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Investigation of Factors Influencing Release of Solid Drug Dispersed in Inert Matrices II

Quantitation of Procedures

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Recently a number of factors governing the rate of release of drug from plastic matrices were investigated. This study showed that while the experimental results were generally in agreement with Higuchi's relationship, they were not always quantitative. The present paper describes a refined experimental procedure for quantitatively studying the various factors. Matrix porosities are determined in two ways so that available and inaccessible pores can be differentiated. Diffusion coefficients are independently determined. The matrix tortuosity can now be quantitatively determined independently of the solid drug release rate data. In addition to these experimental refinements, the limitations of the theory are reviewed and some useful modifications proposed.

A PREVIOUS communication (1) discussed preliminary results on the investigation of the factors influencing drug release from solid drugs dispersed in inert matrices. An attempt was made in that study to compare experimental release rate data to the Higuchi relationship (2). While it was found that qualitative and semiquantitative comparisons between theory and data could easily be made, considerable difficulty was generally encountered when a quantitative test of the theory with data was attempted.

It was believed that much of the difficulty was due to the porosity and the tortuosity of the matrix not being independent of the other variables and changing from experiment to experiment. For example, these studies (1) showed that a small amount of surfactant in the solvent phase could markedly increase the release rate from the polyethylene plastic matrix. It was shown that this was not an increased solubility effect, and therefore, must be related to the porosity or tortuosity factors.

It has now become apparent that, in order to clearly understand the basic mechanisms involved, a more systematic study must be undertaken. Wherever possible, each of the parameters in the theory should be quantitated independently and then incorporated into the theory to see whether the equation accurately predicts the rate. Then when discrepancies occur, real or apparent, physical interpretations that are meaningful may be assigned.

The purpose of this paper is to present details of methods, both theoretical and experimental, designed for the quantitative physical evaluation of the various factors involved in drug release from nondisintegrating matrices. It will be shown that these techniques should permit the unambiguous interpretation of release rate data in most instances.

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THEORY

The basic Higuchi relationship (2) for the rate of diffusional release of drug incorporated as solid drug in an insoluble matrix, from one surface of the matrix, is

$$Q = \left\{\frac{D\epsilon}{\tau}(2A - \epsilon C_s)C_s t\right\}^{1/2} \quad \text{(Eq. 1)}$$

where Q is the grams of drug released per unit area of surface at time, t, D is the diffusion coefficient of drug in the release medium, ϵ is the porosity of the matrix, C_s is the solubility of drug in the release medium, τ is the tortuosity of the matrix, and A is the concentration of drug in the tablet expressed as Gm./ml.

Some comments are now appropriate regarding Eq. 1. Most of these were pointed out in the original work (2).

The porosity, ϵ, refers to the volume fraction that is permeated by the solvent and available for diffusion in the already leached portion of the matrix. Therefore, in general,

$$\epsilon = \epsilon_d + \epsilon_{\text{air}} + \epsilon_{\text{other}} \quad \text{(Eq. 2)}$$

Here $\epsilon_d = \frac{A}{\rho_d}$ is the contribution to the porosity from the dissolved drug where ρ_d is the drug crystal density. The other two terms in Eq. 2 are the contributions to porosity from released air and from the leaching of other soluble additives in the mixture. As we shall see later, ϵ_{air} available for solvent penetration and drug diffusion, is very sensitive to the presence of surfactants with certain matrices.

The tortuosity factor, τ, corrects for the lengthened diffusional path caused by the necessary lateral excursions. In other words, it accounts for, or corrects for the additional distance a molecule must travel due to its circuitous path within the tablet. A straight channel will have a tortuosity of 1, whereas a spherical glass bead column will have a τ value of about 2 to 3.

It will be seen later that in some situations extremely large τ values ($\sim 10^3$ to 10^4) are encountered. In these cases the concept of the average porosity and the average tortuosity does not adequately describe physically the pathways and resistances for diffusion, and a more detailed consideration of the microscopic matrix permeability factors becomes desirable.

As was originally stressed (2), the model leading to Eq. 1 should fail when $\epsilon C_s \gtrsim 2A$. To derive a general analytical expression which includes the large ϵC_s cases appears to be extremely difficult because the pseudo steady-state assumption cannot be made. It appears safe to state that, as long as $2A$ is more than about 3 times greater than ϵC_s, the model should be quantitatively meaningful. The authors' initial quantitative studies of Eq. 1 will therefore be limited to those cases involving solutes of low to moderate solubilities.

