tonine (20), and fusarenon-X (13). One explanation for this is that peptidyl tRNA or methionyl tRNA lowers affinity binding of drug to ribosome (21). Daphnoretin effectively blocked peptidyl transferase activity of the elongation process. The magnitude of inhibition of protein synthesis is of a sufficient degree to account for the cessation of cell growth. It has been reported previously that daphnoretin suppresses DNA synthesis with an $ID_{50} \cong 0.194$ mM (5). The present studies show that daphnoretin only suppresses protein and DNA synthesis in the Ehrlich ascites carcinoma cells, the only tumor screen in which daphnoretin demonstrated antineoplastic activity at 3–12 mg/kg/day. Protein and DNA synthesis of whole cells was not suppressed in normal mouse tissue, *e.g.*, brain, kidney, and lung; but there was a moderate reduction of protein synthesis in the liver. Daphnoretin was isolated from *Wikstroemia indica* C. A. Mey (Thymelaeaceae), which has been used as a herbal remedy to treat human cancer, arthritis, syphilis, and whooping cough (22, 23). This study of the mode of action of daphnoretin may explain some of the pharmacological properties of the plant.

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Square Root of Time Dependence of Matrix Formulations with Low Drug Content

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Abstract □ One of the conditions of derivation of the Higuchi square root law is that $A/\epsilon > S/2$ where A is drug content per cubic centimeter of matrix tablet, ϵ is the porosity, and S is the solubility of the drug in the dissolution medium. In actuality, A/ϵ should be larger than S. It is shown in this work that a similar square root equation can be derived when $A/\epsilon < S$. Experimental data are presented supporting the equation $Q = A(Dt)^{1/2}$, where Q is the amount of drug released per square centimeter at time t and D is the diffusion coefficient.

Keyphrases □ Matrix formulations—square root of time dependence, with low drug content □ Dissolution—square root of time dependence of matrix formulations with low drug content □ Release rate—square root of time dependence of matrix formulations with low drug content

Many sustained-release products are designed around the principle of imbedding the drug in a porous matrix. Liquid will penetrate and dissolve the drug, which will then diffuse out into the exterior liquid (Fig. 1). In general, for the purpose of derivation, a slab is considered which has a unit cross-section, is infinite to the left (Fig. 1), has a porosity ϵ', contains A grams of drug (of density ρ) per cubic centimeter of matrix, and allows penetration and diffusion through the unit surface only. At time t a depth of h is penetrated.

BACKGROUND

Higuchi (1, 2) was the first to derive the following expression for the amount of material released (Q) through the unit surface. He cautions that "the equation would be essentially valid for systems in which A is greater than the solubility S or ϵS by a factor of three or four. Of course,

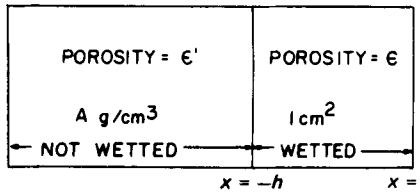

Figure 1—*Schematic of penetration of liquid into a solid matrix. The distance is denoted* x *(cm) and is zero at the surface and* −h *at the border of penetration.*

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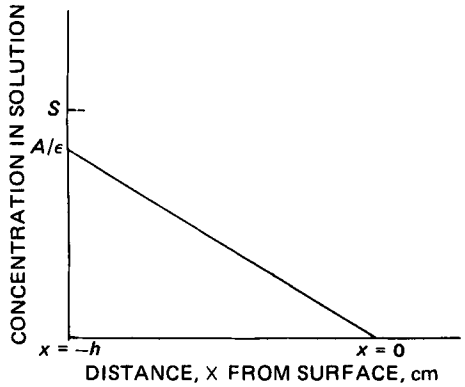

Figure 2—*Assumed concentration profile in the penetrating liquid for the situation in Fig. 1.*

if $A < S$ or ϵS, the drug would no longer be present as a solid and a different equation would apply."

$$Q = [2DS\epsilon(A - 0.5S\epsilon)]^{1/2}t^{1/2} \quad \text{(Eq. 1)}$$

The tortuosity term has been omitted since it does not apply in the following; ϵ is the porosity of the part of the matrix already penetrated by liquid, and S is the solubility (in gram per cubic centimeter) of the drug in the penetrating liquid. The point that A should be greater than S by a factor of three or four has been emphasized previously (3–5). In cases where the above is not the case, *ie.*, when

$$S > A/\epsilon \quad \text{(Eq. 2)}$$

derivations are nevertheless possible. The following sequence follows closely that described previously (1, 2, 5), and the following assumptions are made:

(*a*) sink conditions exist (*i.e.*, $C \sim O$) in the exterior liquid, where C is concentration of drug;

(*b*) the concentration gradient in the liquid in the penetrated space is linear;

(*c*) the diffusion coefficient is concentration independent;

(*d*) the drug content, A, is less than $S\epsilon$;

(*e*) the rate of dissolution is governed by the liquid penetration rate, not the dissolution rate.

