Solution–Solubility Dependency of Controlled Release of Drug from Polymer Matrix: Mathematical Analysis

YIE W. CHIEN ˣ, HOWARD J. LAMBERT, and TENG K. LIN

Abstract □ Two types of drug release mechanisms—matrix controlled ($Q - t^{1/2}$ relationship) and partition controlled ($Q - t$ relationship)—were reported previously. The dependency of the transition between these two processes on the solution solubility of drug is now analyzed. Mathematical expressions are derived to treat the systemic effects of the addition of varying volume fractions of the cosolvent system on the concentration gradients across both the drug depletion zone and hydrodynamic diffusion layer as well as on the partitioning behavior at the polymer–solution interface. The results are in excellent agreement with reported experimental observations.

Keyphrases □ Drug release from polymer matrix, controlled—solution–solubility dependency, equations □ Polymer matrix—controlled drug release, solution–solubility dependency, equations

A rapid *in vitro* drug elution system, which permits direct characterization of drug release mechanisms and rates, was recently reported (1). Two types of release mechanisms—matrix controlled and partition controlled—were observed when the release profiles of ethynodiol diacetate from silicone vaginal devices were followed daily in this system (2). In the region of the partition-controlled process, steady-state drug release profiles were defined by a linear $Q - t$ relationship and found to be linearly dependent on the partition coefficient of drug (K) from polymer toward solution.

In the region of the matrix-controlled process, steady-state drug release profiles were defined by a $Q - t^{1/2}$ linearity and found to be independent of the variation in the magnitude of K. The transition between the matrix-controlled and the partition-controlled processes was observed to be dependent on the solution solubility of drug in the elution medium. This article provides a mathematical analysis of the solution–solubility dependency of the controlled release of drug from a drug-dispersed polymer matrix.

MATHEMATICAL DERIVATION AND EXPERIMENTAL OBSERVATION

For such a system, one can draw a concentration profile, which may exist after a finite time following drug elution, on a unit section of a polymeric device (Fig. 1). In this model, the drug is homogeneously dispersed as solid crystals in the polymer matrix. It is visualized that the solid drug on the surface layer of the device is first eluted; when this layer becomes exhausted, the next layer is then depleted. A depletion zone, with a thickness of δ_m, therefore occurs. The interface of the drug dispersion zone–drug depletion zone moves further into the core of the device for another differential thickness, $d(\delta_m)$, when more solid drug is released.

Microscopically, a thin layer of solution, the hydrodynamic diffusion layer, adheres to the immediate surface of the device. The thickness (δ_D) of this diffusion layer may be controlled at a finite value (3) by a constant angular rotation. In the present study, this diffusion layer thickness ($\leq 70 \times 10^{-4}$ cm) is much smaller than the surface area of the device (33.75 cm^2) available for the diffusion of drug molecules. Therefore, the diffusion of drug molecules to and from the polymeric device across the hydrodynamic diffusion layer may be treated simply as one-dimensional diffusion to a plane surface (4). The flux of diffusional, J_D, across the plane surface of a unit area is defined by Fick's first law of diffusion (5):

$$J_D = -D\frac{dC}{d\chi} \qquad \text{(Eq. 1)}$$

where $dC/d\chi$ is the concentration gradient across the diffusion path of $d\chi$, and D is the diffusivity of a drug species. With the assumptions that: (*a*) diffusion is the primary mode of drug release, (*b*) the diffusion coefficient is constant irrespective of the distance traveled and the difference in concentration, and (*c*) a pseudosteady state exists, Fick's arguments may be extended to describe the mechanisms of drug release from a polymeric device.

Under diffusion laws, the rate of drug diffusion from a point at the drug dispersion zone–depletion zone interface to the polymer–solution interface may be expressed as:

$$\frac{dQ_m}{dt} = \frac{D_m}{\delta_m}(C_p - C_m) \qquad \text{(Eq. 2)}$$

where D_m is the effective diffusivity of drug in the polymer matrix, C_p is the drug concentration at the interface of the drug dispersion zone–depletion zone (that is, the polymer solubility of the drug), and C_m is the drug concentration at the polymer–solution interface.

