Analysis of Data on Drug Release from Emulsions II

Pyridine Release from Water-in-Oil Emulsions as a Function of pH

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The practically important case of the release from an amine–amine hydrochloride solute mixture in a water-in-oil emulsion into an aqueous sink has been studied experimentally and theoretically. All of the parameters entering into the theory have been independently measured and put into the theory. The theoretically predicted release behavior was then determined employing the IBM 7090 computer. These results were then compared to the experimental data obtained over a wide range of conditions. The agreement between the experiments and the physical model was extremely good. These procedures should have extensive application in the future when complex solute–solute, solute–solvent, and solvent–solvent interactions are involved.

$\mathbf{I}$N THE PREVIOUS paper (1), Fick's law of diffusion (Eq. 1) was used to predict medicament release from ointments:

$$\frac{\partial c}{\partial t} = \frac{\partial^2 c}{\partial x^2} \qquad \begin{array}{l} t = 0 \text{ and } x > 0, c = C_0 \\ t > 0 \text{ and } x = 0, c = 0 \end{array} \quad \text{(Eq. 1)}$$

Here C is the drug concentration, D is the diffusion coefficient, t is time, and x is the coordinate. Its solution (Eq. 2) was shown to agree with the experimental data in a satisfactory manner:

$$q = 2C_0 \sqrt{\frac{Dt}{\pi}} \qquad \text{(Eq. 2)}$$

where q is the amount of drug released per unit area.

Among other assumptions involved in these equations is that D must be constant with respect to both time and position. This is a serious limitation, because in many situations involving emulsions the diffusion coefficient is not constant but varies with concentration.

This report deals with such cases, and an attempt is made to predict the drug release from emulsions in which the diffusion coefficient of the drug is a function of concentration. Studies such as this should be helpful in drug formulation practices.

THEORY

The Effective Diffusion Coefficient—It was reported (2) that approximate relationships between the effective permeability constant of a heterogeneous system and the permeability constants and the volume fractions of the individual phases can be obtained by considering the analogous electro-

static problem. The Wagner-Wiener equation (Eq. 3) and the Bruggeman equation (Eq. 4), which were derived originally to express the dielectric behavior of heterogeneous systems, may be employed to evaluate the effective diffusion coefficient:

$$\frac{P_e - P_c}{P_e + 2P_c} = \frac{P_i - P_c}{P_i + 2P_c} \, v_i \qquad \text{(Eq. 3)}$$

$$\frac{P_e - P_i}{P_c - P_i} \left(\frac{P_c}{P_e}\right)^{1/3} = v_c \qquad \text{(Eq. 4)}$$

and

$$P_j = K_j \times D_j \, (j = e, i, c) \qquad \text{(Eq. 5)}$$

where P is a permeability constant, K is a partition coefficient, D is a diffusion coefficient, and v is a volume fraction. The subscripts e, i, and c represent "effective," "internal phase," and "continuous phase," respectively. And K_e is given by Eq. 6:

$$K_e = K_i v_i + K_c v_c \qquad \text{(Eq. 6)}$$

where K_c is unity.

Solving Eqs. 3 or 4 for P_e and dividing by K_e, one obtains an expression for the effective diffusion coefficient, D_e, in the form of Eq. 7:

$$D_e = f(K_i, \, v_i, \, v_c, \, D_i, \, D_c) \qquad \text{(Eq. 7)}$$

where v_i and v_c are constants for a given system. Even when D_i and D_c are constant, D_e is a function of K_i, which may be concentration dependent.

The Partition Coefficient—K_i may change with drug concentration in various ways such as dissociation of the drug, dimerization, complex formation, etc. Let us now examine a situation where dissociation of the drug is involved.

