution rate behavior of benzocaine. R is ratio of rate in polysorbate solution to that without polysorbate (from Desai et al.). *Key: ———, experimental; · · · · · · · , diffusion layer theory; – · – · –, Danckwerts theory; – – – –, Noyes-Whitney theory.*

The reviewer believes that studies by Desai *et al.* represent the first clear-cut demonstration of mechanism differentiation. This technique should have extensive application in the future—particularly in studying the effects of hydrodynamic factors on mechanisms.

Some Comments on the Influence of Additives at the Interface—An interfacially adsorbing agent may help in increasing the dissolution rate. A surfactant may improve the wetting of the surface and effectively increase the available area (27, 28). It may also increase the interfacial rate constant k_i (Eq. 3) by assisting in the release of surface molecules through interfacial tension lowering.

Surface-active agents may play other roles. For example, the formation of a surface adsorbed layer of aliphatic long chain ammonium ions retards the dissolution rate of apatite crystals (29). Also it is expected on theoretical grounds (30) that for very water insoluble drugs ($C_s \lesssim 10^{-8}$ Gm. ml.$^{-1}$) the intrinsic rate of micellar solubilization of a drug may be very low, and the dissolution rate may be much slower than that predicted by Eq. 16. This might occur if, for example, the surfactant micelles have the same charge as the crystal surface (due to, say, the adsorbed surfactant), and the close approach of the micelle to the surface is improbable.

Dissolution Rates Involving Simultaneous Phase Changes—There have been a number of reports in the literature (31, 32) where the formation of a new surface phase was noted during the dissolution of the drug. Invariably the formation of such phases leads to slower dissolution rates than if it did not occur.

The physical model approach involving the consideration of simultaneous diffusion, chemical equilibria, and new phase precipitation has now been employed in a number of instances. The dissolution rate behavior in phosphate buffers of the sodium salt of a relatively water-insoluble weak acid drug was analyzed (33) by this technique. The data were found to be consistent with the model in which a surface coating of the weak acid was formed under certain conditions.

The pamoate salt of an amine drug forms a coating of pamoic acid during its dissolution in HCl solutions (32). Assuming that the diffusion of the protonated amine through this coating is rate determining, a model was constructed and compared to data (34).

The dissolution rate behavior of apatites is important because of its relation to bone and tooth mineral dynamics (35, 36). The possibility of dicalcium phosphate surface phase deposition during apatite dissolution in aqueous lactate buffers was considered (35). More recently (37, 38) the influence of the fluoride ion on the dissolution rate behavior of apatites has been examined by means of models involving surface phases of fluorapatite and CaF_2. The questions of what effects phosphate, calcium, and fluoride ions and pH have on these mechanisms are being answered by these models and the appropriate experiments.

Recently Bernardo (39) examined the problem of the anomalous dissolution rate behavior (40) of the polymorphs of methylprednisolone. A model was considered in which it was assumed that simultaneous surface reversion of polymorph II (the higher energy one) to polymorph I

occurred during the dissolution of polymorph II. This led to equations which were consistent with the experimental observation that at high stirring rates the dissolution rates for forms I and II were indistinguishable.

Dissolution Rates from Mixtures—Recently a mathematical analysis based on a physical model was presented (41) to describe the dissolution rate behavior of polyphase mixtures. For a two phase mixture in which the two components, A and B, do not interact in any way with each other, we may describe the model in the following way. Upon exposure to solvent, both components of the mixture should tend to dissolve at rates proportional to their solubilities and their diffusion coefficients. After some time, usually one of the phases would become depleted at the solid–liquid interface region because N_A/N_B may not be equal to $(D_A C_{SA})/(D_B C_{SB})$, where N_A and N_B are the original amounts of A and B in the mixture, D_A and D_B are the diffusion coefficients, and C_{SA} and C_{SB} are the respective solubilities. As a result, a surface layer is formed that is composed of only one of the phases. The three possible situations after zero time are illustrated in Fig. 3 for the one-dimensional, two-phase mixture problem.

