(230) Y. Olsson, *Acta Physiol. Scand. Suppl. 284*, **69**, 3 (1966).
(231) G. S. Kerkut, R. J. Walker and G. N. Woodruff, *Br. J. Pharmacol.*, **32**, 241 (1968).
(232) N. Ambache and M. B. Zar, *J. Physiol.* **204**, 20 (1969).
(233) E. J. Harris and S. Ochs, *ibid.*, **187**, 5 (1966).
(234) C. A. M. Sampaio, A. J. Lapa, and J. R. Valle, *J. Pharm. Pharmacol.*, **19**, 552 (1967).
(235) M. D. Green, B. Cox, and P. Lomax, *J. Neurosci. Res.*, **1**, 353 (1975).
(236) S. Rashid, *Arch. Int. Pharmacodyn.*, **195**, 247 (1972).
(237) M. Harris, J. M. Hopkin, and M. J. Neal, *Br. J. Pharmacol.*, **47**, 229 (1973).
(238) M. J. Brimble and D. I. Wallis, *Nature (London)*, **246**, 156 (1973).
(239) G. Gardos, U. V. Lassen, and L. Pape, *Biochim. Biophys. Acta*, **448**, 599 (1976).
(240) C. Bell, W. J. Lang, and C. Tsilemanis, *Brain Res.*, **56**, 392 (1973).
(241) J. N. Sinha, M. L. Gupta, and K. P. Bhargawa, *Eur. J. Pharmacol.*, **5**, 235 (1969).
(242) M. Skingle and M. B. Tyers, *J. Pharmacol. Methods*, **2**, 71 (1979).
(243) C. C. Eagleson and I. J. Zeitlin, *J. Physiol. (London)*, **275**, 68 (1978).
(244) National Toxicology Program, Carcinogenesis Testing Program, June 8, 1981.
(245) G. S. Probst and S. B. Neal, *Cancer Lett.*, **10**, 67 (1980).
(246) R. A. Harper and B. A. Flaxman, *J. Invest. Dermatol.*, **65**, 400 (1975).
(247) EMIC, Oak Ridge National Laboratory, Nov. 17, 1980.
(248) P. Naranjo and E. deNaranjo, *Arzneim.-Forsch.*, **18**, 188 (1968).
(249) F. Bovet-Nitti, G. Bignani, and D. Bovet, *Life Sci.*, **5**, 303 (1963).
(250) J. M. Brandon and R. M. Wallis, *J. Reprod. Fert.*, **50**, 251 (1977).
(251) J. Z. Nowak and A. Pilc, *Proc. 2nd Congress of Hungarian Pharmacol. Soc.*, Budapest, 1976, pp. 193–196.
(252) C.-I. Wong and M. B. Roberts, *IRCR Med. Sci.*, **3**, 618 (1975).
(253) ETIC, Oak Ridge National Laboratory, Nov. 17, 1980.

RESEARCH ARTICLES

Diffusion of Phenol in the Presence of a Complexing Agent, Tetrahydrofuran

J. B. DRESSMAN *§, K. J. HIMMELSTEIN *‡§x, and T. HIGUCHI *

Received October 29, 1981, from the **Department of Pharmaceutical Chemistry* and the ‡*Department of Chemical and Petroleum Engineering, The University of Kansas, Lawrence, KS 66045.* Accepted for publication February 19, 1982. §Present address: Inter$_x$ Research Corporation, Lawrence, KS 66044.

Abstract □ The effect of a complexing agent, tetrahydrofuran, on the diffusion of phenol across a stagnant fluid layer has been studied. At a given activity of free phenol, the steady-state flux of phenol appearing in an acceptor phase was greatly enhanced. However, as the fraction of phenol associated with the complexing agent increased, the flux of phenol decreased, since the transport was then controlled by the diffusion of the complex, a larger structure. A mathematical model of simultaneous association and diffusion was derived to determine whether the diffusional behavior of two associating species could be accounted for in terms of the association equilibrium constant and Fick's second law. Experimental results supported the model. It was concluded that the presence of a complexing agent tends to reduce the rate of diffusion, the effect being more pronounced at high concentrations of complexing agent.

Keyphrases □ Phenol—diffusion in a complexing agent, tetrahydrofuran □ Diffusion—phenol in a complexing agent, tetrahydrofuran □

The purpose of this study was to investigate the influence of complexing agents on the diffusional behavior of drugs. The ability of most drugs to undergo association interactions is intrinsically related to their activity, since most drugs exert their action by complexing to a receptor site. Some dosage forms are designed to take advantage of this associative tendency by using a complexing agent to increase the solubility of the drug in the formulation (1, 2). In other cases, complexing agents are used to modify the dissolution rate of a drug at the site of administration (3, 4), as it is known that the dissolution rate can be greatly affected by association in the diffusion layer (5).

