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ACKNOWLEDGMENTS AND ADDRESSES

Received September 17, 1973, from the *Cardiovascular Research Laboratories, Department of Pharmacology, School of Pharmacy, University of Pittsburgh, Pittsburgh, PA 15261*

Accepted for publication December 6, 1973.

Supported in part by the National Institutes of Health Training Grant GM-1217-09 from the National Institutes of General Medical Sciences.

The pentapeptide, SQ 20,475, and the nonapeptide, SQ 20,881, were supplied by Dr. Zola Horowitz, the Squibb Institute for Medical Research, Princeton, N.J. Angiotensin II (Hypertensin) was supplied by Dr. William Wagner, Ciba-Geigy, Summit, N.J.

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Controlled Drug Release from Polymeric Delivery Devices II: Differentiation between Partition-Controlled and Matrix-Controlled Drug Release Mechanisms

YIE W. CHIENˣ **and HOWARD J. LAMBERT**

Abstract □ The drug release pattern of micronized ethynodiol diacetate from silicone devices was thoroughly investigated in polyethylene glycol-containing elution media with a wide range of solubility and partition properties. When high drug solubility was maintained, the drug release pattern followed a $Q - t^{1/2}$ relationship (matrix controlled). Under this matrix-controlled process, the drug release profiles were independent of the variation in partition coefficient magnitude and insensitive to the change in solubility parameters. As the drug solubility in the elution medium was decreased, the drug release process shifted from matrix controlled to partition controlled, and a $Q - t$ (zero-order) relationship was observed. The drug release profile was then a function of the partition coefficient of drug from the polymer matrix to the elution medium. A transition phase was also seen between these two processes. Matrix-controlled and partition-controlled drug release processes were analyzed theoretically. The experimental rates of drug release were in perfect agreement with the values calculated from the theoretical model.

Keyphrases □ Drug release, controlled—differentiation between partition-controlled and matrix-controlled release mechanisms, ethynodiol diacetate from silicone devices in polyethylene glycol 400 media □ Permeation, drug—ethynodiol diacetate from silicone devices in polyethylene glycol 400 media, differentiation between partition- and matrix-controlled release mechanisms □ Ethynodiol diacetate—release from silicone devices in polyethylene glycol 400 media, matrix- and partition-controlled release mechanisms □ Silicone devices—release of ethynodiol diacetate

An *in vitro* drug release system, which is simple in construction and allows rapid characterization of the drug release mechanism, was introduced previously (1). The rate of drug release from silicone devices measured in such a system was found to follow current theoretical models (2–9). The application of such methodology allowed characterization of the mechanism and rate of drug release. In the studies

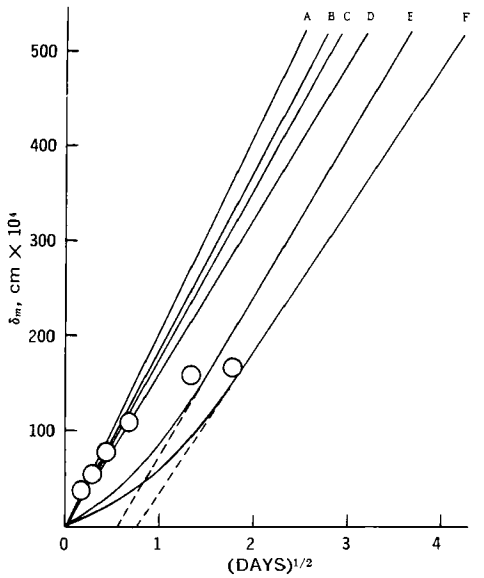

Figure 1—*Relationship between the thickness of depletion zone* (δ_m) *and the square root of time* ($t^{1/2}$) *as estimated from actual drug release data. The lines A, B, C, D, E, and F are the experimental* $\delta_m \sim t^{1/2}$ *profiles in the elution media containing 85, 80, 75, 70, 65, and 62.5% of polyethylene glycol 400, respectively. The circles are the values of* $2D_m\delta_D/KD_s$ *(calculated from the parameters of* D_m, δ_D, K, *and* D_s) *for the corresponding media used.*

(1) reported earlier, the experimental conditions were designed such that matrix-controlled drug release profiles were obtained.