The rate of drug diffusion across the hydrodynamic diffusion layer (with a thickness of δ_D) at the immediate surface of the device may be described by:

$$\frac{dQ_d}{dt} = \frac{D_s}{\delta_D}[C_d - C_b(t)] \qquad \text{(Eq. 3)}$$

where D_s is the diffusivity of the drug in the elution solution, C_d is the drug concentration at the solution–polymer interface, and $C_b(t)$ is the drug concentration in the bulk of the elution medium at a given time.

When a steady state is established, the rate of drug diffusion across the depletion zone, dQ_m/dt, should be equilibrated with the rate of drug diffusion across the hydrodynamic diffusion layer, dQ_d/dt. That is:

$$\frac{D_m}{\delta_m}(C_p - C_m) = \frac{D_s}{\delta_D}[C_d - C_b(t)] \qquad \text{(Eq. 4)}$$

Rearrangement of Eq. 4 gives:

$$\frac{C_p}{C_m} = 1 + \frac{D_s\delta_m}{D_m\delta_D}\left[\frac{C_d}{C_m} - \frac{C_b(t)}{C_m}\right] \qquad \text{(Eq. 5)}$$

According to Eq. 5, if $C_b(t)/C_m$ is equal to C_d/C_m in their magnitudes, the ratio of C_p over C_m is unity. Under such a circumstance, there is no concentration gradient across the depletion zone and no release of drug is detected. In other words, if the magnitude of $C_b(t)/C_m$ is approaching the value of C_d/C_m, the difference between C_p and C_m is becoming smaller and the rate of drug release (dQ_m/dt in Eq. 2) is reduced (since $dQ_d/dt \rightarrow 0$ in Eq. 3). This

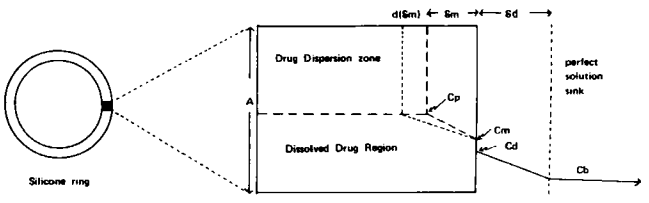

Figure 1—*Theoretical concentration profile existing in a drug-dispersed polymeric device in contact with a perfect solution sink. A is the initial amount of drug impregnated in a unit volume of device. See text for definitions of* C_p, C_m, C_d, $C_b(t)$, δ_m, and δ_D.

Table I—Effect of Polyethylene Glycol 400 on the Solution Solubility (C_s) and Bulk Concentration [$C_b(t)$] of Ethynodiol Diacetate

Volume Fraction of Polyethylene Glycol 400[a], % v/v	C_s, μg/ml	$C_b(t)$[b], μg/ml
0	13.7	—
20	37	6.77
30	64.6	10.66
40	99.7	14.56
50	156	24.18
55	196	36.65
60	437	47.63
62.5	647.5	75.11
65	780	92.0
70	1390	152.9
75	2430	316.7
80	4450	395.2
85	8000	425.8

[a] In distilled water. [b] For maintaining a sink condition, the bulk drug concentration (C_b) in drug elution cells was monitored and the elution solution was renewed daily (Ref. 1). Each value represents the average of the $C_b(t)$ values measured during a 10-day experiment (Ref. 2).

suggests that the magnitude of the $C_b(t)/C_m$ term (Eq. 5) has to be maintained at a level much lower than the value of the C_d/C_m term.

This sink condition may be satisfied either by setting $C_b(t)$ very close to zero or by making C_d much greater than $C_b(t)$. The former approach has been applied in many conventional dissolution and elution studies and is best represented by the use of a large volume (60 liters/day) of distilled water as the elution medium for release studies of medroxyprogesterone acetate (6) (aqueous solubility of 3.25 μg/ml). The other approach was demonstrated by the application of a small volume (150 ml) of cosolvent–water combinations to enhance remarkably the aqueous solubility (13.7 μg/ml) of ethynodiol diacetate by from three- to 584-fold (1, 2), depending on the volume fraction (20–85% v/v) of cosolvent added.

