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ACKNOWLEDGMENTS

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Simultaneous Self-Association and Diffusion of Phenol in Isooctane

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Abstract □ The impact of self-association on mass transport was studied. The model system chosen was the diffusion of phenol through an immobilized layer of isooctane. In the theoretical development, self-associated phenol contributed to diffusion, with the fluxes being interdependent because of the self-association equilibrium. Predictions from theory were then compared with experimental results. It was shown that self-association can significantly affect flux of diffusing species.

Keyphrases □ Phenol—self-association and diffusion in isooctane □ Isooctane—simultaneous self-association and diffusion of phenol □ Diffusion—phenol in isooctane, simultaneous self-association

Associative interactions are of interest to those concerned with pharmaceutics for two reasons. First, associative interactions affect many processes such as dissolution, partitioning, and diffusion, all of which are vitally important to drug delivery. Second, most drugs contain at least one interactive functional group and, thus, are able to participate in associative interactions with many substances found in dosage forms and in the body.

The effects of association and related processes on various aspects of drug delivery have been examined in several studies. Dissolution rate is known to be altered significantly when dissociation reactions (1, 2) or complexation (3) occur within the dissolution layer. It has also been observed that when a diffusing species self-associates (4) or forms micelles (5) there is a pronounced effect on the rate of transport of that substance. Another study (6) has indicated that in a self-associating system, where diffusion of the self-associated species is blocked by its inability to penetrate the membrane used, the observed mass transport behavior can be accounted for by assuming that the compound is transported only in its monomeric form.

Where simultaneous self-association and diffusion occur, the direct application of Fick's laws fails to predict the diffusion rates observed. In the current study, a more comprehensive approach to the theoretical analysis of diffusion under such circumstances is presented. It is postulated that (*a*) by taking into account the interdependence of the fluxes of the associated and unassociated species arising from associative equilibrium within the diffusional layer, (*b*) by applying Fick's laws to each kind of species present, and (*c*) by numerically solving the differential equations derived on this basis, it is possible to predict the mass transport behavior of self-associating systems.

The model system used to test this postulate was one in which phenol was allowed to diffuse from a donor phase of isooctane, through an immobilized layer of isooctane which served as the diffusion layer, into an aqueous receptor phase. Phenol is known to self-associate significantly (>50%) at high concentrations in isooctane (7). This interaction was expected to cause the rate of mass transport into the aqueous phase to deviate markedly from that predicted by simply applying Fick's laws to the overall concentration of phenol present. Using the scheme outlined above, the diffusional behavior of phenol in the model system was predicted mathematically. The predicted results were then compared with the experimental data obtained.

THEORETICAL

Previous studies have shown that when phenol self-associates in isooctane, the dominant species formed is probably the pentamer[1] (7). The equilibrium expression for this interaction has been reported as:

$$5\,P_m \rightleftharpoons P_5$$

where P_m represents monomeric phenol and P_5 represents the pentameric species. The equilibrium constant for this interaction is $K_{1\text{-}5} = 6300\ M^{-4}$ at 25° in isooctane. This model appears to provide an adequate description of self-association of phenol over a wide range of concentrations.

In the present investigation a silanized sintered glass filter with a presilanization pore size range of 4.5–5.5 μm was used to form a diffusional barrier between the donor isooctane and the receptor aqueous phases. Because of the large pore size and equilibration of the filter with the donor phase prior to each experiment, the barrier actually consisted of a layer of isooctane immobilized within the sintered glass filter. As

[1] J. B. Dressman and T. Higuchi, unpublished results.

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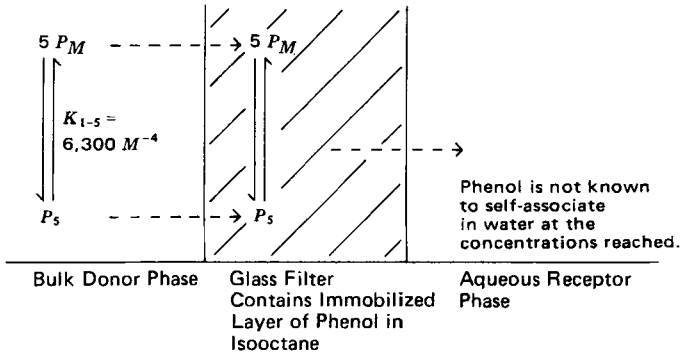

Figure 1—*Interactions of phenol in the silanized sintered glass filter system.*

shown in Fig. 1, self-association would be expected to occur within the diffusional layer as well as in the donor phase. Over the time span of the experiment, phenol concentrations remained sufficiently low in the aqueous phase to allow the assumption that self-association in that phase was negligible.