It is assumed that (a) the drug molecule dissociates in the internal phase, (b) only the nonionized species dissolves in the continuous phase, and (c) equilibrium of nonionized species always exists between the internal and the continuous phases. The water-in-oil emulsion of pyridine hydrochloride is an example of this case. The concentration relationships among the various species for this system are: (a) in the internal phase:

$$K_a = \frac{(A)(H^+)}{(AH^+)}$$

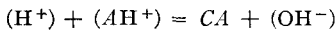$$C_i = (AH^+) + (A)$$

$$K_w = (H^+)(OH^-)$$

$$(H^+) + (AH^+) = CA + (OH^-)$$

(b) in the continuous phase:

$$C_c = (A)_c$$

(c) at the interface:

$$\frac{(A)_i}{(A)_c} = \frac{1}{P_0}$$

where K_a is the acid dissociation constant of drug, and C_1 and C_i are the drug concentrations in the internal phase and the continuous phase, respectively. CA is the hydrochloric acid concentration in internal phase, P_0 is the true partition coefficient of the drug (partition coefficient of the nonionized species), and K_w is the ion product for water.

Solving these equations simultaneously, one can get Eq. 8.

$$K_i = \frac{C_i}{C_c} = \frac{1}{P_0} +$$
$$\frac{CA + \sqrt{CA^2 + \frac{4K_w}{P_0 K_a}(C_c + P_0 K_a)}}{2(C_c + P_0 K_a)} \quad \text{(Eq. 8)}$$

The total drug concentration is given by Eq. 9:

$$C_e = v_c \cdot C_c + v_i \cdot C_i = (v_c + v_i K_i) \cdot C_c \quad \text{(Eq. 9)}$$

From Eqs. 8 and 9, it is clear that the partition coefficient, K_i, is a function of concentration, C_e.

The Time Dependence of the Amount of Drug Released—When the diffusion coefficient, D, is a function of concentration, C (the subscript e is dropped from D_e and C_e), the equation for one-dimensional diffusion is given by Eq. 10, instead of Eq. 1.

$$\frac{\partial C}{\partial t} = \frac{\partial}{\partial x}\left(D\frac{\partial C}{\partial x}\right) \quad \begin{array}{l} t = 0 \text{ and } 0 < x, C = C_0 \\ t > 0 \text{ and } x = 0, C = 0 \end{array}$$
$$\text{(Eq. 10)}$$

Applying Boltzman's method (3), one can obtain Eq. 11:

$$C = a \int_0^\lambda \frac{1}{D} \exp\left(-\int_0^\lambda \frac{\lambda}{2D} d\lambda\right) d\lambda \quad \text{(Eq. 11)}$$

$$a = \frac{C_0}{\int_0^\infty \frac{1}{D} \exp\left(-\int_0^\lambda \frac{\lambda}{2D} d\lambda\right) d\lambda} \quad \text{(Eq. 12)}$$

where $\lambda = x/\sqrt{t}$.

Then the nonsteady state drug release rate per unit area, G, is given by:

$$G = \left(D\frac{\partial C}{\partial x}\right)_{x=0} \quad \text{(Eq. 13)}$$

Integration of Eq. 13, using Eqs. 11 and 14, gives:

$$\left(D\frac{\partial C}{\partial x}\right)_{x=0} = \frac{1}{\sqrt{t}}\left(D\frac{\partial C}{\partial \lambda}\right)_{\lambda=0} \quad \text{(Eq. 14)}$$

$$q = 2a\sqrt{t} \quad \text{(Eq. 15)}$$

where q is the amount of drug released per unit area, and a is the same constant defined by Eq. 12.

These results show that, even if D is concentration dependent, the release pattern is exactly the same as the constant D case. *"Square root" relationship still holds.*

Computation of a—It is quite difficult to solve Eq. 12 and evaluate a, analytically, even though D is a known function of C. Therefore, a numerical calculation method is expedient.

