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ACKNOWLEDGMENTS AND ADDRESSES

Received from the *Division of Organic Chemistry, Department of Medicinal Chemistry, College of Pharmacy, University of Tennessee Center for the Health Sciences, Memphis, TN 38163*

The authors express their appreciation to Dr. Charles E. Kossmann, Dr. James R. Wennemark, and Dr. E. M. Vaughan Williams for useful discussions during the preparation of this review.

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RESEARCH ARTICLES

Programmed Diffusional Release Rate from Encapsulated Cosolvent System

FELIX THEEUWES ˣ, KAZUO ASHIDA*, and TAKERU HIGUCHI ‡

Abstract □ The programmed diffusional release rate of an active agent through a rate-controlling membrane from a cosolvent system is discussed. At initial conditions, the drug is present below saturation in solution in a solvent mixture, enclosed by the rate-controlling membrane; the solvent is composed of the main solvent and a cosolvent, which increases the drug solubility in the main solvent. During operation, the active agent and cosolvent diffuse from the capsule at a rate controlled by the membrane. Equations were derived describing the release rate of the active agent as a function of the permeability of the cosolvent and agent, the capsule dimensions, and the system's initial conditions. A great variety of release rate profiles can be programmed from declining to increasing delivery rate patterns as a function of time. Experimental data are presented for the drug progesterone in solution in cyclohexane with methyl, heptyl, or cetyl alcohol as the cosolvent in a polyethylene capsule. The theory qualitatively predicts the experimental results.

Keyphrases □ Diffusion—progesterone through rate-controlling membrane (polyethylene capsule), programmed release rate, cosolvent system □ Release rate, programmed—progesterone diffusion through rate-controlling membrane (polyethylene capsule) □ Drug delivery systems—progesterone diffusion through rate-controlling membrane (polyethylene capsule) □ Membranes, rate controlling—polyethylene capsule, progesterone diffusion □ Progesterone—diffusion through polyethylene capsule, programmed release rate □ Polyethylene capsule—rate-controlling membrane, progesterone diffusion, programmed release rate

During the past 5 years, considerable effort has been undertaken to achieve embodiments of a new class of dosage form, specified not by the quantity of drug but by the rate and duration of drug release (1). Both rate and duration are parameters that should be designed to be independent of the body environment in which the system is deployed.

The mechanism of diffusion provides one basis for accomplishing this objective. Such systems were discussed in detail in a recent review article (2). The release patterns are governed by Fick's law, and different time profiles are obtained, depending on the system design. Important well-known (2) release rate profiles are:

1. Zero-order release, where the drug is released through a membrane of fixed dimensions from a source at constant thermodynamic activity.

2. Release from dispersed systems, where the release rate is inversely proportional to the square root of time (3, 4).

3. Release from a capsule containing the drug in solution where the release rate (dm/dt) decreases exponentially with time as:

$$\frac{dm}{dt} = A\left(\frac{P}{l}\right)C_0 \exp(-kt) \qquad \text{(Eq. 1)}$$

where A is the membrane area, l is the membrane thickness, P is the drug permeability through the membrane, and C_0 is the drug concentration at time $t = 0$ in the capsule. The rate constant, k, is defined as:

$$k = \frac{AP}{Vl} \qquad \text{(Eq. 2)}$$

where V is the capsule volume.

The three patterns discussed have a time profile constant or decreasing with time. In this paper, a system is discussed that can be programmed at a rate increasing, constant, or decreasing with time. The system consists of the drug in solution in a mixture of two solvents, contained in a capsule composed of a polymeric rate-controlling membrane. One of the two solvents, the main solvent, does not leave the capsule; the second solvent, the cosolvent, permeates through the membrane and, in turn, affects the thermodynamic activity of the drug in solution while the drug concentration continuously decreases.

In the system described here, the cosolvent was selected such that the drug solubility increases linearly in solution as a function of the cosolvent concentration. During the experiment, the capsule was suspended in the main solvent and the capsule wall served as the rate-controlling membrane for the drug and cosolvent.

The model systems studied consisted of a polyethylene capsule containing the drug progesterone in a solution of cyclohexane as the main solvent and methyl, heptyl, or cetyl alcohol as the cosolvent.