Apparently, the magnitude of $C_b(t)$ in the latter case is a finite value and cannot be approximated to zero as in the former approach. This fact is illustrated in Table I, where $C_b(t)$ has various finite values in various elution media, although they are much smaller than their corresponding C_s (solution solubility) values.

The magnitude of $C_b(t)$ is enhanced by the addition of polyethylene glycol 400 in a manner that seems proportional to the increase in the magnitude of the C_s term. The correlation of $C_b(t)$ with C_s becomes quite apparent when one plots $C_b(t)$ values against their corresponding C_s values (Fig. 2). The use of a log–log scale in Fig. 2 allows the complete coverage of a wide range of both

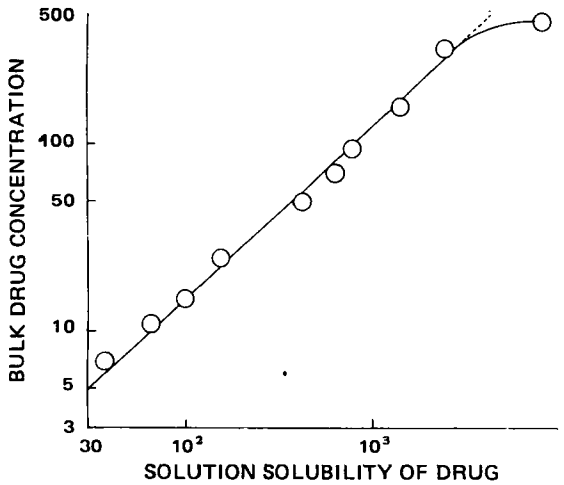

Figure 2—*Logarithmic relationship between the bulk concentration (C_b) of drug in the sink elution medium and the solution solubility of drug (C_s). Slope = 0.933.*

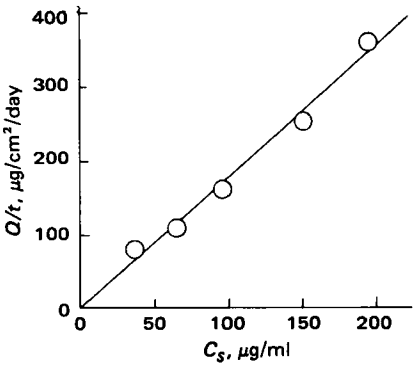

Figure 3—*Linear relationship of the drug release rate (Q/t) with the solution solubility (C_s) of drug following Eq. 24. Slope (kD_s/δ_D) = 1.77 cm/day.*

$C_b(t)$ and C_s values. As expected, a linear relationship with a slope (0.93) close to unity was obtained (Eq. 6a):

$$C_b(t) = \alpha C_s^{(1)} \qquad \text{(Eq. 6a)}$$

Since:

$$C_m = \beta C_p \qquad (\beta \leq 1) \qquad \text{(Eq. 6b)}$$

then:

$$\frac{C_b(t)}{C_m} = \frac{\alpha C_s}{\beta C_p} = k'K \qquad \text{(Eq. 7)}$$

where the partition coefficient, K, for the partitioning of drug molecules from the polymer surface toward the elution solution (6) is expressed as:

$$\frac{C_s}{C_p} = K = \frac{C_d}{C_m} \qquad \text{(Eq. 8)}$$

and:

$$k' = \frac{\alpha}{\beta} \qquad \text{(Eq. 9)}$$

Substituting Eqs. 7 and 8 into Eq. 5 results in:

$$\frac{C_p}{C_m} = 1 + \frac{D_s\delta_m}{D_m\delta_D}[1 - k']K \qquad \text{(Eq. 10a)}$$

or:

$$\frac{C_p}{C_m} = 1 + \frac{D_s\delta_m kK}{D_m\delta_D} \qquad \text{(Eq. 10b)}$$

where:

$$k = 1 - k' \qquad \text{(Eq. 11)}$$

Rearrangement of Eq. 10b gives:

$$C_m = \frac{D_m\delta_D C_p}{D_m\delta_D + D_s\delta_m kK} \qquad \text{(Eq. 12)}$$