Another limitation of Eq. 1 is that it does not explicitly account for the effects of the diffusional movement of the solvent or for the possibility that the solute diffusion coefficient may be concentration dependent in the diffusion barrier. Both of these factors could become important when C_s is moderate to large, say $\gtrsim$ 0.1 Gm./ml. The modified equation (see *Appendix* for the derivation) taking these factors into account may be written

$$Q = \left\{\frac{D'\epsilon C_s}{\tau} t\left[2A - 2\epsilon\int_0^{C_s}\frac{DC\,dC}{D'C_s - KC}\right]\right\}^{1/2} \quad \text{(Eq. 3)}$$

where D' is the effective (or apparent) diffusion coefficient that takes into account both of the effects mentioned above. As will be shown later D' may be conveniently determined by a single run in a conventional diffusion cell.

The term in Eq. 3 involving the integral has the same physical meaning as the $\frac{1}{2}\epsilon C_s$ term in Eq. 1. It represents, therefore, the solution holdup of solute in the leached matrix. This integral term has a value between $\frac{1}{2}\epsilon C_s$ and ϵC_s and may be approximately evaluated by methods discussed in the *Appendix*.

It should be pointed out that Eq. 3, like Eq. 1, breaks down when

$$\epsilon C_s \gtrsim 2A$$

However, it should extend the quantitative applicability of the theory to much larger C_s values than Eq. 1.

The effect of solute binding has not been included in Eq. 1. For the case in which binding to the matrix is linear, *i.e.*, constant partition coefficient, a modified equation may be derived by the same mathematical procedure used previously (2). One has in this case

$$Q = \left\{\frac{\epsilon DC_s}{\tau}[2A - C_s(\epsilon + K - K\epsilon)]t\right\}^{1/2} \quad \text{(Eq. 4)}$$

where $K = \dfrac{\text{(drug in matrix phase)}}{\text{(drug in solvent)}}$ at equilibrium.

Equation 4 assumes equilibrium binding and takes into account the same factors included in Eq. 1. The cases for time dependent binding or nonlinear binding would be much more difficult to handle mathematically.

It can be seen from Eq. 4 that unless the product, KC_s, is a significant fraction of A, the effect of binding should not be very important.

EXPERIMENTAL METHODS

Diffusion Coefficient.—The method used in these studies is, in principle, the same as that employed by McBain (3). Essentially, it involves measurement of the solute transfer rate through a sintered glass disk from one chamber to another.

The apparatus is shown schematically in Fig. 1. It consists of a porous sintered glass disk (E) mounted between two 150-ml. conical flasks (C) with side arms. One of the flasks is closed with a ground glass stopper, and the other with a special adapter (B). Stirring of the solution is achieved by using magnetic stirring bars (D). The entire apparatus is water jacketed (F) to maintain constant temperature.

The following procedure was followed. Before the beginning of each experiment, the glass disk was flushed with water to remove entrapped air. This was accomplished by filling one of the flasks with water and then applying pressure over it or by applying vacuum to the other flask. This step was an important one because it was assumed that identical conditions were maintained from one experiment to another.

Also, a few minutes before the experiment the drug solutions were heated in a flask to boiling and then cooled rapidly to within 10° of the temperature of the experiment. This step greatly helped to eliminate the development of gas bubbles in the solution chamber during the experiment.

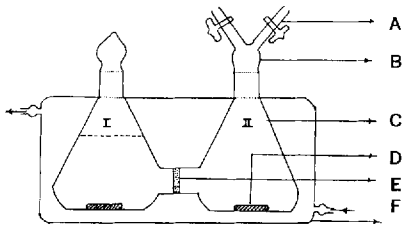

Fig. 1.—Schematic diagram of apparatus used to determine diffusion coefficients. Sintered glass disk diameter = 30 mm., thickness = 2.5 mm., and pore size = 4.0–5.5 μ. (See text for detailed description.)

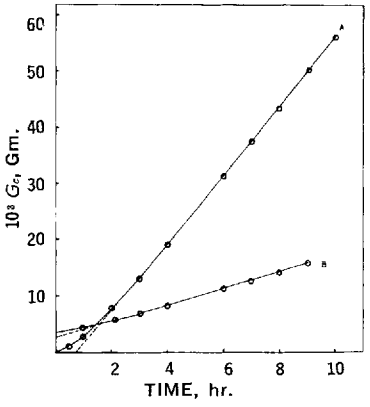

Fig. 2.—Typical diffusion runs with the apparatus. Curve A gives data for 6.8% sodium salicylate solution in flask II and water in flask I initially. Curve B gives data for saturated caffeine solution in flask II and water in flask I initially.