In a previous study (6), the importance of associative interaction on mass transport of drugs was exemplified by the case of simultaneous self-association and diffusion of phenol through an immobilized layer of isooctane. The results of this analysis showed that the self-association of phenol can significantly alter the rate of transport of phenol. The case of simultaneous complexation and diffusion has also been investigated (7). However, those results relied on accurate determination of the forward and reverse rate constants for the associative interaction, parameters which may prove difficult to obtain. It was also assumed that for association equilibrium to be attained within the diffusion layer, it was necessary for the con-

0022-3549/83/0100-0012$01.00/0

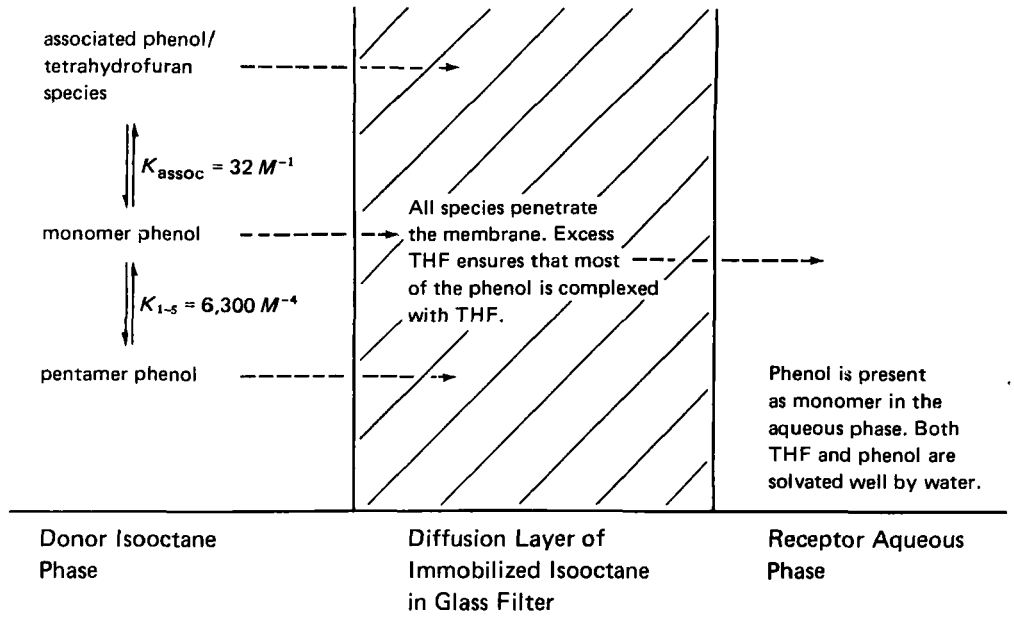

Figure 1—*The influence of tetrahydrofuran on the diffusion of phenol through an unstirred layer of isooctane.*

centration of the complexing agent to be the same at all points in the system.

In the present study, the model system used was the diffusion of phenol from a donor phase solution in isooctane, through a diffusion layer consisting of immobilized isooctane, into an aqueous receptor phase (Fig. 1). The complexing agent used was tetrahydrofuran which, as a cyclic ether, was capable of associating strongly with phenol *via* hydrogen bond formation. A mathematical model of this system was derived to determine whether the experimental diffusional behavior of the two associating species could be accounted for in terms of their association equilibrium constant and Fick's second law. The derivation was based on the following assumptions: (*a*) coupling of the fluxes of free phenol, free tetrahydrofuran, and the complex occurs; (*b*) equilibrium is rapidly attained compared with the rate of diffusion; and (*c*) diffusion of each kind of species is governed by Fick's laws.

THEORETICAL

A silanized sintered glass filter was used in the experimental portion of the present investigation to create an immobilized layer of isooctane between the donor isooctane phase and the receptor aqueous phase, a procedure described previously (6). The immobilized isooctane layer thus formed a stagnant diffusion layer. This arrangement allowed both the phenol and the tetrahydrofuran in the donor isooctane phase to diffuse across the diffusion layer. The association equilibria which occur in the donor phase and the diffusion layer are shown in Fig. 1.

The self-association of phenol in isooctane can be described by the equilibrium (8):

$$5P_m \rightleftharpoons P_5 \text{ with } K_{1-5} \approx 6{,}300\ M^{-4} \text{ at } 25° \qquad \text{(Eq. 1)}$$

where P_m is the concentration of free (monomer) phenol, P_5 is the concentration of self-associated (pentamer) phenol, and K_{1-5} is the equilibrium constant for self-association. The equilibrium governing the association between phenol and tetrahydrofuran is given by:

$$P_m + T \rightleftharpoons [P - T] \text{ with } K_{assoc} = 32\ M^{-1} \text{ at } 25° \qquad \text{(Eq. 2)}$$

where $[P - T]$ is the concentration of associated phenol–tetrahydrofuran species and K_{assoc} is the equilibrium constant for association of phenol and tetrahydrofuran in isooctane. The total concentration of phenol in the presence of tetrahydrofuran is represented by:

$$P_T = P_m + [P - T] + 5P_5 \qquad \text{(Eq. 3)}$$

The total concentration of tetrahydrofuran is given by:

$$T_T = T + [P - T] \qquad \text{(Eq. 4)}$$

where T_T is the total concentration of tetrahydrofuran, similarly expressed. Association in the aqueous phase is assumed to be negligible, since the concentrations of both phenol and tetrahydrofuran in the aqueous phase remained low over the duration of the experiment. Under these conditions, self-association also appears to be negligible[1]. Applying Fick's second law:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2}$$

to each species of phenol present, one obtains:

$$\frac{\partial P_T}{\partial t} = D_M\frac{\partial^2 P_m}{\partial x^2} + 5D_5\frac{\partial^2 P_5}{\partial x^2} + D_{P-T}\frac{\partial^2[P - T]}{\partial x^2} \qquad \text{(Eq. 5)}$$

where D is diffusivity, t is time, C is the concentration of a given species, x is equal to distance, D_m is the diffusivity of free phenol, D_5 is the diffusivity of pentamer phenol, and P_T is expressed as molarity of monomeric phenol.

