Influence of Complex Formation on Drug Transport

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Abstract □ A method of *a priori* prediction of whether complex formation will lead to enhancement or reduction of the transport rate of a drug across biological membranes is presented. It is shown that compounding a drug with substances of lower diffusion coefficients, with which the drug will form a complex, leads to enhancement of the flux of the drug; compounding with substances with similar diffusion coefficients results in a reduction of the transport rate of unassociated drug (flux), provided the rate constants for association–dissociation reactions are of similar magnitude. Detailed methods of computation of fluxes and concentration profiles are included.

Keyphrases □ Complex formation—transport rates, method for predicting enhancement or reduction, equations □ Drug transport—role of complex formation, method for predicting enhancement or reduction, equations □ Diffusion coefficients—used in computing transport rates, influence of complex formation □ Fluxes, drug—method of computation, influence of complex formation on drug transport

It is usually assumed that most drugs pass through biological membranes by passive diffusion processes (1). Studies of the influence of various cations (2) and sugars (3) on passive transfer of some drugs across the everted rat intestine showed the reduced or unaffected transfer rate. On the other hand, the neutral macrocyclic antibiotics appear to enhance significantly the permeability properties of ions across bilayer membranes (4).

The biopharmaceutical implications of complex formation and of potential opportunities for the advantageous modification of GI absorption characteristics of drugs have resulted in a number of experimental investigations (5, 6). Attempts to enhance the rate of absorption by formation of more lipoid-soluble complexes have not, in general, been successful. Therefore, one can find numerous experimental investigations of the interference of either nonmedicinal components of a dosage form or substances normally found in a biological system on the transfer rate of a drug across a specified diffusion barrier. It is of significant theoretical and applied interest to predict *a priori* whether complex formation of a drug with specified substances will lead to enhancement or reduction of the transport rate across a membrane. This aspect was pursued in this investigation. It is shown that, in addition to the required solubility of the components in the diffusion barrier phase, the relative magnitude of diffusion coefficients plays an important role in the enhancement or reduction of fluxes of a specified component as influenced by the complex formation reaction.

To make meaningful progress toward this objective, one must have a clear understanding of the theoretical aspects of the problem. If it is assumed that one is in possession of such knowledge, it is possible in principle to choose judiciously the complexing agents having optimum desirable physicochemical properties to effect desired rates of permeation of a specified drug.

Biological membranes act as an inhomogeneous diffusion barrier for transport of substances from one side to the other. When substances undergoing transport across the membrane can also participate in a chemical reaction, the inhomogeneous character of the medium is able to sustain a reaction rate profile. Experimentally, it is often observed that such reactions influence the magnitude of fluxes of species undergoing transport. Of the various possible chemical reactions occurring in the system, it is assumed in this paper that only an association–dissociation type of reaction takes place in the barrier phase region. The reactant substance with which the permeating species can associate could either be another permeating substance or a substance confined to the membrane region. The analysis presented previously (7), as well as the contents of the following two sections, is mainly applicable when the reactants and products are permeable across the diffusion barrier phase. However, the conventional model for facilitated diffusion (8) across a biological membrane assumes that the diffusion barrier contains an impermeable carrier molecule which combines specifically with the permeating substance and aids its passage across the membrane. This interesting model is analyzed in the *Carrier Transport Model* section. Comparison of the reaction rate profiles obtained as solutions of the nonlinear differential equation with the linearized equation solution of Blumenthal and Katchalsky (9) is also presented in that section.

By assuming that under stationary-state conditions the diffusion coefficients of the species participating in the chemical reaction can be regarded as constants in the diffusion barrier phase, and that one can neglect coupling between fluxes of different species, the problem of computation of profiles of concentrations, reaction rate, and fluxes from knowledge of rate constants, diffusion coefficients, and concentrations at the boundary is analyzed. These considerations complement the analysis presented in a previous paper (7). Illustrative numerical calculations are presented to enable the reader to perform similar calculations for other systems for which relevant experimental information is available.