Consider an infinitesimal element within the diffusion layer. Expressions for the net flux of the monomer and pentamer species into the element can be obtained assuming that the self-association equilibrium between the two species is established very quickly compared to the rate of diffusion, and Fick's laws can be applied to the diffusion of each species within the element. Influx of the monomer can be represented as:

$$\left(\frac{\partial P_m}{\partial t}\right)_{IN} = -D_m\left(\frac{\partial P_m}{\partial h}\right) \qquad \text{(Eq. 1)}$$

where D_m is the diffusivity of the phenol monomer, h is distance, and t is time. The efflux of the monomer from the element can be written as:

$$\left(\frac{\partial P_m}{\partial t}\right)_{OUT} = -D_m\left[\left(\frac{\partial P_m}{\partial h}\right) + \frac{\partial}{\partial h}\left(\frac{\partial P_m}{\partial h}\right)\right] \qquad \text{(Eq. 2)}$$

The net flux of the monomer into the element is given by the difference between the influx and efflux of the monomer from the element:

$$\left(\frac{\partial P_m}{\partial t}\right) = \left(\frac{\partial P_m}{\partial t}\right)_{IN} - \left(\frac{\partial P_m}{\partial t}\right)_{OUT} = D_m\frac{\partial}{\partial h}\left(\frac{\partial P_m}{\partial h}\right) \qquad \text{(Eq. 3)}$$

as given by Fick's second law. Similarly, the following expression is obtained for the net flux of the pentamer:

$$\left(\frac{\partial P_5}{\partial t}\right) = D_5\left(\frac{\partial^2 P_5}{\partial h^2}\right) \qquad \text{(Eq. 4)}$$

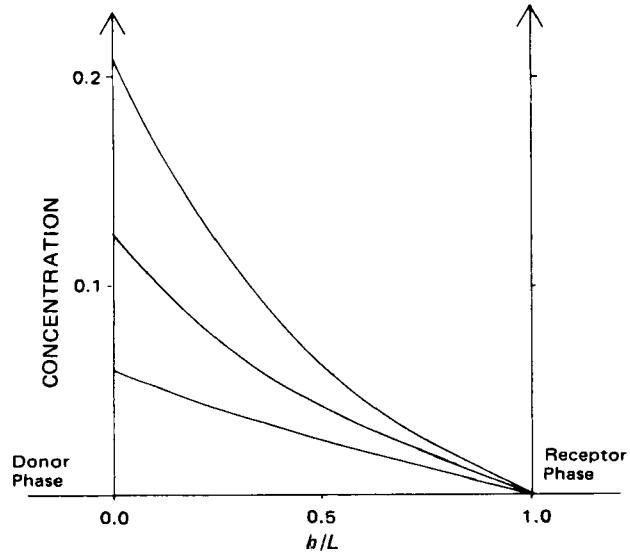

Figure 2—*Profile of total concentration of phenol in the immobilized layer of isooctane constituting the diffusion layer, calculated from Eqs. 9 and 15 for three donor phase concentrations of phenol: 0.2063, 0.1226, and 0.0432* M, *under steady-state and sink conditions.*

