International Journal of Pharmaceutics, 1 (1978) 265–274

THE HIGUCHI SQUARE ROOT EQUATION APPLIED TO MATRICES WITH HIGH CONTENT OF SOLUBLE DRUG SUBSTANCE

H. FESSI, J.-P. MARTY, F. PUISIEUX and J.T. CARSTENSEN

Université de Paris-Sud, Faculté de Pharmacie, Laboratoire de Pharmacie Galénique, 92290 Châtenay-Malabry (France)

(Received January 11th, 1978)
(Accepted February 10th, 1978)

SUMMARY

It is shown that dissolution of a *soluble drug in high concentration* from an insoluble matrix follows the Higuchi square root equation, except an initial lag phase and a terminal diffusion phase exist. The parameters (ϕ) involved in these correspond to one another. The diffusional cross-sectional area is an almost linear function with time. The slopes obtained from square root plots are in reasonable agreement with theoretical values, and the diffusion coefficient for the terminal phase correlates with the actual diffusion coefficient of the drug used (diphenhydramine hydrochloride).

INTRODUCTION

The Higuchi square root law (Higuchi, 1963) has been validated in numerous cases (e.g. Roseman and Higuchi, 1970; Roseman, 1975; Corby et al., 1974a, b; Chien and Lambert, 1974; Chien et al., 1974). The general derivation of the law may be found in standard texts (e.g. Carstensen, 1977), and the law takes the form

$$Q = \{2DS(\epsilon/\tau)[A - 0.5S\epsilon]^2\}^{1/2}\sqrt{t} \qquad (1)$$

where

Q(g) = the amount of drug released per cm^2 of surface at time t (s),
S = the solubility of the drug in g/cm^3 in the dissolution medium,
A = the content of drug in the insoluble matrix,
ϵ = the porosity of the matrix,
D = the diffusion coefficient (cm^2/s) of the drug in the dissolution medium, and
τ = a tortuosity factor.

The main assumptions made are that the two-dimensional cross-sectional 'porosity'