EXPERIMENTAL

Materials—Progesterone samples[1] were recrystallized from methyl alcohol to yield the crystalline form, mp 128°. All solvents were reagent grade and were used as received.

Solubility—The 37° solubility of progesterone in cyclohexane with alcohol as a cosolvent was determined using the solubility technique of Higuchi and Connors (5). Progesterone concentrations were determined spectrophotometrically at 232 nm in cyclohexane.

Diffusion—The permeability coefficients of progesterone, methyl alcohol, heptyl alcohol, and cetyl alcohol from cyclohexane through polyethylene into cyclohexane were determined for each compound separately. The experiments were carried out in a glass diffusion cell with a membrane area of 1.96 cm^2. Both sides of the cell were magnetically stirred. Polyethylene membranes, with a thickness of 5.8×10^{-3} cm, were used in the permeability experiments on the pure compound as well as in the cosolvent system diffusion experiments. The permeated amounts of progesterone were determined spectrophotometrically at 232 nm in cyclohexane. The permeated amounts of cosolvent were determined by GC.

In the cosolvent diffusion experiments, progesterone was dissolved at a known initial concentration, C_{Di}, smaller than the saturated value of C_{DS}, in a mixture of cyclohexane and cosolvent at concentration X_i. This solution was sealed into a polyethylene capsule and suspended in the first of a series of volumetric flasks containing cyclohexane. The flasks were shaken in a 37° bath. At regular time intervals, the capsule was transferred into a fresh flask in the same bath.

The content of each flask was analyzed, and the amount of progesterone released per unit time and area was calculated. The progesterone concentration on the downstream side was maintained at less than 5% of the concentration on the upstream side. The amounts of progesterone released were determined spectrophotometrically as in the solubility studies.

[1] Searle Chemicals.

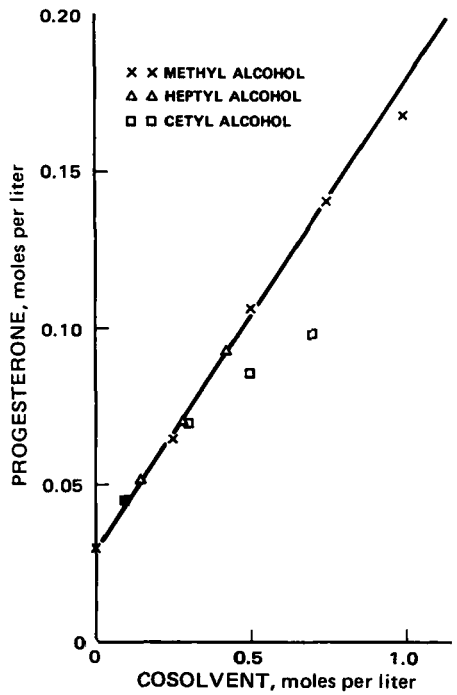

Figure 1—*Solubility of progesterone in cyclohexane as a function of cosolvent (methyl alcohol, heptyl alcohol, and cetyl alcohol) concentration.*

RESULTS

The solubility data of progesterone in the cyclohexane–alcohol cosolvent systems are plotted in Fig. 1. A linear solubility curve was obtained for the three cosolvents: methyl, heptyl, and cetyl alcohols. The intercept and initial slope were the same for the three cosolvents, and the curve can be represented by a single straight line:

$$C_{DS} = C_{DSO} + BX \qquad \text{(Eq. 3)}$$

where C_{DS} is the progesterone solubility in the system with X as the cosolvent concentration in moles per liter, C_{DSO} is the progesterone solubility in cyclohexane equal to 0.025 mole/liter, and $B = 0.15$ (moles per liter of progesterone/moles per liter of cosolvent) is the slope of the solubility curve.