The case where both dissolution and penetration rates play a part has been treated elsewhere (6, 7). Because of (*d*) and (*e*), the drug will, in fact, dissolve immediately when reached by liquid and form an unsaturated solution of concentration A/ϵ ($<S$). It is emphasized here that ϵ is the actual porosity in the penetrated space, *i.e.*, the original porosity, ϵ', and that created by dissolution of drug, A/ρ (presuming that an ideal solution forms). In the following, ϵ will be referred to as actual and ϵ' as measured porosity. It follows that:

$$\epsilon = \epsilon' + (A/\rho) \quad \text{(Eq. 3)}$$

The concentration profile shown in Fig. 2 will therefore apply. The

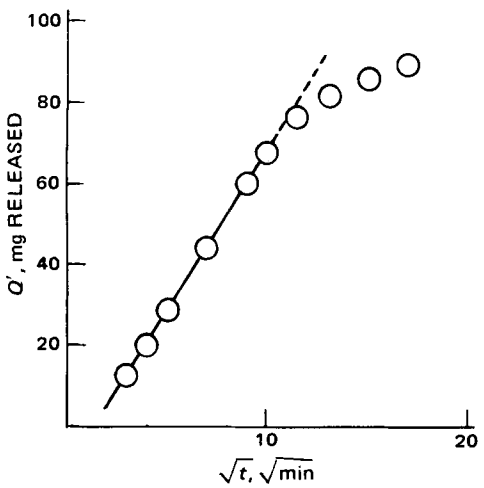

Figure 3—*Release data for Formula II, Table I.*

Table I—Compositions of Formulations Tested

	Formulation Number[a]			
	I	II	III	IV
Diphenhydramine HCl[b]	5	10	15	20
Polyvinyl acetate–polyvinyl chloride copolymer	50	50	50	50
Povidone	1.5	1.5	1.5	1.5
Magnesium stearate	3	3	3	3
Calcium phosphate, tribasic	←a sufficient quantity to 500 mg→			

[a] Percent by weight.
[b] The measured porosities of the formulations were 0.17, 0.16, 0.16, 0.17, and 0.13, respectively, giving drug concentrations on a volume basis of 0.067, 0.142, 0.200, and 0.260, respectively.

amount dissolved at time t is Q grams per square centimeter of surface and is given by:

$$Q = Ah - 0.5(A/\epsilon)h\epsilon = 0.5Ah \quad \text{(Eq. 4)}$$

Ah is the amount present in the matrix in the h-cm thick layer before dissolution started. After penetration to a depth of h, there are ϵ cubic centimeters of liquid per cubic centimeter of matrix and the average concentration is $0.5(A/\epsilon)$, so that the total amount not liberated to the exterior liquid is $h\epsilon(0.5A/\epsilon) = hA/2$.

Differentiation of Eq. 4 with respect to time gives:

$$dQ/dt = (A/2)dh/dt \quad \text{(Eq. 5)}$$

The diffusion of the drug takes place *via* Fick's law:

$$\text{Flux} = -D \times \text{Gradient} \quad \text{(Eq. 6)}$$

The flux is the amount of material passing through a unit cross-section per unit of time (dt). The cross-sectional area available for liquid is ϵ in square centimeters, and the amount of material passing through it is dQ/dt, so that the left hand side of Eq. 6 may be written:

$$\text{Flux} = (1/\epsilon)(dQ/dt) \quad \text{(Eq. 7)}$$

The gradient (dC/dx) is assumed to be constant [condition (*b*)] and drops from $C = A/\epsilon$ at $x = -h$ (Fig. 2) to zero at $x = 0$ [condition (*a*)]. Hence the gradient term in the right hand side of Eq. 6 is:

$$\text{Gradient} = dC/dx = [0 - (A/\epsilon)]/h = -A/(h\epsilon) \quad \text{(Eq. 8)}$$

so that inserting Eqs. 7 and 8 in Eq. 6 gives:

$$(1/\epsilon)dQ/dt = -D\{-[A/(h\epsilon)]\}$$

or

$$dQ/dt = DA/h \quad \text{(Eq. 9)}$$

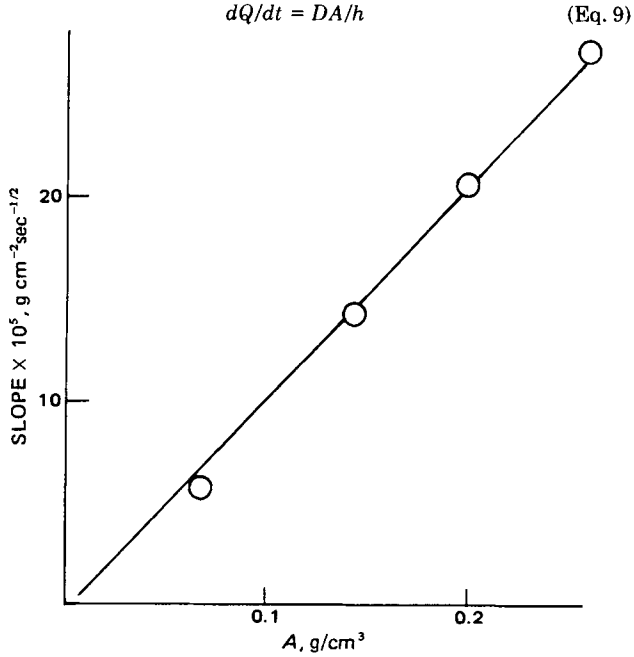

Figure 4—*Slopes of data as shown in Fig. 3 (divided by surface area) as a function of* A, *the drug content (Eq. 13) (data from Table III).*

Table II—Release Rate Data from Matrix Tablets of Four Drug Substances, Using Formula IV from Table I

Compound	S, g/cm³	Tablet Area, cm²	Tablet Volume, cm³	A, g/cm³	Experimental Porosity, ϵ'	Slope, mg min$^{-0.5}$	Adjusted Slope, $10^5 Q$, g cm^{-2} sec$^{-0.5}$	$10^{10} Q^2/S$
Diphenhydramine HCl	0.83	3.54	0.384	0.26	0.13	7.58	27.6	918
Acetaminophen	0.02	3.58	0.4	0.25	0.21	3.60	13	8450
Dyphylline[a]	0.17	3.48	0.37	0.27	0.16	5.26	19.5	2237
Theophylline	0.010	3.48	0.37	0.27	0.16	2.56	9.4	8836

Compound	Density, g/cm³	$\epsilon' + (A/\rho)$	A/ϵ	Molecular Weight
Diphenhydramine HCl	1.20	0.35	0.74	255
Acetaminophen	1.28	0.40	0.63	151
Dyphylline	1.18	0.39	0.69	254
Theophylline	1.28	0.37	0.73	180

[a] 7-(2,3-dihydroxypropyl)-1,3-dimethylxanthine, $C_{10}H_{14}N_4O_4$.

Combining Eqs. 4 and 9 yields:

$$(A/2)dh/dt = AD/h \qquad \text{(Eq. 10)}$$

or

$$hdh = 2Ddt \qquad \text{(Eq. 11)}$$

which integrates (with the initial condition that $h = 0$ at $t = 0$) to:

$$h^2 = 4Dt \qquad \text{(Eq. 12)}$$

Inserting Eq. 12 into Eq. 4 gives:

$$Q = A(Dt)^{0.5} \qquad \text{(Eq. 13)}$$

Equation 13 predicts that Q, the amount released per square centimeter of tablet surface, is proportional to the square root of time, and that the slope of such a plot is independent of porosity and solubility and is directly proportional to the drug content (per cubic centimeter) of the matrix.

As mentioned earlier, the case of (*d*), *i.e.*, of Eq. 2, is the exception rather than the rule. Only one case was reported in literature with drug concentrations where A may approach a low value close to S (8). These data fit fairly well to Eq. 13, but are difficult to analyze, because due to the lack of porosity data, the independence of Eq. 13 of the porosity cannot be tested in that specific case.

EXPERIMENTAL

Matrix tablets of the composition shown in Table I were produced as described in earlier publications (9–11). The matrix is sufficiently insoluble to consider it as completely insoluble (albeit the 1.5% povidone does dissolve to some extent).

Four drugs were tested (Table II) that have solubilities above and below the solubilities dictated by the Higuchi equation (Eqs. 1 and 2). The solubilities were tested by equilibrating excess of drug substance with water at 37 ± 0.2° in a rotating bottle in a waterbath. The concentrations in the supernate were determined spectrophotometrically at the peaks of the respective adsorption spectra. Densities were determined pycnometrically.

