

# Effects of Interacting Colloids on Transport Rates

By W. I. HIGUCHI

A theoretical analysis along with the resulting equations pertinent to the qualitative and quantitative aspects of the dissolution and deposition of solid materials in colloidal solutions and transport of solutes across diffusional barriers is presented.

**I**N A NUMBER of situations involving diffusion of a solute, colloidal agents present may be expected to play important roles, such as dissolution and deposition of solid materials in colloidal solutions and transport of solutes across diffusional barriers, physiological or otherwise.

A survey of the literature has shown that the general problem has not received much theoretical consideration. Because of the frequent occurrence of systems involving colloids, an analysis of this problem appeared to be worthwhile. This report gives such an analysis and the resulting equations, which are relatively simple, should be useful both qualitatively and quantitatively in discussing all problems of transport in which colloids are suspected of being important.

## NO COLLOID CASE

Figure 1 illustrates the problem of the diffusional transport of a single solute at a concentration  $C=C_0$  in compartment I to compartment II where the solute concentration is  $C=C_A$ . We assume that the mixing rates in compartments I and II are sufficiently rapid, so that the rate will be controlled entirely by the barrier in the region  $0 \leq X \leq h$ , where  $X$  is the coordinate and  $h$  is the barrier thickness. Also convection in the barrier is assumed to be negligible.

From the biopharmaceutical standpoint, the barrier may be a membrane, or it may represent the diffusion layer controlling the deposition or dissolution rate of solid materials *in vitro* or *in vivo*. In the latter cases, one of the compartments will be a solid phase.

It is convenient to discuss problems of this type in two portions—the nonsteady state and the steady state.

For the particular case  $C=C_0$ ,  $C=C(x)=0$ , and  $C=C_h=0$  at time = 0, the Fick's law treatment gives (1)

$$\tau = \frac{h^2}{6D} \quad (\text{Eq. 1})$$

for the lag time, where  $D$  is the diffusion coefficient of the solute in the barrier. The lag time corresponds roughly to the initial nonsteady state period during which simultaneous transfer of the solute through the barrier and concentration buildup of the solute in the barrier is taking place. In this case  $\tau$  defines the nonsteady state period. Equation 1 assumes that at all times the total amount of

solute in the barrier phase is small compared to the amounts of solute in compartment I, and that the diffusion coefficient,  $D$ , is independent of concentration in the range of  $C(x)$  encountered in the barrier. In most practical situations involving simple diffusion these assumptions are valid.

At times large compared to  $\tau$ ,  $\partial C(x)/\partial t = 0$  throughout the barrier, and we have the steady state diffusion case. We may then write for the diffusional transport rate (1)

$$G = \frac{D(K_I C_0 - K_{II} C_h)}{h} \quad (\text{Eq. 2})$$

where  $K_I$  and  $K_{II}$  are the equilibrium partition coefficients,  $K_I =$  concentration of solute in barrier/concentration of solute in I and  $K_{II} =$  concentration of solute in barrier/concentration of solute in II.

When  $K_I C_0 \gg K_{II} C_h$

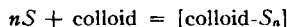
$$G = \frac{D K_I C_0}{h} \quad (\text{Eq. 3})$$

Thus, according to Eq. 3 the transport rate of a drug across a lipid barrier separating two aqueous compartments would be directly proportional to the lipid-water partition coefficient, and the initial diffusion controlled dissolution rate of a solid in pure solvent would be proportional to the solubility,  $K_I C_0$ . As we shall see below, these conclusions may frequently be in serious error when applied to cases involving interacting colloids.

## STEADY STATE DIFFUSION WITH COLLOIDS

In most solute dissolution and deposition problems and in many membrane transport problems the steady state considerations alone should explain the behavior of the system.<sup>1</sup> Therefore, while the nonsteady state case will be considered briefly later, let us first examine the steady state situation in detail.

The steady state treatment here differs from that (2) in which the interaction of the solute with reactant results in only one or a few new products. Here one must consider the possibility of a very large number of "species" resulting from the reactions



where  $S$  is a solute molecule and  $n$  may go from unity to a very large number. For the moment, let us assume that there will be only a single species of free colloid. Also we assume that the barrier (or diffusion layer) is pure liquid, except for the solute and colloid.

