Drug Release from Wax Matrices II

Application of a Mixture Theory to the Sulfanilamide–Wax System

By JOSEPH B. SCHWARTZ, ANTHONY P. SIMONELLI, and WILLIAM I. HIGUCHI

Using the T. Higuchi relationship for the release of a drug from a solid matrix, a hydrogenated castor oil–propylene glycol monostearate–sulfanilamide system has been investigated. Plots of the amount of drug released per unit of tablet surface area exposed as a function of the square root of time enabled comparison of the release for various concentrations of drug, and the calculation of the apparent tortuosity values. A model based on the Bruggeman mixture relationship for a two-phase system has been used and equations were derived for the prediction of theoretical tortuosity values as a function of porosity due to drug. These theoretical values for tortuosity appear to follow a skewed convex parabolic function. The experimental results obtained compared well with the theoretical predictions.

THE APPLICABILITY of applying the basic T. Higuchi relationship (2) for systems incorporating drug in a wax matrix has been previously considered (1). This relationship is given by:

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

where Q is the amount of drug released per unit area of the tablet exposed to the solvent; D is the diffusion coefficient of the drug in the solvent; ϵ is the porosity of the matrix; τ is the tortuosity of the matrix; A is the concentration of solid drug in the matrix; C_s is the solubility of the drug in the solvent; and t is time. Equation 1 predicts a linear relationship between Q and the square root of time. Each of the above variables may be determined experimentally, and these have been reported for two drug–wax systems (1).

In the present communication, a drug–wax system is described in which the drug release behavior is relatively complex. Over one range of drug–wax composition the rate appears to be diffusion controlled through the aqueous pores, but the tortuosity values are extremely high. In the second range (high drug concentrations in the tablet) the mechanism appears to change to one in which the rate is not solute diffusion controlled in the aqueous pores. A quantitative physical model is presented that appears to satisfactorily describe the data in the low drug concentration range.

THEORY

Before a theory can be developed, it is essential to first consider the various possible physical arrangements of drug and matrix and their corresponding tortuosity values. If the matrix is composed of nearly spherical particles, such as one would have in a bed of spheres, the τ values should range between about 1.5 to 3 (2, 3). On the other hand, if the matrix material is less spherical, either because the initial particles are nonspherical or because during preparation of the matrix the particles become distorted (4), then greater τ values would be expected. However, even under extreme conditions, it is difficult to imagine τ values much greater than 10 or 20 when the simple concept (2, 3) underlying the meaning of tortuosity is used.

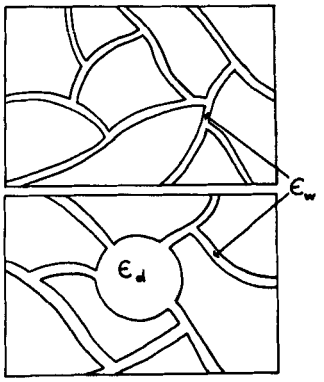

Fig. 1—Schematic diagram of proposed tablet model with air channels through the wax represented by ϵ_w and drug represented by ϵ_d.

As will be seen later, apparent τ values greater than 1,000 have been observed with compressed tablets made of drug–wax combinations. In order to explain such results the following model is proposed.

It is assumed that the drug particles are isolated in a sea of wax. This should be a reasonable approximation at low drug concentrations, since most waxes are extremely soft (plastic) and should flow around the drug particles during compression. Figure 1 schematically illustrates this model. The important feature of this situation is that diffusion is most difficult in the wax regions connecting the pores (left behind after the drug is leached) rather than in the pores themselves as might be generally assumed (2, 5). Thus the permeability of the drug is largely determined by the permeability characteristics of the wax matrix itself.

One equation which gives the permeability char-

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acteristics of a two-phase system is the Bruggeman equation (3, 6).

$$\frac{P_2 - P_e}{P_2 - P_1} = V_1 \left(\frac{P_e}{P_1}\right)^{1/3} \quad \text{(Eq. 2)}$$

where P = permeability,
P_e = permeability of the total system,
V = volume fraction,
1 = external phase,
2 = internal phase.