If the region $(0 \sim C_0)$ is divided into N equal parts, the following relationships hold:

$$C_j = a \int_0^{\lambda_j} \frac{1}{D} \exp\left(-\int_0^\lambda \frac{\lambda}{2D} d\lambda\right) d\lambda$$
$$(j = 1, 2, \ldots N) \quad \text{(Eq. 16)}$$

$$C_N = C_0, \quad \lambda_N = \infty$$

$$C_j - C_{j-1} = \frac{C_0}{N}$$
$$= a \int_0^{\lambda_j} \frac{1}{D} \exp\left(-\int_0^\lambda \frac{\lambda}{2D} d\lambda\right) d\lambda -$$
$$a \int_0^{\lambda_{j-1}} \frac{1}{D} \exp\left(-\int_0^\lambda \frac{\lambda}{2D} d\lambda\right) d\lambda$$
$$\text{(Eq. 17)}$$
$$(j = 1, 2, \ldots N)$$

therefore

$$\int_{\lambda_{j-1}}^{\lambda_j} \frac{1}{D} \exp\left(-\int_0^\lambda \frac{\lambda}{2D} d\lambda\right) d\lambda = \frac{C_0}{aN} =$$
$$\text{constant} \quad \text{(Eq. 18)}$$
$$(j = 1, 2, \ldots N)$$

The constant a is computable from these relationships. The procedure is as follows.

(a) Divide C_0 into N equal parts, C_j,

$$C_j = C_0 \times \frac{j}{N} \; (j = 1, 2, \ldots N) \quad \text{(Eq. 19)}$$

(b) Calculate D_j, which is a known function of C_j, from C_j obtained by the previous step.

(c) Choose arbitrary value for λ_1, and evaluate M_1, given by Eq. 20, applying the proper numerical integration method:

$$M_1 = \int_0^{\lambda_1} \frac{1}{D} \exp\left(-\int_0^\lambda \frac{\lambda}{2D} d\lambda\right) d\lambda \quad \text{(Eq. 20)}$$

With the trapezoidal rule, M_1 is given by:

$$M_1 \simeq \frac{\lambda_1}{2}\left[\frac{1}{D_0} + \frac{1}{D_1} \exp\left(-\frac{\lambda^2_1}{4D_1}\right)\right] \quad \text{(Eq. 21)}$$

(d) Look for the value of λ_2 which satisfies:

$$\int_{\lambda_1}^{\lambda_2} \frac{1}{D} \exp\left(-\int_0^\lambda \frac{\lambda}{2D} d\lambda\right) d\lambda = M_1 \quad \text{(Eq. 22)}$$

(e) Repeat the similar procedure and calculate $\lambda_3, \lambda_4 \ldots \lambda_{N-1}$ which satisfies:

$$\int_{\lambda_{j-1}}^{\lambda_j} \frac{1}{D} \exp\left(-\int_0^\lambda \frac{\lambda}{2D} d\lambda\right) d\lambda = M_1 \quad \text{(Eq. 23)}$$

Applying the trapezoidal rule, integration of Eq. 23 becomes calculable:

$$\int_{\lambda_{j-1}}^{\lambda_j} \frac{1}{D} \exp\left(-\int_0^\lambda \frac{\lambda}{2D} d\lambda\right) d\lambda \simeq$$
$$\left(\frac{\lambda_j - \lambda_{j-1}}{2}\right)(T_j + T_{j-1})$$

$$T_j = \frac{1}{D_j} \exp\left\{-\frac{\lambda_j^2}{4D_j} - \sum_{k=2}^{j} \frac{\lambda_{k-1}\cdot\lambda_k\cdot(D_k - D_{k-1})}{4\cdot D_k\cdot D_{k-1}}\right\}$$
$$\text{(Eq. 24)}$$

(*f*) Calculate the integration from λ_{N-1} to infinity. Assuming D is constant, D_{N-1}, between λ_{N-1} and infinity, and by applying the infinite series for the error function, one obtains Eq. 25:

$$\int_{\lambda_{N-1}}^{\infty} \frac{1}{D} \exp. \left(-\int_0^\lambda \frac{\lambda}{2D} \, d\lambda \right) d\lambda \simeq$$

$$\frac{\sqrt{\pi}}{\sqrt{D_{N-1}}} \left(1 - \sum_{n=0}^{\infty} \frac{(-1)^n \, X^{2n-1}}{(2n+1)n!} \right)$$