In Fig. 2 we have broken down the barrier into

<sup>1</sup> The criteria for this is that we are primarily interested in transport involving amounts of solute much larger than those present in the barrier at any time and that the times for appreciable changes in solute concentration in each of the compartments are large compared to the lag time of the barrier.

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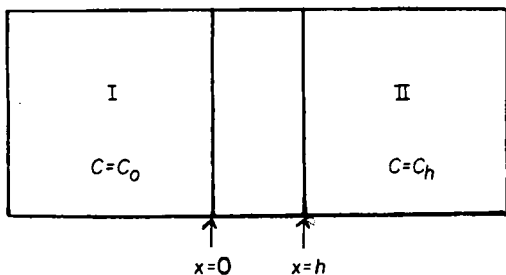


Fig. 1.—Illustration of the problem of diffusion across barrier in the region  $0 < x < h$ .

sublayers of thickness,  $\delta x$ , so that  $\delta x \ll h$ . Now assume that the interaction between the colloid and solute occurs rapidly enough so that in the element of volume  $\delta x$  there is equilibrium<sup>2</sup> between the bound and free solute. The amount of solute bound per mole of colloid particles,  $C_b$ , will then be a function only of the free solute concentration,  $C$ , at constant temperature and pressure. As is well known,  $C_b$  generally increases with increasing  $C$  and goes to zero when  $C$  goes to zero.

Steady state requires that no net changes in solute or colloid concentration occur in any element of volume of the barrier with time. This means that what comes into element from one side must leave at the same rate from the other side. Focusing our attention on the plane at  $x$  and the two adjacent elements of volume, we see that the rate of diffusion of the colloid across the plane  $x$  will be

$$G_c = \frac{D_c(x) [M(x - 1/2\delta x) - M(x + 1/2\delta x)]}{\delta x} \quad (\text{Eq. 4})$$

where  $D_c(x)$  is the average diffusion coefficient for the colloid particle over the two elements of volume and  $M(x - 1/2\delta x)$  and  $M(x + 1/2\delta x)$  are the average concentrations of the colloid in the two elements.

Now the rate of diffusion of total solute across the plane at  $x$  will be

$$G_s = \frac{D_s(x) [C(x - 1/2\delta x) - C(x + 1/2\delta x)]}{\delta x} + \frac{D_s(x) [C_b(x - 1/2\delta x)M(x - 1/2\delta x) - C_b(x + 1/2\delta x)M(x + 1/2\delta x)]}{\delta x} \quad (\text{Eq. 5})$$

where  $D_s$  is the diffusion coefficient of the free solute in the medium,  $C(x - 1/2\delta x)$  and  $C(x + 1/2\delta x)$  are the average free solute concentrations in the two elements, and  $C_b(x - 1/2\delta x)$  and  $C_b(x + 1/2\delta x)$  are the average amounts of the bound solute per mole of colloid in the two elements. The first term in Eq.

<sup>2</sup> Most interactions of interest to us—solubilization and physical adsorption—generally are expected to have small free energies of activation. For these cases, the rate of equilibration would be expected to be determined by how rapidly the free solute molecules will diffuse to or away from the colloid particle in question. The corresponding equilibration times then can be shown to be of the order of  $Ka^2/D_s$ , where  $a$  is of the order of the dimensions of the colloid particle,  $D_s$  is the solute diffusion coefficient, and  $K$  is the colloid-solvent distribution coefficient, treating the colloid as a phase. For commonly occurring values of  $K$  and  $a$ , these times are indeed generally much smaller than the barrier lag times to be discussed later—unless the barrier thickness,  $h$ , is the order of the colloid particle size. This means that there may not be equilibrium for a colloid particle having traveled distances smaller than  $L = a(KD_c/D_s)^{1/2}$ , where  $D_c$  is the diffusion coefficient for the colloid particle; but if  $L$  is small compared to  $h$ , this should be negligible.

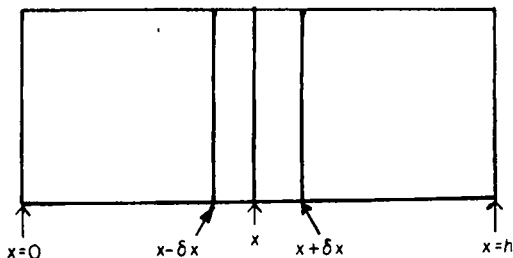


Fig. 2.—Consideration of barrier elements in the region  $0 < x < h$ . (See text for explanation.)

