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MODELS FOR RELEASE OF CHLORPHENIRAMINE AND A NONINTERACTING COMPOUND FROM AN INERT, HETEROGENEOUS MATRIX CONTAINING AN ANIONIC SURFACTANT

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ABSTRACT

Diffusional models in which the mole ratio of surfactant to medicinal compound does not exceed one are applied to the release of chlorpheniramine maleate from chlorinated poly(propylene) matrixes and from matrixes containing anionic surfactants (sodium lauryl sulfate, dioctyl sodium sulfosuccinate) that interact to form a poorly water-soluble complex. The release of a second, noninteracting compound (sodium benzoate) from these matrixes is also considered in the models. The models suggest that the rate of release is slowed by complexation reducing the amount of medicinal compound in solution and concomitantly increasing the tortuosity and decreasing the porosity of the matrix.

INTRODUCTION

The release of highly water-soluble medicinal compounds from an inert, heterogeneous matrix has been characterized (1-4). The addition of surfactants to such matrixes has increased the release presumably due to a lowering of surface tension and decrease of contact angle (5). It was found that with cationic medicinal compounds (procaine hydrochloride, chlorphenirmaine maleate) the addition to the matrix of increasing concentration of an anionic surfactant (sodium lauryl sulfate, dioctyl sodium sulfosuccinate) slowed release to a minimum due to formation of a poorly water-soluble complex; and as the concentration of the anionic surfactant was further increased to mole ratio of surfactant to medicinal compound exceeding one, the release was faster as the complex was solubilized in the micellar phase as an ion-pair (6). This interaction also effected the release profile from a matrix of a second compound that did not interact with the surfactant.

The purpose of this report is to present models representing the release pattern of chlorpheniramine maleate and sodium benzoate from a nonswelling, heterogeneous matrix containing an oppositely charged surfactant (sodium lauryl sulfate, dioctyl sodium sulfosuccinate) (6).

EXPERIMENTAL

The methods of preparation and characterization of the matrixes have been described (5). The conditions and procedure for measuring the release of chlorpheniramine maleate and sodium

TABLE 1

Matrix Formulations of Chlorpheniramine Maleate (CPM), Lactose, Chlorinated Poly(propylene) (CPP), Sodium Benzoate (SB) and Sodium Lauryl Sulfate (SLS) or Dioctyl Sodium Sulfosuccinate (DSS)

Matrix	Milligrams						Percent Surfactant
	CPM	CPP	Lactose	SLS	DSS	SB	
1	40	300	60				0
2	40	300	45	15			3.75
3	60	240	140				0
4	60	240	105		29.75	5.25	6.76
5	60	240	70		59.50	10.50	13.52

benzoate from matrixes of chlorinate poly(propylene) containing sodium lauryl sulfate or dioctyl sodium sulfosuccinate and the data were recently reported (6). The matrix formulations are given in Table 1.

RESULTS AND DISCUSSION

Initially the significance of an aqueous diffusion layer was assessed. The release of chlorpheniramine maleate (CPM) from matrix 1, which contained no surfactant, was measured at 150 and 300 rpm. The difference in agitation had no significant effect on the release profiles. Therefore, the contribution of an aqueous diffusion layer to release from the matrix appears to be negligible.

The original Higuchi model relating the amount released from an inert, heterogeneous matrix to time and to variables of the

matrix may be expressed

$$Q = \sqrt{\frac{D\varepsilon C_s t(2A - \varepsilon C_s)}{\tau}} \qquad \text{(Eq. 1)}$$

in which Q is the amount of compound released per unit area at time t, D is the diffusion coefficient, C_s is the solubility in the dissolution medium, ε is the porosity, τ is the tortuosity and A is the load in g/cm^3. The assumptions and the derivation of the Higuchi equation are well known (7). In this model only one compound is present in the matrix, only one region in the matrix contains dissolved compound, and the concentration profile is linear. If $2A >> \varepsilon C_s$ the Higuchi equation simplifies to

$$Q = \sqrt{2DA\varepsilon C_s t/\tau} \qquad \text{(Eq. 2)}$$

If the compound is highly water-soluble and/or the compound is present at low concentration $(A/\varepsilon < C_s)$, the highest concentration attainable is

$$C = A/\varepsilon \qquad \text{(Eq. 3)}$$

Substituting Eq. 3 into Eq.1 yields

$$Q = A\sqrt{Dt/\tau} \qquad \text{(Eq. 4)}$$

which states that Q is proportional to A in contrast to Eq. 1 that states that Q is proportional to the square root of A.