In a diffusion-controlled system, permeability may be defined as:

$$P = \frac{D\epsilon}{\tau} = KD \quad \text{(Eq. 3)}$$

where $K = \epsilon/\tau$ and where all symbols have been previously defined and all are effective quantities.

The Bruggeman equation (Eq. 2) may be applied to the present system by regarding the matrix "phase" as the external phase. Then the pores left by the leached drug in the tablet constitute the internal phase of the system.

The following relationships are then known for the system:

$$D_2 = D_s \quad \text{(Eq. 4)}$$
$$\therefore P_2 = D_s$$
$$V_1 = (1 - \epsilon_d)$$

where D_2 = diffusion coefficient of internal phase,
D_s = diffusion coefficient of the drug in the solvent,
P_2 = permeability of the internal phase,
V_1 = volume fraction of the external phase,
ϵ_d = porosity due to drug.

Substituting into Eq. 2:

$$\frac{D_s - P_e}{D_s - P_1} = (1 - \epsilon_d)\left(\frac{P_e}{P_1}\right)^{1/3} \quad \text{(Eq. 5)}$$

From Eq. 3 the following relationships may be obtained:

$$P_e = \left(\frac{\epsilon_d + \epsilon_w}{\tau}\right) D_s \quad \text{(Eq. 6)}$$

Table I—Parameters[a] for Sulfanilamide–PGMS–Hydrogenated Castor Oil System

w/w% Drug	% Released by 144 hr.	Slope of Q vs. $t^{1/3}$ Plot	ϵ_d	τ
1	26.02	0.0210	.006	985
2	19.77	0.0357	.013	698
5	15.02	0.0667	.033	707
8.33	12.23	0.0830	.055	1073
10	11.01	0.0863	.067	1287
15	10.83	0.1223	.102	1343
20	11.00	0.1640	.139	1286
25	10.43	0.1910	.176	1444
30	13.87	0.2883	.213	921
35	11.88	0.3200	.257	1030
50	16.62	0.6053	.385	602
60	22.79	1.088	.489	292
70	31.50	1.833	.650	176

[a] Average values for a minimum of three runs.

since the total porosity of the system, ϵ, is composed of that porosity due to drug, ϵ_d, plus that due to air, ϵ_w; and τ is the apparent overall tortuosity.

$$P_1 = \left(\frac{\epsilon_w}{\tau_w}\right) D_s \quad \text{(Eq. 7)}$$

$$\frac{D_s - \frac{(\epsilon_d + \epsilon_w)}{\tau} D_s}{D_s - \left(\frac{\epsilon_w}{\tau_w}\right) D_s} = (1 - \epsilon_d)\left[\frac{\left(\frac{\epsilon_d + \epsilon_w}{\tau}\right) D_s}{\left(\frac{\epsilon_w}{\tau_w}\right) D_s}\right]^{1/3} \quad \text{(Eq. 8)}$$

$$\frac{1 - \left(\frac{\epsilon_d + \epsilon_w}{\tau}\right)}{\left(\frac{\epsilon_d + \epsilon_w}{\tau}\right)^{1/3}} = (1 - \epsilon_d)\frac{\left(1 - \frac{\epsilon_w}{\tau_w}\right)}{\left(\frac{\epsilon_w}{\tau_w}\right)^{1/3}} \quad \text{(Eq. 9)}$$

Letting

$$\theta = \frac{\left(1 - \frac{\epsilon_w}{\tau_w}\right)}{\left(\frac{\epsilon_w}{\tau_w}\right)^{1/3}}$$