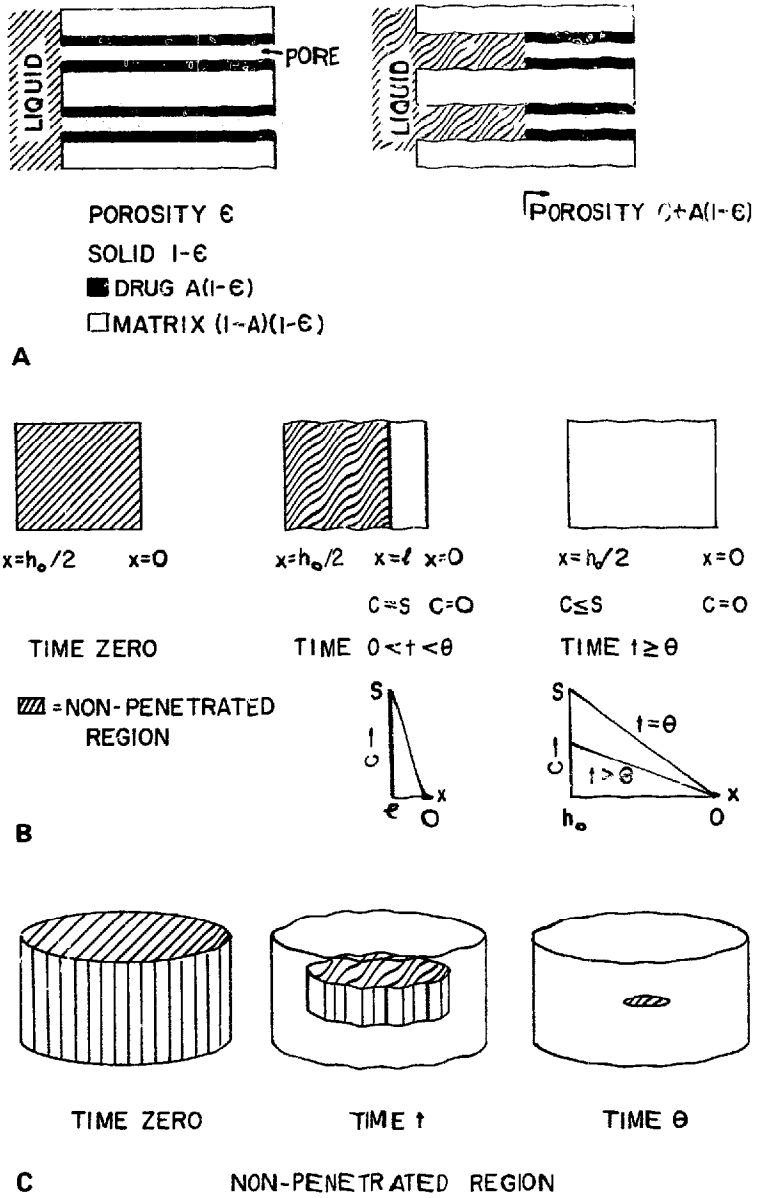

Fig. 1. A: tablet before, during and after drug is dissolved. B: development of ghost section as a function of time in a plate. $t = 0$. $0 < t < \theta$. $t \geq \theta$. C: development of ghost portion (not cross-hatched) as a function of time in a cylinder.

has the same mean as the volumetric porosity, a point validated by Gray (1968), and that the dissolving substance is sufficiently dilute so as not to affect the porosity.

However, in somes pharmaceutical applications, A is large, and as the drug dissolves the porosity increases with the amount dissolved. This might, on the surface, seem to imply that the porosity is time dependent, but it is the porosity in the portion of the matrix which is penetrated which is of importance. As demonstrated in Fig. 1, this will always have a value $\epsilon + [1 - \epsilon]A$ on the average, and hence this is simply introduced

into the expression (Eqn. 1) to obtain the theoretical slope.

The second assumption made in the derivation of Eqn. 1 is that the concentration of drug in the dissolution medium at the plane of penetration is S, and that it is zero (sink condition) in the bulk liquid outside the solid. This tacitly implies that the solid (Fig. 1B) extends ad infinitum to the left. However, in practice this is not so and a critical time, θ, will be reached where the solvent front will just have reached the 'end' (ℓ cm from the surface) of the solid. In an actual tablet (Fig. 1C) this will be the point where the 'center' is reached by the liquid. Beyond this point the concentration at ℓ will decrease below S and hence the release rate will decrease below that predicted by Eqn. 1.

Finally, the surface area from which the release takes place is usually assumed constant, and from, for example, a 'strip' of plastic this is correct. However, a tablet as shown in Fig. 1B will have an area which is a function of time. Lai and Carstensen (1978) have shown that for cylinders, in such cases, there is linear dependence with time of radius, r, and height, h, with common rate constant, k, i.e.

$$2r(t) = 2r_0 - kt \tag{2}$$

$$h(t) = h_0 - kt \tag{3}$$

If the height is less than the diameter then

$$k = h_0/\theta \tag{4}$$

The surface area, at time t, of the interface at the zone of penetration will be given by:

$$2\pi\left(r_0 - \frac{k}{2}t\right)^2 + 2\pi\left(r_0 - \frac{k}{2}t\right)(h_0 - kt) \tag{5}$$

The mean surface area experienced by the diffusing species at time t' is denoted $O(t)$ and is given by

$$O(t) = \frac{2\pi}{t'}\int_0^{t'}\left\{\left(r_0 - \frac{k}{2}t\right)^2 + \left(r_0 - \frac{k}{2}t\right)(h_0 - kt)\right\}dt \tag{6}$$

The time dependence of $O(t)$ can be introduced into the *derivation* of Eqn. 1 (Carstensen, 1977a) by noting that

$$\frac{\partial Q}{\partial t} = \frac{\partial[M/O(t)]}{\partial t} = \frac{\partial M}{O(t)\partial t} - \frac{M\partial O(t)}{[O(t)]^2\partial t} \tag{7}$$

where M is the amount of drug released per tablet at time t. The ensuing equations are cumbersome and a direct means of accounting for the time dependence of $O(t)$ will be developed in the article to follow.

MATERIALS AND METHODS

Tablets were made with the compositions shown in Table 1. The diphenhydramine hydrochloride was mixed with the polymer and the tricalcium phosphate, and granulated with a solution of the polyvinylpyrrolidone dissolved in ethanol at a concentration of 5%. The wet granulation was fluid bed dried at 60°C for 20 min, sized to a particle range of 200 to 800 μm, lubricated and compressed at 500 mg on a single punch tablet machine using cylindrical punches of a diameter of 12 mm. The tablets had a thickness of 0.345–0.350 cm (mean of three batches and five tablets per batch); they had a hardness of 13–14 kg Heberlein and a friability of 0.40–0.60% using an Erweka friabilator at 20 rpm for 5 min.