Roseman and Higuchi (4) proposed that under certain conditions the rate of diffusion from the surface of the matrix to the surrounding bulk solution makes a significant contribution to the total diffusional process. Recently, Haleblian *et al.* (6) also suggested the possibility that the rate of solute transfer across the matrix–solution interface may control the release. Both reports, therefore, pointed out the possible existence of a partition-controlled model of drug release flux. Unfortunately, no experimental observations pertinent to this model were reported. By using the same drug release system developed earlier (1), the studies have been extended to the low partition coefficient region to gain an insight into the partition-controlled drug release mechanism. A completely different pattern of drug release was discovered. This paper reports these new observations and provides a theoretical analysis of the differentiation between partition-controlled and matrix-controlled drug release mechanisms.

EXPERIMENTAL

The apparatus for drug release studies, the drug-impregnated silicone devices, the polyethylene glycol 400–water cosolvent system for drug elution, and the analysis of drug samples utilized in the present investigation were essentially the same as those reported previously (1).

One additional study involved the determination of partition coefficients. A ring-shaped silicone device containing no drug was rotated in the same manner as those for drug release studies in 150 ml of elution medium containing a fixed concentration of ethynodiol diacetate at 37° for 24 hr. The drug concentration before and after the partitioning study was measured and used to calculate the partition coefficient (K) of ethynodiol diacetate from the matrix phase to the solution phase as follows:

$$K = \frac{V_p C_e}{V_s(C_i - C_e)} \qquad \text{(Eq. 1)}$$

where V_s and V_p are the volumes of elution solutions and of polymeric devices, respectively; and C_i and C_e are the initial and equilibrium drug concentrations in solution, respectively. The 24-hr period was adequate to ensure equilibrium.

For the elution media containing high volume fractions (≥60% v/v) of polyethylene glycol 400, the following relationship may also be used to calculate the pertinent high partition coefficients (5):

$$K = \frac{C_s}{C_p} \qquad \text{(Eq. 2)}$$

where C_s and C_p are the solubilities of drug in elution solutions and in polymeric devices, respectively.

THEORETICAL ANALYSIS

The mechanisms of drug release from various polymeric matrix systems have been extensively discussed (2–4). In the present study, the thickness of the hydrodynamic diffusion layer ($\leq 70 \times 10^{-4}$ cm) was much smaller than the surface area of the matrix (33.75 cm^2) available for the diffusion of drug species. Therefore, the diffusion of drug molecules to and from the matrix across the hydrodynamic diffusion layer may be treated as one-dimensional diffusion to a plane surface (10). From earlier theoretical treatments (3, 4), the following general equations describing the release of drug from a polymeric matrix are obtained:

$$\delta_m^2 + \frac{2D_m\delta_D\delta_m}{KD_s} = \frac{4C_pD_mt}{(2A - C_s)} \qquad \text{(Eq. 3)}$$

$$Q = (A - C_s/2)\delta_m \qquad \text{(Eq. 4)}$$

where δ_m and δ_D are the thicknesses of the depletion zone and the hydrodynamic diffusion layer, respectively; D_m and D_s are the diffusivities of drug in the matrix phase and the solution phase, respectively; A is the total amount of solid drug impregnated per unit volume of polymeric matrix; C_p and C_s are the drug solubilities in the polymer and in the solution, respectively; K is the partition coefficient of the drug species from the matrix phase to the elution medium; Q is the amount of drug released per unit surface area of devices; and t is time.