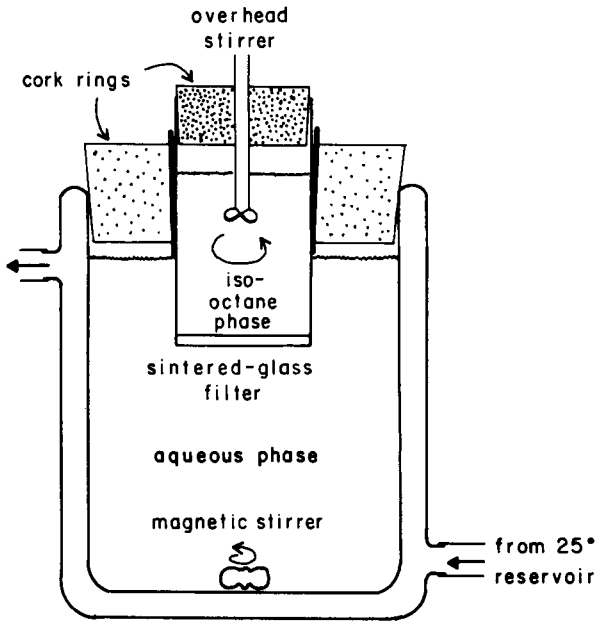

Figure 3—*Apparatus for diffusion studies.*

where D_5 is the diffusivity of the pentamer species. Given that P_T is the total concentration of phenol present, one can write:

$$P_T = P_m + 5P_5 \qquad \text{(Eq. 5)}$$

The expressions for the flux of the monomer and pentamer can therefore be combined into one expression as follows:

$$\left(\frac{\partial P_T}{\partial t}\right) = D_m\left(\frac{\partial^2 P_m}{\partial h^2}\right) + 5D_5\left(\frac{\partial^2 P_5}{\partial h^2}\right) \qquad \text{(Eq. 6)}$$

Using the equilibrium expression:

$$P_5 = K_{1-5}P_m^5 \qquad \text{(Eq. 7)}$$

it can be shown then by repeated application of the chain rule that:

$$\left(\frac{\partial^2 P_5}{\partial h^2}\right) = 20K_{1-5}P_m^3\left(\frac{\partial P_m}{\partial h}\right)^2 + 5K_{1-5}P_m^4\left(\frac{\partial^2 P_m}{\partial h^2}\right) \qquad \text{(Eq. 8)}$$

By substituting Eq. 7 into Eq. 5 one obtains the expression:

$$P_T = P_m + 5K_{1-5}P_m^5 \qquad \text{(Eq. 9)}$$

Taking the derivative of both sides of Eq. 9 with respect to time it can be shown that:

$$\left(\frac{\partial P_T}{\partial t}\right) = \left(\frac{\partial P_m}{\partial t}\right)(1 + 25K_{1-5}P_m^4) \qquad \text{(Eq. 10)}$$

Then, by substituting Eqs. 8 and 10 into Eq. 6 one can produce a partial differential equation in terms of the monomer concentration only:

$$\left(\frac{\partial P_m}{\partial t}\right)(1 + 25K_{1-5}P_m^4) = \left(\frac{\partial^2 P_m}{\partial h^2}\right)(D_m + 25D_5K_{1-5}P_m^4) + \left(\frac{\partial P_m}{\partial h}\right)^2 100D_5K_{1-5}P_m^3 \qquad \text{(Eq. 11)}$$

Steady-State Solution Under Sink Conditions—At steady state there is no net accumulation of either form of phenol at any point within the diffusion layer, so there is no net flux into any element, *i.e.*, $\partial P_T/\partial t = 0$. Applying this condition to Eq. 11 one finds that:

$$\left(\frac{\partial P_T}{\partial t}\right) = \left(\frac{\partial^2 P_m}{\partial h^2}\right)(D_m + 25D_5K_{1-5}P_m^4) + \left(\frac{\partial P_m}{\partial h}\right)^2 100K_{1-5}K_5P_m^3 = 0 \qquad \text{(Eq. 12)}$$

Letting $y = (dP_m/dh)$ in the above expression and then separating the variables and integrating, one obtains:

$$\left(\frac{dy}{y}\right) = -\left(\frac{100K_{1-5}D_5P_m^3}{D_m + 25K_{1-5}D_5P_m^4}\right)dP_m$$