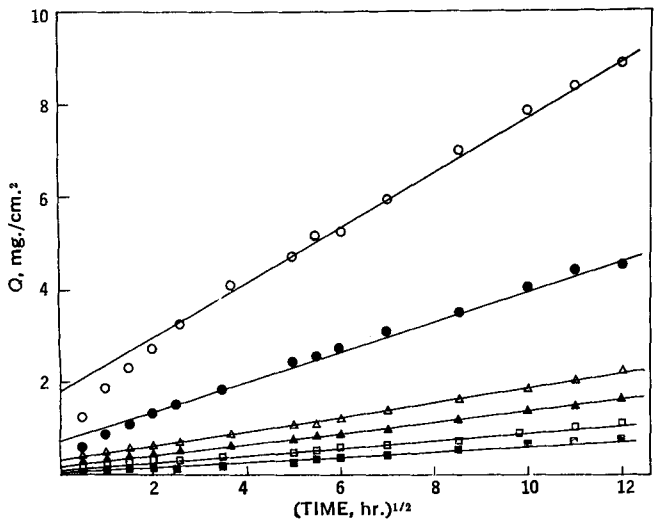

Fig. 2—Q versus $t^{1/2}$ plots for tablets with varying concentrations of drug released in distilled water. Key: ■, 5%; □, 10%; ▲, 15%; △, 20%; ●, 35%; ○, 50%.

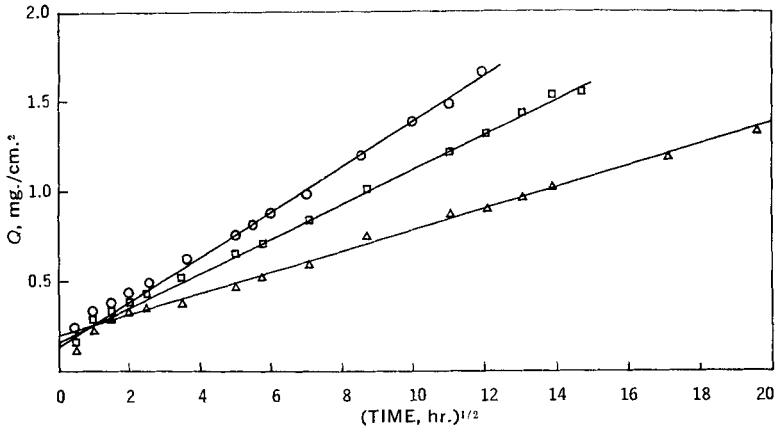

Fig. 3—Comparison of released profiles for 15% sulfanilamide released in different solvents. Key: ○, distilled water; □, 0.5 M NaCl; △, 5.0 M NaCl.

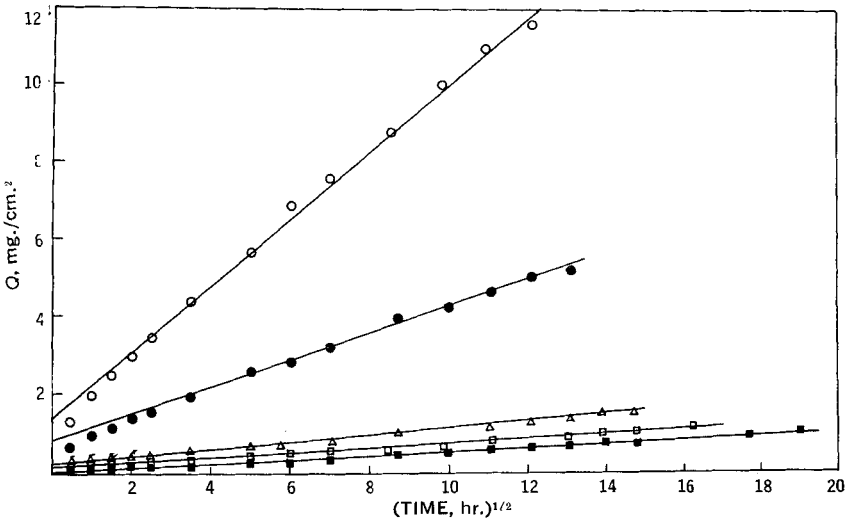

Fig. 4—Q versus $t^{1/2}$ plots for tablets with varying concentrations of drug released in 0.5 M NaCl. Key: ■, 5%; □, 10%; △, 15%; ●, 35%; ○, 50%.