It is appropriate to emphasize the main conclusions of this paper. Given that one has knowledge of diffusion coefficients of the three species α, β, and γ participating in a chemical reaction of Eq. 1, and given that one has knowledge of concentrations of the reactants at the boundary (or concentrations in bulk homogeneous phases weighted by partition coefficients, the fluxes,

concentration profiles, and reaction rate profile can be computed quantitatively. From such calculations the effect of the ratio of diffusion coefficients and rate constants on the flux of a specified permeating substance is discussed as an illustrative example. These considerations are believed valid for artificial lipoid barriers. Whether these considerations are applicable for a real biological membrane system is open to question and subject to verification dependent upon the validity of the assumptions. If it is assumed that a carrier mechanism prevails in biological membranes for certain permeant molecules, the present analysis is probably a step in the right direction.

THEORETICAL

It is assumed that in the diffusion barrier there occurs a reaction of the type (7):

$$\alpha + \beta \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \gamma \qquad \text{(Eq. 1)}$$

where α, β, and γ are three species present in the diffusion barrier whose fluxes, as influenced by chemical reaction under stationary-state conditions, is our concern; k_1 and k_2 are, respectively, position-independent rate constants for the association and dissociation reactions. The reaction rate at location x in the barrier phase is given by:

$$J_R(x) = k_1 C_\alpha(x) C_\beta(x) - k_2 C_\gamma(x) \qquad \text{(Eq. 2)}$$

$C_\sigma(x)$ denotes the concentration of species σ at location x. For convenience, the relevant mathematical considerations are presented in Appendix 2. The reaction rate profile can be expressed as a Taylor series:

$$J_R(x) = \sum_{i=0} S_i x^i \qquad \text{(Eq. 3}a\text{)}$$

$$S_i = (1/i!)\{d^i J_R(x)/dx^i\}|_{x=0} \qquad \text{(Eq. 3}b\text{)}$$

When one may regard the diffusion coefficients as constants and neglect coupling between fluxes, the first few Taylor expansion coefficients of Eqs. 3*a* and 3*b* can be expressed as:

$$S_0 = k_1 C_\alpha(0) C_\beta(0) - k_2 C_\gamma(0) \qquad \text{(Eq. 4}a\text{)}$$

$$S_1 = \eta^2 \theta + H \qquad \text{(Eq. 4}b\text{)}$$

$$S_2 = (\eta^2 S_0/2) + \mu[\theta^2 - X^2] \qquad \text{(Eq. 4}c\text{)}$$

$$S_3 = (\eta^2 S_1/6) + \mu S_0 \theta \qquad \text{(Eq. 4}d\text{)}$$

$$S_4 = (\eta^2 S_2/12) + (\mu/4) S_0^2 + (\mu/3) S_1 \theta \qquad \text{(Eq. 4}e\text{)}$$

$$H = -(k_2/2D_\gamma h)\{2D_\gamma \Delta C_\gamma + D_\alpha \Delta C_\alpha + D_\beta \Delta C_\beta\} + \mu X[C_\beta(0) D_\beta - C_\alpha(0) D_\alpha] \qquad \text{(Eq. 4}f\text{)}$$

$$X = (q_\alpha - q_\beta)/2 = (D_\alpha \Delta C_\alpha - D_\beta \Delta C_\beta)/h2 \qquad \text{(Eq. 4}g\text{)}$$

$$\mu = (k_1/D_\alpha D_\beta);\ \eta^2 = \mu[C_\alpha(0) D_\alpha + C_\beta(0) D_\beta] + (k_2/D_\gamma) \qquad \text{(Eq. 4}h\text{)}$$

The derivation of Eqs. 4*a*–4*h* is presented in Appendix 2; x is the position variable defined along the axis of transport normal to the plane of the membrane, and h is the thickness of the membrane. As may be seen from Eqs. 4*a*–4*h*, one can compute the first five coefficients of Eq. 3*a* from knowledge of rate constants and concentrations at the boundary and diffusion coefficients in the barrier phase, provided that one has knowledge of yet undefined parameter θ. As shown previously (7), knowledge of the first few Taylor expansion coefficients enables one to compute higher order coefficients. Thus, in essence, computation of reaction rate profile reduces to evaluation of θ; θ is a constant quantity defined by the relation:

$$2\theta = D_\alpha a_1 + D_\beta b_1 \qquad \text{(Eq. 5)}$$

where a_1 and b_1 are, respectively, concentration gradients of species α and β at location $x = 0$. ΔC_σ equals $C_\sigma(h) - C_\sigma(0)$. [The expression for θ as equal to $(k_2 q_\gamma/D_\gamma \eta^2)$ presented in Eq. 55 of *Reference 7* resulted from the negative sign of (q_γ/D_γ) of Eq. 17*c*. This negative sign is inconsistant with Eq. 38 of *Reference 7*.] θ should be and can be evaluated using appropriate boundary conditions and Eq. 26.