5 is the diffusion rate of the free solute across plane  $x$ , and the second term<sup>3</sup> is the rate of solute transport by the "carrier" mechanism.

In the case  $\delta x \rightarrow 0$  the above equations may be approximated by

$$G_c = D_c(x) \left( \frac{dM}{dx} \right)_x \quad (\text{Eq. 6})$$

and

$$G_s = D_s(x) \left( \frac{dC}{dx} \right)_x + D_s(x) \left( \frac{d[C_b M]}{dx} \right)_x \quad [\text{Eq. 7}]$$

Equation 7 may also be

$$G_s = D_s(x) \left( \frac{dC}{dx} \right)_x + D_s(x) \left[ C_b \frac{dM}{dx} + M \frac{dC_b}{dx} \right]_x \quad (\text{Eq. 8})$$

It is worthwhile to point out that Eq. 8 shows that even when  $G_c = 0$ , *i.e.*, no net diffusion of the colloid, there may be a contribution to solute diffusion by the colloid. This is an important special case discussed below.

**Special Case of  $G_c = 0$ ,  $D_c$  and  $D_s$  Independent of  $C$ .**—This case would apply to the many situations in which there is no net transfer of the colloid itself. Thus, in the dissolution or deposition of a solid the colloid must not be a part of the solid, but acts only as a "carrier" in the solution phase. The assumption of constant  $D_s$  would be a good one for dilute solutions (no solute-solute interactions). For  $D_c$  to be constant, it would be necessary that the size

(hydrodynamic radius) of the colloid be relatively insensitive both to the colloid concentration and to the amount of solute bound in the range of  $C$  encountered in the barrier (or diffusion layer). If the colloid is a flexible chain organic polyelectrolyte, if the organic solute is an ion with opposite charge, and if the ionic strength of the medium is low, this assumption may be very poor because the extent of expansion of the polyelectrolyte-solute complex may be very sensitive (3) to the degree of binding. On the other hand, if the colloid is relatively rigid or, if a micelle does not swell appreciably with increased

<sup>3</sup> This assumes that the bound solute is transported without loss or gain from one element to the next. Thus,  $\delta x$  must be taken small compared to  $L = a\sqrt{KD_c/D_s}$  (see Footnote 2), but large compared to Brownian motion distances. This can be done because the latter are much smaller than  $L$ . However,  $C_b$  now must be interpreted as both a space average (over  $\delta x$ ) and a number average (over different extents of equilibration of bound and free solute).

binding and if intercolloidal interactions are negligible,  $D_c$  may not vary much.

For this case Eq. 7 becomes

$$G_s = D_s \frac{dC}{dx} + D_c M \frac{dC_b}{dx} \quad (\text{Eq. 9})$$

Integration over the boundary conditions consistent with Fig. 1 then gives

$$G_s = \frac{D_s}{h} [K_1 C_0 - K_2 C_h] + \frac{D_c M}{h} [K_1 C_{b0} - K_2 C_{bh}] \quad (\text{Eq. 10})$$

where  $K_1$ ,  $K_2$ , and  $D_s$  refer to the solvents<sup>4</sup> in the two compartments and the barrier as before.  $C_{b0}$  and  $C_{bh}$  are the values for  $C_b$  at  $x = 0$  and  $x = h$ , respectively.

For two reasons Eq. 10 shows that the conclusions following Eq. 3 may not apply to situations involving colloids. First,  $D_c$  may be much smaller<sup>5</sup> than  $D_s$ . Second, the binding function  $C_b$  may not be linear with respect to  $C$ ; therefore,  $C_{b0} - C_{bh}$  may not be proportional to  $C_0 - C_h$ .

An extreme example of the first may be obtained from the studies of Wurster and Polli (6). From their experiments on the effect of Norite A on the dissolution rate of benzoic acid, these investigators pointed out that the adsorbent did not influence the dissolution rate as long as  $C_h \ll C_0$ ; *i.e.*, only free solute contributed to the transport rate under these conditions. Equation 10 is consistent with these conclusions if we note that  $D_c$  in this case was several orders of magnitude smaller than  $D_s$ . This more than offset the effect of the factor ( $MC_{b0}$ ) which may have otherwise increased the dissolution rate significantly.