$$\exp. \left(-\sum_{n=2}^{N-1} \frac{\lambda_{n-1}\lambda_n(D_n - D_{n-1})}{4 \cdot D_{n-1} \cdot D_n} \right) \quad \text{(Eq. 25)}$$

where $X = \lambda_{N-1}/2\sqrt{D_{N-1}}$

(*g*) If the value obtained at (*f*) is equal to M_1 within the allowable accuracy, *a* is calculated by:

$$a = \frac{C_0}{NM_1} \qquad \text{(Eq. 26)}$$

(*h*) If (*g*) is not true, modify λ_1 according to the result of the comparison, *i.e.*, when the value of (*f*) is greater than M_1, increase λ_1. Repeat the whole procedure from (*c*) to (*f*) until (*g*) becomes true.

EXPERIMENTS

In order to test the validity of the theory, the release rates of pyridine from w/o emulsions were determined.

Apparatus—The apparatus used to determine drug release from emulsions is shown in Fig. 1. Compartments A and B are made of glass. Compartment B contains 345 ml. of water (or hydrochloric acid) and behaves as a sink for releasing drug. Solution samples are taken through C with a pipet. The emulsion is placed in compartment A at zero time. M is a cellophane membrane[1] separating the emulsion from the aqueous sink. The whole set-up is immersed in a constant-temperature water bath at 30°.

Emulsion—Water-in-oil emulsions of pyridine hydrochloride were made using sorbitan sesquioleate, HLB 3.7,[2] as emulsifier and hexadecane as the oil phase. Fifteen milliliters of a 2% solution of pyridine in water or in hydrochloric acid (0.063 *N*, 0.084 *N*, 0.126 *N*, 0.189 *N*, and 0.252 *N*) was added to a 50-ml. test tube containing 5 ml. of hexadecane and the weighed amount of sorbitan sesquioleate (0.64 Gm.). Stoppered tightly, the test tube was shaken vigorously for 20 min. This procedure gave a thick, stable emulsion, and the type of the emulsion was determined to be w/o by electric conductivity.

Ten milliliters of the emulsion was put into compartment A of the cell, and the release of pyridine was determined as a function of time. To make the sink more effective, the same concentrations of hydrochloric acid as the internal phase of emulsions were used in the B compartment of the cell. Samples of the solution were taken at predetermined periods. Drug content was determined by UV absorbance measurement (at 255 mμ). Amount of drug released, *Q*, was plotted against the square root of time. Results are shown in Fig. 2.

Diffusion Coefficient of Pyridine in Homogeneous System—Diffusion coefficients of pyridine in hexa-

[1] Visking Co., Chicago, Ill.
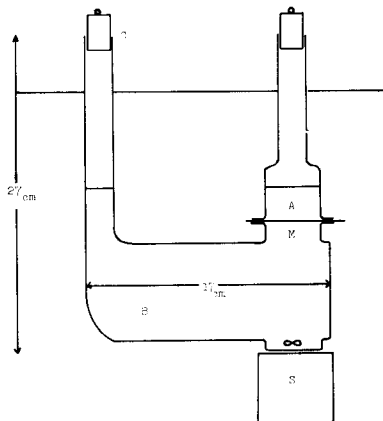[2] Arlacel C, Atlas Chemical Co., Wilmington, Del.

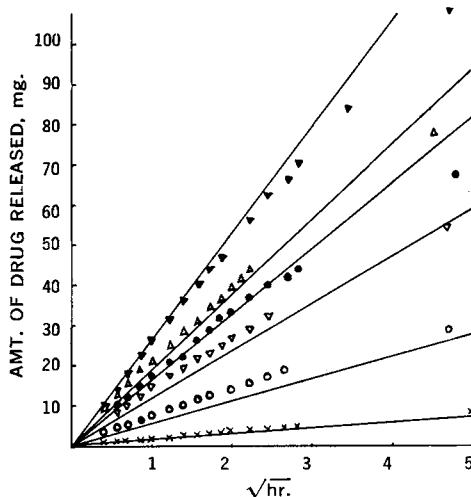*Fig. 1—Apparatus for drug release from emulsions. See text for discussion.*