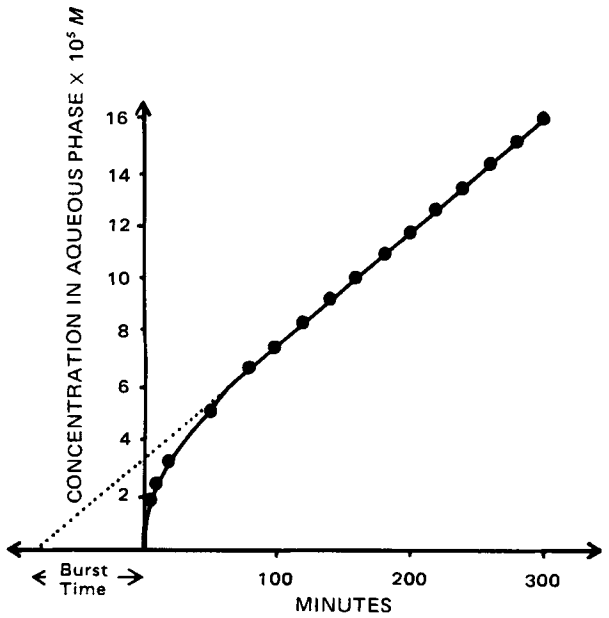

Figure 4—*Cumulative concentration of phenol in the aqueous phase* versus *time for diffusion through a sintered glass filter from a 0.1403* M *solution of phenol in isooctane. Key: (●) experimental data; (—) results obtained by numerical solution of Eq. 11.*

which leads to:

$$y = \left(\frac{dP_m}{d\,h}\right) = \frac{C_1}{D_m + 25\,K_{1\text{-}5}\,D_5 P_m^4} \qquad \text{(Eq. 13)}$$

where C_1 is the first constant of integration. Separating variables and integrating again gives the equation:

$$D_m P_m + 5\,K_{1\text{-}5}\,D_5 P_m^5 = C_1\,h + C_2 \qquad \text{(Eq. 14)}$$

where C_2 is the second constant of integration.

Appropriate boundary conditions can then be applied to solve for the constants of integration. Since the concentration in the bulk of the donor phase remains effectively constant during the course of the experiment, one can write:

$$P_m = P_0 \text{ at } h = 0$$

The second constant of integration C_2 can be found by substituting this condition into Eq. 14 to give:

$$C_2 = D_m\,P_0 + 5\,K_{1\text{-}5}\,D_5\,P_0^5$$

If sink conditions are assumed to hold at the aqueous interface, *i.e.*, $P_m = 0$ at $h = L$ where L is the distance across the diffusion barrier, this condition can be used in conjunction with the expression for C_2 in Eq. 14 to obtain the first constant of integration, which is thus given by:

$$C_1 = \frac{-D_m\,P_0 - 5\,K_{1\text{-}5}\,D_5\,P_0^5}{L}$$

Substituting for C_1 and C_2 in Eq. 14 gives the expression:

$$\frac{h}{L} = \frac{D_m(P_0 - P_m) + 5\,K_{1\text{-}5}\,D_5\,(P_0^5 - P_m^5)}{D_m\,P_0 + 5\,K_{1\text{-}5}\,D_5 P_0^5} \qquad \text{(Eq. 15)}$$

Equation 15 can be used to find the concentration of monomer and total phenol at any point in the diffusion layer at steady state, under sink conditions. Using Eq. 9 and the monomer concentration obtained using Eq. 15, the total concentration profile can be calculated. Figure 2 shows the total concentration profiles at three representative donor phase concentrations of phenol. These plots show that at higher concentrations of phenol where the self-associated species accounts for a large percentage of phenol present, the concentration profile is predicted to deviate from linearity in a pronounced manner. The values of D_m and D_5 were 5.5×10^{-6} and 2.0×10^{-6} cm²/sec, respectively. They were obtained initially from the Stokes–Einstein equation and then adjusted to give a reasonable representation of the experimental data. Filter tortuosity characterization with a substance with a known diffusion coefficient would have allowed a more accurate determination of D_m, at least at low concentrations.

Nonsteady-State Solution—To determine whether the self-association model can be used to successfully predict the data obtained for the cumulative amount of phenol in the aqueous phase over the course of the experiment and subsequently to predict burst time and steady-state flux data, it was necessary to obtain solutions to Eq. 11 for both presteady-state and steady-state behavior under nonsink conditions.

