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Keyphrases

Monoamine oxidase inhibitors
β-carbolines–synthesis
Methyl and methoxy substitution–activity effect
Ethyl substitution–activity effect
Propyl substitution–activity effect
IR spectrophotometry–structure
UV spectrophotometry–structure

Drug Release from Wax Matrices I

Analysis of Data with First-Order Kinetics and with the Diffusion-Controlled Model

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

The release of drug into aqueous media from wax matrices has been investigated using benzoic acid and salicylic acid as the active ingredients. The data have been examined from the viewpoint of the first-order kinetic theory and that of a diffusion-controlled process. It was found that the experimental data are best analyzed using a diffusion-controlled model and square root of time release profiles. Parameters controlling the release are presented.

SEVERAL WORKERS (1–4) have recently reported the results of investigations regarding the factors influencing drug release from inert, insoluble matrices. Matrices composed of plastic polymers have been shown to exhibit release profiles which are best described by the linear square root of time dependence indicating that a diffusion-controlled mechanism is operative (2). Waxes, on the other hand, present a much more complicated system, both experimentally and theoretically, due to various physical-chemical factors and properties not present in the plastic systems.

As a result, the mechanism of release from wax matrices has not been as firmly established. In view of the large number of patents issued in this area, it would be highly desirable that the release rates from these systems also be quantitated by use of the diffusion model and the determination of the necessary controlling parameters made.

Theoretical treatment has shown that drug release from an insoluble, inert matrix is described by the T. Higuchi equation (5) if the rate-determining process is diffusion; and this 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 disk 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. Each of the above variables lends itself to experimental determination. Any units may be used for the above variables and constants, provided they are mutually consistent.

It was the purpose of this study to establish the applicability of the diffusion model to wax systems and to determine the controlling variables.

EXPERIMENTAL

Tablets composed of a drug homogeneously distributed throughout a wax matrix were prepared by the following method. The drug was suspended or dissolved in the melted waxes contained in an evaporating dish. Following the removal of heat, continual stirring until complete solidification had

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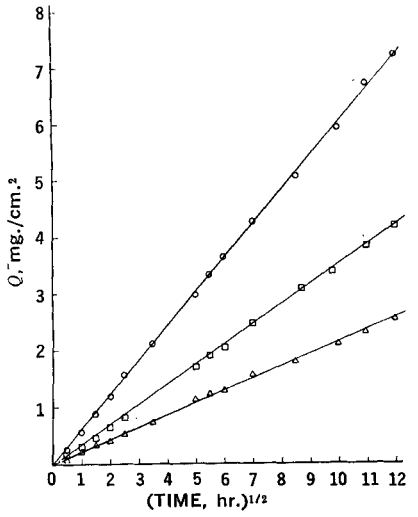

Fig. 1—Release profile of various concentrations of salicylic acid when plotted according to the diffusion model. Key: Δ, 5%; □, 10%; ○, 20%.

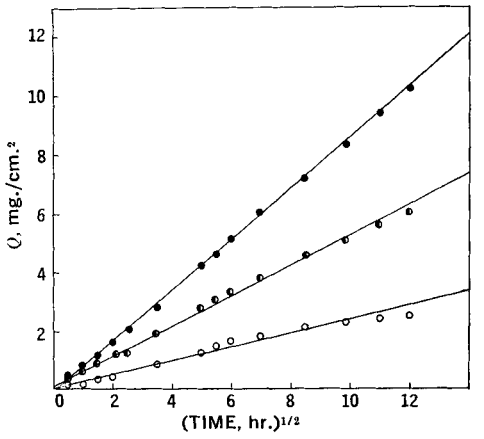

Fig. 2—Release profiles of various concentrations of benzoic acid when plotted according to the diffusion model. Key: ○, 5%; ◐, 10%; ●, 20%.

occurred prevented any separation of drug and wax. To facilitate compression, this solid was then granulated by means of a 16-mesh screen and a spatula. Tablets of approximately 250 mg. with a $^3/_8$-in. diameter were compressed from this granulation using a Carver press at a compressional force of 5,000 lb.