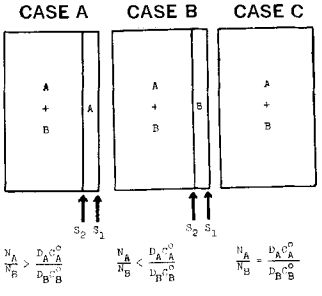

Fig. 3—Dissolution behavior of two-phase mixture of A *and* B. *In case* A, *phase* B *dissolves fast enough to leave a layer of pure* A *behind; in case* B, *the reverse is true; while in case* C, *dissolution rates of* A *and* B *are proportional to their relative amounts in the mixture.*

The following dissolution rate equations based on this model were derived[3] for each of the situations given in Fig. 3.

When

$$N_A/N_B > (D_A C_{SA})/(D_B C_{SB}),$$

$$\left.\begin{aligned} G_A &= \frac{D_A C_{SA}}{h} \\ \text{and} \\ G_B &= \frac{N_B}{N_A} G_A \end{aligned}\right\} \quad \text{(Eq. 19)}$$

When

$$N_A/N_B < (D_A C_{SA})/(D_B C_{SB}),$$

$$\left.\begin{aligned} G_B &= \frac{D_B C_{SB}}{h} \\ \text{and} \\ G_A &= \frac{N_A}{N_B} G_B \end{aligned}\right\} \quad \text{(Eq. 20)}$$

When

$$N_A/N_B = (D_A C_{SA})/(D_B C_{SB}),$$

$$\left.\begin{aligned} G_A &= \frac{D_A C_{SA}}{h} \\ \text{and} \\ G_B &= \frac{D_B C_{SB}}{h} \end{aligned}\right\} \quad \text{(Eq. 21)}$$

Equations 19–21 were applied (41) to the data on benzoic acid–salicylic acid tablet mixtures dissolving in water. Excellent agreement between data and theory was found in this case.

The above equations have a restriction in that they are quantitatively applicable in the steady state only. This requires that the C_{SA} and C_{SB} do not differ too greatly, say no more than a factor of 100 if, for example, the tablet thickness is on the order of millimeters.

If one of the components is very much less soluble than the other, *i.e.*, if either $C_{SA}/C_{SB} \to 0$ or ∞, then the problem reduces to that of solute release from an inert matrix which is discussed under *Drug Release Out of Matrix Systems*. The intermediate ranges have been treated also (41).

This two-phase model has been extended (41) to the case in which the components, A and B, may interact to form a complex, $A \cdot B$, in solution. The resulting equations for this case very nicely agreed with data on the dissolution rate behavior of caffeine–benzocaine mixtures in water. The same basic model was used (39) to derive equations that accurately described the dissolution rate behavior of mixtures of different crystalline forms of drugs. Experimental data with sulfathiazole forms I and II and with methylprednisolone polymorphs agreed well with the theory. The model was also employed in the re-examination of Nelson's data (42) on the dissolution rate behavior of benzoic acid–trisodium phosphate mixtures in water.

The simple nature of this model should allow extension to mixture problems involving more than two phases.

DRUG RELEASE OUT OF MATRIX SYSTEMS

General Considerations—This portion of the

[3] While the diffusion layer theory was used to express the dissolution rate behavior of the surface phases in Eqs. 19–21, the Danckwerts theory could have been used instead.

review[4] is concerned with drug release problems in which the external geometry of the dosage form remains essentially unchanged during drug release. Therefore, cases in this category include drug release from ointments, nondisintegrating tableted matrices, and perhaps from injections of the depot type. The discussion is directed toward the recent *in vitro* type work where attempts have been primarily made to understand the roles played by those factors associated with the dosage form itself. The question of whether conclusions from studies such as these truly reflect the *in vivo* availability is not under scrutiny here.

Special mention should be made that the most significant applications of the physical model approach in this area in recent times are those presented in the reports by T. Higuchi (44–47). These studies form the basis for much of the discussion here. They are also reflected in much of the thinking and research being done today on diffusion controlled release of drugs.

Diffusion Controlled Solute Release Obeying Fick's Law—When Fick's law is obeyed, the diffusion coefficient, D, is constant. For the one-dimensional diffusion of a single solute, we may write

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \qquad \text{(Eq. 22)}$$

Here C is the solute concentration at time t and at position x.