The parameters of matrix 1 are given in Table 2 (6). The diffusion coefficient was calculated by the Stokes-Einstein relationship (8). $A\ \tau = 44$ provided the best fit of the experimental and calculated values of Q. The experimental

TABLE 2
Parameters of Matrixes Used to Calculate Release of Chlorpheniramine

Parameter	Matrix	
	1	2
A, g/cm^3	0.146	0.145
10^6 D, cm^2/s	7.664	
10^6 D_2, cm^2/s		7.281
τ	44	
τ_2		50
ε	0.374	
ε_2		0.272
C_2, g/cm^3		0.262

release and the release calculated by Eq. 4 of chlorpheniramine maleate (CPM) from a chlorinated poly(propylene) matrix containing no surfactant are shown in Figure 1.

Release of Chlorpheniramine Maleate from Matrixes Containing an Oppositely Charged Surfactant. In a matrix containing a infinitesimal concentration of an oppositely charged surfactant that complexes with the medicinal compound the load of the surfactant is extremely small compared to the load of the medicinal compound. Theoretically, at an infinitesimal concentration of the surfactant, the product of the free medicinal compound and free surfactant does not exceed the

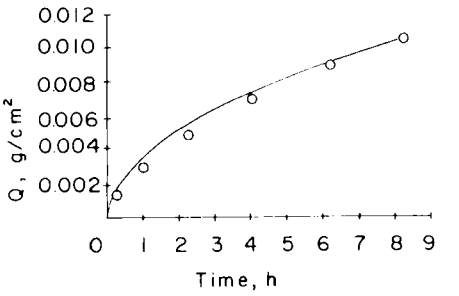
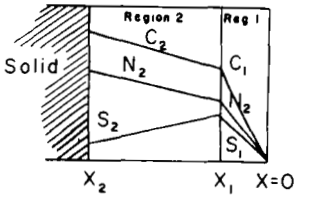


FIGURE 1

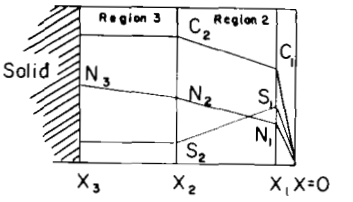
Experimental and calculated release of CPM from matrix 1. Solid line represents values calculated using Eq. 4.

solubility product, and the minute amount of complex formed would not precipitate. Experimentally this would be difficult to demonstrate as the solubility product is very small (9).

When the medicinal compound and surfactant interact to form a poorly soluble complex and the load of surfactant is less than the critical concentration required for solubilization of the complex, the concentration profiles of free medicinal compound and free surfactant can be represented by a two regions model shown in Figure 2a. In the region 1 from X_1 to X_0 the concentration of the free medicinal compound and free surfactant are increasing as the matrix is penetrated. The concentration of free medicinal compound continues to increase as penetration continues to X_2; however, the concentration of free surfactant decreases as complexation occurs. If the concentrations of free medicinal compound, C_1, and free surfactant, S_1, in region 1 are much less than in region 2 and the concentrations in region 2



(a) Two Regions



(b) Three Regions

FIGURE 2

Two and three regions models of concentration gradient in a inert, heterogeneous matrix with C the concentration of free medicinal compound, S the concentration of surfactant and N the concentration of noninteracting compound. Subscripts refer to region.

are increasing concurrently, the contribution to the flux of region 1 is insignificant compared to region 2.