For a matrix-controlled process:

$$\delta_m^2 \gg \frac{2D_m\delta_D\delta_m}{KD_s} \qquad \text{(Eq. 5)}$$

Then Eq. 3 is reduced to:

$$\delta_m^2 = \frac{4C_pD_mt}{(2A - C_s)} \qquad \text{(Eq. 6}a\text{)}$$

or:

$$\delta_m = 2\sqrt{\frac{C_pD_mt}{(2A - C_s)}} \qquad \text{(Eq. 6}b\text{)}$$

Substituting Eq. 6*b* for δ_m in Eq. 4 results in:

$$Q = \sqrt{D_m(2A - C_s)C_pt} \qquad \text{(Eq. 7)}$$

Equation 7 was analyzed extensively in the first report of this series (1). Similar equations have been developed and correlated with the experimental observations in a number of studies (2–9). In matrix-controlled drug release mechanisms, Eq. 7 was followed perfectly in all investigations that were carried out in this laboratory (1).

It is obvious that Eq. 7 will be valid only under the condition that Eq. 5 is existing experimentally. The validity of Eq. 5 may be confirmed by comparing the $\delta_m \sim t^{1/2}$ profiles (estimated from the drug release data) with the magnitudes of $2D_m\delta_D/KD_s$ (calculated from the parameters of D_m, δ_D, K, and D_s) (Fig. 1). Except for the cases where 65 and 62.5% polyethylene glycol 400

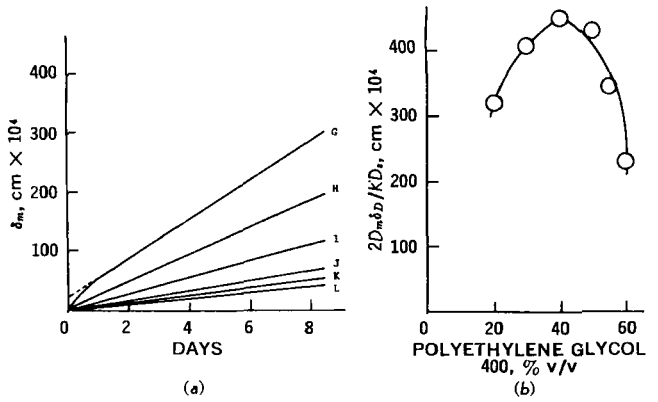

Figure 2—*Comparison of the magnitudes of* $2D_m\delta_D/KD_s$ *to those of* δ_m *in the region of low partition coefficient.* (a) *Linear relationship between the thickness of depletion zone* (δ_m) *and time* (t) *as computed from actual drug release data. The lines G, H, I, J, K, and L are the experimental* $\delta_m \sim t$ *profiles in the elution media containing 60, 55, 50, 40, 30, and 20% of polyethylene glycol 400, respectively.* (b) *Calculated values of* $2D_m\delta_D/KD_s$ *for the corresponding elution medium. The scales for* δ_m *and* $2D_m\delta_D/KD_s$ *are drawn in the same magnitude for a convenient comparison.*

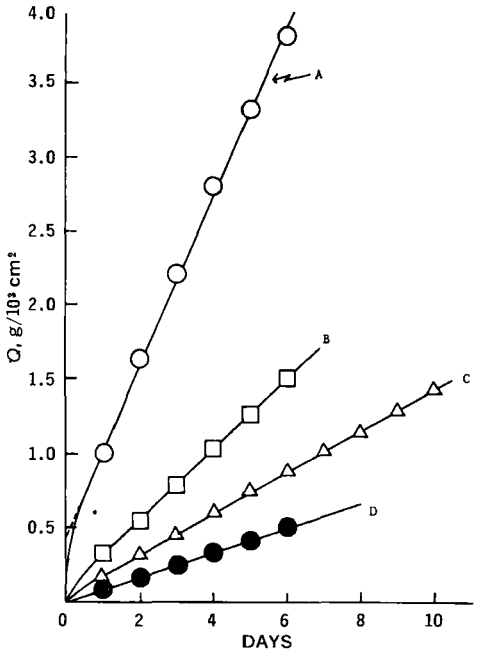

Figure 3—*Linear relationship between the cumulative amount of drug released* (Q) *from per unit area of devices and the time (days) in the elution media with partition coefficients of: (A) 0.2873, (B) 0.099, (C) 0.061, and (D) 0.036.*

were used as the elution media, all other drug release fluxes took only 1 day to satisfy Eq. 5. In the 65 and 62.5% cases, 1–2 more days was required to reach the experimental condition defined by Eq. 5. Equation 5 was apparently followed quite well in the present study.