The tablets made were produced at various, controlled compression forces on an instrumented single punch machine (11). The porosities were measured using a mercury intrusion porosimeter[1]. The surface areas and volumes of the tablets were obtained from their dimensions. The dissolution rates were determined using a flow cell as described previously (6, 7, 9).

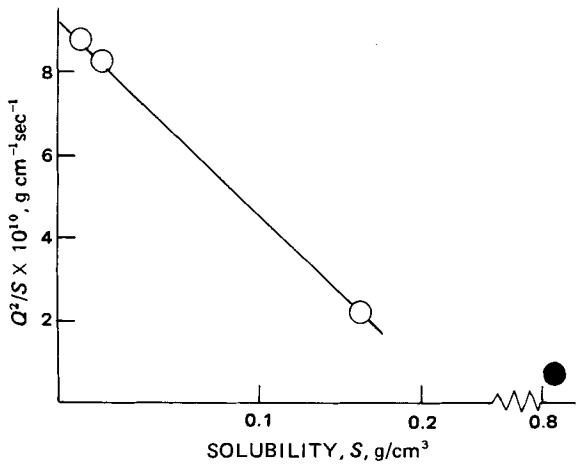

Figure 5—*Data from Table II plotted according to Eq. 18.*

RESULTS AND DISCUSSION

Figure 3 shows an example of dissolution of diphenhydramine hydrochloride from formulas as shown in Table I. It is seen that the amount released is linear in the square root of time up to the critical time (9, 10) when the tablet is completely penetrated by liquid. There is also a slight lag time, also explained in previous publications (9, 10). Slopes from four concentrations of drug are shown in Table III. The data in the last column are obtained by converting the slopes from plots like Fig. 3 to g sec^{-1} cm^{-2}, by multiplying by $10^{-3}/\sqrt{60}$ and dividing by the surface area of the tablet. This latter, in the case cited, is 3.54 cm², as it is in most of the tablets in question. An exception to this is the data leading to the Heckel plot mentioned at a later point[2]. Data of the type in Table III are plotted in Fig. 4, where the specific release rates (in grams per square centimeter sec$^{-0.5}$) are plotted as a function of A. According to Eq. 13 this should be a straight proportionality, which is borne out by the graph. The least squares fit line is:

$$y = 1.13 \times 10^{-3}x - 2 \times 10^{-6} \qquad \text{(Eq. 14)}$$

where $y = Qt^{-0.5}$ (g cm^{-2} sec$^{-1/2}$) and $x = A$ (g cm^{-3}). The intercept does not differ significantly from zero ($p = 0.001$) as predicted by Eq. 13. If this latter case is correct, then the slope of the plot in Fig. 4 should equal $D^{0.5}$, *i.e.*, $D^{0.5} = 1.13 \times 10^{-3}$ cm sec$^{-0.5}$ or $D \cong 10^{-6}$ cm² sec^{-1}, which is

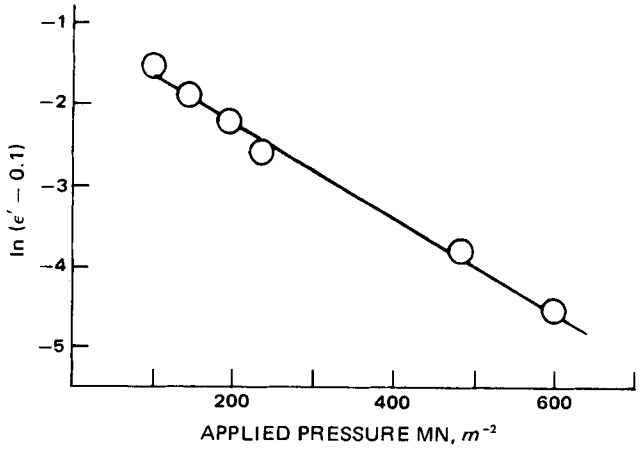

Figure 6—*Data from Table IV plotted as a Heckel function.*

[1] J. T. Carstensen and M. A. Zoglio, *J. Pharm Sci.*, Submitted for publication.
[2] The low porosity points in Table IV have slightly larger surface areas per tablet, due to a larger thickness.

Table III—Data for Diphenhydramine HCl Square Root Dissolution Rate Constants in a Series of Compositions[a]

Tablet Volume, cm^3	Drug, g/500-mg Tablet	A, g/cm^3	ϵ' Experimental	$\epsilon = \epsilon' + (A/\rho)$	Slope $\times 10^5$, $g\ cm^{-2}\ sec^{-1/2}$
0.375	0.025	0.067	0.173	0.23	5.82
0.351	0.050	0.142	0.163	0.28	14.4
0.375	0.075	0.20	0.164	0.33	20.8
0.384	0.100	0.26	0.13	0.38	27.6

[a] Porosity has been kept constant.