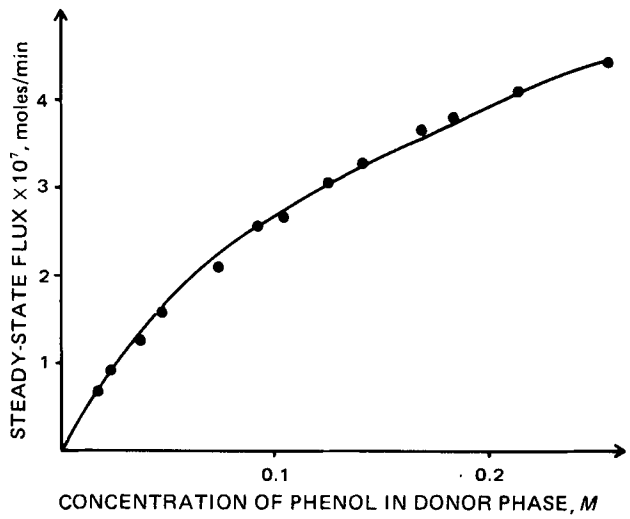

Figure 5—*Steady-state flux (moles per minute) over the entire diffusion layer surface area* versus *total concentration of phenol in the donor phase. Key: (●) mean of the experimental data at a given concentration of phenol; (—) results obtained by numerical solution of Eq. 11.*

Equation 11 is a nonlinear second-order partial differential equation and cannot be conveniently solved analytically under the required conditions. Therefore, it was necessary to transform the equation into an approximate algebraic expression that could be solved numerically. The derivatives were expressed as finite differences using the central and backward difference formulas outlined in a previous report (8) for use in implicit solution methods. The square term in the first derivative of P_m with respect to distance was handled by splitting it into two parts: a constant coefficient calculated on the previous time step and a backward difference expression for the derivative calculated on the current time step. This enabled a set of linear equations to be established for each time step, the coefficients of which were arranged in a tridiagonal matrix. This matrix system was then solved using a Gaussian elimination method as described previously (8). The nonlinear elements of the equation could then be updated from the solution obtained. The entire procedure was repeated until the solution obtained did not differ from the assumed elements by more than a predetermined tolerance. However, it was found that the first approximation used for the nonlinear elements was within the desired tolerance and the iterative solution was not employed subsequently.

Burst Time—Burst time methodology was employed because of the apparatus design. That is, the glass filter initially contained phenol at the same concentration as the bulk isooctane phase. As with the more commonly used lag time, the burst time should be independent of the donor phase concentration in a system where only one species is responsible for the total observed rate of diffusion. This can be shown by following the derivation presented in a previous report (9) and applying boundary and initial conditions appropriate for burst effect conditions to obtain:

$$t_{\text{burst}} = \frac{-L^2}{3.1\,D} \qquad \text{(Eq. 16)}$$

where L is the distance across the diffusion layer and D is the diffusivity (10). Deviation from this relationship was predicted in the current study as it was postulated that more than one species contributed to the overall rate of diffusion.

EXPERIMENTAL

Materials—Phenol[2] (Analytical reagent grade) was fractionally distilled under vacuum to remove the preservative and other contaminants, then stored under nitrogen in a desiccator. Certified ACS isooctane (2,2,4-trimethylpentane)[3] was used without further purification.

[2] Mallinckrodt.
[3] Fisher Scientific Co.

Table I—Experimental and Calculated Steady-State Flux and Burst Time Values for Diffusion of Phenol Through an Immobilized Layer of Isooctane in a Sintered Glass Filter

Concentration in Donor Phase, M	N^a	Steady-State Flux × 10^7, moles/min		Burst Time, min	
		Computer	Experimental ±SEM	Computer	Experimental ±SEM
0.0132	1	0.500	0.467	34.6	40
0.0166	1	0.630	0.689	34.8	39
0.0233	1	0.881	0.922	35	51
0.0365	4	1.332	1.270 ± 0.02	36	45 ± 3
0.0461	4	1.625	1.584 ± 0.05	39	51 ± 3
0.0913	4	2.556	2.576 ± 0.03	54	66 ± 3
0.1030	4	2.741	2.687 ± 0.06	57.5	69 ± 5
0.1240	4	3.010	3.069 ± 0.01	64	68 ± 3
0.1403	4	3.244	3.269 ± 0.07	69	86 ± 9
0.1680	4	3.592	3.676 ± 0.04	76	81 ± 5
0.1826	4	3.740	3.824 ± 0.10	80.5	92 ± 5
0.2130	4	4.018	4.109 ± 0.05	87	88 ± 3
0.2550	1	4.460	4.440	97	111

[a] Number of experiments.