However, situations where δ_m^2 is smaller than $2D_m\delta_D\delta_m/KD_s$ are also possible[1] when K, the partition coefficient, is very small (partition-controlled process) and/or δ_D is much larger than δ_m (diffusion layer-controlled process). The comparison made in Fig. 2 clearly demonstrates that, except for the elution medium containing 60% polyethylene glycol 400 (K = 0.287), Eq. 8 is obeyed perfectly. In the elution medium containing 60% polyethylene glycol 400, Eq. 8 is followed only before the 6th experimental day. This special case will be discussed later.

For the partition-controlled process:

$$\delta_m^2 \ll \frac{2D_m\delta_D\delta_m}{KD_s} \qquad \text{(Eq. 8)}$$

Then Eq. 3 is reduced to:

$$\frac{2D_m\delta_D\delta_m}{KD_s} = \frac{4C_pD_mt}{(2A - C_s)} \qquad \text{(Eq. 9}a\text{)}$$

or:

$$\delta_m = \frac{2KD_sC_pt}{\delta_D(2A - C_s)} \qquad \text{(Eq. 9}b\text{)}$$

Substituting Eq. 9*b* for δ_m in Eq. 4 results in:

$$Q = \frac{KD_sC_p}{\delta_D}t \qquad \text{(Eq. 10}a\text{)}$$

or:

$$Q = \frac{KD_sC_s}{\delta_D}t \qquad \text{(Eq. 10}b\text{)}$$

if the dissolution of drug species into the elution medium is a slower step than the solubilization of the solid drug into the polymer phase, *e.g.*, $C_p \gg C_s$.

It is obvious that under matrix control, the drug release profile follows a $Q - t^{1/2}$ relationship (Eq. 7) while under partition control the drug release profile shifts to follow $Q - t$ linearity (Eq. 10). According to Eq. 7, the drug solubility (C_s) in the elution medium, the partition coefficient (K) of the solution–polymer system, and the thickness of diffusion layer (δ_D) do not make any major contribution to the drug release rate. On the other hand, according to Eq. 10*b*, the parameters mentioned become highly significant in determining the magnitude of drug release fluxes.

RESULTS AND DISCUSSION

The experimental observations on matrix-controlled drug release processes were previously presented and analyzed thoroughly (1). The present investigation was devoted to partition-controlled processes and the drug release patterns were compared to those of matrix-controlled processes.

As stated earlier, the drug release studies were extended to the low polyethylene glycol 400 concentration region (≤60%) in which the magnitude of the partition coefficient is very low (≤0.287). The results on the pattern of drug release in these elution media with low partition coefficients are illustrated in Fig. 3. Obviously, a $Q - t$ relationship is obeyed perfectly, as expected from Eq. 10*b*. The drug release profiles in Fig. 3 also indicate that the magnitude of the slopes is a function of the partition coefficients of drug from the polymer phase to the elution medium. From Eq. 10*b* the slope of $Q - t$ profiles may be defined as:

$$\frac{Q}{t} = \frac{KD_sC_s}{\delta_D} \qquad \text{(Eq. 11)}$$

A linear relationship should therefore exist between the slope of the $Q - t$ profile (Q/t) and the partition coefficient (K). The data shown in Fig. 4 demonstrate this $Q/t \sim K$ linearity (bottom scale). The Q/t value for the K = 0.287 case is apparently lower than that expected from Eq. 11. This lower Q/t value is explained by the fact that the values of δ_m are close to the magnitude of $2D_m\delta_D/KD_s$ at K = 0.287 (Fig. 2). In other words, Eq. 8 is no longer well established. This deviation may indicate the approach of a transition state.

Equation 11 also points out the possible existence of another linear relationship of the rate of drug release (Q/t) to the drug solubility (C_s) in the elution medium. Experimentally, this linearity is also followed as expected in the low C_s range (Fig. 4, upper scale). As the $Q/t \sim K$ profile illustrated earlier, when the drug solubility (C_s) in the elution medium was raised from 200 to 437 μg/cm³, the $Q/t \sim C_s$ linearity was lost. As stated before, this probably indicates a transition state.