The permeability coefficients for progesterone (P_D) and cosolvents (P_X) from cyclohexane through polyethylene are listed in Table I. The remaining parameters affecting the release phenome-

Table I—Experimental Permeability Coefficients through Polyethylene from Cyclohexane

Compound	Permeability Coefficient, cm^2/sec × 10^8
Progesterone	3.9
Methyl alcohol	5.1
Heptyl alcohol	1.9
Cetyl alcohol	0.45

Table II—Initial Progesterone and Cosolvent Concentrations and Capsule Dimensions

Cosolvent	Initial Concentration: Progesterone, C_{Di}, mole/liter	Initial Concentration: Cosolvent, X_i, mole/liter	Capsule Volume, cm^3	Membrane: Area, cm^2	Membrane: Thickness, cm
None	0.025	0	0.5	5.07	5.8×10^{-3}
Methyl alcohol	0.053	0.50	0.3	3.5	5.8×10^{-3}
Heptyl alcohol	0.053	0.50	0.35	4.0	5.8×10^{-3}
Cetyl alcohol	0.053	0.50	0.3	3.7	5.8×10^{-3}

non are listed in Table II, which gives the dimensions of the capsules and initial concentrations of cosolvent, X_i, and progesterone, C_{Di}, for each cosolvent experiment.

In the experiment listed in the first row of Table II, no cosolvent was used and the release rate declined exponentially according to Eq. 1. The experimental data are collectively presented in Fig. 2, in which the release rates are plotted for the cyclohexane and cosolvent systems. In these experiments, the same initial conditions and about the same capsule sizes were chosen. As seen earlier, the solubility curve represented by Eq. 3 is the same for each cosolvent system.

THEORETICAL

Derivation of Working Equations—In the following calculations, it is assumed that the cosolvent has no plasticizing effect on the membrane and that the cosolvent permeates from the capsule at a rate independent of the drug. It also is assumed that concentrations of the drugs and cosolvents in the membrane are in equilibrium with the inside and outside of the capsule at all times so that the bulk concentrations are directly related to the membrane surface concentrations[2] and the membrane can be treated as a thin membrane.

Under steady-state conditions in the membrane, it has been shown (6) that the drug permeation rate, dm/dt, is proportional to the fraction of saturation for a system obeying Henry's law:

$$\frac{dm}{dt} = \left(\frac{A}{l}\right) \bar{T} \left(\frac{C_D}{C_{DS}}\right) \quad \text{(Eq. 4)}$$

where A is the membrane area, l is the membrane thickness, and $\bar{T}$ is the transference coefficient (6):

$$\bar{T} = \frac{l}{A}\left(\frac{dm}{dt}\right)_{sat} = P_D C_{DS} \quad \text{(Eq. 5)}$$

In Eqs. 4 and 5, C_D and C_{DS} are the drug concentration and the drug concentration at saturation, respectively; $(dm/dt)_{sat}$ is the limiting mass permeation rate occurring from a saturated drug solution. The cosolvent system, progesterone–alcohol, has a saturated concentration, C_{DS}, represented by Eq. 3. Hence, Eqs. 4 and 3 result in:

$$\frac{dm}{dt} = \left(\frac{A}{l}\right) \bar{T} \left[\frac{C_D}{(C_{DSO} + BX)}\right] \quad \text{(Eq. 6)}$$

Since a steady state is assumed for the cosolvent as well as progesterone, Eq. 1 also applies to the cosolvent as long as the cosolvent leaves as an independent species. Thus, the concentration of cosolvent can be expressed by:

$$X = X_i \exp(-k_x t) \quad \text{(Eq. 7)}$$

where X_i is the initial cosolvent concentration, and k_x is:

$$k_x = \frac{AP_x}{Vl} \quad \text{(Eq. 8)}$$

For a capsule volume, V, the relation between the mass, m, of drug in solution and drug concentration, C_D, is given by:

$$m = C_D V \quad \text{(Eq. 9)}$$

Substituting Eqs. 9 and 7 into Eq. 6 results in:

$$\frac{dC_D}{C_D} = -\left(\frac{A}{l}\right)\left(\frac{\bar{T}}{V}\right) \frac{dt}{C_{DSO} + BX_i \exp(-k_x t)} \quad \text{(Eq. 10)}$$

The drug concentration, C_D, at each time, t, is obtained by integrating Eq. 10 from $t = 0$ from the initial drug concentration, C_{Di}, to C_D:

$$\int_{C_{Di}}^{C_D} \frac{dC_D}{C_D} = -\left(\frac{A}{l}\right)\left(\frac{\bar{T}}{V}\right) \int_0^t \frac{dt}{C_{DSO} + BX_i \exp(-k_x t)} \quad \text{(Eq. 11)}$$