One particular batch (IV) was made using isopropanol as granulating fluid and this batch was prepared three times consecutively to establish repreducibility.

The dissolution rates were tested in a Desaga flow cell, using a peristaltic proportioning pump to pump the liquid. One tablet was placed in the cell which was positioned in a thermostatic bath at 37°C. The exiting liquid was collected in an Erlenmeyer flask, and assayed at various points of time; the liquid composition was first changed in time according to the half change method described in U.S.P. XVIII, and the pumping speed was 2 cm^3 of liquid/min. The results obtained in this fashion were identical to those obtained with distilled water, and the results reported here were all obtained with this latter solvent. The assay used consisted of addition of sulfuric acid, appropriate dilution, and determination of absorption at 440 nm.

Porosities of the tablets were measured by means of a mercury porosimiter. The solubility of diphenhydramine hydrochloride at 37°C was determined by exposing an excess of solid to water in a constant temperature bath, and assaying the supernatant from time to time, until a constant value was obtained (72 hr).

Viscosities of saturated solution and semisaturated solution were determined by means of a Rheomat 30 recording viscometer.

TABLE 1

FORMULAE USED IN DISSOLUTION STUDIES

Formula	I	II	III	IV [a]	V	VI	VII	VIII	IX
Diphenhydramine hydrochloride	20%	20%	20%	20%	20%	20%	20%	20%	20%
Solvic	50%	60%	70%	50%	60%	70%	50%	60%	70%
Polyvinylpyrrolidone	0%	0%	0%	1.5%	1.5%	1.5%	3%	3%	3%
Tricalcium phosphate	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Magnesium stearate	3%	3%	3%	3%	3%	3%	3%	3%	3%
Slope (mg $min^{-0.5}$), M vs $t^{1/2}$	8.58	5.95	6.85	5.08	5.33	4.65	6.45	9.68	8.57
Porosity (measured)	0.37	0.28	0.26	0.31	0.22	0.22	0.19	0.13	0.15
Porosity (total)	0.50	0.43	0.41	0.45	0.37	0.37	0.36	0.31	0.32

[a] Three separate batches of this formula were made using isopropanol as granulating liquid.

TABLE 2

PHYSICAL PARAMETERS OF DIPHENHYDRAMINE HYDROCHLORIDE

Density of saturated solution at 37°C:	1.045 g/cm^3
Saturation concentration in water at 37°C:	112 g/100 g of water = 0.55 g/cm^3
Viscosity of saturated solution (37°C):	0.423 Poise
Viscosity of semisaturated solution (37°C):	0.041 Poise
Density of solid (37°C)	1.211 g/cm^3
Molar volume (molecular weight = 291.8)	290 cm^3
Molecular radius (from molecular volume)	7.75 × 10^{-8} cm
Diffusion coefficient (Stokes-Einstein) [a]	3 × 10^{-6} cm^2/s

[a] Based on the viscosity of water.

The density of the saturated solution was determined pycnometrically (Carstensen, 1977b). The density of solid diphenhydramine hydrochloride was determined pycnometrically using cyclohexane as pycnometer liquid. Values obtained in these studies are summarized in Table 2.

RESULTS AND DISCUSSION

Fig. 2 shows the results of the dissolution tests on batch plotted according to Eqn. 1. It is noted that linearity of the amount, M, released as a function of square root of time