Since region 1 is minute and the concentration of free surfactant is zero at $X = 0$ and has a finite value at X_2, the total flux of free surfactant is from the matrix. Assuming that $C_2 >> C_1$ and $X_2 >> X_1$, the flux of medicinal compound from the matrix is

$$dQ/dt = (D_2 \varepsilon_2 C_2) / (\tau_2 X_2) \qquad \text{(Eq. 5)}$$

The cumulative amount, Q, of medicinal compound released per unit surface area of matrix exposed to the dissolution medium is equal to the load, A, of medicinal compound multiplied by the

depth of penetration, X_2, minus the amount of medicinal compound still in solution in the pores of the matrix ($1/2\ \varepsilon_2 C_2 X_2$). Thus,

$$Q = (A - 1/2\ \varepsilon_2 C_2)X_2 \qquad \text{(Eq. 6)}$$

The derivative of Eq. 6 with respect to time is

$$dQ/dt = (A - 1/2\ \varepsilon_2 C_2)dX_2/dt \qquad \text{(Eq. 7)}$$

Equating Eq. 5 and 7 and rearranging yields

$$\int_0^{X_2} X_2 dX_2 = \int_0^{t} \frac{D_2 \varepsilon_2 C_2}{\tau_2 (A - 1/2\ \varepsilon_2 C_2)}\, dt \qquad \text{(Eq. 8)}$$

Integrating Eq. 8 and solving for X_2 yields

$$x_2 = \sqrt{\frac{2 D_2 \varepsilon_2 C_2 t}{\tau_2 (A - 1/2\ \varepsilon_2 C_2)}} \qquad \text{(Eq. 9)}$$

Substituting Eq. 9 into Eq. 6

$$Q = \sqrt{D_2 \varepsilon_2 C_2 \frac{t}{\tau_2} (2A - \varepsilon_2 C_2)} \qquad \text{(Eq. 10)}$$

Equation 10 has the form of the Higuchi equation except the parameters refer to region 2. Although Eq. 10 does not explicitly address complexation, complexation is accounted for in the C_2 term that is a function of the solubility product of the complex. To test the applicability of Eq. 10 to release of

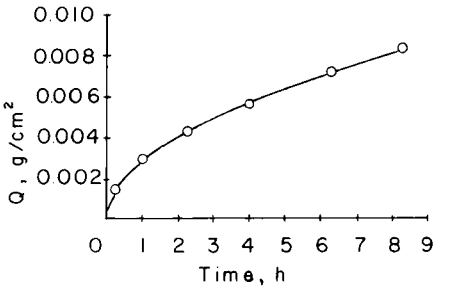


FIGURE 3

Experimental and calculated release of CPM from matrix 2 containing SLS. Solid line represents values calculated by Eq. 10.

CPM from matrixes containing mole ratios of SLS to CPM less than 1, the calculated and experimental values of Q from matrix 2 are compared in Figure 3.

The parameters are given in Table 2. It was assumed that the surfactant was converted into the complex. Therefore, the moles of SLS present in the matrix were subtracted from the moles of CPM present and divide by the volume due to air and excipient in the matrix. The porosity of region 2 was estimated. Knowing the moles of SLS and CPM precipitating as the complex, the volume of complex was estimated using the densities of SLS and CPM (5). This volume was subtracted from the volume due to air, SLS and CPM and divided by the total volume of the matrix. Using ε_2 the initial estimated C_2 was corrected for this reduction in porosity. A tortuosity was selected that best fit the experimental and calculated values of Q. Logically, the value

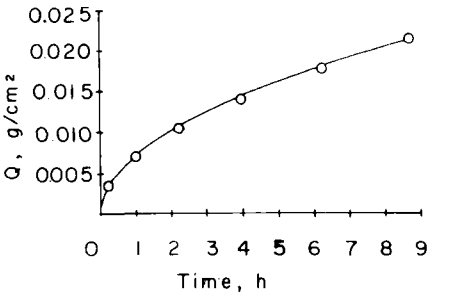


FIGURE 4

Experimental and calculated release of CPM from matrix 3. Solid line represents values calculated by Eq. 4.

$\tau_2 = 50$ would be greater than the $\tau = 44$ for the matrix containing no surfactant because complexation would cause a more tortuous diffusional pathway.

Simultaneous Release of a Noninteracting Compound and Chlorpheniramine from a Matrix Containing an Oppositely Charged Surfactant. Using Eq. 4 the values of Q were calculated for matrix 3 containing no surfactant and are compared to the experimental values in Figure 4. Parameters of matrix 3 are given in Table 3.