Fig. 2—Comparison of experimental data with theory. Amount of pyridine released from w/o emulsion vs. square root of time. Key: ▼, △, ●, ▽, ○, *and* × *represent CA = 0, 0.063, 0.084, 0.126, 0.189, and 0.252 mole/L., respectively. Straight lines are theoretical values computed using Brugeman's equation.* $V_c = 0.25$; $V_i = 0.75$; $P_0 = 0.570$; $D_c = 1.42 \times 10^{-5}$ cm.²/sec.; $D_i = 1.19 \times 10^{-5}$ cm.²/sec.; $C_0 = 0.189$ mole/L.; $K_a = 5.89 \times 10^{-6}$ mole/L.

decane, D_c, and in water, D_i, were determined with the apparatus (above) applying Eq. 2 for calculation. A small amount of glass wool was used in compartment A in order to prevent convection currents setting up (when the emulsions were used, the viscosities were high enough to prevent convection and such precautions were unnecessary). The amount of drug released, *Q*, was plotted against square root of time. Results are shown in Fig. 3. Diffusion coefficients were calculated from the slope of the straight line of Fig. 3 by Eq. 27:

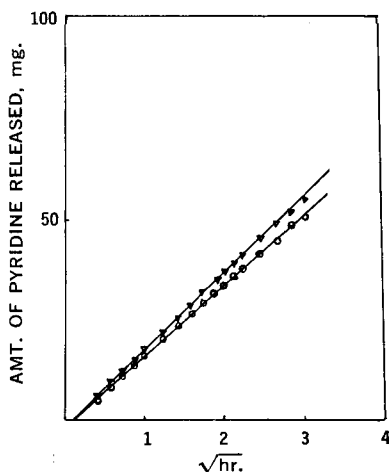$$D = \left(\frac{\text{slope}}{2 \cdot C_0 \cdot A} \right)^2 \pi \qquad \text{(Eq. 27)}$$

Fig. 3—Amount of pyridine released from homogeneous solutions. Key: ▽, *hexadecane;* ○, *water.* Cross-sectional area of cell, A, is 7.54 cm.².
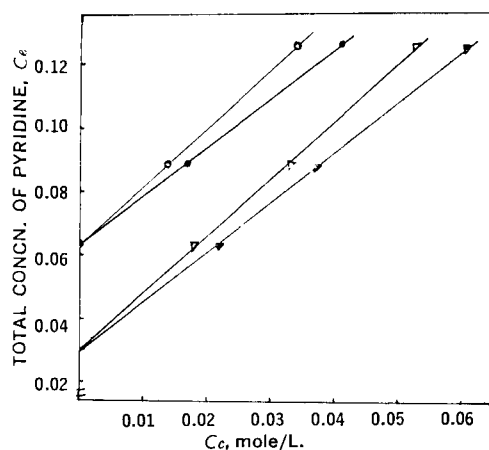

Fig. 4—Plots of C_e *vs.* C_c. *See text. Key:* ○, ●, CA = 0.126 mole/L.; △, ▲, CA = 0.063 mole/L.; ○, △, sorbitan sesquioleate 0.16 Gm./10 ml. hexadecane; ●, ▲, sorbitan sesquioleate 0.64 Gm./10 ml. hexadecane; $V_i = V_e = 0.5$.

where A is the cross-sectional area (cm.²) of the diffusion compartment and a constant for a given cell. A was determined from the release rate of 0.05 N hydrochloric acid for which the diffusion coefficient is known to be 2.93 × 10⁻⁵ cm.²/sec. at 25° and 3.61 × 10⁻⁵ cm.²/sec. at 35° (4). A value of 1.42 × 10⁻⁵ cm.²/sec. was obtained for the diffusion coefficient of pyridine in hexadecane, D_e, at 30°, and 1.19 × 10⁻⁵ cm.²/sec. was obtained for pyridine in water or in 0.252 N HCl (1% pyridine), D_i, at 30°.