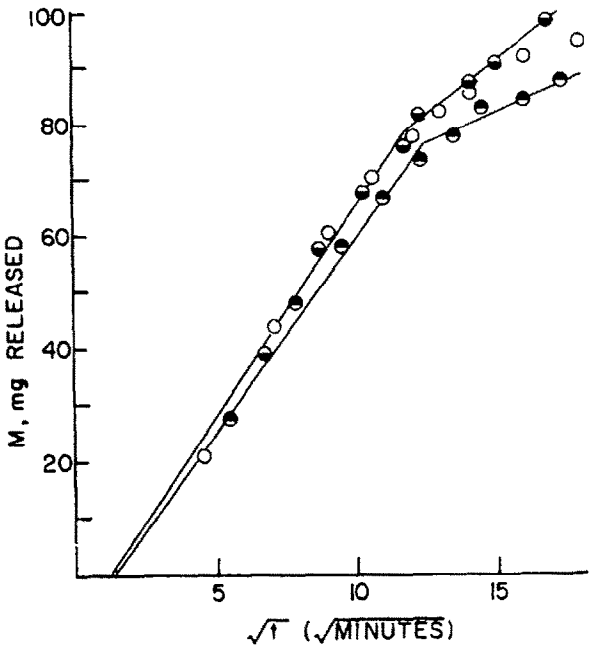

Fig. 2. Square root plots of formulae IV, a, b, and c (three batches of identical formula) plotted as amount released, M mg, versus the square root of time (min$^{1/2}$). ○ = a; ● = b; ◐ = c.

TABLE 3

LEAST SQUARES PARAMETERS OF DATA IN FIGS. 2, 3 AND 4

		Formula		
		a	b	c
M versus $\sqrt{t}$	R_1^2	0.986	0.987	0.994
Constant surface (Fig. 2)	$Slope_1$ (mg $min^{-0.5}$)	7.03	7.58	8.15
	$Intercept_1$ (mg)	−9.62	−10.25	−14.33
	t_1(lag) (min)	1.87	1.83	3.10
	R_2^2	0.964	0.996	0.936
	$Slope_2$ (mg $min^{-0.5}$)	2.02	3.29	2.40
	$Intercept_2$ (mg)	52.7	41.0	51.3
	θ(min)	155	143	130
	10^3 k (cm/min)	2.69	2.45	2.26
Q versus $\sqrt{t}$	R_3^2	0.998	0.9995	0.999
Variable surface (Fig. 4)	$Slope_3$	3.57	3.84	3.28
	$Intercept_3$	−10.1	−13.4	−9.7
	t_3(lag) (min)	8.0	12.2	8.7
O(t) versus time (Fig. 3)	$O(0)$ (cm^2), Fig. 3	3.56	3.55	3.56
	γ (cm^2/min), Fig. 3	−0.0097	−0.0087	−0.0092
	R^2 Fig. 3 (individual)	0.997	0.995	0.993

applies up to a certain time, θ, (about 14^2 min), after which the slopes change. It is also noted that reproducibility is fairly good: the coefficients of variation are above 0.98 for the individual batches.

Least squares parameters for the two linear portions are shown in Table 3; subscript '1' refers to the initial part of the square root plot, and the lag time observed (ϕ min, i.e. the x-intercept squared) is shown. The second portion is recorded with subscript '2' and the least squares intercept calculated; the square of this abscissa value is the critical time θ. The least squares slopes of the data as plotted in Fig. 2, for all the batches, are shown in Table 3.

To get an *overall* estimate of the adherance of the data to Eqn. 1, it is noted from Table 1 that the porosity on the average is 0.39 ± 0.05. The volume of the tablet is $0.35\,\pi\,0.6^2 = 0.396\ cm^3$ and since the tablet contains 0.1 g diphenhydramine hydrochloride it follows that A in Eqn. 1 is equal to $0.1/0.396 = 0.25\ g/cm^3$ of *solid*. In the Higuchi equation the A term is introduced in the derivation as the amount of material in 1 cm^3 of total matrix (Roseman, 1975). The average measured porosity from Table 1 is 0.24 ± 0.06, hence the spatial concentration of drug is $A = 0.25\,(1 - 0.24) = 0.19\ g/cm^3$. From Table 2 it is seen that $D = 3 \times 10^{-6}\ cm^2/s$ and that $S = 0.55\ g/cm^3$, and inserting these values into Eqn. 1 gives:

$$Q/\sqrt{t} = \sqrt{2 \times 3 \times 10^{-6} \times 0.39 \times 0.55[0.19 - (0.5 - 0.55 \times 0.39)]}\,[1/\tau]^{1/2} \times 3.3 \times 10^{-4}\ g\,s^{-1/2}\,cm^{-2} \quad (8)$$