Assuming that the association equilibria are established quickly compared with the rate of diffusion, P_5 and $[P - T]$ can be substituted in Eq. 3 by the equilibrium expressions:

$$P_5 = K_{1-5}P_m{}^5 \qquad \text{(Eq. 6)}$$

$$[P - T] = K_{assoc}TP_m \qquad \text{(Eq. 7)}$$

resulting in:

$$\frac{\partial P_T}{\partial t} = D_M\frac{\partial^2 P_m}{\partial x^2} + 5D_5K_{1-5}\frac{\partial^2 P_m{}^5}{\partial x^2} + D_{P-T}K_{assoc}\frac{\partial^2(TP_m)}{\partial x^2} \qquad \text{(Eq. 8)}$$

The second term in Eq. 8 can be reexpressed as:

$$\frac{\partial^2(P_m{}^5)}{\partial x^2} = 5P_m{}^4\frac{\partial^2 P_m}{\partial x^2} + 20\,P_m{}^3\left(\frac{\partial P_m}{\partial x}\right)^2 \qquad \text{(Eq. 9)}$$

The third term in Eq. 8 can be reexpressed as:

$$\frac{\partial(TP_m)}{\partial x^2} = P_m\frac{\partial^2 T}{\partial x^2} + T\frac{\partial^2 P_m}{\partial x^2} + 2\frac{\partial P_m}{\partial x}\frac{\partial T}{\partial x} \qquad \text{(Eq. 10)}$$

Also, by substituting Eqs. 6 and 7 into Eq. 3:

$$P_T = P_m + 25K_{1-5}P_m{}^5 + K_{assoc}TP_m \qquad \text{(Eq. 11)}$$

Taking the derivative of both sides with respect to time one obtains the expression:

$$\frac{\partial P_T}{\partial t} = \frac{\partial P_m}{\partial t} + 25K_{1-5}P_m{}^4\frac{\partial P_m}{\partial t} + K_{assoc}T\frac{\partial P_m}{\partial t} + K_{assoc}P_m\frac{\partial T}{\partial t}$$

[1] Personal communication, M. Tobin.

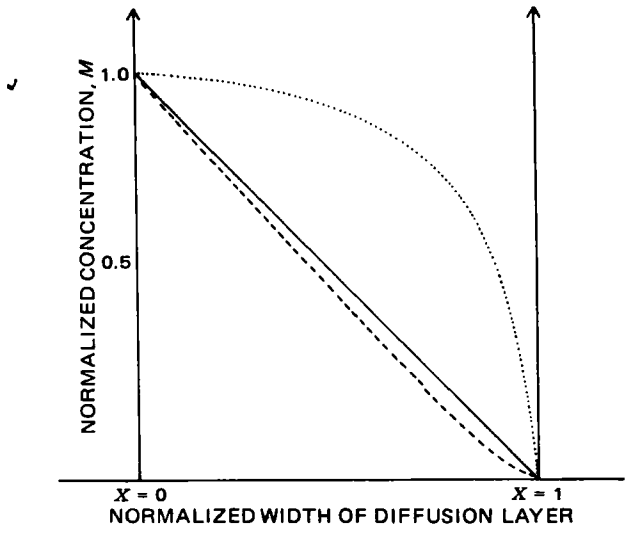

Figure 2—*Normalized steady-state concentration profiles in the diffusion layer, at total phenol concentration of 0.1403* M *and total tetrahydrofuran concentration of 4.76% (v/v) in the donor phase. Key: (——) free tetrahydrofuran concentration scaled up by a factor of 2.194; (- - - - -) associated phenol concentration scaled up by a factor of 7.616; (. . . . .) concentration of free phenol scaled up by a factor of 111.11.*

This expression can be rearranged to give:

$$\frac{\partial P_T}{\partial t} = \frac{\partial P_m}{\partial t}(1 + 25K_{1\text{-}5}P_m^4 + K_{assoc}T) + K_{assoc}P_m\frac{\partial T}{\partial t} \quad \text{(Eq. 12)}$$

By substituting Eqs. 9, 10, and 12 into Eq. 8 the following is derived:

$$\frac{\partial P_m}{\partial t}[1 + 25K_{1\text{-}5}P_m^4 + K_{assoc}T] = D_M\frac{\partial^2 P_m}{\partial x^2} + D_5K_{1\text{-}5}5P_m^4\frac{\partial^2 P_m}{\partial x^2} + 20P_m^3\left(\frac{\partial P_m}{\partial x}\right)^2 + P_m\frac{^2T}{\partial x^2} + T\frac{\partial^2 P_m}{\partial x^2} + 2\frac{\partial P_m}{\partial x}\frac{\partial T}{\partial x}D_{P\text{-}T}K_{assoc} - K_{assoc}P_m\frac{\partial T}{\partial t} \quad \text{(Eq. 13)}$$

Equation 13 can be rearranged to produce the following in terms of monomer phenol only:

$$\frac{\partial P_m}{\partial t} = \frac{\left[D_M\frac{\partial^2 P_m}{\partial x^2} + D_5K_{1\text{-}5}5P_m^4\frac{\partial^2 P_m}{\partial x^2} + 20P_m^3\left(\frac{\partial P_m}{\partial x}\right)^2 - K_{assoc}P_m\frac{\partial T}{\partial t} + D_{P\text{-}T}K_{assoc}P_m\frac{\partial^2 T}{\partial x^2} + T\frac{\partial^2 P_m}{\partial x^2} + 2\frac{\partial P_m}{\partial x}\frac{\partial T}{\partial x}\right]}{[1 + 25K_{1\text{-}5}P_m^4 + K_{assoc}T]} \quad \text{(Eq. 14)}$$