If the dissolution of the drug particles into the surrounding polymer matrix in the drug dispersion zone (Fig. 1) is the first step in drug release dynamics (prior to the diffusion of solvated drug molecules across the depletion zone), then the cumulative amounts (Q and Q') of drug released from a unit surface area of device with a thickness of δ_m or ($\delta_m + d\delta_m$) are expressed, respectively, by:

$$Q = \left(A - \frac{C_p + C_m}{2}\right)\delta_m \qquad \text{(Eq. 13a)}$$

$$Q' = \left(A - \frac{C_p + C_m}{2}\right)(\delta_m + d\delta_m) \qquad \text{(Eq. 13b)}$$

The differential cumulative amount (dQ) of drug released due to the formation of a differential zone ($d\delta_m$) of depletion can be calculated from the difference between Q' and Q as follows:

$$dQ = Q' - Q \qquad \text{(Eq. 14a)}$$

$$dQ = \left(A - \frac{C_p + C_m}{2}\right)d\delta_m \qquad \text{(Eq. 14b)}$$

The rate of expansion, dQ/dt, of this differential zone of depletion is then described by:

Table II—Calculation of k

Volume Fraction of Polyethylene Glycol 400, % v/v	D_S/δ_D, cm/day	k[a]
20	56.66	0.031
30	36.82	0.048
40	23.87	0.074
50	15.39	0.114
55	14.30	0.123
60	9.92	0.177
62.5	8.77	0.201
65	8.03	0.219
70	6.44	0.273
75	5.27	0.334
80	4.12	0.427
85	3.38	0.521

[a] Calculated from the relation of $k = 1.77/(D_S/\delta_D)$ (Eq. 24).

$$\frac{dQ}{dt} = \left(A - \frac{C_p + C_m}{2}\right)\frac{d\delta_m}{dt} \qquad \text{(Eq. 14c)}$$

where A is the initial amount of solid drug impregnated homogeneously in a unit volume of device.

The theoretical model shown in Fig. 1 indicates that the rate of expansion (dQ/dt) of the depletion zone will have a finite value only if the surface concentration of drug, C_m, on the polymeric device is maintained at a constantly smaller level than C_p (the polymer solubility of drug) throughout an observation.

Substituting Eq. 12 for the C_m term in Eqs. 2 and 14c and then equating them at a steady state result in:

$$\frac{D_m}{\delta_m}\left[C_p - \frac{D_m\delta_D C_p}{D_m\delta_D + D_s\delta_m kK}\right] = \left[A - \frac{C_p}{2} - \frac{D_m\delta_D C_p}{2(D_m\delta_D + D_s\delta_m kK)}\right]\frac{d\delta_m}{dt} \qquad \text{(Eq. 15a)}$$

Rearrangement of Eq. 15a and integration yield:

$$C_m D_s D_m kK \int_0^t dt = (A - C_p)D_m\delta_D \int_0^{\delta_m} d\delta_m + \left(A - \frac{C_p}{2}\right)D_s kK \int_0^{\delta_m} \delta_m d\delta_m \qquad \text{(Eq. 15b)}$$

and then:

$$\delta_m{}^2 + \frac{2(A - C_p)D_m\delta_D\delta_m}{(A - C_p/2)D_s kK} = \frac{2C_p D_m}{(A - C_p/2)}t \qquad \text{(Eq. 16)}$$

Experimentally, the system was designed so that the initial amount of solid drug (A) dispersed homogeneously in a unit volume of polymer matrix was much larger than the polymer solubility (C_p) of the drug ($A \geq 98.8$ g/10^3 cm^3 and $C_p = 1.4791$ g/10^3 ml). Therefore, $2A \gg (C_p + C_m)$ may be established (since $C_m = \beta C_p$ and $\beta \leq 1$) and Eq. 13a may be approximated:

$$Q \simeq \left(A - \frac{C_p}{2}\right)\delta_m \qquad \text{(Eq. 13c)}$$

or:

$$Q \simeq A\delta_m \qquad \text{(Eq. 13d)}$$

without any significant error involved as long as the condition $2A \gg (C_p + C_m)$ is satisfied.