$$\frac{[\tau - (\epsilon_d + \epsilon_w)]\tau^{1/3}}{\tau(\epsilon_d + \epsilon_w)^{1/3}} = (1 - \epsilon_d)\,\theta \quad \text{(Eq. 10)}$$

$$\tau^{2/3}[\tau - (\epsilon_d + \epsilon_w)] = \theta\,(1 - \epsilon_d)(\epsilon_d + \epsilon_w)^{1/3} \quad \text{(Eq. 11)}$$

If it is assumed that $\tau \gg \epsilon_d + \epsilon_w$, then the following relationship holds:

$$\tau^{1/3} = \theta\,(1 - \epsilon_d)(\epsilon_d + \epsilon_w)^{1/3} \quad \text{(Eq. 12)}$$

$$\tau = \theta^3\,(1 - \epsilon_d)^3(\epsilon_d + \epsilon_w) \quad \text{(Eq. 13)}$$

Thus, the apparent tortuosity of the system is given theoretically as a function of the permeability factors of the matrix alone, θ; the porosity due to drug, ϵ_d; and the porosity due to air, ϵ_w. It should be noted that the apparent tortuosity is independent of the diffusion coefficient of the drug in the solvent.

EXPERIMENTAL

The procedure used for these experiments is essentially the same as that presented in a previous paper in this series (1). The same components, PGMS[1] and hydrogenated castor oil,[2] were used as the matrix material and in the same 1:1 ratio. The drug used in this study was sulfanilamide which was spectrophotometrically assayed in the UV region. In addition to the usual solvent, distilled water, varying concentrations of sodium chloride solution were used to test the C_s effect.

RESULTS AND DISCUSSION

Figure 2 shows the release profiles of the tablets in water for various concentrations of sulfanilamide as a function of the square root of time. It is noted that the initial points appear to deviate from linearity, and we have tentatively attributed this to the release of surface drug before the matrix diffusion model takes control. To analyze the data, the best straight lines were drawn through the points after $t^{1/2} = 3$. The experiments had been carried out for much longer periods of time. Based on the observed slopes, the apparent values for tortuosity, τ, were calculated according to Eq. 1, these are listed in Table I along with several other parameters for the system.

Because of the surprisingly high values obtained for τ, it was decided to see whether diffusion in the aqueous phase was rate determining. This was done by changing the C_s factor (see Eq. 1). Tablets were run in NaCl solutions instead of water; because of the salting out effect, the solubility of sulfanilamide

[1] Propylene glycol monostearate, Glyco Chemicals Inc.
[2] Castorwax, Baker Castor Oil Co.

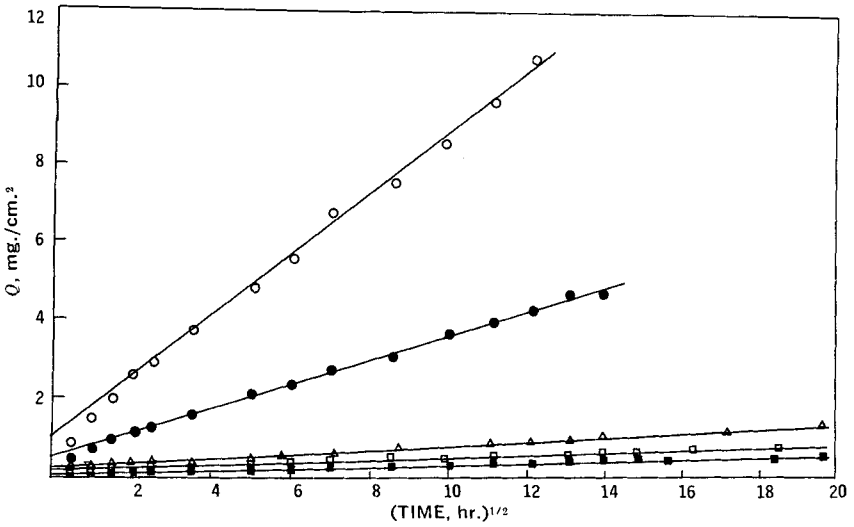

Fig. 5—Q versus $t^{1/2}$ *plots for tablets with varying concentrations of drug released in 5.0 M NaCl. Key:* ■, *5%;* □, *10%;* △, *15%;* ●, *35%;* ○, *50%.*