Partition Coefficient—*Absence of Surfactant*—Ten milliliters of the aqueous solution of pyridine was added to a 50-ml. centrifuge tube, containing 10 ml. of hexadecane, which was stoppered tightly and shaken vigorously until equilibrium was reached. The mixture was centrifuged and the aqueous phase was separated from the oil phase. The pyridine contents of both phases were determined as well as the pH of the water phase. The concentration of the nonionized species in the water phase was calculated from the pH and the acid dissociation constant. The partition coefficient of the non-ionized species, P_0, was calculated from the results. The data are shown in Table I.

Presence of Surfactant (5)—When a surfactant which is necessary for making the emulsion is present, its effects have to be taken into account. However, it is difficult to define K_i exactly in this situation.

For the practical purpose, however, it is con-

venient and reasonable to assume that the surfactant changes P_0, but nothing else, by solubilizing more pyridine into the hexadecane phase. Therefore:

$$P_0^* = P_0 + K\ (S) \qquad \text{(Eq. 28)}$$

where P_0^* is the partition coefficient of nonionized species in the presence of a surfactant. Here (S) is the surfactant concentration and K is constant. Because of the low solubility of sorbitan sesquioleate in water, all of the sorbitan sesquioleate used to make the emulsion is assumed to exist in the hexadecane phase.

Ten milliliters of the aqueous solution of pyridine was added to a 50-ml. centrifuge tube containing 10 ml. of hexadecane and the weighed amount (0.64 Gm.) of sorbitan sesquioleate. Stoppered tightly, the tube was shaken until equilibrium was reached. When the surfactant was used, centrifugation (7,000 r.p.m., 5 hr.) separated the oil phase but did not clear the water phase. Consequently, the determination of pyridine in the water phase was difficult.

In Eq. 8 as $4K_w/P_0K_a\ (C_c + P_0K_a)$ is less than 10^{-7} mole/L. and negligible compared to C_A, which is greater than 6.3 × 10⁻² mole/L., Eq. 29 may be used instead of Eq. 8.

$$K_i = \frac{C_i}{C_c} = \frac{1}{P_0} + \frac{C_A}{C_c + P_0K_a} \qquad \text{(Eq. 29)}$$

TABLE I—PARTITION COEFFICIENT, P_0, OF PYRIDINE BETWEEN HEXADECANE AND WATER
IN THE ABSENCE OF SURFACTANT

	Pyridine Concn. in Water Phase, mole/L.	Pyridine Concn. in Hexadecane Phase, mole/L.	pH of Water Phase	Nonionized[b] Pyridine Concn. in Water Phase, mole/L.	P_0 Partition Coefficient of Non-ionized Species
1[a]	0.1095	0.0141	5.10	0.0418	0.337
2[a]	0.1106	0.0142	5.10	0.0422	0.336
3	0.0188	0.0058	6.20	0.0163	0.356
4	0.0895	0.0287	6.66	0.0820	0.350
5	0.1799	0.0587	6.87	0.1765	0.333

[a] Water phase is 0.063 N HCl.   [b] Nonionized concentration = total concn. in water × $[K_a/K_a + (H^+)]$, $K_a = 5.89 × 10^{-6}$ mole/L.

TABLE II—PARTITION COEFFICIENT, P_0*, OF PYRIDINE BETWEEN HEXADECANE AND WATER IN THE PRESENCE OF SURFACTANT

Sorbitan Sesquioleate Concn. (S) Gm./10 ml. Hexadecane	V_i	V_c	HCl Concn. in Water Phase CA mole/L.	Slope	$P_0*\ V_i/$ Slope $-\ V_c$	$P_0* - P_0^a$	K
0.16	0.500	0.500	0.063	1.84	0.37	0.03	0.19
0.16	0.500	0.500	0.126	1.86	0.37	0.03	0.19
0.64	0.500	0.500	0	1.64	0.44	0.10	0.16
0.64	0.500	0.500	0.063	1.61	0.45	0.11	0.17
0.64	0.500	0.500	0.126	1.55	0.48	0.14	0.22
1.28	0.667	0.333	0.063	1.53	0.56	0.22	0.17

[a] 0.34 was used as the value of P_0 (cf. Table I).