To measure release rate, a volumetric flask (250 ml.) containing a tablet was filled with 100 ml. of the solvent and was placed in a shaking water bath maintained at 30°. Aliquot samples were withdrawn at various times and replaced with fresh solvent. After proper dilution with water, these samples were assayed using a Beckman DU spectrophotometer (salicylic acid, 294 mμ; benzoic acid, 259 mμ).

RESULTS AND DISCUSSION

Preliminary investigations were carried out with several waxes and their combinations. The matrix chosen for these studies was composed of PGMS[1] and hydrogenated castor oil[2] in a 1:1 ratio. It was observed that either wax, when used alone, had disadvantages which disappeared when the two were combined. Tablets of PGMS exhibited relatively rapid release rates but showed a tendency to flake when run for any length of time under experimental conditions. Tablets of hydrogenated castor oil did not flake but gave an extremely slow release. The 1:1 ratio provided the optimum matrix.

Tablets containing either salicylic or benzoic acid were studied. Figures 1 and 2 show linear square root of time plots indicating that these systems are diffusion controlled. Average slopes (3 or more runs) of these curves, listed in Table I, are proportional to the concentration of drug in the tablet as predicted by Eq. 1 and support the above mechanism.

Interestingly, the data also yielded an apparently straight line when the log of the drug left in the matrix was plotted as a function of time as predicted by first-order release:

$$\log W = \frac{kt}{2.303} + \log W_0 \qquad \text{(Eq. 2)}$$

where W = amount of drug left in tablet,
W_0 = initial amount of drug in tablet,
k = first-order rate constant,
t = time.

Figure 3 illustrates the release profiles of the salicylic acid data when plotted this way. The initial curvature can be attributed to the presence of surface drug and can be ignored. This same figure shows that the rate constant appears to remain relatively constant with a change in concentration of the drug in the tablet; this fact is in agreement with a first-order analysis.

Since both first-order and square root of time plots are acceptably linear, a more stringent test was developed to distinguish between the mechanisms. The use of the predicted rate equations corresponding to Eqs. 1 and 2 can be used for this purpose as shown by the following treatment.

Equation 1 can be reduced to the following:

$$Q' = KSt^{1/2} \qquad \text{(Eq. 3)}$$

where Q' = amount released = $Q \times S$,
S = surface area of tablet,
$K = \left[\frac{D\epsilon}{\tau}(2A - \epsilon C_s)\, C_s\right]^{1/2}$

By differentiation of the above reduced equation and appropriate substitution, Eq. 4 can be obtained:

$$\frac{dQ'}{dt} = \text{rate} = \frac{K^2S^2}{2Q'} \qquad \text{(Eq. 4)}$$

which indicates that the rate will be inversely proportional to the amount of drug released, Q'.

The rate predicted by first-order kinetics, however, is given by the following relationship:

$$\frac{dQ'}{dt} = \text{rate} = kW_0 - kQ' \qquad \text{(Eq. 5)}$$

since

$$-\frac{dW}{dt} = \frac{dQ'}{dt} = kW \qquad \text{(Eq. 6)}$$

[1] Propylene glycol monostearate, Glyco Chemicals, Inc.

[2] Castorwax, Baker Castor Oil Co.