Various mathematical solutions to Eq. 22 have provided useful quantitative methods for studying the drug release problem. For planar diffusion to a perfect sink at $x = 0$ from a region, $0 \angle x \angle h$, at a uniform initial ($t = 0$) concentration of C_0, the solution to Eq. 22 is (45, 48–50)

$$Q = hC_0\left[1 - \frac{8}{\pi^2}\sum_{m=0}^{\infty} \times \frac{1}{(2m+1)^2}\exp.\left(\frac{-D(2m+1)^2\pi^2 t}{4h^2}\right)\right] \qquad \text{(Eq. 23)}$$

where Q = amount of drug released to the sink per unit area. It can be shown (51) that Eq. 23 may be approximated rather well by Eq. 24 up to about 30 to 50% drug release,

$$Q = 2C_0\left(\frac{Dt}{\pi}\right)^{1/2} \qquad \text{(Eq. 24)}$$

where Eq. 24 is the solution to the case for h at infinity.

Figure 4 shows how the drug concentration profiles may change with time in the region, $0 < x < h$. It is noteworthy that the slopes of these curves at $x = 0$ give the rate of release at the various times, *i.e.*,

$$\text{rate} = \frac{dQ}{dt} = D\left(\frac{dC}{dx}\right)_{x=0} \qquad \text{(Eq. 25)}$$

and may be obtained by simply differentiating Eqs. 23 or 24 with times.

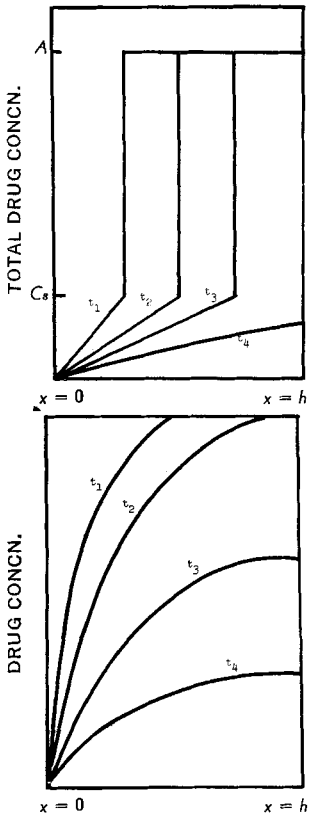

Fig. 4—Concentration profiles for the two situations during drug release to a perfect sink. Solid in matrix (top); solution in matrix (bottom).

It can be seen that if D is known we may easily predict the release rate behavior by means of Eqs. 23–25. While D may always be determined experimentally, it is of interest from the mechanism standpoint to consider the various theoretical methods for predicting D for the different situations.

First of all, there is the well known Stokes-Einstein relation,

$$D = \frac{kT}{6\pi na} \qquad \text{(Eq. 26)}$$

where k is the Boltzmann constant, T is temperature, n is the viscosity of the matrix, and a is the hydrodynamic radius of the diffusing drug molecule. This equation is practically quantitatively applicable when the matrix is composed

[4] The readers are referred to an earlier review (43) on this subject for background.

of solvent molecules that are comparable to or smaller than the diffusing drug molecules so that the microscopic viscosity is close to the macroscopic viscosity. The case when the situation is reversed, *i.e.*, drug diffusion out of polymer solutions or gels, will be discussed later.

The meaning of D when the matrix is heterogeneous has received much attention recently (51–57). A number of approximate relationships have been considered and compared with experimental data.

When the matrix is a suspension or an emulsion, the effective diffusion coefficient, D_e, must be used instead of D in Eqs. 23 and 24. D_e may be obtained from mixture formulas based on analogous electrostatic situations (52, 58–61). Equations 27 and 28 are, respectively, the Bruggeman (59) and the Maxwell-Rayleigh-Lorentz-Clausius-Mosotti-Wagner-Wiener relations for the effective permeability constant, P_e, for a two-phase system consisting of an internal phase of spherical particles dispersed in a continuous phase.

$$\left(\frac{P_e - P_i}{P_c - P_i}\right)\left(\frac{P_c}{P_e}\right)^{1/3} = V_c \qquad \text{(Eq. 27)}$$

and

$$\frac{P_e - P_c}{P_e + 2P_c} = \left(\frac{P_i - P_c}{P_i + 2P_c}\right) V_i \qquad \text{(Eq. 28)}$$

Here the P's are the permeability constants and the V's are the volume fractions of the phases. The subscripts i and c refer to the internal phase and the continuous phase, respectively. Equations 27 and 28 are the two most popular mixture formulas discussed in the literature. Other formulas are available (52), including those which take into account shape effects and the effects of a "coating" of the internal phase. Higuchi (52) considered a semiquantitative mixture relationship that correlated well with literature data.