The two regions model shown in Figure 2a represents the concentration profiles of chlorpheniramine maleate, an oppositely charged surfactant and noninteracting sodium benzoate. The release of the sodium benzoate is expressed by Eq. 10. If sodium benzoate is present in low load, $A/\varepsilon_2 < C_s$ and substituting A/ε_2

$$Q = A\sqrt{D_2 t/\tau_2} \qquad \text{(Eq. 11)}$$

TABLE 3

Parameters of Matrixes Used to Calculate Release of Chlorpheniramine Maleate and Sodium Benzoate from Two Regions Model

Parameters	Matrixes				
	3	4	5	4	5
	Chlorpheniramine			Sodium Benzoate	
A, g/cm^3	0.196	0.190	0.189	0.017	0.033
10^6 D, cm^2/s	7.664				
10^6 D_2, cm^2/s		6.898	6.898	10.75	10.750
τ	20				
τ_2		30	40	30	40
ε	0.559				
ε_2		0.412	0.271		
C_2, g/cm^3		0.259	0.088		

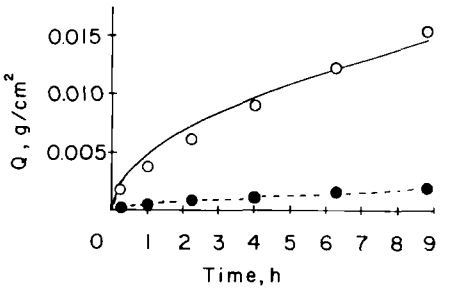


FIGURE 5

Experimental and calculated release of CPM and SB from matrix 4. Key: (○) CPM; and (●) SB. Solid and dashed lines represent values calculated by Eq. 10 and 24, respectively.

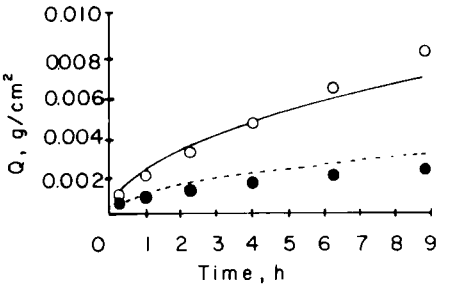


FIGURE 6

Experimental and calculated release of CPM and SB from matrix 5. Key: (○) CPM; and (●) SB. Solid and dashed lines represent values calculated by Eq. 10 and 24, respectively.

The release of chlorpheniramine and sodium benzoate was calculated for matrix 4 using the values of the parameters given Table 3. If $\tau = 30$ for region 2, the experimental and calculated values are in good agreement as shown in Figure 5. This tortuosity appears reasonable as it is greater than that of surfactant-free matrix 3, because precipitation of the poorly soluble complex produces a more tortuous diffusional path for all compounds.

Similarly, for matrix 5 the calculated and experimental values of Q for chlorpheniramine and sodium benzoate are compared in Figure 6. A $\tau = 40$ provided the best fit of the data. This appears reasonable as with a greater concentration of surfactant more complex is formed increasing the tortuosity.

The three regions model shown in Figure 2b has in region 3 a zero concentration gradient of the medicinal compound and oppositely charged surfactant and the concentration gradient of

the noninteracting compound is increasing. The existence of region 3 was suggested by the fact that experimentally the percent of SB released from the matrix was greater than the percent of CPM released at the same time. Although region 2 and 3 contain complex, region 3 is more tortuous and less porous.

The release of CPM may be described by Eq. 10; however, a derivation is required to describe the release of SB. The flux, F_2, of the noninteracting compound is

$$F_2 = \frac{D_2\varepsilon_2(N_2 - N_1)}{\tau_2 (X_2 - X_1)} \qquad \text{(Eq. 12)}$$

Similarly, the flux, F_3, of the noninteracting compound through region 3 may be written

$$F_3 = \frac{D_3\varepsilon_3(N_3 - N_2)}{\tau_3 (X_3 - X_2)} \qquad \text{(Eq. 13)}$$

Assuming diffusional continuity at the boundaries, Eq 12 and 13 may be equated and solved for C_2. If $N_2 >> N_1$ and $X_2 >> X_1$,

$$N_2 = \frac{D_3\varepsilon_3\tau_2X_2N_3}{D_2\varepsilon_2\tau_3(X_3 - X_2) + D_3\varepsilon_3\tau_2X_2} \qquad \text{(Eq. 14)}$$