Recent studies (7) on the dissolution rate of dibutyl phthalate droplets in normal saline containing 0.10% polysorbate<sup>6</sup> 20 show that the rate is at least 1 order of magnitude slower than predicted by solubility data. These observations are consistent with the formation of highly swollen micelles or "microemulsions" that diffuse slowly.

It is of interest to note that the above point concerning nonlinearity of rates with respect to  $C_0 - C_h$  leads to equations which have been able to describe the phenomenon of "facilitated" diffusion (8) in biological membranes. If the function,  $C_b$ , is assumed to be of the Langmuir type, *i.e.*

$$C_b = \frac{k_1 C}{1 + k_2 C}$$

where  $k_1$  and  $k_2$  are the conventional constants, then Eq. 10 becomes

<sup>4</sup> The local heterogeneous nature of the medium due to the presence of the colloid may be ignored for present purposes if the colloid concentration is low (a few per cent or so). Actually the permeability constant  $P = D_s K_1$  in Eq. 10 should be  $D_m K_m$ , where  $D_m$  is the effective diffusion coefficient of the solute in the colloid solution, and  $K_m$  is the partition coefficient for the compartment I phase and the colloid solution. However,  $D_s K_1$  and  $D_m K_m$  do not differ much for dilute solutions (4). For nonsteady state considerations, this matter must be taken into account because  $D_m$  may be much smaller than  $D_s$ , even though  $D_s K_1 \approx D_m K_m$ .

<sup>5</sup> By about one order of magnitude for high molecular weight macromolecules (3) and micelles (5) and perhaps by two to three orders of magnitude when larger colloidal agents are involved. This follows from the Stokes-Einstein relation,  $D_c = kT/6\pi\eta a$ , where  $k$  is the Boltzmann constant,  $T$  is absolute temperature,  $a$  is the hydrodynamic radius of the colloid, and  $\eta$  is viscosity.

<sup>6</sup> Marketed as Tween 20 by the Atlas Powder Co., Wilmington, Del.

$$G_s = \frac{D_s}{h} (K_1 C_0 - K_2 C_h) + \frac{D_c M}{h} \left( \frac{K_1 k_1 C_0}{1 + k_2 C_0} - \frac{K_2 k_1 C_h}{1 + k_2 C_h} \right) \quad (\text{Eq. 11})$$

The expression in which only the second term of Eq. 11 is important has been employed to explain the transport of sugars through membranes (8).

**Other Steady State Cases.**—Let us briefly consider other possible situations of interest which follow from the general Eqs. 7 and 8. If in a solid deposition process the colloid is deposited to some extent along with the solute, then the  $dM/dx$  term will contribute toward a greater rate. Similarly, the dissolution rate of a solid material containing an interacting colloid will be greater by this term when other conditions (solute solubility,  $C_h$ , colloid concentration in solution) remain the same. In both of these instances, if the solid composition and solubilities are known, Eq. 8 may be integrated to give an equation analogous to Eq. 10.

As Eq. 7 applies to the single colloid species problem, it will be necessary to write the following equation for the general case

$$G_s = D_s \frac{dC}{dx} + \sum_i D_{ci} \frac{d[C_{bi} M_i]}{dx} \quad (\text{Eq. 12})$$

and if ( $dM_i/dx$ ) = 0 for all  $i$ , *i.e.*, no net colloid transport, we obtain

$$G_s = D_s \frac{dC}{dx} + \sum_i D_{ci} M_i \left( \frac{dC_{bi}}{dx} \right) \quad (\text{Eq. 13})$$

Therefore, if a mixture of colloidal particles is present, Eq. 13 states that the importance of the particular species in transport is directly proportional to its concentration, diffusion coefficient, and the gradient of its solute binding. On the basis of Eq. 13 one would expect that, for example, deposition of cholesterol in the human body would not be greatly facilitated by high cholesterol levels if most of the cholesterol is distributed among large particles in the physiological fluids, but would be if the solute is bound to the smaller molecules present. Also the *in vivo* release of drugs by dissolution in the gastrointestinal tract may be facilitated by the smaller interacting agents in the intestinal fluids if sufficient binding is present, but to a much lesser extent if the important binding agents are large particles.