Therefore:

$$C_e = \left(v_c + \frac{v_i}{P_0} \right) C_c + \frac{v_i C_c C_A}{C_c + P_0 K_a} \qquad \text{(Eq. 30)}$$

Equation 30 shows that when C_c is large enough compared to $P_0 K_a$, the relationship between C_c and C_e is linear. The slope is $v_c + v_i/P_0$, and the intercept is $v_i C_A$.

The pyridine concentration in the hexadecane phase, C_c, was determined and plotted against the total concentration, C_e. Figure 4 shows the results. P_0* was calculated from the slope of the straight line, namely:

$$P_0* = \frac{v_i}{\text{slope} - v_c} \qquad \text{(Eq. 31)}$$

The P_0* values at various surfactant concentrations are shown in Table II. K is fairly constant at the different concentrations of surfactant, and therefore Eq. 28 holds reasonably well in this situation. The average value of K, 0.18, was used for the theoretical computations of pyridine release rate from emulsion.

Computation of the Theoretical Slopes—The computations were executed by the IBM 7090 digital computer. The flow chart is shown in Fig. 5. Results are in Table III and are shown also in Fig. 2.

Discussion—The relatively good linearity of the data shown in Fig. 2 supports the validity of "square root" relationship for the variable diffusion coefficient case. Leveling off of the curve at large t is due to the finite thickness of emulsion in the diffusion compartment.

In Fig. 3, which shows the release of pyridine from homogeneous solution, the curve did not start from the origin but gave a short lag time. It is believed that this time lag of 0.6 min. was caused by the initial diffusion of pyridine in the membrane as well as by the initial absorption of pyridine by the membrane. Details of the lag time phenomenon are discussed under *Appendix*.

The Bruggeman equation (Eq. 4) appears to be better than the Wagner-Wiener equation (Eq. 3) for estimating effective diffusion coefficient in the present situation.

Considering the fact that the theoretical slope is computed from independently determined parameters, agreement of theoretical and experimental results is extremely satisfactory.

From these results, it is obvious that quantitative theory is quite useful and should have extensive applications in the future.

APPENDIX

One of the time-lag phenomena that is involved in the experimental situations of this report is the well-known lag time of Barrer (6) which is a measure of the period required for the absorption of the drug by the membrane.

Fig. 5—Flow diagram showing the procedure for the computation of a. ϵ = *accuracy allowance (allowable error);* M_1 = *calculated value of Eq. 21;* M_J = *calculated value of Eq. 24;* M_∞ = *calculated value of Eq. 25.*

TABLE III—THEORETICAL VALUES OF a^a

CA mole/L.	N	60	80	100
0	B	0.022318	0.022321	0.022323
	W	0.022311	0.022313	0.022315
0.063	B	0.015728	0.015752	0.015764
	W	0.015106	0.015132	0.015146
0.084	B	0.013720	0.013749	0.013760
	W	0.012978	0.013003	0.013014
0.126	B	0.0099014	0.0099215	0.0099319
	W	0.0089659	0.0089859	0.0089960
0.189	B	0.0046754	0.0046931	0.0047020
	W	0.0036538	0.0036719	0.0036809
0.252	B	0.0012180	0.0012220	0.0012244
	W	0.00048505	0.00048687	0.00048798