EVALUATION OF θ

If the condition that flux of species β, for example, vanishes at location $x = 0$ is utilized, then:

$$\theta = (q_\alpha - q_\beta)/2 \qquad \text{(Eq. 6)}$$

The boundary condition of Eq. 6 is applicable, for example, in the absorption and transport of gaseous oxygen facilitated by hemoglobin in the simple artificial system of Scholander (10), when one side of the diffusion barrier contains gaseous oxygen and the other side of the diffusion barrier contains an aqueous solution of hemoglobin.

If the condition that at location $x = 0$ the fluxes of α and β are equal in magnitude but opposite in direction is used, one obtains:

$$\theta = 0 \quad \text{since } D_\alpha a_1 = D_\beta b_1 \qquad \text{(Eq. 7)}$$

Another useful condition which can be utilized for evaluation of θ, when the reactant molecule β is confined to the membrane phase, was suggested by Blumenthal and Katchalsky (9)—*viz.:*

$$\int_0^h J_R(x)dx = 0 \qquad \text{(Eq. 8)}$$

where the diffusion barrier extends from $x = 0$ to $x = h$. The condition expressed by Eq. 8 is valid when the reaction takes place only in the diffusion barrier, as in Scholander's (10) experiments, and no discernible chemical reaction occurs in the surrounding solution. Evaluation of θ using Eq. 8 is presented later in this paper. Since quantities such as flux, concentration, and reaction rate at an arbitrary location in the membrane phase do not vary with time under conditions of stationary state, the reaction adjusts the energy supply and production or consumption of species to maintain the concentration difference and flux difference between two arbitrary locations in the system invariant with time. This concept leads to the nontrivial condition:

$$\Delta J_R = k_1[C_\alpha(0)\Delta C_\beta + C_\beta(0)\Delta C_\alpha + \Delta C_\alpha \Delta C_\beta] - k_2 \Delta C_\gamma \qquad \text{(Eq. 9)}$$

which may also be utilized to evaluate θ.

CRITERIA FOR ENHANCEMENT OR REDUCTION OF PERMEANT FLUXES

Since one has means to obtain θ using appropriate boundary conditions, one may state with confidence that the reaction rate and concentration profiles in the diffusion barrier can be computed quantitatively in terms of experimentally available quantities. One is now in a position to answer the question about the conditions under which complexation of a specified drug with another substance will lead to enhancement or reduction of the drug transport rate across a biological membrane.

Consider the case when the drug α is compounded in dosage form with a nonmedicinal substance β. The substance β is chosen so that it can form a complex γ by the reaction of Eq. 1. Assume that both α and β are not normally found in biological membranes.

Administration of this dose produces a transport process across the biological diffusion barrier, where both α and β, as well as the complex γ, transport passively. Evidently, both α and β will have fluxes in the same direction. Thus, the ratio of fluxes of α and β at the beginning of inhomogeneity of the diffusion barrier is positive definite and:

$$(D_\alpha a_1)/(D_\beta b_1) > 0 \qquad \text{(Eq. 10)}$$

From Eq. A8*b* of Appendix 2, one has:

$$(\theta + X)/(\theta - X) > 0 \qquad \text{(Eq. 11)}$$

Since a_1 and b_1 are negative, θ is negative definite. Since in general

X could be either positive or negative, the validity of Eq. 11 requires that $|\theta| > |X|$. The flux of the unassociated form of drug α at location $x = 0$ is $-D_\alpha a_1 = -(\theta + X)$. The flux of drug α at location $x = h$ is given by:

$$J_\alpha(h) = -(q_\alpha + m_1) - \sum_{i=0} T_i h^{i+1} \qquad \text{(Eq. 12a)}$$

$$T_i = S_i/(i + 1) \qquad \text{(Eq. 12b)}$$

One will, therefore, observe an enhancement of the rate of transport of (unassociated form of) drug α due to complexation with the substance β across the diffusion barrier due to the chemical reaction if:

$$J_\alpha(h) - J_\alpha(0) = \Delta J_\alpha > 0 \qquad \text{(Eq. 13)}$$

One will observe no effect due to complexation if $\Delta J_\alpha = 0$ and will observe a reduction if ΔJ_α is negative.