## NONSTEADY STATE ASPECTS

Let us examine the lag time,  $\tau$ , for solute diffusion involving colloids for the single colloid species case in which the colloid concentration is constant in the barrier with time and position and where the solute binding is proportional to the free solute concentration. We may write two expressions for the lag time. One is used when the free solute transport is more important, and the other when the "carrier" transport is more important.

When  $D_s C_0 \gg D_c M C_{b0}$ , the lag time problem would be the same as that for solute diffusion into and through an absorbing emulsion layer (4). Therefore, we may write

$$\tau \approx \frac{h^2}{6D_m} \quad (\text{Eq. 14})$$

for the same problem leading to Eq. 1, but with the

barrier containing an interacting colloid material. Now  $D_m$  is given by (4)

$$D_m = \frac{P_m}{K_m}$$

where  $P_m$  and  $K_m$  are the permeability coefficient and partition coefficient for the compartment I phase and the colloid solution barrier phase. It has been shown (4) that  $P_m$  and  $P = D_s K_1$  would be about the same for dilute colloid solutions, *i.e.*, the steady state rates of the free solute contribution to transport and of the zero colloid case would be essentially the same. However,  $K_m$  would be greater than  $K_1$  by the factor

$$\frac{C_0 + MC_{b0}}{C_0}$$

Therefore,  $\tau$  in Eq. 14 would be greater than the  $\tau$  given by Eq. 1 by approximately this factor.

When  $D_s MC_{b0} \gg D_s C_0$ , the lag time for the same problem will be determined by the transport rate of the colloid and we may write

$$\tau \sim \frac{h^2}{3D_c} \quad (\text{Eq. 15})$$

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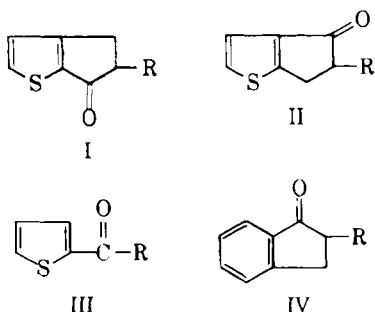
# Thiaindanones II

## Nitration, Acetylation, and Mannich Reactions

By JOSEPH SAM and ALONZO C. THOMPSON

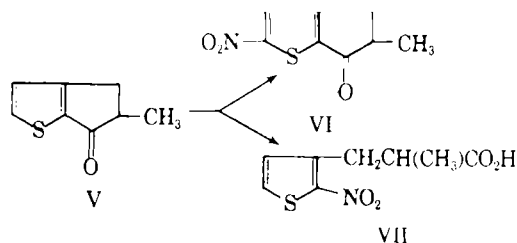
The nitration, acetylation, and Mannich reactions with thiaindanones are described. These reactions were observed to be analogous to similar reactions with 2-acylthiophenes and 1-indanone.

THIAINDANONES, represented by structures I and II, were observed to undergo reactions similar to those encountered with acylthiophenes (III) and indanones (IV).



The nitration of 5-methylthiaindanone (V) resulted in both ring substitution (VI) and in ring cleavage (VII). The ratio of nuclear substitution to carbonyl displacement was dependent

upon the temperature at which the nitration was performed. At a temperature below  $-6^\circ$  ( $-6$  to  $-15^\circ$ ) only the nuclear substituted nitro derivative was isolated, whereas above  $0^\circ$  ( $0$  to  $10^\circ$ ) both carbonyl displacement and ring substitution occurred (Table I).



Structures VI and VII were assigned to the nitration products on the basis of analysis, neutralization equivalent in the case of VII, and analogy to the nitration products of 2-acetylthiophene.

Rinkes (1) had shown earlier that replacement of the carbonyl group by the nitro group takes

TABLE I.—NITRATION OF 0.1 MOLE OF 5-METHYLTHIAINDAN-6-ONE

Temp., °C.	Ratio of VI/VII, Gm.
-15	10:0
-6	12:0
0	5:2
10	5:3

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