An expression for diffusion of tetrahydrofuran can be derived in a similar manner. The concentration of tetrahydrofuran in associated form can be calculated using Eq. 15:

$$[P - T] = K_{assoc}TP_m \quad \text{(Eq. 15)}$$

By applying Fick's second law to the species of tetrahydrofuran present, an expression for flux of tetrahydrofuran across a small distance within the diffusion layer can be obtained:

$$\frac{\partial T_T}{\partial t} = D_T\frac{\partial^2 T}{\partial x^2} + D_{P\text{-}T}\frac{\partial^2[P - T]}{\partial x^2} \quad \text{(Eq. 16)}$$

By appropriate substitution and rearrangement, the following expression is derived:

$$\frac{\partial T}{\partial t} = \frac{\left[\frac{\partial^2 T}{\partial x^2}[D_T + D_{P\text{-}T}K_{assoc}P_m] + D_{P\text{-}T}K_{assoc}T\frac{\partial^2 P_m}{\partial x^2} + 2\frac{\partial P_m}{\partial x}\frac{\partial T}{\partial x} - K_{assoc}T\frac{\partial P_m}{\partial t}\right]}{[1 + K_{assoc}P_m]} \quad \text{(Eq. 17)}$$

In view of the great excess of tetrahydrofuran present in all experiments

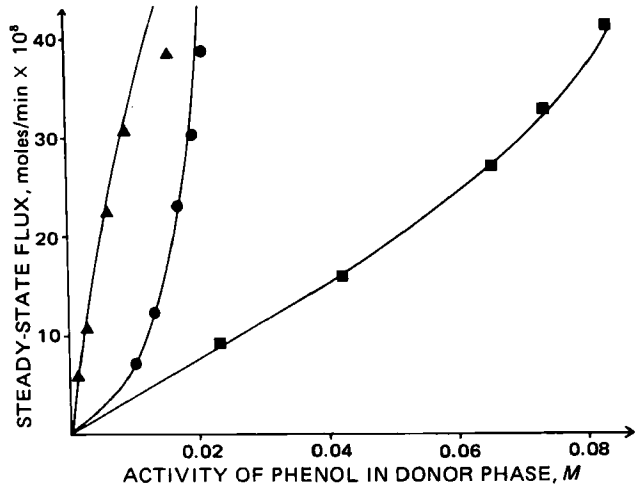

Figure 3—*Steady-state flux* versus *activity of phenol (free concentration) in the donor phase. Solid lines represent computer-generated results. Key: (▲) data from experiments in which 4.76% (v/v) tetrahydrofuran was used; (●) data from experiments in which an approximately 2:1 ratio of tetrahydrofuran to phenol was used; (■) control experiments in which no tetrahydrofuran was used.*

in which this complexing agent was used and also the magnitude of the association constant between phenol and tetrahydrofuran, it is reasonable to assume that the self-association of phenol was negligible in these experiments. For example, at $T_T = 0.5872\ M$ and $P_T = 0.1403\ M$, $[P_5] = 3.7 \times 10^{-7}\ M$.

Neglecting the contribution of the pentamer allowed the terms for diffusion of the self-associated species to be omitted. Eq. 13 is then simplified to give the following expression:

$$\frac{\partial P_m}{\partial t} = \frac{\left[\frac{\partial^2 P_m}{\partial x^2}[D_P + D_{P\text{-}T}K_{assoc}T] + D_{P\text{-}T}K_{assoc}P_m\frac{\partial^2 T}{\partial x^2} + 2\frac{\partial P_m}{\partial x}\frac{\partial T}{\partial x} - K_{assoc}P_m\frac{\partial T}{\partial t}\right]}{[1 + K_{assoc}T]} \quad \text{(Eq. 18)}$$

Since Eq. 18 is in the same form as Eq. 17, these two interdependent equations can then be solved simultaneously to determine the concentration profiles of phenol and tetrahydrofuran in the diffusion layer at a given time. Owing to the complexity of the equations involved, it was convenient to use numerical methods to obtain the required solutions. The computer program, based on the approaches described previously (9), used an implicit method of solution of differential equations of similar form. Approximate algebraic expressions, written on the $(n + 1)$ time step, were found by applying the central difference approximation to the derivative term which were thus converted to finite difference expressions. Equations 17 and 18 are nonlinear and coupled equations. To linearize and effectively decouple the equations, the following approximations were used for Eq. 17:

$$T\frac{\partial^2 P_m}{\partial x^2} = \frac{P_{n,i-1} - 2P_{n,i} + P_{n,i+1}}{\Delta x^2}T_{n+1,i}$$

$$\frac{\partial P_m}{\partial x}\frac{\partial T}{\partial x} = \frac{P_{n,i} - P_{n,i-1}}{\Delta x}\frac{T_{n+1,i} - T_{n+1,i-1}}{\Delta x}$$

$$T\frac{\partial P_m}{\partial t} = T_{n+1,i}\frac{P_{n,i} - P_{n-1,i}}{\Delta t}$$

Analogous approximations were made for the equivalent expressions in the equation governing phenol transport (Eq. 18). Since the tetrahydrofuran concentration profile was solved first for a given time step, the current values of $T_{n,i}$ were retained rather than substituting those from the previous time step:

$$P\frac{\partial T}{\partial t} = P_{n+1,i}\frac{T_{n+1,i} - T_{n,i}}{\Delta t}$$

From these expressions, it can be seen that the dependent variable on which the equation was written, *e.g.*, T in Eq. 17, was always taken to be the variable on which the terms were written implicitly. This effectively decoupled Eqs. 17 and 18, allowing them to be solved separately as sets of linear algebraic expressions to give the concentration profiles for phenol and tetrahydrofuran in the diffusion layer at a given time.