This implies a value of $M/\sqrt{t}$ of $3.3-3.58 \times 10^{-4}\ [1/\tau]^{1/2} = 11.8 \times 10^{-4}\ [1/\tau]^{1/2}$ g $s^{-1/2}$. The average value of $M/\sqrt{t}$ from Table 1 is $\{6.79 \pm 1.30\}$ mg $min^{-1/2} = \{8.7 \pm 0.2\}10^{-4}$ g $s^{-0.5}$, giving a value of τ of 2. This is a reasonable value, because with the high total porosity (in the ghost portion), τ should be low and close to unity, since the diffusion path should be rather unobstructed. The value of the diffusion constant used is that obtained from the Stokes-Einstein equation where, properly, the viscosity of the solvent (not the solution) is used. At high concentration (as seen in Table 2) the viscosity of the solution increases considerably. D in such systems is probably smaller than the value used, and this would make the value of τ larger.

Q in Eqn. 1 is the amount of drug released per unit surface area of an infinite plate. This diffusional cross-section does not change in time in this type geometry, but in the case of a cylinder, as shown in Fig. 1B, the diffusional cross-section is not time independent. It has been shown (Lai and Carstensen, 1978) that the ghost portion of a cylinder will adhere to Eqns. 2 and 3. As seen from Fig. 2, θ can be estimated graphically (Table 3). The time required for h to reduce from 0.35 cm to zero is θ so that $k = 0.35/\theta$ (Eqn. 3). It is now possible to calculate the surface area of the boundary of the ghost portion (L) (the cross-hatched area in Fig. 1C) as a function of time. The diffusional cross-section, $O(t)$, at any time point will be a figure in between this area, L, and the surface area of the tablet (3.58 cm^2) as shown in Eqn. 6. Assuming that one can approximate $O(t)$ by $(L + 3.58)/2$, i.e. the average of these two figures, one can find the time dependence of the diffusional cross-sectional area for the formulae a, b and c in Table 3. These are shown in Fig. 3, and it seen from the figure that $O(t)$ is almost linear in time, i.e. with a regression constant of γ

$$O(t) = O(0) - \gamma t \qquad (9)$$

The least squares fit for the pooled data gives $O(0) = 3.50$ as opposed to the theoretical

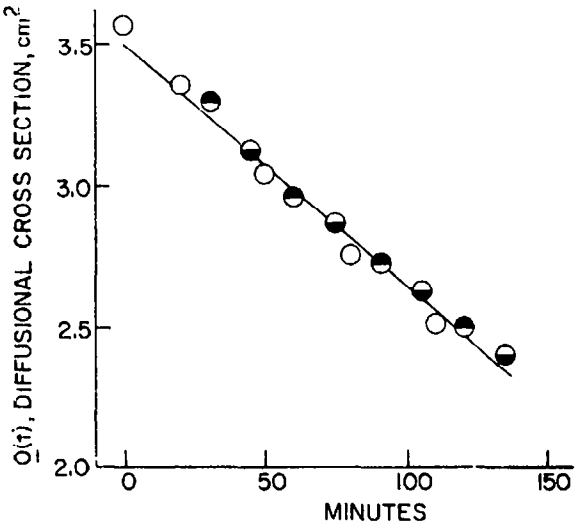

Fig. 3. Diffusional cross-sectional area as a function of time. ○ = a; ◒ = b; ◓ = c.

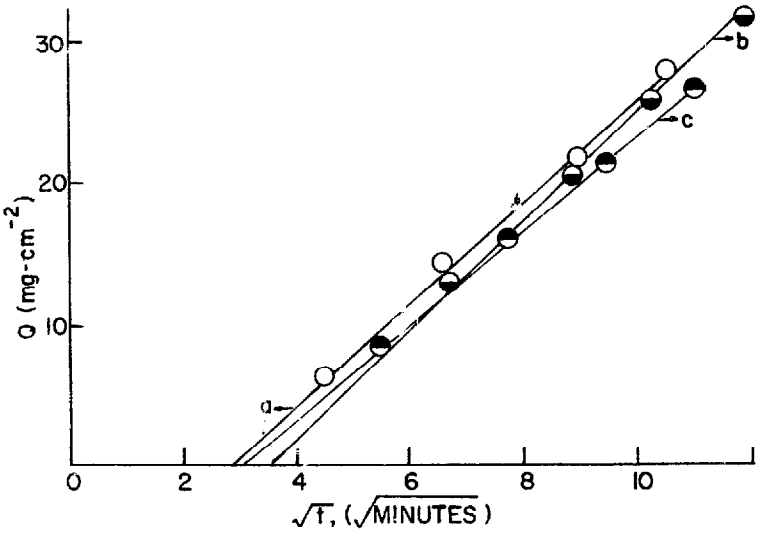

Fig. 4. Data from Fig. 2 plotted as Q versus $\sqrt{t}$. ○ = a; ● = b; ⊖ = c.