Now D_e may be calculated (52, 53) with either Eqs. 27 or 28 if we note further that

$$D_e = \frac{P_e}{K_e} \qquad \text{(Eq. 29)}$$

and

$$K_e = K_i V_i + V_c \qquad \text{(Eq. 30)}$$

where K_i is the partition coefficient of the solute between the internal and the external phases.

Koizumi (53) has tested Eqs. 23 and 24 and 27–30 with data on pyridine release from water-in-oil emulsions into an aqueous sink. Agreement of both Eqs. 27 and 28 with data was satisfactory. However, Koizumi's more critical tests were carried out with solute mixtures of pyridine and pyridine hydrochloride to be discussed later.

Higuchi analyzed data on drug release from oil-in-water emulsions. Good consistency of the data (62) with Eqs. 23 and 24 and with the Higuchi mixture formula (52) was found in this instance.

Drug release from inert plastic matrices initially saturated with a drug solution of concentration, C_0, may follow equations similar to Eqs. 23 and 24. Here, for example, instead of Eq. 24 we may write (54)

$$Q = 2\epsilon C_0 \left(\frac{Dt}{\tau\pi}\right)^{1/2} \qquad \text{(Eq. 31)}$$

where $\epsilon \equiv V_c$ = porosity, and τ = tortuosity. The quantity τ may be calculated by means of Eqs. 27 or 28 if the internal phase particles are spherical and impermeable. Thus, if $V_i = V_c = 0.5$, we get $P_e = 0.35P_c$ and $\tau = 1.43$, according to Eq. 27, and $P_e = 0.40P_c$ and $\tau = 1.25$ according to Eq. 28. The Higuchi mixture formula (52) gives $P_e = 0.35P_c$ and $\tau = 1.43$ for this situation.

Desai *et al.* (55) employing Eq. 31 found experimental τ values mainly in the range of 1.3 to 3.0 for polyvinyl chloride compressed tablet matrices when $V_i \simeq 0.60$ to 0.70. This is in very good agreement with the expected values of about 1.4 to 2.0 according to Eqs. 27, 28, and the Higuchi formula (52). When polyethylene plastic tablet matrices were used (55),[5] higher τ values of 6 to 10 were found. This difference in general behavior has been explained (55) on the basis of the much greater plasticity of the polyethylene and the much greater elasticity of the polyvinyl chloride influencing the structures of their respective matrices when the materials are subjected to compaction.

It is worthwhile to point out that both Eqs. 27 and 28 lead to Eq. 32 when V_i is small.

$$D_e = \frac{D_1}{V_c + K_i V_i}\left[1 + 3V_i \frac{K_i D_i - D_c}{K_i D_i + 2D_c}\right] \qquad \text{(Eq. 32)}$$

This equation is not only useful in estimating accurate values of D_e for dilute suspensions and emulsions but also when the matrix is a dilute polymer solution or a gel.

If a gel forming polymer does not bind the drug but acts only to provide some "mechanical" resistance to drug diffusion, Eq. 22 becomes

$$D_e = \frac{D_1}{V_c}\left(1 - \frac{3}{2} V_i\right) \qquad \text{(Eq. 33)}$$

Equation 33 appears to accurately describe (63)

[5] See also Desai, S. J., Ph.D. thesis, University of Michigan, Ann Arbor, Mich., 1966.

the diffusion of sodium and cesium ions in aqueous agar gels.

Suppose a viscous but dilute polymer solution is the matrix with the polymer binding the drug according to a linear law, *i.e.*,

$$M = k_0 C_c \qquad \text{(Eq. 34)}$$

where M = amount of drug bound per unit volume of polymer, C_c = concentration of the drug in the "continuous" phase, and k_0 = constant. Then Eq. 32 should be used with $D_i = 0$ and

$$K_i = \frac{M}{C_c} \qquad \text{(Eq. 35)}$$

If the binding does not obey Eq. 34, then Fick's law will not be obeyed and other methods must be considered. (See under *Diffusion Controlled Release Not Obeying Fick's Law.*)