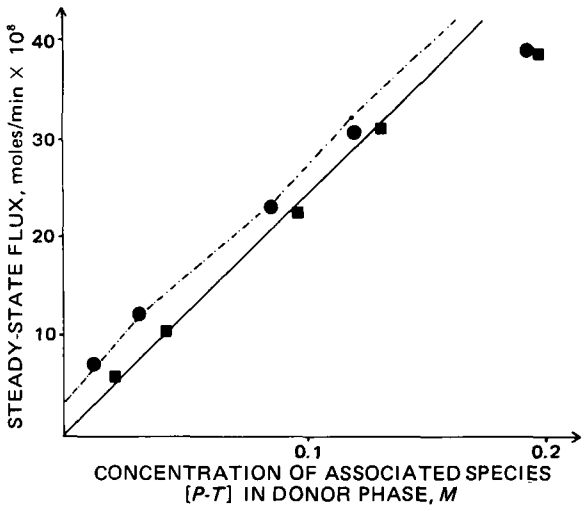

Figure 4—*Steady-state flux* versus *concentration of associated phenol in the donor phase for experiments in which 4.76% (v/v) tetrahydrofuran was used. Key: (■) the experimental data and (——) the computer-generated results. For experiments in which an approximate 2:1 ratio of tetrahydrofuran to phenol was used; (●) the experimental data and (- - -) joins computer-generated data points. Standard deviations for experimental data are incorporated into the size of the symbol.*

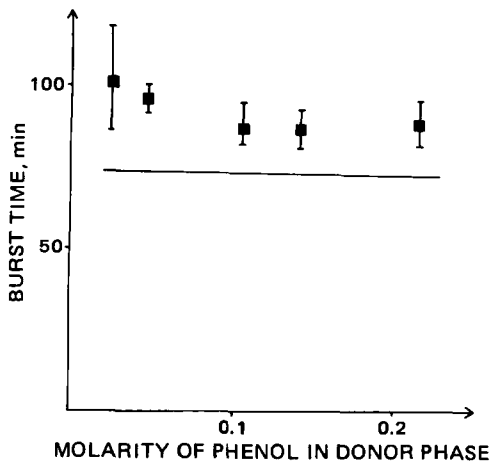

Figure 5—*Burst time* versus *concentration of phenol in the donor phase, for experiments in which 4.76% (v/v) tetrahydrofuran was used. Key: (——) computer-generated results; (■) average values observed; (⊥) ranges observed.*

It should be noted that the sets of linearized decoupled equations for Eqs. 17 and 18 can be solved iteratively for T_{n+1}^{j+1} and P_{n+1}^{j+1} such that the jth solution of the two sets of equations allows for the more accurate approximations of the nonlinear portions of the expressions. However, by choosing sufficiently small values of t, the assumed and calculated values of the derivatives differed only by a tolerably small amount after the first iteration, and therefore, iterative solutions were not required.

The coefficients of the set of linear equations for tetrahydrofuran were arranged in a matrix and solved by a method equivalent to Gaussian elimination using the subroutine TRIDAG (9) to give the current diffusion layer concentration profile of tetrahydrofuran. The same method was then applied to determine current concentrations of phenol in the diffusion layer.

From the gradients of phenol and tetrahydrofuran concentrations at the interface between the immobilized isooctane layer and the aqueous phase, the flux into the aqueous phase and subsequently the cumulative concentration in the aqueous phase was determined for each species at successive times. Since the concentrations in the aqueous phase remained consistently low, sink conditions were applied at the isooctane–aqueous phase interface for the purpose of calculating flux into the aqueous phase. This assumption may have introduced some error into the calculated steady-state flux predictions, especially at the higher donor phase concentration of phenol, and into the burst time calculations.

Typical computer-generated concentration profiles within the membrane at steady state are shown in Fig. 2 for donor phase concentrations of 0.1043 M phenol and 0.5872 M tetrahydrofuran. The gradient of the free tetrahydrofuran is linear due to the large excess of tetrahydrofuran present, but the profiles of both the associated and free phenol are nonlinear owing to the association equilibrium with tetrahydrofuran.

EXPERIMENTAL

Materials—Commercially obtained analytical reagent grade phenol[2] was fractionally distilled under vacuum to remove the preservative and other contaminants and then stored under nitrogen in a desiccator.

Tetrahydrofuran[3], containing 0.025% butylated hydroxytoluene as a preservative, was distilled from benzophenone and sodium under nitrogen, and then collected over activated 4-Å molecular sieves[4]. Batches were discarded 4 days after distillation.

Certified ACS isooctane (2,2,4-trimethylpentane)[3] was used without further purification.