[1] T. J. Roseman, The Upjohn Co., Kalamazoo, Mich., personal communication.

Table I—Comparison of Experimental Rates of Drug Release to Theoretical Values and Their Relationship to $C_b(t)/C_s$

Polyethylene Glycol 400, %	$C_b(t)/C_s$	Rate of Drug Release, g/10⁶ cm²/day		
		$(Q/t)_T$[a]	$(Q/t)_E$[b]	$(Q/t)_T/(Q/t)_E$
20	0.183	75.5	82.6	1.09
30	0.165	103.95	109.8	1.05
40	0.146	145.2	141.3	0.97
50	0.155	237.65	245.7	1.03
55	0.187	371.31	360.0	0.97
60	0.109	1245.0	550.0	0.442
62.5	0.116	2209.3	728.8[c]	0.330

[a] Theoretical rate of drug release, $(Q/t)_T$, is estimated from Eq. 11. [b] $(Q/t)_E$, the experimentally observed rate of drug release. [c] Rate of drug release calculated from the initial 4-day drug release data.

If Eq. 11 is really the theoretical model defining the partition-controlled drug release mechanisms, then $(Q/t)_T$, the theoretical rate of drug release, calculated from the parameters of K, C_s, D_s, and δ_D following Eq. 11 should be comparable in magnitude to the values measured experimentally, $(Q/t)_E$. A comparison is made in Table I. The agreement between $(Q/t)_T$ and $(Q/t)_E$ data is remarkable except for the case in which more than 60% polyethylene glycol 400 was used as the elution medium. The lower $(Q/t)_E$ values obtained in the elution media containing 60 and 62.5% polyethylene glycol 400 solutions further demonstrate the invalidity of Eq. 8 in these two cases. As illustrated in Figs. 1 and 2 for the 60% case (G in Fig. 2), Eq. 8 is valid only earlier than 5 experimental days; for the 62.5% case (F in Fig. 1), Eq. 8 is substituted by Eq. 5 after the 3rd experimental day. Obviously, the drug release fluxes in the elution medium containing 60–62.5% polyethylene glycol 400 are close to the neighborhood of a transition phase where both Eqs. 5 and 8 do not apply.

Haleblian *et al.* (6) proposed that a constant release rate would be observed if the release of drug was controlled by either the rate of drug dissolution into the matrix or the rate of solute transfer across the matrix-solution interface. They observed that the rate of drug release from devices containing micronized drug particles was four times higher than those containing macrosized drug. In the present investigations, micronized ethynodiol diacetate particles were used. Therefore, the possibility of a dissolution-controlled release mechanism may be ruled out, and the rate of partitioning of drug species across the matrix-solution interface may be considered as rate determining.

In developing Eq. 3, the necessary condition that a perfect sink

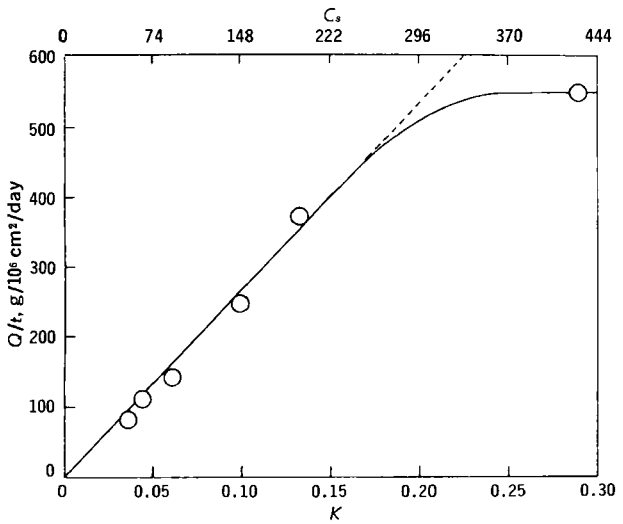

Figure 4—*Rate of drug release* (Q/t), *as a function of the partition coefficient* (K, *bottom scale*) *and the solubility* (C_s) *in the elution medium* (*upper scale*).