TABLE II—TEST FOR DIFFUSION-CONTROLLED MODEL SULFANILAMIDE-PGMS-HYDROGENATED CASTOR OIL

w/w%	Solvent	C_s (mg./ml.)	η[a]	Slope	Ratio to H_2O	Predicted[b] Ratio
5	H_2O	10.70	1	0.06667	1	1
	0.5 *M* NaCl	9.92	1.05	0.05300	0.7949	0.9396
	5.0 *M* NaCl	5.46	1.70	0.02500	0.3749	0.5479
10	H_2O	10.70	1	0.08633	1	1
	0.5 *M* NaCl	9.92	1.05	0.06900	0.7992	0.9396
	5.0 *M* NaCl	5.46	1.70	0.03410	0.3950	0.5479
15	H_2O	10.70	1	0.12233	1	1
	0.5 *M* NaCl	9.92	1.05	0.09500	0.7765	0.9396
	5.0 *M* NaCl	5.46	1.70	0 05667	0.4632	0.5479

[a] Compared to water = unity. [b] On basis of η and C_s.

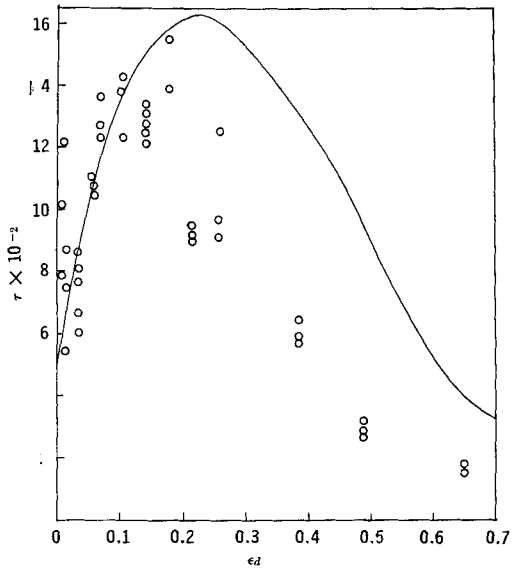

Fig. 6—Comparison of experimental values with the theoretical curve obtained by applying the Bruggeman theory.

is reduced appreciably by high concentrations of NaCl The reduced solubility was expected to reduce the slope of the *Q versus* $t^{1/2}$ plots in accordance with the predictions of Eq. 1. As can be seen in Fig. 3 and also by comparing Fig. 2 with Figs. 4 and 5, this effect was seen for those experiments at low drug concentrations.

The salt effects were not observed, however, with the tablets containing high concentrations ($\gtrsim$35%) of drug. This suggests a basic change in the mechanism of release at the high drug concentrations. Thus the proposed model would be expected to hold only at drug concentrations of less than about 35%.

Table II shows the slopes obtained in the various solvents and the slopes normalized to the distilled water values. According to the Stokes-Einstein equation, the diffusion coefficient, D, is affected by the viscosity of the solvent. Therefore, both the effect of the salt upon D and the effect upon C_s were taken into account in Table II. While the agreement is not exactly quantitative, the comparison strongly supports the diffusion-controlled concept for the low drug concentration cases.

Figure 6 shows the comparison of the experimental τ values with the Bruggeman relationship (Eq. 13). An experimentally determined (1) value for ϵ_w = .0374 was used and a τ_w value of 500 was used to give the fit as shown. A different choice of τ_w would only raise or lower the theoretical curve in Fig. 6; the shape would remain unchanged. Differentiation with respect to ϵ_d and proper analysis of Eq. 13 reveals that the maximum, calculated at 0.222, is independent of τ_w. Treatment of the second derivative, moreover, showed an inflection point at ϵ_d = 0.481 which gives the theoretical curve (see Fig. 6) a skewed convex parabolic shape.