Solving Eq. 13 for N_2 and equating with Eq. 14 yields

$$F_3 = \frac{D_3\varepsilon_3N_3}{X_2\tau_3[(X_3 - X_2)/X_2]} \qquad \text{(Eq. 15)}$$

$$\frac{D_3^2\varepsilon_3^2\tau_2N_3}{\tau_3(X_3 - X_2)[D_2\varepsilon_2\tau_3(X_3 - X_2)/X_2) + D_3\varepsilon_3\tau_2]}$$

Combining X_3 and X_2 into a constant and assuming that K does not vary with time (10)

$$K = (X_3 - X_2)/X_2 \qquad \text{(Eq. 16)}$$

Substituting of Eq. 16 into Eq. 15 in region 3 and solving

$$F_3 = \frac{D_3\varepsilon_3N_3\ (1 + K)}{X_3[\tau_3K + (D_3\varepsilon_3\tau_2)/(D_2\varepsilon_2)]} \qquad \text{(Eq. 17)}$$

By mass balance the total amount of compound released per unit area is equal to the load of the compound multiplied by the depth of penetration of the solvent minus the amount of compound still in solution within the pores of the matrix. Assuming the amount of noninteracting compound in solution in region 1 is negligible, the mass balance

$$Q = AX_3 - 1/2\ \varepsilon_3N_3X_3 + 1/2\ \varepsilon_3N_3X_2 - 1/2\ \varepsilon_3N_2X_3 + 1/2\ \varepsilon_3N_2X_2 - 1/2\ \varepsilon_2N_2X_2 \qquad \text{(Eq. 18)}$$

Assuming that the last four terms are negligible, the derivative with respect to time is

$$dQ/dt = [A - 1/2\ \varepsilon_3N_3](dX_3/dt) \qquad \text{(Eq. 19)}$$

As $dQ/dt = F_3$, Eq. 19 may be equated to Eq. 17

$$\int_0^{X_3} X_3 dX_3 = \int_0^t \frac{D_3\varepsilon_3 N_3(1 + K)}{[A - 1/2\ \varepsilon_3 N_3][\tau_3 K + (D_3\varepsilon_3\tau_2)/(D_2\varepsilon_2)]} \quad \text{(Eq. 20)}$$

Integrating and solving for X_3

$$X_3 = \frac{2D_3\varepsilon_3 N_3(1 + K)t}{[A - 1/2\ \varepsilon_3 N_3][\tau_3 K + (D_3\varepsilon_3\tau_2/(D_2\varepsilon_2)]} \quad \text{(Eq. 21)}$$

Substituting Eq. 21 into Eq. 22

$$Q = \sqrt{\frac{D_3(1 + K)[2A - \varepsilon_3 N_3]\varepsilon_3 N_3 t}{\tau_3 K + (D_3\varepsilon_3\tau_2)/(D_2\varepsilon_2)}} \quad \text{(Eq. 22)}$$

As the concentration of surfactant, which complexes with a medicinal compound, is increased the difference between region 2 and 3 becomes negligible. Consequently, K becomes smaller as more surfactant is added to the matrix. Thus, in matrix 3, K is larger than in matrix 4 and 5. As region 3 is more tortuous and less porous than region 2 it may be assumed that in Eq. 22, $D_3/D_2 \leq 1$ and $\varepsilon_3/\varepsilon_2 < 1$ in the right hand term. For the same reason τ_3 in the left hand term is greater than τ_2 in the right hand term in the denominator. If K is larger in the matrix without surfactant than in the matrix containing surfactant, the right hand term may be ignored with respect to the left hand term in the denominator. If $K >> 1$ in the numerator, then the K terms cancel yielding

$$Q = \sqrt{[(D_3/\tau_3)(2A - \varepsilon_3 N_3)\varepsilon_3 N_3 t]} \quad \text{(Eq. 23)}$$

TABLE 4

Parameters of Matrixes Used to Calculate Release of Chlorpheniramine Maleate and Sodium Benzoate from Three Regions Model

	Matrixes			
Parameters	4	5	4	5
	Chlorpheniramine		Sodium Benzoate	
A, g/cm^3	0.190	0.189	0.017	0.033
$10^6 D_2$, cm^2/s	7.281	7.281		
$10^6 D_3$, cm^2/s			10.78	10.78
τ_2	25	35	25	35
τ_3			30	40
ε_2	0.486	0.417		
C_2	0.220	0.057		
D_3/D_2			0.95	0.95
$\varepsilon_3/\varepsilon_2$			0.848	0.65

which has the form of the Higuchi equation for a matrix without surfactant.