Table IV—Release Data of Diphenhydramine HCl as a Function of Porosity

Compression Force, MPa	$Q \times 10^5$ $g\ cm^{-2}\ sec^{-0.5}$	ϵ'	ϵ	$\ln(\epsilon' - 0.1)$
98	43	0.302	0.48	−1.600
147	39	0.260	0.45	−1.900
196	27	0.207	0.42	−2.235
234	25	0.169	0.39	−2.674
490	24	0.123	0.35	−3.772
588	24.3	0.111	0.34	−4.510

the right order of magnitude. The formulations listed in Table I all adhere to the inequality in Eq. 2, and they demonstrate the utility of the modification of the Higuchi equation in low concentration regions.

To further test the correctness of the developments described, it is noted that Eq. 1 may be written:

$$Q^2 = aS - bS^2 \qquad \text{(Eq. 15)}$$

where

$$a = 2D\epsilon A \qquad \text{(Eq. 16)}$$

and

$$b = D\epsilon^2 \qquad \text{(Eq. 17)}$$

This solubility dependence of the Higuchi equation has been checked and verified with three drug substances, the latter three listed in Table II. It is noted from the table that the A-values have been kept constant. If D is the same for the three substances, then a plot of Q^2/S *versus* S should give a straight line:

$$Q^2/S = a - bS \qquad \text{(Eq. 18)}$$

The slope and intercept should give the same value for D. It should be noted that according to the Stokes-Einstein equation:

$$D = kT/(6\pi\eta r) \qquad \text{(Eq. 19)}$$

where η is viscosity, k is Boltzmann's constant, T is absolute temperature, and r is the molecular radius. The value r should be proportional (roughly) to the cube root of the molar volume, so that the D-values should vary at the most by a factor of $(254/151)^{1/3} = 1.19$, *i.e.*, ~20%. It is assumed that the D-values of the three compounds are identical.

The data from the last three entries in Table II have been plotted according to Eq. 18, and are shown in Fig. 5; it can be seen that a straight line ensues. The least-squares fit equation is

$$10^{10}Q^2/S = -42{,}000\,S + 9300 \qquad \text{(Eq. 20)}$$

Hence, from the slope:

$$b = D\epsilon^2 = 0.42 \times 10^{-5} \qquad \text{(Eq. 21)}$$

so that setting $\epsilon = 0.38$ (Table III) gives $D = 3 \times 10^{-5}\ cm^2/sec$. From the intercept:

$$a = 9.3 \times 10^{-7} = 2D\epsilon A \qquad \text{(Eq. 22)}$$

so that setting $\epsilon = 0.38$ (Table III) gives $D = 10^{-5}\ cm^2/sec$. This demonstrates that substances adhering to the Higuchi requirements, in the system tested and using the test methods described, adhere to the Higuchi equation and give reasonable parameter values.

From the point of view of the present study, the most important point is that diphenhydramine has a Q^2/S value out of line with the remaining compounds.

An important difference between Eqs. 1 and 13 is that the latter is independent of the porosity, ϵ. This point is difficult to investigate, as shown below. Preparations were made at different preparative porosities, ϵ'. This was accomplished by varying the applied compression force at which the tablets were made.

The data are tabulated in Table IV. The force *versus* porosity data are consistent as demonstrated in the Heckel plot in Fig. 6. Of the preparations, the three made at the low pressures disintegrated, and hence, from a point of view of release, do not fall into the described models. The last three entries in Table IV, however, show that Q is not drastically a function of ϵ: Q is 24–25 $g\ cm^{-2}\ sec^{-0.5}$ over a range of initial porosity values of $\epsilon' = 0.11$–0.17 (*i.e.*, a 60% spread). However, due to the A-contribution to the porosity ϵ, the overall porosity, is 0.34–0.39, which is only at best a 20% variation. It would appear that a 20% variation in actual porosity, ϵ, causes a change of <4% in the slope (Q) of the square root plot, so that the effect of ϵ is small. Experimentally, it would have been desirable to have a wider spread of ϵ-values, but the disintegration is a problem at the lower end and the A-values a problem at the upper end.

It has been shown that when $A < S\epsilon$ the release rate for a matrix should be $Q = AD^{0.5}t^{0.5}$. Release plots of drug in situations where $A < S\epsilon$ have been shown to follow a square root law with slopes that are proportional to A. The proportionality constant gives a reasonable value of D ($2 \times 10^{-6}\ cm^2/sec$). Evidence is presented that the proportionality constant is independent of solubility, S, and porosity, ϵ.

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