The solution to Eq. 11 is given by:

$$\ln \frac{C_D}{C_{Di}} = -\left(\frac{A}{l}\right)\left(\frac{\bar{T}}{V}\right)\left[\frac{t}{C_{DSO}} + \frac{1}{C_{DSO}k_x} \ln \frac{C_{DSO} + BX_i \exp(-k_x t)}{C_{DSO} + BX_i}\right] \quad \text{(Eq. 12)}$$

To reduce the size of the expressions, substitute $\phi(t)$:

$$\phi(t) = t + \frac{1}{k_x} \ln \frac{C_{DSO} + BX_i \exp(-k_x t)}{C_{DSO} + BX_i} \quad \text{(Eq. 13)}$$

where $\bar{T}$ is the transference obtained from the system at unit activity and is given by:

$$\bar{T} = P_D C_{DSO} \quad \text{(Eq. 14)}$$

The final form of the delivery rate obtained from Eqs. 6 and 12–14 is given by:

$$\frac{dm}{dt} = \left(\frac{A}{l}\right)\bar{T} \frac{C_{Di} \exp[-k_D \phi(t)]}{C_{DSO} + BX_i \exp(-k_x t)} \quad \text{(Eq. 15)}$$

Equation 15 is the general expression for the delivery rate from a capsule containing drug in solution in a cosolvent system with a linear solubility curve. At $t = 0$, $\phi(t)$ reduces to zero and dm/dt reduces to Eq. 4 for $C_D = C_{Di}$. At $t \to \infty$, $\phi(t) \to \infty$ and dm/dt goes to zero. At $X_i = 0$, $\phi(t)$ is equal to t and Eq. 15 reduces to the simple case for a single solvent given by Eq. 1.

The maximum in the delivery rate is obtained when Eq. 16 holds:

$$\frac{d}{dt}\left(\frac{dm}{dt}\right) = 0 \quad \text{(Eq. 16)}$$

By differentiating Eq. 15 and equating to zero, the time, t_R, at which the maximum occurs is found to be:

$$t_R = \frac{lV}{AP_x} \ln \frac{P_x B X_i}{P_D C_{DSO}} \quad \text{(Eq. 17)}$$

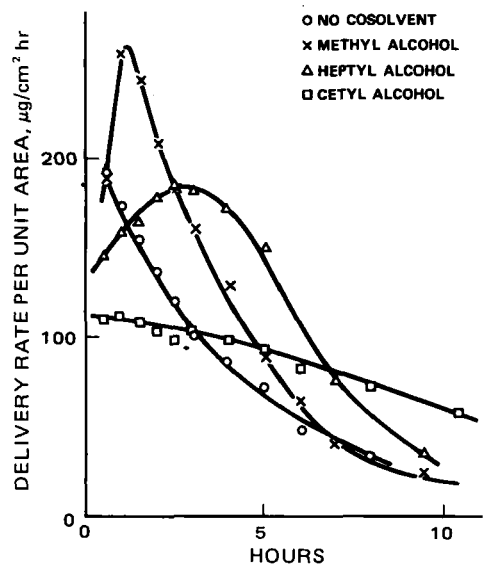

Figure 2—*Experimental release rates of progesterone from polyethylene capsules, containing cyclohexane as a primary solvent and an alcohol as the cosolvent, into cyclohexane.*

[2] This assumption will only be approximately true as hydrodynamic boundaries must be "crossed" at the interfaces (Ref. 7). Given the small permeability coefficients through the membrane and with the assumption that partition coefficients ≤1, these fluid boundaries would contribute negligibly to the diffusional resistance.