If the noninteracting compound is present at a low load so that saturation solubility within the pores of the matrix is not attained, substitution of $N_3 = A/\varepsilon_3$ in Eq. 22 yields

$$Q = A\sqrt{\frac{D_3(1 + K)t}{\tau_3 K + (D_3\varepsilon_3\tau_2)/(D_2\varepsilon_2)}} \qquad \text{(Eq. 24)}$$

Likewise, if the right hand term in the denominator can be

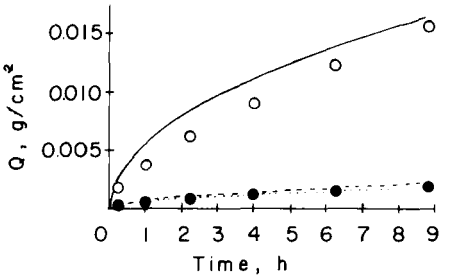


FIGURE 7

Experimental and calculated release of CPM and SB from matrix 4. Key: (○) CPM; and (●) SB. Solid line represents values calculated by Eq. 10 and broken lines represent values calculated by Eq. 24 with K = 0.05 (---) and K = 500 (•••).

ignored with respect to the left hand term in the denominator, and the 1 ignored with respect to K in the numerator, the K terms cancel yielding

$$Q = A\sqrt{D_s t/\tau_s} \qquad \text{(Eq. 25)}$$

which is the Higuchi equation for the release of a compound having a high solubility or a low load.

The three regions model was applied to describe the release of CPM and SB from matrix 4 using the parameters given in Table 4. A $\tau = 25$ seems reasonable as the tortuosity of matrix 3 without surfactant is 20. The values of Q for CPM and SB were calculated using Eq. 10 and 24, respectively. A comparison of the experimental and calculated values of Q for CPM and SB is shown in Figure 7. The release of SB appears insensitive to the

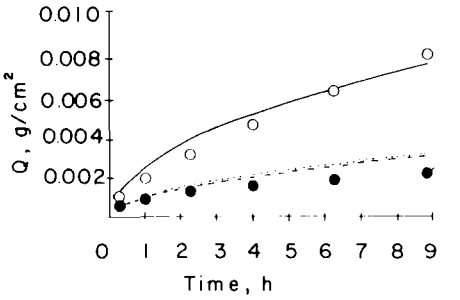


FIGURE 8

Experimental and calculated release of CPM and SB from matrix 5. Key: (○) CPM; and (●) SB. Solid line represents values calculated by Eq. 10 and broken lines represent values calculated by Eq. 24 with K = 0.05 (•••) and K = 500 (---).

value of K as four orders of magnitude produced little change in the calculated release of SB.

The three regions model was also applied to describe the release of CPM and SB from matrix 5 using the parameters given in Table 4. The tortuosity that best fit the observed data was 35 and 40 for regions 2 and 3, respectively. The greater tortuosity in region 3 seems reasonable as more surfactant is present to complex with the CPM to produce a more tortuous diffusional path. A comparison of the experimental and calculated values of Q for CPM and SB is shown in Figure 8.

CONCLUSION

The two and three regions models appear to describe the release of CPM and SB from an inert, heterogeneous matrix; however, the three regions model has the disadvantage of requiring additional assumptions, less certainty of the value of

some parameters, and initially requiring a two regions model to determine reasonable values of some parameters.

For matrixes in which the mole ratios of interacting surfactant to medicinal compound does not exceed one models support the premise that complexation not only reduces the amount of medicinal compound in solution slowing its release, but also produces a more tortuous and less porous diffusional path for its release and for the release of a second, noninteracting compound.

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