The value of δ_m is a time-dependent variable and may be estimated by measuring the size of the formed depletion zone by microscopy after sectioning a device (6). The δ_m term in Eqs. 13a, 13c, and 13d also may be calculated from the time-independent parameters, *e.g.*, A, C_p, D_s, D_m, δ_D, and K. These release rate-limiting physicochemical parameters can be measured easily from a diffusion experiment.

Table III—Comparison of k[a] with K[b] for Partition-Controlled Processes

Volume Fraction of Polyethylene glycol 400, % v/v	k	K	k/K
20	0.031	0.036	0.86
30	0.048	0.044	1.10
40	0.074	0.061	1.21
50	0.114	0.099	1.15
55	0.123	0.133	0.93
		Mean ($\pm SD$)	1.05 (0.15)

[a] Defined in Eq. 11. [b] Defined in Eq. 8.

Table IV—Calculated *versus* Observed Rates of Drug Release (Q/t)

Volume Fraction of Polyethylene Glycol 400, % v/v	Q/t, μg/cm²/day	
	Calculated[a]	Observed
20	65.5	82.6
30	114.2	109.8
40	176.1	141.3
50	273.7	245.7
55	344.7	360.0

[a] Calculated from Eq. 24. The C_S data are from Table I, and the D_S/δ_D and k data are from Table II.

In these studies, the magnitude of K was a variable depending on the volume fraction of cosolvent in the elution medium. The following two cases were observed as the value of K was varied to make the magnitude of the $\delta_m{}^2$ term (Eq. 16) either much greater or much smaller than the second term in Eq. 16.

Case 1—For a matrix-controlled process, K is very large; therefore:

$$\delta_m{}^2 \gg \frac{2(A - C_p)D_m\delta_D}{(A - C_p/2)D_s kK}\delta_m \qquad \text{(Eq. 17)}$$

and Eq. 16 is reduced to a $t^{1/2}$-dependent δ_m:

$$\delta_m = \sqrt{4C_p D_m t/(2A - C_p)} \qquad \text{(Eq. 18)}$$

Substituting Eq. 18 for the δ_m term in Eq. 13c results in:

$$Q = \sqrt{D_m(2A - C_p)C_p t} \qquad \text{(Eq. 19)}$$

which is the equation developed earlier by Higuchi (7). Equation 19 is slightly different from Eq. 3 of Ref. 1. In the earlier derivation, the contribution due to the penetration of elution solution in the microscopic channels (formed after the depletion of drug particles) was considered. In the present derivation of Eq. 19, this contribution was considered to be very small in comparison with the contribution from the diffusion across the polymer structure. The difference in the magnitudes of the resultant $Q/t^{1/2}$ values was

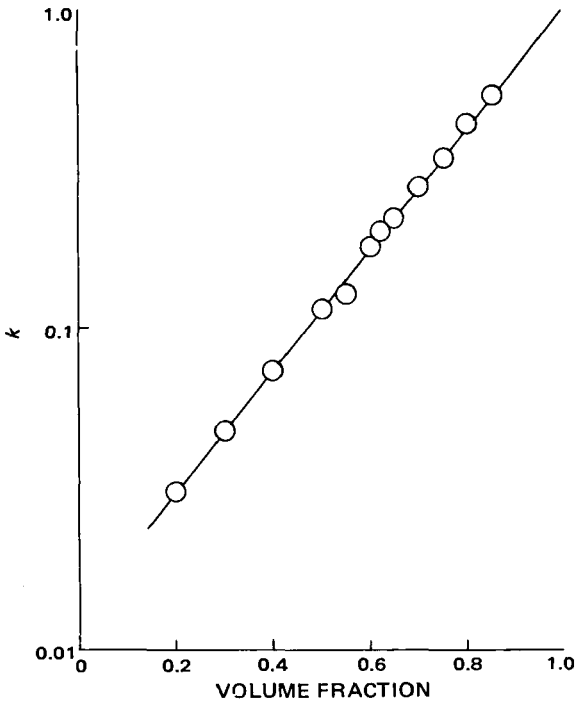

Figure 4—*Semilogarithmic relationship between* k *and the volume fraction of polyethylene glycol 400. Slope* (m) = *1.87.*