The single sintered glass filter (pore size 4.5–5.5 μm; 2-mm thick; 30-mm radius) was obtained commercially[4] and silanized by soaking overnight in a solution of dichloromethylsilane in toluene. Excess silanizing agent was later removed with a solution of acetic acid in hexane.

Analytical Method—Two-milliliter samples were removed from the aqueous phase at suitable time intervals up to 300 min. At the conclusion of the experiment the UV absorbance at 269 nm, the wavelength of maximum absorbance for phenol in the UV region, was determined for each sample[5]. Deoxygenated, distilled water was used as the reference solution. In the aqueous solution with ~pH 6 ionization was >99.9% suppressed.

Diffusion Apparatus and Study—The experimental apparatus is depicted in Fig. 3. Five hundred milliliters of freshly deoxygenated distilled water was placed in a water-jacketed beaker connected to a controlled-temperature reservoir which was used to maintain the temperature of the system at 25°. A magnetic stirrer was used to keep the aqueous phase well mixed. Fifty milliliters of a solution of phenol in isooctane was poured into the tube containing the silanized sintered glass filter and allowed to sit for 3 min. The lower side of the filter was then wiped dry and the tube placed in the aqueous phase in such a position that bulging of the isooctane phase down into the aqueous phase was avoided. Silanization of the filter prevented the hydrostatic pressure of the aqueous phase forcing any water up into the filter. Cork rings fitted above both phases prevented evaporation. The isooctane phase was stirred from above. Optimal stirring rates for the isooctane and aqueous phases were used to ensure even mixing without vortexing problems. This allowed the assumption to be made that the boundary layers in the bulk isooctane and aqueous phases were a negligible barrier to diffusion compared to the immobilized isooctane layer in the sintered glass filter. Thus, the principal barrier to diffusion was the layer of isooctane immobilized in the sintered glass filter.

At suitable time intervals, 2-ml samples were removed from the aqueous phase and the volume replaced with deoxygenated distilled water. The samples were analyzed by UV spectroscopy at the conclusion of each experiment on the same day, so that chemical stability was not a problem.

RESULTS AND DISCUSSION

Phenol was diffused from a donor phase solution in isooctane (at concentrations ranging from 0.0123 to 0.255 M) through a layer of isooctane immobilized within a sintered glass filter into an aqueous phase. The concentration of phenol was determined in the aqueous phase at times up to 300 min. Figure 4 shows a typical plot of the data obtained. For all donor phase concentrations studied, the plot became linear for times >100 min as the system reached a pseudo steady state. Data for these points were analyzed by linear regression to determine the steady-state flux and burst time values. Results from runs in which the correlation coefficient was <0.999 were discarded to minimize uncertainty in calculations of steady-state flux. Extrapolation of the best-fitting linear relationship to zero phenol concentration in the aqueous phase provided the burst time measurement. The slope of the line was used to calculate the steady-state flux in moles per minute over the entire surface area of the diffusion layer (7.069 cm^2) after adjusting the units from molarity per minute by using the aqueous phase volume. Table I summarizes steady-state flux and burst time values obtained.