TABLE I—VALUES OF PARAMETERS FOR THE RELEASE OF SALICYLIC AND BENZOIC ACID FROM A PGMS–HYDROGENATED CASTOR OIL MATRIX IN WATER

Drug	w/w, %	ϵ	A (mg./ml.)	Slope of Q vs. $t^{1/2}$ Plot	τ
Salicylic acid	5	0.11212	47.47	0.220	16.9
$D = 3.852 \times 10^{-2}$ cm.²/hr.	10	0.12087	99.03	0.380	12.8
$C_s = 2.0$ mg./ml.	20	0.20352	201.70	0.640	15.9
Benzoic acid	5	0.09040	48.27	0.278	18.9
$D = 3.96 \times 10^{-2}$ cm.²/hr.	10	0.11745	99.33	0.513	14.7
$C_s = 4.2$ mg./ml.	20	0.19218	204.64	0.870	17.2

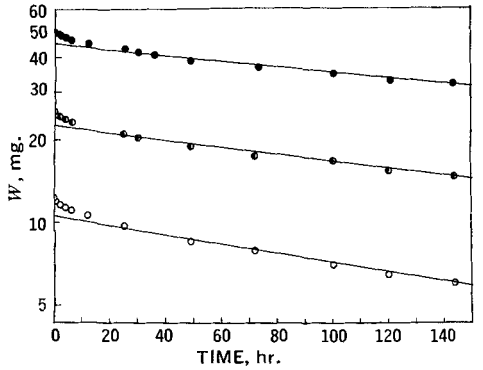

Fig. 3—Release profiles of various concentrations of salicylic acid when plotted according to first-order kinetics. Key: ○, 5%; ◐, 10%; ●, 20%.

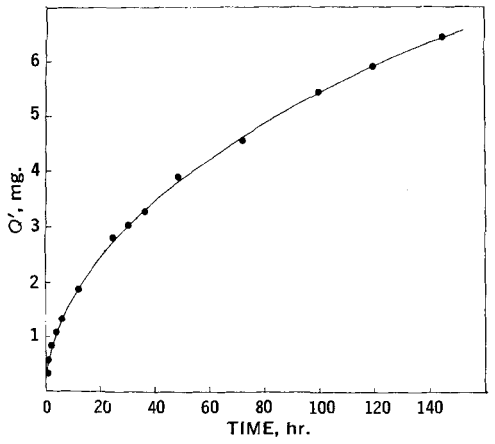

Fig. 4—Amount of drug released from the matrix as a function of time for 5% salicylic acid.

TABLE II—VALUES FOR RATE, AMOUNT RELEASED, AND THE CORRESPONDING RECIPROCAL FOR THE RELEASE OF 5% SALICYLIC ACID

Rate = dQ'/dt	Q'(mg.)	$1/Q'$(mg.)
0.3400	0.480	2.083
0.2250	0.700	1.429
0.1670	0.850	1.176
0.1185	1.105	0.905
0.0940	1.520	0.658
0.0650	2.350	0.426
0.0400	3.520	0.284
0.0290	4.670	0.214
0.0225	5.580	0.179
0.0215	6.180	0.162

and

$$W = W_0 - Q' \qquad \text{(Eq. 7)}$$

which indicates that the rate is proportional to Q' rather than inversely proportional as predicted by the diffusion model.

The rates of release were determined by obtaining slopes of a Q' *versus* time plot (see Fig. 4). These values are tabulated along with Q' and reciprocal Q' values in Table II.

By comparison of Eqs. 4 and 5, it is clear that the first predicts a linear plot when *rate* is plotted as a function of $1/Q'$ and that the second predicts a linear plot when *rate* is plotted as a function of Q'. Figures 5 and 6 show that the two mechanisms can indeed be differentiated by this rate treatment as only Fig. 5 is linear indicating a diffusion-controlled mechanism. In addition, it should be noted that the slope of the line in Fig. 5 was found to be equal to $K^2S^2/2$ as predicted by Eq. 4.