If a suspension type matrix with $D_i = 0$ is able to adsorb drug according to a linear relation similar to Eq. 34, then equations analogous to 34 and 35 may be used (43) with Eqs. 32, 27, or 28 and Q calculated with Eqs. 23 or 24. Again if the adsorption isotherm is not linear, then the mathematics cannot be handled analytically and numerical methods become necessary. (See under *Diffusion Controlled Release Not Obeying Fick's Law.*)

In all of the preceding discussion involving Eqs. 23 and 24 and the mixture relations, Eqs. 27–30, we have assumed that local equilibrium (52) is maintained, *i.e.*, partitioning or binding occurs rapidly. If local equilibrium is not maintained the equations may not be correct. In this connection, Koizumi (64) has theoretically treated the case where the rate of oil–water interfacial transport becomes important in influencing the rate of drug release from emulsions. It appears safe to state (52) that in most situations the assumption of local equilibrium will be a good one for the small particle sizes normally involved in most emulsions.

Diffusion Controlled Release Not Obeying Fick's Law—For many situations in drug release rate problems, Eq. 22 alone cannot describe the process. In the following we shall consider some of those cases that have been studied.

Diffusion controlled drug release when the drug is dispersed as a solid in a matrix was first studied by Higuchi (45–47). If the matrix is a homogeneous liquid, the one-dimensional theory (planar release) gives

$$Q = \sqrt{D(2A - C_s)C_s t} \qquad \text{(Eq. 36)}$$

where D is the drug molecule diffusion coefficient in the matrix, A is the total amount of drug present in the matrix per unit volume, and C_s is the solubility of the drug in the matrix substance.

If the matrix is heterogeneous and diffusion takes place in the intergranular pores, *e. g.*, drug dispersed in an inert plastic matrix with aqueous pores, instead of Eq. 36 we get

$$Q = \sqrt{\frac{D\epsilon}{\tau}(2A - \epsilon C_s)C_s t} \qquad \text{(Eq. 37)}$$

where D is the diffusion coefficient in the solvent, ϵ = porosity of the matrix, and τ, as before, is the tortuosity.

Figure 4 shows the drug concentration profiles in the matrix at different times in accordance with the theory leading to Eqs. 36 and 37. The concentration gradients from the solid-drug boundary ($x = s$) to the matrix boundary ($x = 0$) are linear as long as $2A \gg C_s$ (for Eq. 36) or $\epsilon C_s \ll 2A$ (for Eq. 37) which is the key assumption in the derivation of these two equations.

Desai *et al.* (54, 55) and Singh *et al.* (56) have made extensive experimental and further theoretical studies of Eq. 37. In their approach several different plastics and several drugs were involved. They independently determined the appropriate D (diffusion cell experiments), the solubility C_s, the appropriate ϵ (two ways), and τ by an independent experiment with the same matrix utilizing Eq. 31. Under the expected conditions (good penetration of the pores and when $\epsilon C_s \ll 2A$) Eq. 37 agreed quantitatively with the experimental data over a wide range of variables.

These investigators also showed (55) that in some instances (polyethylene matrices without surfactant in the solvent) wetting may be poor and therefore the effective τ values may be in the tens of thousands. More recent studies (56) show that in these cases the diffusion controlled model probably fails, and the release rate is determined by the channel penetration rate of the solvent. In other instances (polyvinyl chloride matrices in water) wetting was efficient, but air removal from the matrix significantly altered the drug release pattern.

Desai *et al.* (55) have extended Eq. 37 to take into account the hydrodynamic flow of the solvent in the pores. This refinement was necessary to explain the behavior of moderately soluble solutes.

These investigators have also further extended the same model taking into account the effect of a concentration dependent D and the possibility of linear binding of the drug onto the plastic during the release of drug.

Very recently Singh *et al.* (56) extended the theory to describe the release from mixtures of drugs in an inert matrix. They have derived equations which also take into account the possibility of complex formation between the

components of the phases. The theory is being used to evaluate the data on mixtures currently being gathered in these laboratories.

A very important situation where Eq. 22 fails is in the release of drugs when the partition coefficient, K_i (see Eqs. 30 and 35), is not constant but is dependent on the drug concentration. K_i may vary with drug concentration if (*a*) the drug is a weak acid or a weak base and therefore K_i would be pH dependent, (*b*) the drug molecule associates as carboxylic acids do in mineral oil, or (*c*) the drug binds or complexes according to some nonlinear law, *e.g.*, Langmuir binding, to some component in the system.