Diffusion Apparatus and Study—The diffusion apparatus and the analytical procedure for phenol were described in a previous paper (6). The cutoff point for tetrahydrofuran in the UV region was 220 nm. It did not interfere with the assay of samples for phenol. Three different solution compositions were used at each concentration of phenol studied:

1. Fifty milliliters of the phenol in isooctane solution plus 2.5 ml of isooctane were used. Experiments in which solutions of this composition were used provided control data for comparison with diffusion data from experiments in which tetrahydrofuran was used.
2. Fifty milliliters of the phenol in isooctane solution, sufficient tetrahydrofuran to provide a ratio of ~ 2:1 tetrahydrofuran to phenol, and 2.5 ml (less the volume of tetrahydrofuran used) of isooctane were used.
3. Fifty milliliters of the phenol in isooctane solution plus 2.5 ml of tetrahydrofuran were used. The concentration of tetrahydrofuran present in these solutions was 0.5872 M (4.76% v/v).

The solutions required were prepared and added immediately to the tube containing the silanized sintered glass filter. Each solution was allowed to equilibrate with the filter for 3 min, enabling an immobilized layer of solution to be established within the filter. At the end of 3 min, the lower face of the filter was carefully wiped dry and the tube lowered into the jacketed beaker containing the aqueous phase, the temperature of which was maintained at 25°. When overhead and aqueous phase stirrers were turned on, the study was begun. Samples were taken from the aqueous phase at convenient times, replacing the volume removed with distilled, deoxygenated water. At the conclusion of the experiment the samples were analyzed for phenol. Further experimental details were presented in a previous study (6).

RESULTS AND DISCUSSION

Diffusion of phenol from the donor isooctane phase, through an immobilized layer of isooctane within the silanized sintered glass filter, into an aqueous receptor phase was followed by determination of the cumulative concentration of phenol in the aqueous phase at times ≤300 min. When tetrahydrofuran was used, it was present initially in both the donor phase solution and the diffusion layer. It was assumed that the association equilibrium between phenol and tetrahydrofuran was established in both the diffusion layer and the donor phase and that all species were capable of diffusing through the immobilized isooctane layer into the aqueous phase. For each type of experiment, four runs were made at each of the five phenol concentrations studied. Steady-state flux was calculated from the slope of the concentration *versus* time plot using vaues obtained at times of 100 min or longer. Runs were rejected if the linear regression correlation coefficient for the data used to calculate the slope fell below 0.999, to minimize variation in the steady-state flux and burst time values.

Steady-State Flux—When simultaneous association and diffusion occur, the rate of diffusion may increase, decrease, or remain the same. The change in the diffusion rate depends on the size of the associated species formed, its ability to penetrate or partition into the diffusion layer, and the extent to which complexation occurs.

Figure 3 shows a plot of steady-state flux *versus* concentration of free phenol (defined as activity) present in the donor phase. In the control experiments, there was a positive deviation from linearity at high phenol activities. This was accounted for by the contribution of the diffusion of

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

Table I—Concentrations of Various Species in Solution at Given Total Concentrations of Phenol and Tetrahydrofuran (Molar)

$[T_T]$	$[P_T]$	P	$5P_5$	$[P-T]$	$[T]$	$[T_T]:[P_T]$
0.5872	0.0233	0.0012	8.5×10^{-11}	0.0220	0.5651	-
0.5872	0.0461	0.0025	3.0×10^{-9}	0.0436	0.5435	-
0.5872	0.1034	0.0062	2.9×10^{-7}	0.0972	0.4900	-
0.5872	0.1403	0.0090	1.9×10^{-6}	0.1313	0.4559	-
0.5872	0.2130	0.0158	3.3×10^{-5}	0.1988	0.3900	-
0.0534	0.0233	0.0102	3.5×10^{-6}	0.0131	0.04026	2.29
0.1100	0.0461	0.0133	1.3×10^{-5}	0.0328	0.0772	2.39
0.2460	0.1034	0.0170	4.5×10^{-5}	0.0867	0.1493	2.39
0.3160	0.1403	0.0193	8.4×10^{-5}	0.1206	0.1954	2.25
0.4834	0.2130	0.0207	1.2×10^{-4}	0.1926	0.2908	2.27

the self-associated pentameric phenol to the overall rate of flux. In the presence of tetrahydrofuran, the steady-state flux at a given activity of phenol was greatly enhanced. The effect was more pronounced when 4.76% (v/v) tetrahydrofuran was present than when a 2:1 ratio of tetrahydrofuran to phenol was added. In both cases the increase in steady-state flux could be attributed to diffusion of the phenol–tetrahydrofuran-associated species. When 4.76% (v/v) tetrahydrofuran was used, the extent of association was greater owing to the larger excess of complexing agent present. This led to a greater enhancement of the steady-state flux values than observed for the 2:1 excess experiments, in which a significant proportion of phenol present remained unassociated.

In the 4.76% (v/v) tetrahydrofuran experiments, almost all of the phenol was expected to be associated with tetrahydrofuran (Table I). Therefore, the steady-state flux was expected to have an approximately linear relationship to the concentration of associated species present as shown in Fig. 4. Except at the highest concentration of phenol, the 4.76% (v/v) tetrahydrofuran data fall along a straight line within experimental error. This deviation at the higher donor phase phenol concentrations may arise from changes in the composition of the neighborhood of molecules surrounding each molecule. Since the theoretical development does not account for changes in the activity coefficient of the free phenol, a deviation of this nature is not surprising.