A measured amount of water was added to flask I, and simultaneously the drug solution was added to flask II keeping the levels of the liquids in the two flasks approximately the same. When the water addition to flask I was completed, flask II was quickly filled to the top and the adapter (B) was placed in position. More solution was added through one of the arms (A) keeping the stopcock of the other arm open for air displacement. Because the last traces of air were difficult to remove, the last few milliliters of solution were added by means of a fine-tipped pipet passed through the bore of the stopcock. After all of the visible air had been removed, the stoppers of the adapter were closed tightly and the magnetic stirring bars were started in both flasks. Samples were withdrawn at various time intervals for analysis.

The solution concentration in flask II was determined before and after each experiment. In most instances the changes, as expected, were negligible during the runs.

The cell constant, L, was determined using KCl solutions and the following relationship,

$$L = \frac{G_{KCl}}{D_{KCl}(C_2 - C_1)}$$

where C_2 and C_1 (with $C_1 \approx 0$) were the KCl concentrations in flasks II and I, respectively, D_{KCl} is the diffusion coefficient for KCl, and G_{KCl} is the KCl transport rate in the experiment.

A D_{KCl} value of 2.09×10^{-5} cm.^{2} sec.$^{-1}$ (4) was used with 0.10 M KCl solutions. G_{KCl} was determined by K^+ analysis using the Perkin-Elmer atomic absorption spectrophotometer model 303.

For the present apparatus it was found that at 30°

$$L = 2.45 \pm 0.10 \text{ cm.}$$

This value was also checked with benzoic acid solutions and the agreement was satisfactory using King's value for the diffusion coefficient for benzoic acid (5).

For the unknown solutes the diffusion coefficients were calculated from the data using the equation

$$D_e = \frac{G_e}{L\Delta C} \qquad \text{(Eq. 5)}$$

where G_e is the rate of solute transport and ΔC is the concentration difference between the two flasks.

It must now be pointed out that the D_e value obtained by means of experiment and Eq. 5 is the appropriate apparent diffusion coefficient to be used in either Eqs. 1 or 3 when $\Delta C = C_s$. This identity can easily be seen (Eq. 17a in *Appendix*) by examining the theory for the diffusion cell experiment in the same way as was done in the derivation of Eq. 3.

The direct use of the experimentally obtainable diffusion coefficient, D_e, in the theory for drug release from the matrix conveniently allows the absolute test of Eqs. 1 or 3 when ϵ and τ values are available from the measurements described later.

In Fig. 2 are given typical diffusion cell experimental data for two experiments. If the linear portions of the curves are extrapolated, it can be seen that in one curve (B) a positive intercept is obtained, while in the other curve (A) the intercept is negative. The magnitude of the intercept and whether it is positive or negative depends upon how the diffusion experiment is started. In the calculation of D_e the intercept is disregarded and only the straight line, steady-state portion of the data, is used.

Table I presents some D_e values determined by this method.

Solubility Determination.—An amount of drug, in excess of its reported solubility was placed in

Table I.—Diffusion Coefficients and Solubilities of Some Compounds Used in This Work

Drug	Solubility 10^2 Gm./ml.	Diff. Coeff. 10^6 cm.^{2}/sec.	Concn. of Soln. Used to Determine Diff. Coeff.
Sulfanilamide	1.08	12.9	1.08%[a]
Caffeine	2.50	6.3	2.50%[a]
Potassium acid phthalate	11.60	18.2	11.60%[a]
Sodium salicylate	65.00	23.1	65.00%[a]
Sodium salicylate	65.00	10.0	6.80%

[a] Saturated solutions.

TABLE II.—DATA INVOLVED IN THE DETERMINATION OF POROSITY FROM PHYSICAL MEASUREMENTS OF THE TABLET AND ITS COMPONENTS

Tablet Compn.	Wt. of Tablet, Gm.	I Vol. of Drug w/ρ	II Vol. of Plastic w/ρ	III Vol. of Tablet $\pi r^2 h$	IV Vol. of Air III − (I + II)	V Vol. of Air + Drug I + IV	ϵ V/III
5% Sodium salicylate	0.500	0.0159	0.5000	0.5820	0.0661	0.0820	0.113
10% Sodium salicylate	0.500	0.0318	0.4737	0.5625	0.0570	0.0888	0.158
20% Sodium salicylate	0.500	0.0637	0.4210	0.5340	0.0493	0.1130	0.211
20% Potassium acid phthalate	0.300	0.0368	0.2500	0.3310	0.0546	0.0914	0.275
20% Caffeine	0.300	0.0422	0.2500	0.3351	0.0429	0.0851	0.254
20% Sulfanilamide	0.300	0.0400	0.2500	0.3280	0.0380	0.0780	0.237