intercept (the area of the tablet) of 3.58. The least squares fit slope is –0.009. This should theoretically be –0.012 if the relation were strictly linear, because at the average θ value (142.7 min in Table 3) the diffusional cross-section is (3.58 + 0)/2 = 1.79 so that the slope should be (1.79–3.58)/142.7 = –0.012.

When the data in Fig. 2, which represent M, the mg of drug released at each time point, t, as a function of $\sqrt{t}$, are converted to Q values by dividing the $O(t)$ value at each time point, the data in Fig. 4 ensue. The fits here are somewhat better, since the correlation coefficients are *consistently* higher (Table 3). In this case, using 3.45 mg min$^{-0.5}$ cm^{-2} as the average slope it is found that

$$Q/\sqrt{t} = 4.5 \times 10^{-4} \text{ g s}^{-1/2} \text{ cm}^{-2} \tag{10}$$

Comparing this with Eqn. 8 also gives a τ value of 2. The physical presentation leading to Eqn. 10 is more realistic than straightforward plotting.

It is obvious from both Fig. 2 and Fig. 4 that there is a lag time, ϕ. Lag times are usually not important in penetration kinetics because in most cases the dissolution of the drug is not the rate-determining step. In the case of a *soluble drug in high concentration* as treated here, the situation will be as shown in Fig. 5. Here, in oversimplification, a linear capillary is considered walled by active material. As liquid enters the capillary, the situations in Fig. 5B through D will ensue. At a particular point (Fig. 5C) the fluid penetration rate will match the dissolution rate so that from this point on the profile shown will persist (Fig. 5D).

The profile portion has a thickness of δ cm as shown in Fig. 5C and 5D. It has been shown that the rate of height reduction (Eqn. 3) is 2.46 10^{-3} cm/min. The penetration rate is one half of this (since penetration takes place from two sides), and since the average lag time (Fig. 4 and Table 3 subscripts 3) is 9.7 min, then δ is of the order of 1.23×10^{-3} 9.7 = 0.012 cm. This is considerable, since it is about 7% of the ultimate penetration (0.175 cm).

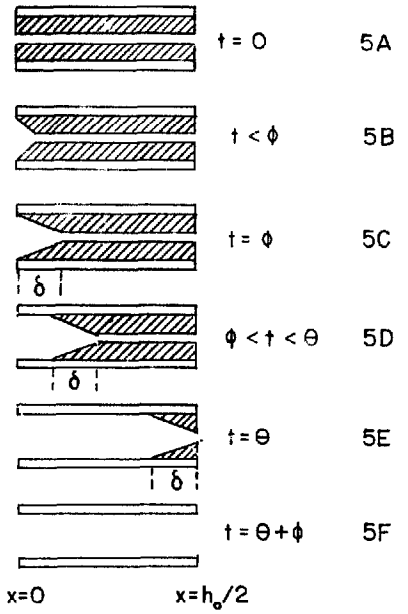

Fig. 5. Idealized spatial composition of a capillary in a matrix. A at t = 0. B at $0 < t < \phi$, i.e. before the lag time C at the lag time $t = \phi$. D at $\phi < t < \theta$, i.e. after the lag time but prior to complete penetration. E at $t = \theta$, i.e. at complete penetration. F at $t = \theta + \phi$, i.e. at complete dissolution (but not complete release).