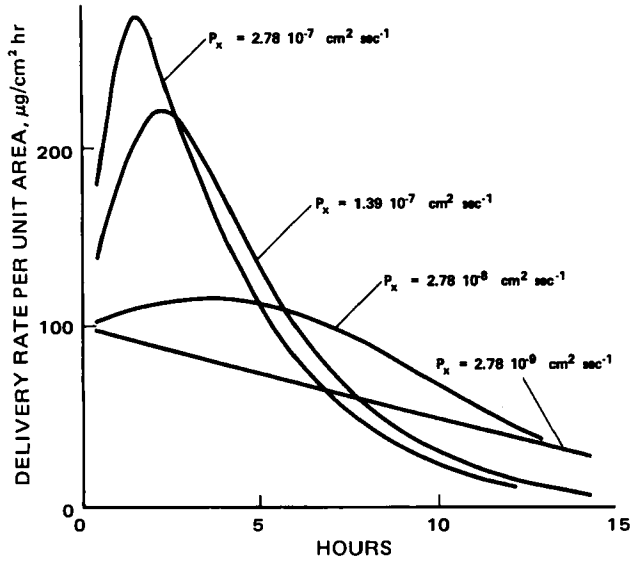

Figure 3—*Theoretical release rates of progesterone from polyethylene capsules calculated from Eq. 15 for different values of cosolvent permeability,* P_x.

From Eq. 17, it can be seen that t_R values exist only when $P_xBX_i > \bar{T}$. In other words, if $\bar{T} > P_xBX_i$, t_R is negative and no maximum exists. In this case, only decreasing rates are obtained.

It is notable that, if $P_xBX_i > \bar{T}$, the condition $t_R > 0$ is independent of the initial drug concentration, C_{Di}. Also, the time dependency of the rate in Eq. 15 is independent of C_{Di} and only the magnitude of the rate depends on C_{Di}.

As can be seen from Eq. 17, the maximum in the delivery rate can be programmed by selecting different cosolvents, in an homologous series, affecting mainly the permeability P_x. In Eq. 17, P_x appears both in the nominator and the denominator, resulting in a maximum value of t_R as a function of P_x; t_R is shortest for large values of P_x and increases with smaller P_x values to reach a maximum $t_{R,max}$ at P_{xm} before decreasing and becoming negative or ceasing to be real. The value P_{xm} at which the time t_R reaches a maximum can be obtained by differentiating Eq. 17 with respect to P_x and equating to zero. The value of P_{xm} is given by Eq. 18:

$$P_{xm} = e\left(\frac{\bar{T}}{BX_i}\right) \qquad \text{(Eq. 18)}$$

where e is the base of the natural logarithm.

The maximum time $t_{R,max}$ for a maximum rate is obtained by substituting Eq. 18 into Eq. 17, resulting in:

$$t_{R,max} = \frac{1}{e}\frac{lV}{A}\frac{BX_i}{\bar{T}} \qquad \text{(Eq. 19)}$$

$$t_{R,max} = \frac{lV}{AP_{xm}} \qquad \text{(Eq. 20)}$$

For cosolvent permeabilities P_x smaller than P_{xm}, $t_{R,max}$ decreases to reach the zero value at the cosolvent permeability P_{x0} given by:

$$P_{x0} = \frac{\bar{T}}{BX_i} \qquad \text{(Eq. 21)}$$

Numerical Calculations—The delivery rate per unit area, $(1/A)\ (dm/dt)$, was calculated from Eq. 15 using P_D given in Table I for an average sized capsule corresponding to Table II with V = 0.3 cm³, A = 3.7 cm², and $l = 5.8 \times 10^{-3}$ cm; initial conditions are C_{Di} = 0.053 mole/liter and X_i = 0.50 mole/liter. The cosolvent permeability was chosen at $P_x = 2.78 \times 10^{-9}$, 2.78×10^{-7}, 1.39×10^{-7}, and 2.78×10^{-9} cm²/sec. The theoretical curves are shown in Fig. 3.

Qualitatively, the experimental results of Fig. 2 agree with Fig. 3. At decreasing permeability of the cosolvent, the maximum in delivery rate decreases and shifts toward longer times as predicted by Eq. 17. At sufficiently low cosolvent permeability, the delivery rate decreases continuously and almost linearly with time, and a t_R does not exist.