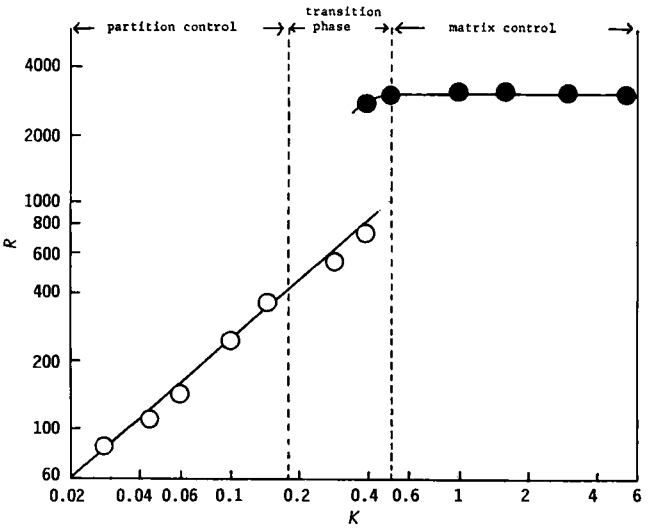

Figure 5—*Relationship between the steady-state drug release rate constant and the partition coefficient. In the region of partition control, the rate constant of drug release* (Q/t, *g/10⁶ cm²/day*) *is a linear function of the partition coefficient* (*slope = 0.88*). *In the region of matrix control, the rate constant of drug release* (Q/t$^{1/2}$, *g/10⁶ cm²/day*$^{1/2}$) *is independent of the partition coefficient* (*slope = 0*).

condition has to be maintained throughout the study was assumed (3, 4). In other words, $C_b(t)$, the drug concentration in the elution medium at a given time, has to be much smaller than C_s, the drug solubility in the elution medium. The data on $C_b(t)/C_s$ (Table I) indicate that the magnitudes of $C_b(t)$ are well below those of C_s, *i.e.*, $[C_b(t)/C_s < 0.2]$, and the requirement that $C_s \gg C_b(t)$ is satisfied. Where more than 60% polyethylene glycol 400 was used as the elution medium, the experimental rate of drug release (listed in the fourth column of Table I) reached only 33–44% of the theoretical value (calculated from Eq. 11 and shown in the third column of Table I) although a perfect sink condition, *e.g.*, $C_b(t)/C_s$ = 0.109–0.116, was maintained. This result rules out the possibility that the deviation of the drug release rate from theory might be due to the effect of nonsink conditions, *e.g.*, $C_b(t)/C_s \simeq 1$.

On the other hand, when the ratio of $C_b(t)/C_s$ becomes larger, a different type of deviation may be observed. The data in Table II demonstrate that a zero-order $(Q \sim t)$ relationship (Eq. 10b) was maintained, but the experimental Q/t values were found to be smaller than the values estimated from Eq. 11. The larger the ratio of $C_b(t)/C_s$, the greater is the deviation of experimental value from theory. The results (Tables I and II) illustrate the importance of maintaining a sink condition for all drug release studies.

The relationship of drug release fluxes in both partition-controlled and matrix-controlled processes to the partition coefficients of drug species (from the matrix to the elution medium) is analyzed further in Fig. 5. In Fig. 5, the most noticeable observa-

Table II—Deviation of Experimental Drug Release Rates from Theoretical Values as a Function of the Ratio of $C_b(t)/C_s$

Sample Renewing Speed[a], ml/day	$C_b(t)/C_s$[b]	Rate of Drug Release, g/10⁶ cm²/day		
		Theoretical[c]	Experimental	Ratio[d]
25	0.588	237.65	162.5	0.684
50	0.402	237.65	197.2	0.830
100	0.155	237.65	245.7	1.03

[a] The total volume of the elution medium is 150 ml. [b] The maximum solubility of ethynodiol diacetate in the elution medium containing 50% polyethylene glycol 400 is 156.0 μg/cm³. [c] Calculated from Eq. 11. [d] Ratio of experimental drug release rates over theoretical values.