For a given concentration of associated phenol, a higher steady-state flux was predicted and observed when a 2:1 ratio of tetrahydrofuran to phenol was used than when 4.76% (v/v) tetrahydrofuran was present. This result was accounted for by the following model. In the 4.76% (v/v) tetrahydrofuran experiments virtually all flux was due to diffusion of the associated species. However, in the 2:1 ratio experiments, a significant proportion of phenol was present as free phenol. Since free phenol was able to diffuse across the immobilized isooctane layer at a faster rate than that of the larger associated species, it was able to contribute significantly to the overall flux into the aqueous phase. This resulted in a larger steady-state flux than would be predicted by considering only the contribution of the associated phenol. The differences in the steady-state flux data were most pronounced at low total concentrations of phenol. At those concentrations, the disparity in percentage of phenol present in unassociated form was also greatest (Table I), supporting the arguments derived from the model.

Overall, the steady-state flux results showed that for a system in which the associated species can penetrate the diffusion layer, the flux for a given total concentration of drug decreases as the concentration of complexing agent present increases. This is accounted for by the lower diffusivity of the larger associated species.

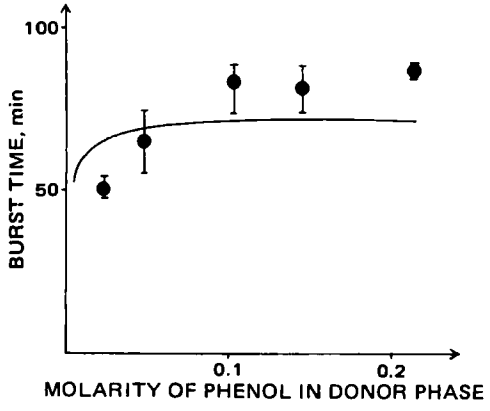

Figure 6—*Burst time* versus *concentration of phenol in the donor phase for experiments in which an approximate 2:1 ratio of tetrahydrofuran of phenol was used. Key: (——) computer-generated results; (●) experimentally observed results; (⊥) ranges.*

Transient Behavior (Burst Time)—As for the more commonly reported time lag, the burst time is inversely proportional to the diffusivity of the diffusing species. When diffusion of one species accounts for the entire flux observed, the burst time is related to the diffusivity of that species. In such cases, the burst time is independent of the donor phase concentration of the diffusing species.

Figure 5 shows the plot of burst time *versus* concentration of phenol in the donor phase in the presence of 4.76% (v/v) tetrahydrofuran. Burst time was calculated by extrapolating the steady-state portion of the concentration *versus* time plot back to zero concentration. Although there is considerable scatter in the results, the burst time was essentially independent of concentration, indicating that one species accounted for most of the mass transport observed. The excess of tetrahydrofuran was large enough in these experiments to ensure that virtually all phenol (93–98%) present was associated with tetrahydrofuran. It was proposed, therefore, that the diffusion of the associated species accounted for the greater fraction of the flux. The large value for the burst time observed in the 4.76% tetrahydrofuran experiments supported this proposal. Since large molecules have lower diffusivities, burst time tends to increase with molecular size. The average burst time observed in these experiments was ~90 min. This time was much greater than the burst time of ~35 min which was calculated for a diffusion system in which only monomer phenol was present (6).

Figure 6 depicts the burst time *versus* the donor phase concentration data for experiments in which a 2:1 ratio of tetrahydrofuran to phenol was used. The theory predicted that the burst time would be shorter at low donor phase phenol concentrations, since in those cases the percentage of phenol in the associated form was considerably lower than at high phenol concentrations (Table I). The smaller free phenol molecules were able to diffuse faster than the associated species so that when free phenol was present in significant quantities, the system came to steady state more rapidly and exhibited a shorter burst time. The observed burst times were similar to the predicted relationship. However, the effects were magnified somewhat.

The failure of the numerical solution of the derived equations to predict exactly the overall burst time was probably due partly to the boundary condition used for the aqueous phase–diffusion layer interface in the computer program (*i.e.*, sink conditions) and partly to an artifact of the experimental method. As in the phenol experiments described previously (7), small amounts of phenol on the lower face of the sintered glass filter may have been released immediately upon contact with the aqueous phase. This would result in high values for cumulative concentration in the aqueous phase and higher burst times than predicted. Build-up of tetrahydrofuran in the aqueous phase may also have affected partitioning of phenol between the diffusion layer and the aqueous phase, which would again alter the concentration of phenol attained in the aqueous phase.

Despite the great reduction in activity of phenol caused by the addition of a complexing agent, the overall transport rate of phenol for a given total concentration of phenol was almost as fast as in a complexing agent-free system. This consistency in transport rates was attributed to the ability of the associated tetrahydrofuran–phenol complex to form in and diffuse through the diffusion layer. A set of equations derived in terms of readily obtainable parameters were found to adequately account for all the data except that obtained at high concentration of phenol. Thus, it was possible to explain the seemingly complicated relationship between steady-state flux diffusional behavior and donor-phase concentration of phenol in the presence of a codiffusing species using the familiar concept of associative interactions.

In the system studied, all species formed were capable of penetrating the diffusion layer. Comparing the results of the 4.76% (v/v) tetrahydrofuran and the twofold excess tetrahydrofuran experiments, it appears

that the excessive use of an excipient capable of complexing with a drug could result in a markedly reduced rate of delivery of that drug by simultaneously lowering the drug's activity and apparent diffusivity. Although such an effect is undesirable in most circumstances, it may be possible to use this effect to advantage in the design of slow-release preparations.