The transference, $\bar{T}$, of progesterone through polyethylene submersed in cyclohexane is found to be 9.7×10^{-13} mole/cm sec, and

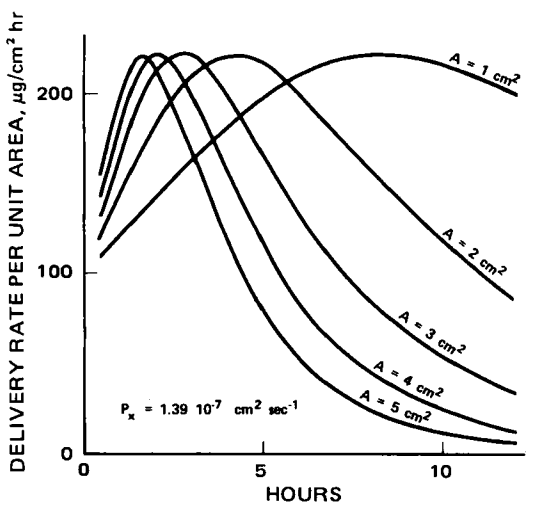

Figure 4—*Theoretical release rates of progesterone from polyethylene capsules calculated from Eq. 15 for different values of membrane area for the case satisfying* $P_xBX_i > \bar{T}$.

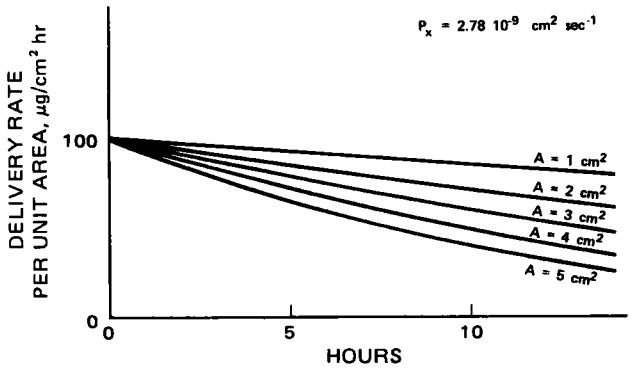

Figure 5—*Theoretical release rate of progesterone from polyethylene capsules calculated from Eq. 15 for different values of membrane area for the case satisfying* $\bar{T} > P_xBX_i$.

the progesterone flux at saturation, $(1/A)\ (dm/dt)_{sat}$, is 190 μg/cm² hr. This finding indicates, as shown in Figs. 2–4, that a supersaturated state is produced *in situ* and that supersaturation can be induced *via* facile equilibrium from the solvent into the membrane phase (6).

The cosolvent permeability, P_{xm}, for the alcohol series was calculated from Eq. 18 as $P_{xm} = 3.5 \times 10^{-8}$ cm²/sec, which would result in $t_{R,max}$ = 3.7 hr as calculated from Eq. 20. The cosolvent permeability at which $t_{R,max} = 0$ is calculated from Eq. 21: $P_{x0} = 1.3 \times 10^{-8}$ cm²/sec. The time at which the maximum in progesterone delivery rate occurs as a function of the alcohol cosolvent permeability is shown in Fig. 6. The calculations were carried out based on the initial experimental condition X_i = 0.5 mole/liter and an average sized capsule (Table II) using Eq. 17.

The membrane surface to capsule volume ratio of the system is very important for programming the device. In Figs. 4 and 5, typical fluxes are shown for systems characterized by $P_D = 3.9 \times 10^{-8}$ cm²/sec, V = 0.3 cm², and $l = 5.8 \times 10^{-3}$ cm. Initial concentrations are C_{Di} = 0.053 mole/liter and X_i = 0.50 mole/liter, and the membrane area was selected to be A = 1, 2, 3, 4, or 5 cm².

For Fig. 4, the cosolvent permeability was taken to be $P_x = 1.39 \times 10^{-7}$ cm²/sec. A P_x of 2.78×10^{-9} cm²/sec was assumed for Fig. 5. In Fig. 4, the maximum flux obtained is independent of membrane area. However, the onset of the maximum in flux occurs at longer times as the membrane area is reduced as predicted by Eq. 17. At low cosolvent permeability (Fig. 5), the flux becomes relatively invarient (zero-order rate) as the membrane area is reduced.