At time θ, the liquid has penetrated to the center, and at time $\theta + \phi$ the drug is all dissolved. After this point in time the amount remaining in the matrix should diminish by a diffusion process. It is convenient to employ a spherical approximation (Pitkin and Carstensen, 1973) and in the order of magnitude calculation to follow, it is assumed that the tablet (which has a volume of 0.396 cm^3) is actually a sphere of radius a = 0.456 cm (which also has a volume of 0.396 cm^3). With this assumption, the amount remaining in the tablet is given by:

$$\ln[\{M(t) - M(\infty)\}/\{M(\theta) - M(\infty)\}] = -\psi[t - \theta - \Phi] \tag{11}$$

where

$$\psi = 4\pi^2 D/a^2 \tag{12}$$

Data plotted in this fashion are shown in Fig. 6. Least squares fitting yields

$$\text{Slope} = \psi = 0.0138\ \text{min}^{-1} = 3 \times 10^{-4}\ \text{s}^{-1} \tag{13}$$

$$\text{Intercept} = \psi\phi = 0.287 \tag{14}$$

so that the lag time can be calculated as

$$\phi = \text{Intercept/Slope} = 20\ \text{min} \tag{15}$$

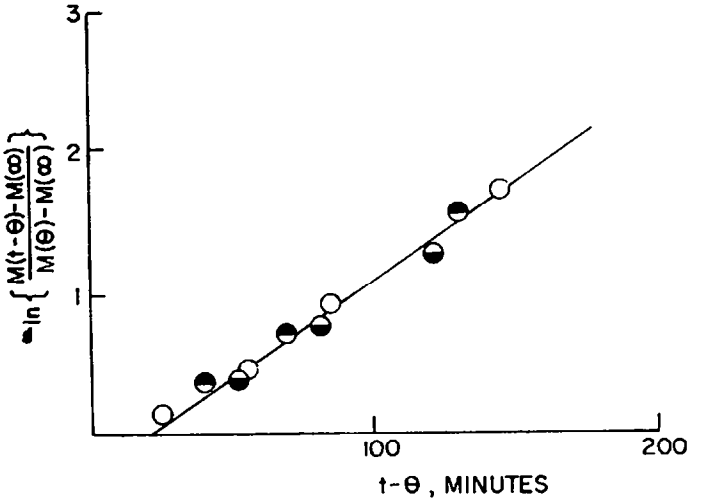

Fig. 6. Data from Fig. 2 plotted according to Eqn. 11. ○ = a; ◒ = b; ● = c.

This compares favorably with the lag times reported in Table 3 (subscripts 3). By inserting the slope and the radius, a, in Eqn. 12 one obtains that the diffusion coefficient is:

$$D = \psi a^2/4\pi^2 = 1.6 \times 10^{-6}\ cm^2/s \qquad (16)$$

This figure is in good order of magnitude agreement with the figure for D reported in Table 2.

REFERENCES

Carstensen, J.T., Pharmaceutics of Solids and Solid Dosage Forms, John Wiley and Sons, New York, 1977a, p. 173.

Carstensen, J.T., Pharmaceutics of Solids and Solid Dosage Forms, John Wiley and Sons, New York, 1977b, p. 230.

Chien, Y.W. and Lambert, H.J., Controlled drug release from polymeric delivery devices. II: Differentiation between partition-controlled drug release mechanisms. J. Pharm. Sci., 63 (1974) 515.

Chien, Y.W., Lambert, H.J. and Grant, D.E., Controlled drug release from polymeric delivery devices. I: Techniques for rapid in vitro release studies. J. Pharm. Sci., 63 (1974) 365.

Corby, J., Mayersohn, M. and Walker, G.C., Influence of shape factors on kinetics of drug release for matrix tablets. I: Therory. J. Pharm. Sci., 63 (1974a) 725.

Corby, J., Mayersohn, M. and Walker, G.C., Influence of shape factors on kinetics of drug release for matrix tablets. II: Experimental. J. Pharm. Sci., 63 (1974b) 732.

Gray, W.A., The Packing of Solid Particles, Chapman and Hall, London, 1968, p. 129.

Higuchi, T., Mechanism of sustained action medication. Theoretical analysis of rate of release of solid drug dispersed in solid matrices. J. Pharm. Sci., 52 (1963) 1145.

Lai, T.Y.-F. and Carstensen, J.T., Effect of shape factor on cube root dissolution behavior. Int. J. Pharm., 1 (1978) 33–40.

Pitkin, C. and Carstensen, J.T., Moisture content of granulations, J. Pharm. Sci., 62 (1973) 1215.

Roseman, T.J., Controlled release from matrix systems. J. Pharm. Sci., 64 (1975) 1731.

Roseman, T.J. and Higuchi, W.I., Release of medroxyprogesterone acetate from a silicone polymer. J. Pharm. Sci., 59 (1970) 353.