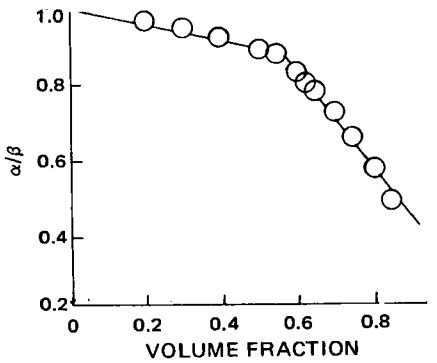

Figure 5—*Biphasic relationship of α/β (relative concentration gradient across diffusion layer over that across depletion zone) with volume fraction of polyethylene glycol 400. The slopes were 0.22 [volume fraction ≤55% (v/v)] and 1.30 [volume fraction ≥60% (v/v)], respectively.*

negligibly small between Eq. 3 ($Q/t^{1/2}$ = 3.03–3.09 mg/cm^2/day$^{1/2}$) and Eq. 19 ($Q/t^{1/2}$ = 3.08 mg/cm^2/day$^{1/2}$).

Case 2—For a partition-controlled process, K is very small; therefore:

$$\delta_m^2 \ll \frac{2(A - C_p)D_m\delta_D}{(A - C_p/2)D_sK}\,\delta_m \qquad \text{(Eq. 20)}$$

and Eq. 16 is reduced to:

$$\delta_m = \frac{kKD_sC_p}{(A - C_p)\delta_D}\,t \qquad \text{(Eq. 21}a\text{)}$$

or:

$$\delta_m \simeq \frac{kKD_sC_p}{A\delta_D}\,t \qquad \text{(Eq. 21}b\text{)}$$

Substituting Eq. 21b for the δ_m term in Eq. 13d gives the following relationship:

$$Q = \frac{kKD_sC_p}{\delta_D}\,t \qquad \text{(Eq. 22)}$$

From Eq. 7, $KC_p = C_s$. Therefore, Eq. 22 is expressed alternatively as:

$$Q = \frac{kD_sC_s}{\delta_D}\,t \qquad \text{(Eq. 23)}$$

The experimental observations on the linear $Q - t$ relationship (Eq. 23) were presented previously (2).

The rate of drug release (Q/t) for a partition-controlled process may be calculated from the slope of the linear Q *versus* t plots and is defined as:

$$\frac{Q}{t} = \frac{kD_s}{\delta_D}C_s \qquad \text{(Eq. 24)}$$

According to Eq. 24, the rate of drug release (Q/t) should be linearly proportional to the magnitude of drug solubility (C_s) in the elution medium used. This linearity is demonstrated in Fig. 3. The slope (kD_s/δ_D) of this linear plot was estimated to be 1.77 cm/day.

Following the addition of polyethylene glycol 400 as a cosolvent, the viscosity of the elution medium was increased. This increase in solution viscosity resulted in an increase in the thickness of the diffusion layer (δ_D) and a decrease in the magnitude of the solution diffusivity (D_s). Therefore, k should be a variable while the overall kD_s/δ_D term is constant (1.77 cm/day) experimentally.

The magnitude of k at various combinations of D_s/δ_D values may be easily calculated (Table II). As expected, the magnitude of k increases as the ratio of D_s over δ_D decreases. Furthermore, a proportionality appears to exist between the values of k and the volume fraction of cosolvent used in the elution medium. This proportionality is plotted semilogarithmically in Fig. 4. Attention is called to the result that k = 1 was obtained at 100% (v/v) of polyethylene glycol 400 (volume fraction = 1). The linear relationship of k with the volume fraction of polyethylene glycol 400 may be expressed as:

$$\log k = m\,(\text{volume fraction of polyethylene glycol 400}) + \text{constant} \qquad \text{(Eq. 25)}$$

with a slope (m = 1.87) very close to 2.