DISCUSSION

A cosolvent that enhances the drug solubility can be used to formulate the drug release rate in a controlled fashion. The drug re-

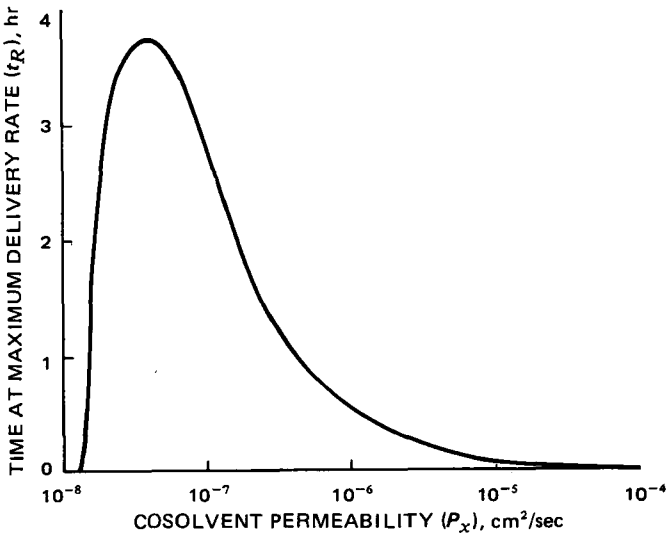

Figure 6—*Theoretical time at which a maximum in delivery rate occurs as calculated from Eq. 17 for progesterone diffusing from a polyethylene capsule (X_i = 0.5 mole/liter).*

lease rate from a cosolvent system with linear solubility characteristics is described by Eq. 15 as a first approximation. The release rate is equal to the product of the limiting rate, initial drug concentration, and a function of time. This time function is dependent on capsule dimensions, on drug and cosolvent permeabilities and solubility characteristics, and on the initial cosolvent concentration. The time function is independent of initial drug loading. The time function is flexible and can be programmed into shapes exhibiting a maximum at a predetermined time or into a declining time pattern. In the limit at zero cosolvent concentration, the time function reduces to a simple first-order (exponential decay) release.

Different release rate profiles were experimentally produced which are in qualitative agreement with the theory. It follows from the theory that no maximum is expected in the cetyl alcohol system, which has a P_x smaller than P_{x0}; for methyl and heptyl alcohols, a maximum is expected at 3.7 and 2.8 hr, respectively. The experimental permeability of heptyl alcohol is smaller than P_{xm} and, therefore, the maximum is expected to lie between 0 and 3.7 hr, the latter time being the maximum time, for maximum rate, expected for the system geometry. Experimental t_R times in excess of the theoretical maximum were not observed.

Since the theory as developed does not account for back-diffusion of cyclohexane, the influence of the cosolvent on membrane permeability characteristics, or for drug–cosolvent complexing (among other things), deviations can be expected where the membrane is affected by the presence of the cosolvent or where a strong cosolvent–drug interaction exists such that the complex diffuses as a separate species.

The release function predicts the attainment of a metastable, supersaturated state under certain tailored system conditions. A dosage form so designed could deliver a drug at rates exceeding those obtained from saturated solutions. During storage, the drug would remain in a stable solution state. When applied, a state of high thermodynamic activity can be produced *in situ* in a preprogrammed fashion.

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ACKNOWLEDGMENTS AND ADDRESSES

Received May 30, 1975, from *ALZA Research, Palo Alto, CA 94304*

Accepted for publication August 11, 1975.

F. Theeuwes thanks Dr. A. S. Michaels and Dr. R. W. Baker for their stimulating discussions on this subject and Scott Hamilton for the numerical computer evaluation of Eq. 15.

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Bioavailability of 17 Ampicillin Products

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Abstract □ The bioavailability of single lots of 250-mg ampicillin capsules, available from 17 distributors and/or manufacturers, was determined. Each product was evaluated in terms of the serum ampicillin levels achieved at 1, 2, 3, 4, 6, and 8 hr postadministration, the peak serum levels, the time of peak serum level, and the area under the serum level–time curve. There was no statistically significant difference ($p > 0.05$) between any of the 17 products tested.

Keyphrases □ Ampicillin—bioavailability of 17 products compared □ Bioavailability—ampicillin, 17 products compared □ Antibiotics—ampicillin, bioavailability of 17 products compared

It is well documented that while simple quantitative analysis of various drug dosage forms may indicate essentially identical drug content, the quantity of drug absorbed from the dosage form following oral administration may differ significantly from product to product (1–4). Ampicillin recently was categorized as a drug with "moderate risk potential" for bioavailability failures (5). Furthermore, the statement by