This conclusion can be further confirmed by the use of Eq. 8, which is obtained by taking logs of Eq. 3:

$$\log Q = \log K + {}^1/_2 \log t \qquad \text{(Eq. 8)}$$

This predicts that a plot of log Q *versus* log t must not only give a straight line, but must have a slope

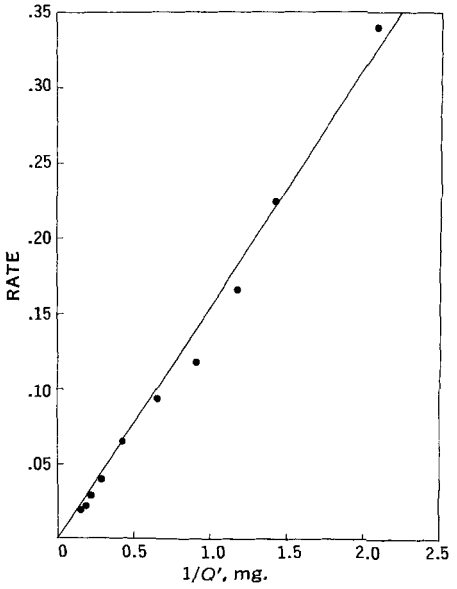

Fig. 5—Rate as a function of reciprocal drug released for 5% salicylic acid.

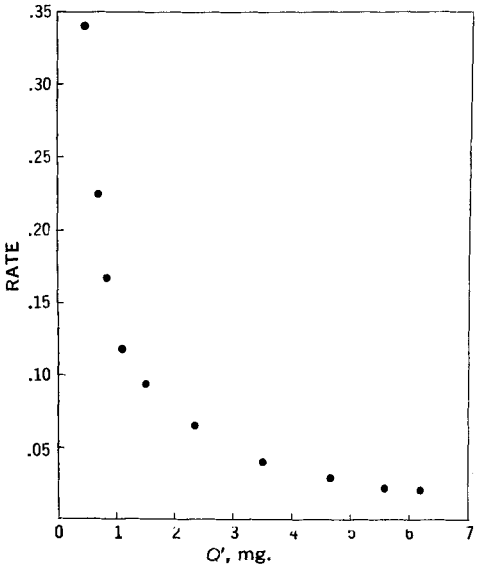

Fig. 6—Rate as a function of amount of drug released for 5% salicylic acid.

of $^1/_2$. This was found to be true and is illustrated by Fig. 7.

In addition, the various parameters for all systems were calculated by use of methods previously reported (6, 7) and are presented in Table I. The values for tortuosity, τ, are relatively constant and reasonable, as one would expect slightly higher τ values when the matrix components are relatively plastic and easily distorted.

CONCLUSIONS

Although the systems studied demonstrated apparently linear semilog plots with slopes that were apparently independent of the concentration of drug embedded in the wax matrix, more stringent tests clearly showed that the diffusion-controlled mechanism was operative and that a first-order release was incorrect.

It should be noted that one must use studies which are sufficiently long to properly evaluate matrix systems. First-order processes demand three or more half-life intervals, and the diffusion model requires an exponential increase in time with each successive sample due to the $t^{1/2}$ dependence. These studies utilized a minimum of 6 days and yet only 50 to 60% was released and can account for the linear semilog plots. This also explains the lack of significant curvature predicted in the latter points of the $t^{1/2}$ plots due to finite changes in the effective area of drug release of a whole tablet since these do not occur until greater than 60 to 70% is released.

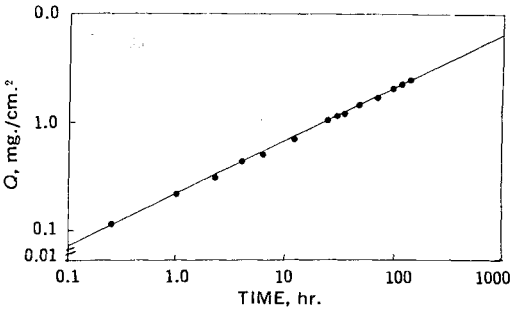

Fig. 7—Plot of the log of the amount of drug released per unit surface area against the log of time for 5% salicylic acid.

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Keyphrases

Drug release
Matrices–wax
Diffusion controlled model
UV spectrophotometry–analysis