each of several 100-ml. volumetric flasks and 50 ml. of solvent was added. The flasks were shaken in a Burrell wrist action shaker for 24 hr. and immersed in a water bath maintained at 30°. These were then filtered with a Millipore filtering unit and the filtrate was analyzed spectrophotometrically. A rapid filtering process was adopted to prevent the precipitation of drug from the saturated solution during filtration. Solubility of the compounds investigated are reported in column 2 of Table I.

Drug-Matrix Partition Tendencies.—Where distribution of drug in the matrix was suspected, saturated solutions of the drug were shaken overnight with the matrix material. High slurry densities were generally employed to increase the sensitivity of this method for estimating K (Eq. 4).

Porosity.—In order to have a porosity value that could be reliably used in Eqs. 1 or 3, two independent methods were used to estimate this quantity. The first method involved calculating the maximum possible contribution to ϵ by air in the tablets. The resulting ϵ value would be the correct one to use in Eqs. 1 or 3 only if all of the air spaces were permeated by the solvent and became available during the drug release process.

From knowledge of the tablet volume, the densities of the drug and matrix material (and other additives, if any), and the weight percentages of all the components, these calculations were carried out. The tablet volumes were computed from tablet dimensions determined with a micrometer and the densities were determined with the Beckman air compression pycnometer.

Some typical data for polyethylene matrix–drug tablets are presented in Table II. The last column gives the porosities calculated by this procedure.

In the second method for estimating ϵ the tablets were completely leached of the solute, and the empty matrices were equilibrated with a dilute solution of a known concentration. The equilibration times depended upon the matrix permeabilities, but usually 1 to 2 weeks was adequate. These resaturated matrices were then exposed to fresh solvent after a brief rinse, and the total amount of solute released determined from the release time data (Figs. 3 and 4). These steps were carried out as described under *Tortuosity*.

Table III presents some of the data with the polyethylene plastic matrix. Columns 4 and 5 of Table

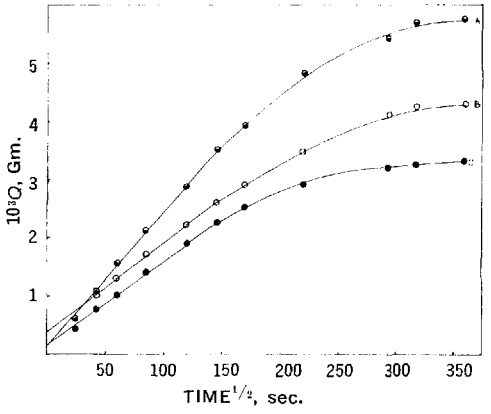

Fig. 3.—Solute release data from polyethylene plastic matrices used in the calculations of porosity and tortuosity. Solute release into 0.2% benzalkonium chloride of sodium salicylate from matrices equilibrated with 5% sodium salicylate solutions. Curves A, B, and C correspond to disks that originally contained 20, 10, and 5% solid sodium salicylate, respectively, and which were leached completely in 0.20% benzalkonium chloride solution.

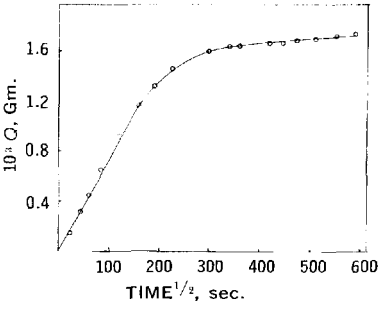

Fig. 4.—Release of caffeine into 0.10% dioctyl sodium sulfosuccinate (AOT) from a polyethylene plastic matrix which was equilibrated with a saturated caffeine solution. The matrix originally contained 20% solid caffeine which was leached completely in 0.10% dioctyl sodium sulfosuccinate (AOT) solution.