Including terms of the order of h^5 and neglecting terms of higher order, one obtains from Eqs. 4*a*–4*h* and 13 that:

$$-\Delta J_\alpha = P\theta^2 + Q\theta + R \qquad \text{(Eq. 14a)}$$

$$P = (\mu h^3/3)\{1 + (\eta^2 h^2/4)\} \qquad \text{(Eq. 14b)}$$

$$Q = (\eta^2 h^2/2)\{1 + (\eta^2 h^2/12)\} + (\mu h^4/60) \times [4Hh + 15S_0] \qquad \text{(Eq. 14c)}$$

$$R = (S_0 h)[1 + (\eta^2 h^2/3!) + (\eta^4 h^4/5!) + (\mu S_0 h^4/20)] + (Hh^2/2)[1 + (\eta^2 h^2/12)] - (\mu h^3/12) \times (q_\alpha - q_\beta)^2\{1 + (\eta^2 h^2/20)\} \qquad \text{(Eq. 14d)}$$

Since one can compute P, Q, and R of these equations from knowledge of diffusion coefficients, rate constants, concentrations at the boundary, and realistic reasonable values of thickness of the diffusion barrier, one can compute ΔJ_α using Eq. 14*a*.

An appreciation of the numerical values of terms involved in Eqs. 14*a*–14*d* is in order at this time. Biological membranes have, in general, a thickness of about 100 Å. For the purpose of illustrative numerical calculations, let us assume that the concentrations at location $x = 0$ of the drug $C_\alpha(0) = 2.1 \times 10^{-4}$ mole cm.$^{-3}$, complexing agent $C_\beta(0) = 1 \times 10^{-4}$ mole cm.$^{-3}$. If the diffusion coefficients in membranes are about 10% of the corresponding values observed in aqueous solutions, it is reasonable to assume that $D_\alpha = 6 \times 10^{-6}$, $D_\beta = 1 \times 10^{-6}$, and $D_\gamma = 0.9 \times 10^{-6}$ (in cm.^{2} sec.$^{-1}$) and compute η^2 as equal to 3.8311×10^6 cm.$^{-2}$, when $k_1 = 12 \times 10^3$ moles^{-1} cm.^{3} sec.$^{-1}$ and $k_2 = 1$ sec.$^{-1}$. The equilibrium constant for the reaction has been assumed to equal $K = k_1/k_2 = 12$ l. mole^{-1}, a value that is of the same order as that observed in many reactions. Thus, the dimensionless parameter ηh equals 1.957×10^{-3}, a quantity much smaller than unity. The parameter P of Eqs. 14*a*–14*b* can be thus computed as 6.6666×10^{-4} cm.^{2} sec. mole^{-1}.

If one assumes $C_\gamma(0) = 1 \times 10^{-4}$, S_0, the reaction rate at location $x = 0$, can be calculated to be 1.52×10^{-4} mole cm.$^{-3}$ sec.$^{-1}$. If one approximates $J_\alpha = -\Delta C_\alpha D_\alpha/h$, one obtains a value of 12×10^{-4} mole cm.$^{-2}$ sec.$^{-1}$, when h equals 1×10^{-6} cm. and $C_\alpha(h) = 1 \times 10^{-5}$. It is, therefore, reasonable to assume a value of -1.0×10^{-3} for $(q_\alpha - q_\beta)$, assuming $q_\beta = -2 \times 10^{-4}$ and $q_\alpha = -12 \times 10^{-4}$. Assuming $q_\beta = q_\gamma$, one computes H as equal to 1.5799×10^3. The quantity $[S_0 h + (Hh^2/2)] = 9.4199 \times 10^{-10}$ and R = about 7.7534×10^{-10}. One can compute $(\mu h^4/60)[4Hh + 15S_0]$ as 2.8666×10^{-13}, a quantity much smaller in magnitude than $(\eta^2 h^2/2)$; thus, Q of Eq. 14*c* $= 1.9155 \times 10^{-6}$. By inserting these values of P, Q, and R in Eq. 14*a*, the roots of the equation when $\Delta J_\alpha = 0$ can be evaluated as $\theta^* = -0.23857$ or $\theta^* = -4.872 \times 10^{-2}$. Both the values of θ^* are negative as anticipated. With the assumed value of $X = -5 \times 10^{-4}$, one evaluates $a_1 = -3.9845 \times 10^4$ and $b_1 = -2.3807 \times 10^5$, when $\theta^* = -0.23857$; $a_1 = -8.2033 \times 10^3$ and $b_1 = -4.822 \times 10^4$ for the other value of θ^*.