Steady-State Flux—The experimentally observed relationship between steady-state flux and total concentration in the donor phase obtained in these studies is shown in Fig. 5. This relationship may be compared with classical behavior predicted from Fick's laws. Fick's first law is given by:

$$J = -D\frac{\partial C}{\partial h} \qquad \text{(Eq. 17)}$$

$$J \approx -D\left(\frac{C_0 - C_L}{h}\right) \qquad \text{(Eq. 18)}$$

where J is the flux across the diffusion layer, D is the diffusivity, C_0 is the concentration at $h = 0$ (the donor phase interface), C_L is the concentration at $h = L$ (the receptor phase interface), and h is distance. Provided the receptor phase concentration remains low, *i.e.*, $C_L \approx 0$, the flux can be written as:

$$J \propto C_0 \qquad \text{(Eq. 19)}$$

Under these conditions, one would expect the steady-state flux to increase linearly with increasing concentration in the donor phase. Figure 5 shows, however, that steady-state flux is not directly proportional to donor phase concentration, since the plot deviates significantly from linearity. Anomalous behavior of this type has also been noted for diffusion of phenol through high-density polyethylene membranes by

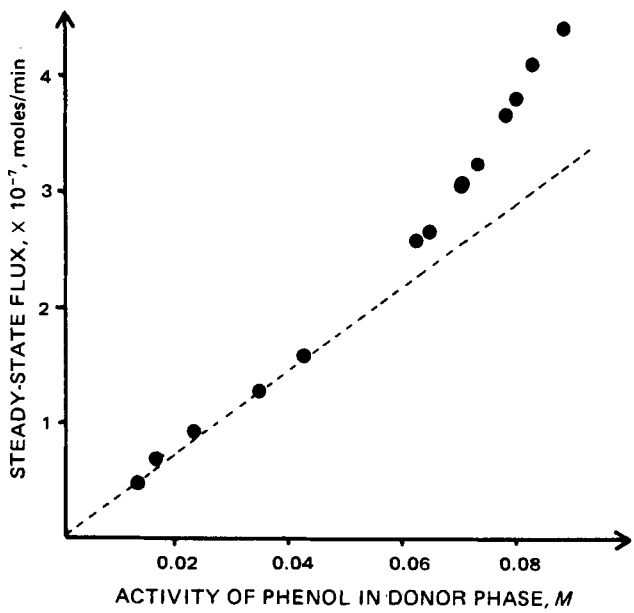

Figure 6—*Steady-state flux (moles per minute) over the entire diffusion layer surface area* versus *activity of phenol (concentration of monomeric phenol) in the donor phase. Key: (●) experimental data; (- - -) linear plot which would be expected if only the monomer species was contributing to the observed flux.*

[4] Lab glass.
[5] Cary 118 model UV/VIS spectrophotometer.

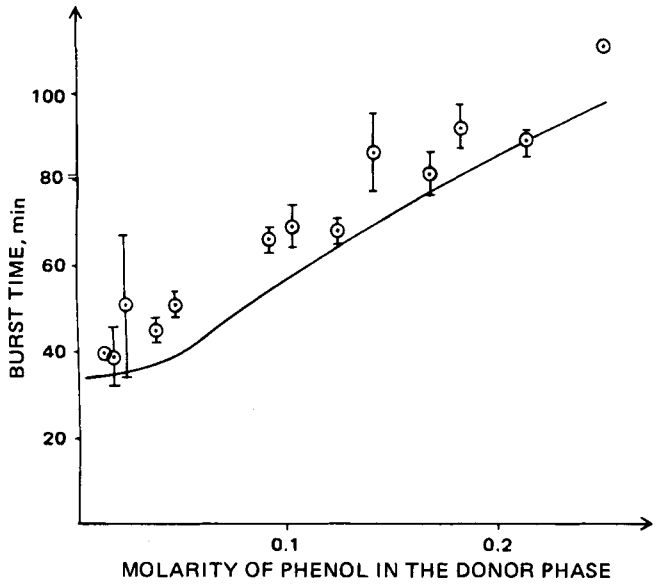

Figure 7—*Burst time (minutes)* versus *total concentration of phenol in the donor phase. Key: (O) experimental data points; (—) obtained from the numerical solution of Eq. 11.*

Mikkelson *et al.* (6) who were subsequently able to obtain a linear relationship by plotting the steady-state flux *versus* activity of phenol present. For that system it was suggested that only the monomeric phenol could partition into the membrane and, hence, contribute to the observed rate of flux. The steady-state flux data for the sintered glass filter system used in the current study was replotted *versus* activity of phenol (defined as the concentration of monomeric phenol) as shown in Fig. 6. The plot exhibits pronounced positive deviation from linearity which indicates that the monomeric portion of the phenol was not solely responsible for the transport of phenol into the aqueous phase in this system. The fraction of phenol present as monomer is ~0.35 at a total phenol concentration of 0.255 *M* as compared to >0.99 at 0.0132 *M*.