REFERENCES

(1) T. Higuchi and M. Ikeda, *J. Pharm. Sci.*, **63**, 809 (1974).

(2) B. Kreilgaard, T. Higuchi, and A. J. Repta, *ibid.*, **64**, 1850 (1975).

(3) J. W. McGinity and J. L. Lach, *ibid.*, **66**, 63 (1977).

(4) W. L. Hayton, D. E. Guttman, and G. Levy, *ibid.*, **59**, 575 (1970).

(5) M. Donbrow and E. Touitou, *ibid.*, **67**, 95 (1978).

(6) J. B. Dressman, K. J. Himmelstein, and T. Higuchi, *ibid.*, **71**, 1226 (1982).

(7) V. S. Vaidhyanathan, *ibid.*, **61**, 894 (1972).

(8) B. D. Anderson, J. H. Rytting, and T. Higuchi, *J. Am. Chem. Soc.*, **101**, 5194 (1979).

(9) B. Carnahan, H. A. Luther, and J. O. Wilkes, "Applied Numerical Methods," Wiley, New York, N.Y., 1969, pp. 440–442, 464.

ACKNOWLEDGMENTS

This work was supported by Grant GM-22357 from the National Institutes of Health.

Zero-Order Controlled-Release Polymer Matrices for Micro- and Macromolecules

DEAN S. T. HSIEH *, WILLIAM D. RHINE, and ROBERT LANGER ˣ

Received May 20, 1981, from the *Department of Nutrition and Food Science, Massachusetts Institute of Technology, Cambridge, MA 02139,* the *Department of Surgery, Children's Hospital Medical Center, Boston, MA 02115,* and the *Harvard Medical School, Boston, MA 02115.* Accepted for publication February 26, 1982. *Present address: Department of Pharmaceutics, Rutgers University, Piscataway, N.J.

Abstract □ Theoretical and experimental analyses demonstrate that a hemispheric polymer–drug matrix laminated with an impermeable coating, except for an exposed cavity in the center face, can be used to achieve zero-order release kinetics. Hemispheric systems for low molecular weight drugs were prepared by heating and compressing polyethylene and drug (sodium salicylate) in a brass mold. Hemispheric systems for high molecular weight drugs were prepared by casting ethylene–vinyl acetate copolymer and protein in a hemispheric mold at −80°, followed by a two-step drying procedure (−20 and 20°). In both systems, cavities were made in the center face of the hemispheres and the remainder of the matrices coated with an impermeable material. Zero-order release for 60 days at a rate of 0.5 mg/day was achieved from polymer matrices containing bovine serum albumin (mol. wt. 68,000).

Keyphrases □ Drug delivery system—zero-order controlled-release polymer matrices, micro- and macromolecules □ Controlled-release delivery—zero-order, polymer matrices, micro- and macromolecules □ Polymers—matrices, zero-order controlled-release, micro- and macromolecules □ Sustained-release delivery—zero-order controlled-release polymer matrices, micro- and macromolecules

Diffusion-controlled matrix devices have been among the most widely used drug delivery systems, but a disadvantage frequently cited is their inability to achieve zero-order release kinetics (1–3). Most matrix devices have been designed in the form of a rectangular slab, and it has been observed that the cumulative release of drug is inversely proportional to the square root of time (4–8).

One possible means of altering release kinetics from matrix systems is to vary the matrix geometry. The influence of shape on kinetics of drug release from matrix tablets in spherical, cylindrical, and biconvex shapes has been evaluated (9, 10). It was predicted (11) that a matrix in the shape of a sector of a right circular cylinder would release drug at a zero-order rate. This analysis was more critically evaluated, and it was found that true zero-order kinetics were not achieved in practical cases but that this shape resulted in release rates that were initially high and then began to approach, but not achieve, linearity (12). A limitation cited in both studies was the need for effective procedures to fabricate these delivery systems and the requirement for further experimental testing.

In a previous study, a theoretical analysis suggested that a hemisphere with all portions laminated with an impermeable coating, except for a small cavity cut into the center of the flat surface, could achieve zero-order release kinetics (13).

In the present study, experimental results have been obtained that provide support for the theoretical analysis. Two types of fabrication procedures are presented here to demonstrate that the hemisphere design is universally suitable for either low or high molecular weight drugs.

THEORETICAL

Assuming that the drug is released from a solid matrix device by diffusion, a steady-state condition exists, and the area for mass transport,

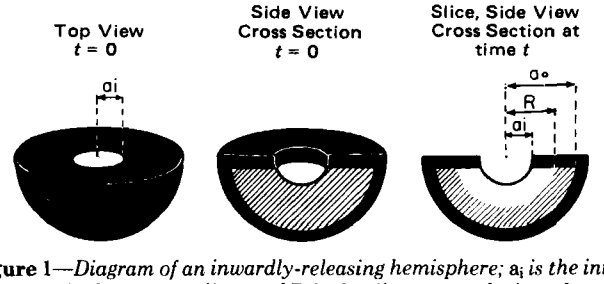

Figure 1—*Diagram of an inwardly-releasing hemisphere;* a_i *is the inner radius,* a_o *is the outer radius, and* R *is the distance to the interface between the dissolved region (white area) and the dispersed zone (diagonal lines). Black represents laminated regions through which release cannot occur.*

0022-3549/83/0100-0017$01.00/0