[a] The parameters are: $D_c = 1.42 \times 10^{-5}$ cm.^{2}/sec., $C_0 = 0.189$ mole/l.., $D_i = 1.19 \times 10^{-5}$ cm.^{2}/sec., $K_a = 5.89 \times 10^{-6}$ mole/L., $P_0* = 0.570$, B = Bruggeman equation, W = Wagner-Wiener equation.
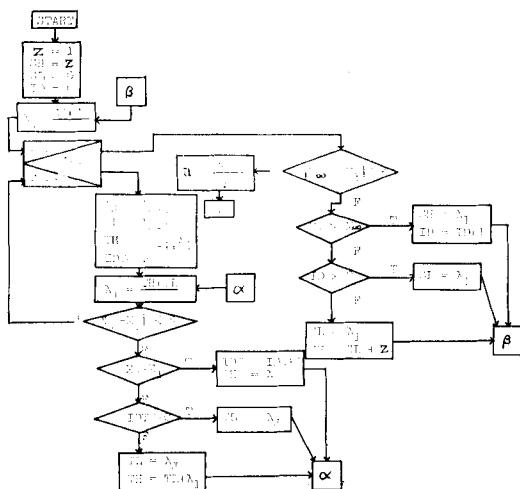
Barrer's lag time is given by:

$$\tau_B = \frac{h^2}{6D} \qquad \text{(Eq. 32)}$$

where h is the thickness of the membrane and D is diffusion coefficient.

Another lag time is present because the diffusion coefficient of the drug in the membrane is smaller than that in the bulk.

Let D_1 be the diffusion coefficient in the membrane, the thickness of which is h, and D_2 that in the bulk. Also, let C_1 be the concentration in the membrane and C_2 in the bulk. Then assume that the diffusion is expressed by the following equations:

$$\text{at } t = 0 \qquad C_1 = C_0 \qquad -h \le x \le 0$$

$$C_2 = C_0 \qquad 0 \le x$$

$$\text{at } t > 0 \qquad \frac{\partial C_1}{\partial t} = D_1 \frac{\partial^2 C_1}{\partial x^2} \qquad -h < x < 0$$

$$\frac{\partial C_2}{\partial t} = D_2 \frac{\partial^2 C_2}{\partial x^2} \qquad 0 < x$$

$$D_1 \frac{\partial C_1}{\partial x} = D_2 \frac{\partial C_2}{\partial x} \text{ and } C_1 = C_2$$

$$\text{at } x = 0 \quad \text{and} \quad C_1 = 0 \text{ at } x = -h$$

Solutions to these equations with the indicated boundary conditions are given by Carslaw (7).

The amount of drug released from this system, q, is given by Eq. 33:

$$q = \int_0^t \left(D_1 \frac{\partial C_1}{\partial x} \right)_{x = -h} dt = \int_0^t \times$$

$$\frac{C_0 \sqrt{D_1}}{\sqrt{\pi t}} \left\{ 1 + 2 \sum_{n=1}^{\infty} \alpha^n \exp. -n^2 h^2/D_1 t \right\} dt$$

$$\text{(Eq. 33)}$$

where $\alpha = \dfrac{\sqrt{D_2} - \sqrt{D_1}}{\sqrt{D_2} + \sqrt{D_1}}$

At large t, Eq. 34 is obtained:

$$q = \frac{2C_0\sqrt{D_2}}{\sqrt{\pi}} \left\{ \sqrt{t} - \frac{h\sqrt{\pi}}{2\sqrt{D_2}} \left(\frac{D_2}{D_1} - 1 \right) \right\} \quad \text{(Eq. 34)}$$

Therefore the lag time due to slow membrane diffusion, τ_M, is expressed by:

$$\tau_M = \frac{h^2 \pi}{4 D_2} \left(\frac{D_2}{D_1} - 1 \right)^2 \qquad \text{(Eq. 35)}$$

From steady-state diffusion experiments of pyridine through a cellophane membrane (other than those reported in this paper), a value of 3.43×10^{-4} cm./sec. was obtained for the value of D_1/h. If the thickness of the cellophane membrane is 0.015 cm., τ_B is calculated to be 3 sec., and τ_M to be 39 sec.

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⌐⊙⊸⊸ *Keyphrases*

Pyridine release from emulsions

pH effect on pyridine release—w/o emulsions

Diffusion coefficient—homogeneous system

Partition coefficient—pyridine

Diffusion coefficient equations

Computer flow chart—theoretical slopes for pyridine release