The good agreement of the data with the theory at the lower ($\lesssim$20%) drug concentrations strongly

supports the proposed model in this concentration range. The large deviations from the theory at high drug concentration are consistent with the idea that a more rapid process takes over that does not appear to be aqueous diffusion controlled. More work is needed to explain the latter behavior.

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Keyphrases

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Sulfanilamide–wax system
Tortuosity values–apparent
UV spectrophotometry–analysis

Alpha-Chymotrypsin-Catalyzed Hydrolysis of Some Carbonate Esters

By ATUL A. SHAH* and KENNETH A. CONNORS

The kinetics of the α-chymotrypsin-catalyzed hydrolysis of several carbonate diesters, ROCOOR′, can be described by the Michaelis-Menten equation. *p*-Acetamidophenyltrichloroethyl carbonate shows a sigmoid pH-rate curve with a kinetic dependence on an enzyme function of pKa 7.2. The limiting values of the catalytic rate constant at high pH are, for *p*-acetamidophenyltrichloroethyl carbonate, 8.0×10^{-2} sec.$^{-1}$; for *p*-nitrophenyltrichloroethyl carbonate, 8.2×10^{-2} sec.$^{-1}$; for *p*-nitrophenylethyl carbonate, 0.2×10^{-2} sec.$^{-1}$. The evidence is consistent with the intermediate formation of an alkyl enzyme carbonate, the hydrolysis of which is rate controlling.

CARBONATE DIESTERS are derivatives of carbonic acid, the two hydrogens of the acid being formally replaced by alkyl or aryl groups to give the general structure ROCOOR′. The suggestion has recently been made (1) that such esters may be useful "prodrugs" because they may possess desirable pharmaceutical properties and can release the parent pharmacologically active compounds (ROH and R′OH) upon hydrolysis in the body. The mechanism of enzymatic hydrolysis of carbonate esters is therefore of pharmaceutical interest.

The enzymatic hydrolysis of carbonate esters is also of considerable fundamental importance. α-Chymotrypsin has been selected as the enzyme in the present study because it is commercially available in crystalline form, a good assay method is known, and especially because more is known about the catalytic behavior of chymotrypsin than of any other enzyme. Chymotrypsin is a member of a group of related enzymes known as the serine hydrolases; these enzymes catalyze the hydrolysis of proteins, peptides, amides, and esters. It is now well established that chymotrypsin (and probably other closely related enzymes) functions catalytically by a double displacement type of reaction. With an ester substrate, for example, the reaction may be written as shown in Scheme I.

$$\text{En—OH} + \text{RCOOR}' \rightleftarrows \text{En—OH}\cdot\text{RCOOR}'$$

$$\text{En—OH}\cdot\text{RCOOR}' \xrightarrow{\text{acylation}} \text{EnOCOR} + \text{R}'\text{OH}$$

$$\text{EnOCOR} + \text{H}_2\text{O} \xrightarrow{\text{deacylation}} \text{En—OH} + \text{RCOOH}$$

Scheme I

Here En—OH represents the enzyme, with a serine hydroxyl group specifically indicated. En—OH · RCOOR′ is the enzyme–substrate complex. In the acylation step, the enzyme is acylated with the release of the alcohol portion of the substrate. Deacylation involves hydrolysis of the acyl–enzyme intermediate EnOCOR to give the carboxylic acid portion of the substrate and to regenerate the enzyme. The evidence supporting this interpretation of chymotrypsin-catalyzed reactions has recently been reviewed by Bruice and Benkovic (2). It is now of interest to consider the possible mode of action of chymotrypsin when the substrate is a carbonate ester, ROCOOR′. It is obvious that two possible

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* Present address: Parke Davis & Co., Detroit, MI 48232