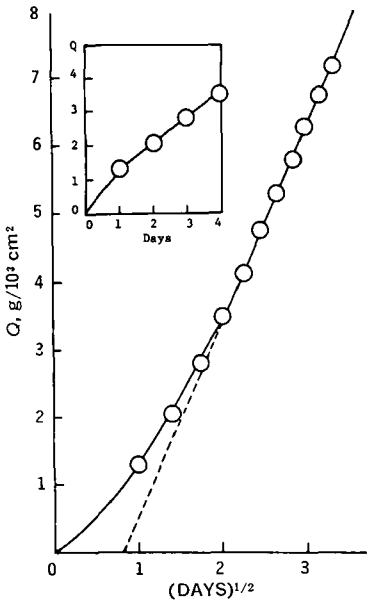

Figure 6—*Drug release profile for ethynodiol diacetate in the 62.5% polyethylene glycol 400 solution. The* Q ~ t *relationship is followed in the initial 4-day data (inserted plot) and the* Q ~ $t^{1/2}$ *relationship is followed thereafter. The slopes are 728.8* $g/10^6$ cm^2/day *and 2.79* $g/10^3$ $cm^2/day^{1/2}$, *respectively.*

tion is that steady-state drug release rates are linear with increasing partition coefficients only up to a certain point ($K \simeq 0.4$) beyond which the matrix-controlled mechanism is observed and the steady-state drug release profiles are virtually independent of variation in partition coefficient. The dependency of the drug release rate on the partition coefficients of drug from polymeric devices to the elution medium may be expressed (11) by the following relationship:

$$\text{rate constant of drug release} = R = K^{\gamma} \qquad \text{(Eq. 12)}$$

where K is the partition coefficient of the drug investigated, and γ is the slope of log $R \sim$ log K profiles. The plot in Fig. 5 indicates that γ is 0.88 for the partition-controlled process and is essentially zero for the matrix-controlled process.

Figure 5 also points out that, in between these two processes, an overlapping transition phase is seen where both conditions (Eqs. 5 and 8) do not exist and may be replaced by a new condition:

$$\delta_m^2 \approx \frac{2D_m\delta_D\delta_m}{KD_s} \qquad \text{(Eq. 13)}$$

Therefore, the general model described by Eq. 3 should be applied to define the drug release profile in the transition phase where both Eqs. 7 and 10*b* fail to give a satisfactory expression.

The drug release profile in the elution medium containing 62.5% polyethylene glycol 400 solution (with a partition coefficient of 0.387) is plotted in Fig. 6. The $Q - t$ relationship was followed in the initial 4 experimental days and the $Q - t^{1/2}$ relationship was followed thereafter. The transition point is located around the 3rd to 4th experimental day where the calculated value of $2D_m\delta_D/KD_s$ is approximately 165×10^{-4} cm (line F in Fig. 1). When δ_m is smaller than this magnitude, the $Q - t$ relationship is observed. As the value of δ_m gets larger, the $Q - t^{1/2}$ relationship becomes apparent (Figs. 1 and 6) and then overweighs the $Q - t$ relationship.

A similar relationship as that demonstrated in Fig. 5 was also reported (12) for the lag time–carbon chain length profile and was derived (13) for the steady-state flux–partition coefficient profile. The marked change in slope from the total partition-control region to the total matrix-control region observed in the present investigation was also seen in both reports (12, 13).

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ACKNOWLEDGMENTS AND ADDRESSES

Received June 22, 1973, from the *Pharmaceutical Research and Development Department, Searle Laboratories, Division of G. D. Searle & Co, Skokie, IL 60076*

Accepted for publication October 29, 1973.

Appreciation is extended to Dr. Theodore D. Sokoloski, Ohio State University, and to Dr. David T. K. Lin, G. D. Searle & Co., for their constructive discussions.

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