Table V—Calculation of α, β, and C_m

Volume Fraction of Polyethylene Glycol 400, % v/v	α[a]	β[b]	C_m[c], μg/ml	C_s, μg/ml
20	0.183	0.189	279.3	37.0
30	0.165	0.173	256.4	64.6
40	0.146	0.158	233.2	99.7
50	0.155	0.173	258.8	156
55	0.187	0.213	315.4	196
60	0.109	0.132	195.9	437
62.5	0.116	0.145	214.7	647.5
65	0.118	0.151	223.5	780
70	0.110	0.151	223.8	1390
75	0.130	0.195	288.7	2430
80	0.089	0.155	229.7	4450
85	0.053	0.111	163.7	8000
$\bar{x}$ (±SD)(n = 12)		0.162 (0.028)	240.3 (±41.9)	

[a] Calculated from Eq. 6a; $\alpha = C_b(t)/C_s$. [b] Calculated from Eq. 26; $\beta = \alpha/(1 - k)$. [c] Calculated from Eq. 8; $C_m = \beta C_p$; C_p = 1.4791 × 10^3 μg/ml.

The magnitude of k for the partition-controlled process was essentially equal to that of K, the partition coefficient of drug from the polymer surface toward the elution medium (Table III). The coincidence of k with K ($k/K \simeq 1$) may provide an explanation for previous observations on the linear relationship between the rate of drug release (Q/t) and the partition coefficient for the partition-controlled process. The validity of Eq. 24 is evident when one compares the rates of drug release in various elution solutions with those calculated from the values of C_s, D_s, δ_D, and k (Table IV).

The following relationship may be derived from Eqs. 9 and 11:

$$\beta = \frac{\alpha}{1 - k} \qquad \text{(Eq. 26)}$$

From Eq. 26, the proportionality (β) between the drug concentration (C_m) at the polymer–solution interface and that (C_p) at the interface of the drug dispersion–drug depletion zone (Eq. 8) may be calculated (Table V). A mean value of 0.162 ± 0.028 was obtained. As predicted, the magnitude of β is considerably smaller than unity ($\beta \leq 1$ in Eq. 8). This result indicates that an effective concentration gradient ($C_p - C_m$) was maintained across the depletion zone (Eq. 2) for all volume fractions of polyethylene glycol 400 used.

The drug concentration (C_m) at the polymer–solution interface can be calculated from Eq. 8, using an experimentally predetermined C_p value (1.4791 × 10^3 μg/cm^3) (Table V), and the C_m values found are substantially smaller than C_p. Unlike the behavior demonstrated by both C_s and $C_b(t)$, the magnitude of C_m is quite independent of the variation in the volume fraction of cosolvent added (a mean of 240.3 ± 41.9 μg/ml). The value of C_m is greater than the value of C_s (Table V) for the partition-controlled process [volume fraction of polyethylene glycol ≤55% (v/v)] but smaller than the value of C_s in the region of the matrix-controlled process [volume fraction of polyethylene glycol ≥60% (v/v)].

The effect of cosolvent on the concentration gradient (α) across the diffusion layer relative to that (β) across the depletion zone is significant (Fig. 5). The effect of cosolvent is considerably smaller when its volume fraction is equal to or smaller than 55% (v/v) (slope = 0.22). The magnitude of this effect is enhanced sixfold (from 0.22 to 1.30) when the volume fraction of cosolvent used is increased above 60% (v/v). These observations may provide some insights into the mechanism of the transition between matrix-controlled and partition-controlled processes reported previously (2).

From the enclosed analysis, it was concluded that the variation in the magnitude of solution solubility (C_s) dictates the mechanism and rate of drug release from a drug dispersed in a polymer matrix.

REFERENCES

(1) Y. W. Chien, H. J. Lambert, and D. E. Grant, *J. Pharm. Sci.*, **63**, 365(1974).

(2) Y. W. Chien and H. J. Lambert, *ibid.*, **63**, 515(1974).
(3) Y. W. Chien, T. D. Sokoloski, and C. L. Olson, *ibid.*, **62**, 435(1973).
(4) W. G. Perkins and D. R. Begeal, *J. Chem. Phys.*, **54**, 1683(1971).
(5) J. Grank and G. S. Park, "Diffusion in Polymers," Academic, New York, N.Y., 1968.
(6) T. J. Roseman and W. I. Higuchi, *J. Pharm. Sci.*, **59**, 353(1970).
(7) T. Higuchi, *ibid.*, **50**, 874(1961).