On the basis of the pentamer model for self-association of phenol in isooctane, it was proposed that both the monomer and the pentamer species of phenol contribute to the overall observed flux according to Eq. 11. This equation was solved numerically as outlined in the *Theoretical* section and the results compared with the experimental data. For both the individual plots of cumulative concentration in the aqueous phase *versus* time (Fig. 4) and the overall plot of steady-state flux *versus* total concentration of phenol on the donor phase (Fig. 5), the numerical solution is in good agreement with the observed results, indicating that the pentamer species was able to form in the diffusion layer and, hence, contribute proportionately to the flux into the aqueous phase.

Transient Behavior—A second way to study the effect of self-association on diffusion is to analyze the transient (burst time) data. The burst time for a single diffusing species should be independent of the concentration in the donor phase when the diffusion of one species accounts for the observed flux. Burst time data for the system under study are presented in Table I. Figure 7 shows a plot of measured burst time *versus* concentration in the donor phase. The burst time increased with increasing concentration rather than being entirely concentration independent. Since burst time is inversely proportional to diffusivity, the apparent diffusivity appears to have become smaller as the concentration in the donor phase increased. This type of behavior has also been noted for solutions of phenol in carbon tetrachloride (11).

An explanation can be offered for this behavior by considering the monomer–pentamer equilibrium. As the total concentration of phenol increased in the donor phase, the percentage present in the self-associated form increased. Since diffusivity is inversely related to the size of the diffusing species, one would expect that when the pentamer accounts for a large percentage of the phenol present, the apparent diffusivity would be lower, and thus, the burst time would be longer than at low concentrations where the much smaller monomer species accounts for virtually all of the phenol in solution.

The solid line in Fig. 7 represents burst time values calculated from the computer-generated data by applying linear regression analysis to predicted steady-state cumulative concentrations of phenol in the aqueous phase and extrapolating back to zero phenol concentration. Although there is considerable scatter in the experimental data, they appear to follow the same trend as the results derived from Eq. 11. In most instances the observed burst time tends to be greater than the theoretical value. This is probably due to a small amount of phenol solution on the lower face of the glass filter when it was positioned into the aqueous phase. This would have caused the immediate release of phenol into the aqueous phase by nondiffusive means, which in turn would result in falsely high observed values for the cumulative amount in the aqueous phase and, therefore, for the burst time.

The burst time and the steady-state flux data both support the conclusion that the apparent deviation of the diffusion characteristics of phenol in isooctane from Fick's laws can be entirely accounted for by considering the self-association equilibrium of phenol in isooctane. From Eq. 11 one can note that the diffusion of each species, monomer and pentamer, fundamentally obeys Fick's laws and that the diffusivity of each species is constant. The apparent diffusivity, as reflected in the burst time, only changes because of the variation with concentration of the relative proportions of the monomer and pentamer present.

CONCLUSIONS

In these studies it has been shown that the apparent deviation from classical behavior of the diffusion of phenol through an immobilized solution of isooctane can be explained by the specific interaction effects rather than needing to resort to an empirical description in terms of the apparent diffusivity of the overall system. This approach to describe concomitant self-association and mass transport can be used to help predict delivery rates of drugs for which diffusion is the rate-controlling step in release from the dosage form or in the absorption process, and self-association occurs under physiological conditions. Caffeine (4) and some analgesics and antihistamines (12–17) have been shown to self-associate at high concentrations in aqueous solution.

The rate of transport of these drugs across the dissolution layer when they are released from solid dosage forms, therefore, may be affected by the self-association interaction. Other substances such as alcohols and carboxylic acids are known to self-associate in organic solvents (18). Absorption through lipoidal membrane barriers or release from dosage forms which are coated with polymeric films are examples of steps in the drug delivery process at which self-association of drugs containing such groups may significantly affect the rate of transport.

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