TABLE III.—POROSITY AND TORTUOSITY VALUES FOR SOME DRUG–POLYETHYLENE SYSTEMS DETERMINED BY RELEASE FROM SOLUTION SATURATED MATRIX METHOD

Tablet Compn.	Leached Out, mg.	Concn. of Saturated Soln., 10^2 Gm./ml.	ϵ by Liquid Leaching Method	ϵ by Physical Measurement	τ from Liquid Leaching
20% Caffeine in polyethylene	2.21	2.50	0.264	0.254	6.4
20% Sodium salicylate in polyethylene	7.09	5.12	0.258	0.211	2.9
10% Sodium salicylate in polyethylene	4.75	5.12	0.164	0.158	4.6
5% Sodium salicylate in polyethylene	3.92	5.12	0.130	0.113	4.8

III compare the two methods for determining ϵ. The agreement of this instance was very satisfactory.

As will be seen in a later communication, the agreement between the two procedures is not always so good. In these cases incomplete displacement of air appears to be the cause of the discrepancies.

It should be pointed out that good agreement between these two methods does not guarantee correctness of the ϵ value for the solid leaching process because air release may occur but only slowly during the solid release experiment. Good agreement between the two methods for determining ϵ does assure, however, a good reference point for evaluating the data by means of Eqs. 1 or 3.

Tortuosity.—The procedure for the determination of the tortuosity, τ, has been described previously (1). It is based upon the use of the following equation for the release of solute from one planar surface of a solution-saturated matrix

$$Q' = 2\epsilon C_0 \left(\frac{Dt}{\tau\pi}\right)^{1/2} \qquad \text{(Eq. 6)}$$

Here Q' is the amount of solute released per cm.^{2} at time, t, ϵ is, as before, the porosity defined by Eq. 2 and determined by the procedures described above, D is the diffusion coefficient obtainable by the experiment described earlier, and C_0 is the solution concentration.

Equation 6 was deduced for the present situation from the general equation for the release from a semi-infinite medium (6). Therefore, it would be quantitatively applicable for initial rates ($\simeq$ up to 30% release) only.

From the slopes of the initial linear portions of the Q' *versus* $t^{1/2}$ plots, τ may be calculated by means of Eq. 6 as

$$\tau = \frac{4\epsilon^2 C_0^2 D}{\pi\,(\text{slope})^2} \qquad \text{(Eq. 7)}$$

A typical plot is presented in Fig. 3 and some calculated τ values are given in the last column of Table III.

APPENDIX

Derivation of Eq. 3.—When steady-state diffusion takes place from a region of relatively high solute concentration toward essentially pure solvent, the movement of the solvent must be considered also in the problem. In the present problem when the solute is diffusing from $X = s$ to $X = 0$, the solvent, which is usually water in the authors' studies, will set up a concentration gradient, $\frac{dC_w}{dX}$ in the opposite direction and a tendency for solvent diffusion will be established.

However, the net movement of the solvent, G_w, must be zero, because at $X = s$ the solvent is not diffusing into the unleached region at steady state. Consequently, this must result in a bulk solution flow in the channels of velocity, v, from $X = s$ to $X = 0$. The important consequence of this bulk flow is that the solute transport rate is greater by $\frac{\epsilon}{\tau} vC$ than that given by Fickian diffusion alone. Mathematically we may write

$$0 = G_w = \frac{\epsilon}{\tau} D_w \frac{dC_w}{dX} + \frac{\epsilon}{\tau} vC_w \qquad \text{(Eq. 1}a\text{)}$$

and

$$G = \frac{\epsilon}{\tau} D \frac{dC}{dX} + \frac{\epsilon}{\tau} vC \qquad \text{(Eq. 2}a\text{)}$$

Here G is the solute transport rate, D_w is the diffusion coefficient of the solvent, C_w and C are, respectively, the solvent and the solute concentrations at X, and the other terms have already been defined.

Let us solve these equations assuming that both D and D_w are concentration dependent. The final results would then be more general and applicable even when appreciable viscosity changes are encountered or when significant solute–solute interactions occur.

Integrating Eq. 1a from $X = 0$ to $X = s$ one obtains

$$v \int_0^s dx = -\int_{C_w^0}^{C_w^s} D_w \frac{dC_w}{C_w}$$

whence,

$$vs = \int_{C_w^s}^{C_w^0} \frac{D_w dC_w}{C_w} = K \qquad \text{(Eq. 3}a\text{)}$$

where C_w^0 and C_w^s are the solvent concentrations at $X = 0$ and $X = s$, respectively. K is constant for a given solvent–solute pair at a given temperature when diffusion takes places from a saturated solution into pure solvent—the situation which is of most interest.