Koizumi (53) has investigated the theoretical and experimental methods for handling this situation. By applying Boltzmann's method (48, 49) and employing Eqs. 27 and 28, he numerically computed the drug release rates from emulsions into aqueous sinks when Eq. 37

$$\frac{\partial C}{\partial t} = \frac{\partial}{\partial x}\left(D\frac{\partial C}{\partial x}\right) \qquad \text{(Eq. 37)}$$

rather than Eq. 22 was obeyed. The theoretical predictions agreed very well with experimental data on the release of solute from pyridine–pyridine hydrochloride solute mixtures in water-in-oil emulsions. As expected, the Bruggeman Eq. 27 agreed better with the data than Eq. 26 over a wide range of the solute mixture ratio. The agreement of theory with data was particularly significant because all parameters entering into the theory were determined independently of the rate experiments themselves.

Koizumi also investigated theoretically and experimentally the effect of a membrane (*e.g.*, cellophane) separating the emulsion from the aqueous sink. This is an important practical factor in many *in vitro* experimental methods. This modification gave better agreement of the data with theory under certain expected conditions.

The reviewer believes that with the use of such numerical methods in conjunction with modern computers there is practically no problem that is inaccessible to theoretical analysis. There will be many examples of such attacks on diffusion problems in the future.

REFERENCES

(1) Wurster, D. E., and Taylor, P. W., *J. Pharm. Sci.*, **54**, 169(1965).
(2) Wagner, J. G., *ibid.*, **50**, 359(1961).
(3) Nernst, W., and Brunner, E., *Z. Physik. Chem.*, **47**, 52(1904); **47**, 56(1904).
(4) Danckwerts, P. V., *Ind. Eng. Chem.*, **43**, 1460(1951).
(5) Toor, H. L., and Marchello, J. M., *A. I. Ch. E. J.*, **4**, 97(1958).
(6) Huang, C. J., and Kuo, C. H., *ibid.*, **9**, 161(1965); **11**, 901(1965).
(7) Johnson, A. I., and Huang, C. S., *ibid.*, **2**, 412(1956).
(8) Hanratty, T. J., *ibid.*, **2**, 359(1956).
(9) Noyes, A., and Whitney, W., *J. Am. Chem. Soc.*, **19**, 930(1897); Noyes, A., and Whitney, W., *Z. Physik. Chem.*, **23**, 689(1897).
(10) Desai, S. J., Singh, P., Simonelli, A. P., and Higuchi, W. I., *J. Pharm. Sci.*, unpublished data.
(11) Wurster, D. E., and Taylor, P. W., *ibid.*, **54**, 670 (1965).
(12) Tawashi, R., and Higuchi, W. I., unpublished data.
(13) Mehta, S. C., and Higuchi, W. I., unpublished data.
(14) Goyan, J. E., *J. Pharm. Sci.*, **54**, 645(1965).
(15) Niebergall, P. J., Milosovich, G., and Goyan, J. E., *ibid.*, **52**, 236(1963).
(16) Higuchi, W. I., *ibid.*, **53**, 405(1964).
(17) Higuchi, W. I., and Hiestand, E. N., *ibid.*, **52**, 67 (1963).
(18) Higuchi, W. I., Rowe, E. L., and Hiestand, E. N., *ibid.*, **52**, 162(1963).
(19) Higuchi, W. I., Parrott, E. L., Wurster, D. E., and Higuchi, T., *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 376(1958).
(20) Olander, D. R., *A. I. Ch. E. J.*, **6**, 233(1960).
(21) Higuchi, W. I., Nelson, E., and Wagner, J. G., *J. Pharm., Sci.*, **53**, 333(1964).
(22) Nelson, E., *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 607 (1957).
(23) *Ibid.*, **48**, 96(1959).
(24) Hamlin, W. E., Northam, J. I., and Wagner, J. G., *J. Pharm. Sci.*, **54**, 1651(1965).