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Effects of Selected Drugs on an Auditory or Thalamic Conditioned Stimulus Eliciting Recruitment in the Cat

B. DUBINSKY [x], W. J. KINNARD, Jr. [*], and J. P. BUCKLEY [‡]

Abstract □ Minimally effective oral doses of chlorpromazine, imipramine, and pentobarbital necessary to block a discrete trial (bar-press) conditioned avoidance response were compared in cats chronically implanted with electrodes over the cerebral cortex and in the nucleus centralis medialis of the thalamus. Three conditioned stimulus contingencies consisting of tone and low or high voltage thalamic stimulation were presented. Minimal conditioned response blocking doses of these agents produced only slight qualitative changes in cortically recorded recruitment. Drug treatment affected the conditioned stimulus contingencies differentially, and the rank order in terms of ease of disruption of the conditioned avoidance response was high voltage thalamic conditioned stimulus > low voltage thalamic conditioned stimulus > auditory conditioned stimulus. The differential effect of these drugs might have been due to the additive inhibition of these agents and the thalamic conditioned stimulus on performance. With the exception of chlorpromazine, the behavioral effects of these drugs and their effects on recruitment were dissociated.

Keyphrases □ Chlorpromazine—effects on conditioned avoidance response, conscious cat □ Imipramine—effects on conditioned avoidance response, conscious cat □ Pentobarbital—effects on conditioned avoidance response, conscious cat □ Thalamic recruitment—effects of chlorpromazine, imipramine, and pentobarbital, conditioned avoidance response, conscious cat

Electrical stimulation of midline thalamic nuclei and other subcortical sites evokes potentials which, when recorded cortically, resemble spontaneous spindle bursts. Since these potentials increase in amplitude with time, apparently through the recruitment of additional responsive neurons, the recorded event has come to be known as the recruiting response. Several studies (1–3) defined these properties and examined the sites of origin of the recruiting response. Since these classic studies, many investigators have studied the behavioral effects of electrical stimulation of regions of the brain from which cortical recruitment may be elicited.

Midline thalamic stimulation has been shown to act as a conditioned stimulus for the formation of a conditioned avoidance response in cats (4–6), dogs (7), and squirrel monkeys (8). Changes in the amplitude of recruitment during learning and performance have been variously interpreted as reflecting behavioral facilitatory or inhibitory processes (6). However, Pecci-Saavedra *et al.* (8) attributed these changes to alterations in the level of arousal associated with learning.

The effects of psychotropic drugs which modify learned behavior on the recruiting system have been extensively tested; however, the relationship between the effects of these agents on recruitment and their effects on behavior is unknown since all studies have been done in paralyzed or anesthetized preparations (9–14). The present study was designed to bridge the gap between these studies and, thus, to examine the mutual alterations in behavior induced by stimulation of the recruiting system and the action of psychotropic drugs. The effects of selected drugs on avoidance behavior conditioned by either tone or midline thalamic stimulation were studied to compare directly the behavioral effects of these agents to their effects on recruitment.

EXPERIMENTAL

Adult female cats, 2.5–3.5 kg, were chronically implanted with cortical and subcortical electrodes under aseptic conditions. Stainless steel rivets (3-mm diameter heads) insulated with epoxy varnish (except at their tips) were positioned on the dura through burr holes in the skull, and an uninsulated rivet was cemented in the bone overlying the frontal sinus as a connection to ground. A bipolar concentric electrode, consisting of an outer 23-gauge stainless steel cannula and an inner insulated stainless steel wire [0.01 cm (0.005 in.) diameter], was placed in the region of the nucleus centralis medialis of the thalamus according to reported stereotaxic coordinates (anterior, 9.5 mm; lateral, 0.0 mm; horizontal, 1.0 mm) (15). The electrode was insulated with epoxy varnish, and the tips were bared 0.5 mm and separated by 1.0 mm.

The position of this electrode was considered satisfactory if, during surgery, recruiting potentials could be recorded from the cortical leads upon stimulation of the medial thalamus. The parameters of stimulation[1] are given under *Results*. The electrodes were wired to a connector[2], and the assembly was secured to the skull with dental acrylate.

Experiments were initiated no sooner than 2 weeks following

[1] Grass model S-4 stimulator and SIU-4 isolation unit were used.
[2] Amphenol No. 57-40140.