Equation 2*a* may now be solved after substituting for v from Eq. 3*a*. Integrating Eq. 2*a* from $X = 0$ to $X = s$ where $C = 0$ and $C = C_s$, one obtains

$$\int_0^s dX = \frac{\epsilon}{\tau}\int_0^{C_s} \frac{DdC}{G - \frac{\epsilon K}{\tau s}C} \qquad \text{(Eq. 4a)}$$

Since the left side of Eq. 4*a* becomes s, we have

$$s = \frac{\epsilon s}{\tau}\int_0^{C_s} \frac{DdC}{Gs - \frac{\epsilon}{\tau}KC} \qquad \text{(Eq. 5a)}$$

The s cancels, and

$$1 = \frac{\epsilon}{\tau}\int_0^{C_s} \frac{DdC}{Gs - \frac{\epsilon}{\tau}KC} \qquad \text{(Eq. 6a)}$$

For Eq. 6*a* to be true the product Gs must not be a function of C. Therefore,

$$Gs = K', \text{ a constant}$$

Now we may proceed as was done previously (2) for the derivation of Eq. 1. The amount of solute release from the matrix per unit area, Q, is

$$Q = As - M \qquad \text{(Eq. 7a)}$$

where M is the amount of drug in the pores from $X = 0$ to $X = s$ as solution. M then is given by

$$M = \epsilon\int_0^s CdX \qquad \text{(Eq. 8a)}$$

Since from Eq. 2*a*, dX is given by

$$dX = \frac{\epsilon D\,dC}{\tau\left(G - \frac{\epsilon K}{\tau s}C\right)} \qquad \text{(Eq. 9a)}$$

$$M = s\epsilon\int_0^{C_s} \frac{\epsilon DCdC}{\tau\left(sG - \frac{\epsilon K}{\tau}C\right)} \qquad \text{(Eq. 10a)}$$

Therefore,

$$Q = s\left\{A - \epsilon^2\int_0^{C_s} \frac{DCdC}{\tau\left(sG - \frac{\epsilon}{\tau}KC\right)}\right\} \qquad \text{(Eq. 11a)}$$

Differentiation of Eq. 11*a* with respect to time gives

$$\frac{dQ}{dt} = \left\{A - \epsilon^2\int_0^{C_s} \frac{DCdC}{\tau\left(sG - \frac{\epsilon}{\tau}KC\right)}\right\}\frac{ds}{dt} \qquad \text{(Eq. 12a)}$$

But

$$\frac{dQ}{dt} = G = \frac{K'}{s} \qquad \text{(Eq. 13a)}$$

Now Eqs. 12*a* and 13*a* may be solved by integrating from $t = 0$ to $t = t$ and from $s = 0$ to $s = s$ to give

$$Q = \left\{2K't\left[A - \frac{\epsilon^2}{\tau}\int_0^{C_s} \frac{DCdC}{K' - \frac{\epsilon}{\tau}KC}\right]\right\}^{1/2} \qquad \text{(Eq. 14a)}$$

If Eq. 14*a* is compared to Eq. 1, we find that K' may be associated with the factor $\frac{D\epsilon}{\tau}C_s$ of Eq. 1. Therefore, an effective (or an apparent) diffusion coefficient, D', may be defined as

$$D' = \frac{K'\tau}{\epsilon C_s} = \frac{Gs\tau}{\epsilon C_s} \qquad \text{(Eq. 15a)}$$

Therefore, Eq. 14*a* becomes

$$Q = \left\{\frac{D'\epsilon C_s}{\tau}t\left[2A - 2\epsilon\int_0^{C_s} \frac{DCdC}{D'C_s - KC}\right]\right\}^{1/2} \qquad \text{(Eq. 16a)}$$

Because Eq. 15*a* is general, this relation may be used to calculate D' from experimental data obtained with a conventional diffusion cell. Thus,

$$D' = \frac{G_c S_c \tau_c}{\epsilon_c C_s} \qquad \text{(Eq. 17a)}$$

where G_c is the measured solute transport rate per unit area of the barrier in a diffusion chamber with a diffusion barrier of thickness, S_c, porosity ϵ_c, and tortuosity, τ_c.

To accurately determine the value of the term involving the integral may be difficult unless accurate D *versus* C data are available. If such data are available and if ϵ and τ are known, then K should first be determined by means of Eq. 6*a* by a numerical integration procedure. Then, again by numerical integration, the integral term in Eq. 16*a* could be computed.

A reasonably accurate estimate of the integral term in Eq. 16*a* could frequently be made by employing a constant D value obtained from a diffusion experiment at low concentration.

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