(25) Hamlin, W. E., and Higuchi, W. I., *ibid.*, **55**, 205 (1966).
(26) Higuchi, W. I., *ibid.*, **53**, 532(1964).
(27) Wurster, D. E., and Seitz, J. A., *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 335(1960).
(28) Taylor, P. W., and Wurster, D. E., *J. Pharm. Sci.*, **54**, 1654(1965).
(29) Roseman, T. J., and Higuchi, W. I., to be published.
(30) Higuchi, W. I., unpublished data.
(31) Levy, G., and Procknal, J. A., *J. Pharm. Sci.*, **51**, 294 (1962).
(32) Morozowich, W., Chulski, T., Hamlin, W. E., Jones, P. M., Northam, J. I., Purmalis, A., and Wagner, J. G., *ibid.*, **51**, 933(1962).
(33) Higuchi, W. I., Mir, N. A., Parker, A. P., and Hamlin, W. E., *ibid.*, **54**, 8(1965).
(34) Higuchi, W. I., and Hamlin, W. E., *ibid.*, **52**, 575 (1963).
(35) Higuchi, W. I., Gray, J. A., Hefferren, J. J., and Patel, P. R., *J. Dental Res.*, **44**, 330(1965).
(36) Higuchi, W. I., Patel, P. R., and Hefferren, J. J., *J. Pharm. Sci.*, **54**, 587(1965).
(37) Mir, N. A., and Higuchi, W. I., to be published.
(38) Nelson, K. G., and Higuchi, W. I., to be published.
(39) Higuchi, W. I., Mehta, S. C., and Bernardo, P. D., *J. Pharm. Sci.*, **56**, 200(1967).
(40) Hamlin, W. E., Nelson, E., Ballard, B. E., and Wagner, J. G., *ibid.*, **51**, 432(1962).
(41) Higuchi, W. I., Mir, N. A., and Desai, S. J., *ibid.*, **54**, 1405(1965).
(42) Nelson, E., *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 300 (1958).
(43) Higuchi, W. I., *Proc. Am. Assoc. Colleges Pharm. Teachers' Seminar*, **1961**, 13.
(44) Higuchi, T., "Permeation of Mechanical Barriers by Chemical Agents," Medical Laboratories contract report No. 32, contract No. DA-18-108-CML-2576, May 1954, Chemical Corps Medical Laboratories, Army Chemical Center, Md.
(45) Higuchi, T., *J. Soc. Cosmetic Chemists*, **11**, 85(1960).
(46) Higuchi, T., *J. Pharm. Sci.*, **52**, 1145(1963).
(47) *Ibid.*, **50**, 874(1961).
(48) Barrier, R. M., "Diffusion In and Through Solids," Cambridge University Press, London, England, 1951.
(49) Jost, W., "Diffusion in Solids, Liquids, and Gases," Academic Press Inc., New York, N. Y., 1952.
(50) Crank, J., "Mathematics of Diffusion," Oxford University Press, London, England, 1964.
(51) Higuchi, W. I., *J. Pharm. Sci.*, **51**, 802(1962).
(52) Higuchi, W. I., and Higuchi, T., *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 598(1960).
(53) Koizumi, T., and Higuchi, W. I., *J. Pharm. Sci.*, unpublished data.
(54) Desai, S. J., Simonelli, A. P., and Higuchi, W. I., *ibid.*, **54**, 1495(1965).
(55) Desai, S. J., Singh, P., Simonelli, A. P., and Higuchi, W. I., *ibid.*, **55**, 1230(1966).
(56) Singh, P., Desai, S. J., Simonelli, A. P., and Higuchi, W. I., *ibid.*, unpublished data.
(57) Schwartz, J., Simonelli, A. P., and Higuchi, W. I., to be published.
(58) Fricke, H., *Physiol. Rev.*, **24**, 575(1924).
(59) Bruggeman, D. A. G., *Ann. Physik.*, **24**, 636(1935).
(60) Hanai, T., Koizumi, N., and Gotoh, R., *Kolloid Z.*, **167**, 41(1959).
(61) Higuchi, W. I., *J. Phys. Chem.*, **62**, 649(1958).
(62) Patel, K. C., Banker, G. S., and DeKay, H. G., *J. Pharm. Sci.*, **50**, 300(1961).
(63) Slade, A. L., Cremers, A. E., and Thomas, H. C., *J. Phys. Chem.*, **70**, 2840(1966).
(64) Koizumi, T., to be published.