For the system under consideration, ΔJ_α does not vanish. Let θ for the system be distinct from θ^* by a quantity $\Delta\theta = \theta - \theta$. Whenever $\Delta\theta$ is positive, ΔJ_α will be positive, if $P\,\Delta\theta + Q$ is less than $2P\theta^*$, and there will be an enhancement in the flux of α across the membrane phase due to complex formation reaction. Whenever $\Delta\theta$ is negative for the system, ΔJ_α will be negative, provided $Q < \{2P\theta^* + P\,\Delta\theta\}$, and there will be a reduction in the flux of α (unassociated form) due to complexing with β.

If the diffusion barrier includes, in addition to the membrane, the inhomogeneous boundary layers such that the thickness of the diffusion barrier may be regarded as equal to 1×10^{-5} cm., one computes for the above assumed values of initial concentrations the values of θ^*, a_1, and b_1 as:

θ^*:	-2.3857×10^{-4}	or	-4.872×10^{-5}
a_1:	-16.48	or	-48.095
b_1:	$+1.28$	or	-188.57

For the cases just considered, one obtains negative values for θ^*. However, the ratio (a_1/b_1) is negative in one case and positive in the other three cases. Since diffusion coefficients are assumed positive definite in this analysis (11), positive values for (a_1/b_1) imply that the fluxes of α and β in the diffusion barrier at location $x = 0$ have the same direction. Since the drug α and the complexing agent β are not normally found in the membrane, one suspects that fluxes of α and β should have the same direction and a_1 should be negative since $C_\alpha(0) > C_\alpha(h)$. The case where (a_1/b_1) is negative is of interest in the analysis of the carrier transport model, especially when β is a substance normally found in the membrane. In the above-mentioned calculations, ηh was a very small fraction of unity. For ηh to be of the order of unity for membranes of thickness 1×10^{-6} cm., the diffusion coefficients in the diffusion barrier need to be of the order of 10^{-12} cm.^{2} sec.$^{-1}$ or less.

The question to which one would like to find an answer is by what criteria one can hope to increase the drug transport across a biological diffusion barrier by compounding the drug with another nonmedicinal substance, β, with which α can participate in an association–dissociation reaction. In terms of dosage design, one has little control over the thickness of the diffusion barrier and the nature of the drug and its diffusion coefficients. However, one can influence the rate of transport of drug α by judiciously choosing the compound with which α can associate, when choice is available. To illustrate this point, assume that α can associate with any of the four species: ω, δ, ϵ, or β. The diffusion coefficients of these species in the membrane are assumed to have values $D_\omega = 1 \times 10^{-5}$, $D_\delta = 2 \times 10^{-6}$, $D_\epsilon = 1 \times 10^{-6}$, and $D_\beta = 1 \times 10^{-7}$, while the diffusion coefficient of α is assumed to be 6×10^{-6} cm.^{2} sec.$^{-1}$. It is assumed that the concentrations of drug α at location $x = 0$ in the diffusion barrier is 2.1×10^{-4} mole cm.$^{-3}$ and that of the complexing substances is 1×10^{-4} mole cm.$^{-3}$. For the purpose of illustrative calculation, it is assumed that the equilibrium constants for all four complexing reactions are the same and equal 12 l./mole. The computed values of η^2, H, P, Q, and R, assuming that the diffusion barrier is of thickness 1×10^{-5} cm., are listed in Table I. If one assumes that the reaction is at equilibrium at location $x = 0$, one can compute the value of θ using the relation:

$$\theta = (k_2/2)\,[\{D_\alpha(q_\alpha + q_\gamma)/Z_1\} + \{D_\beta(q_\beta + q_\gamma)/Z_2\}] \qquad \text{(Eq. 15a)}$$

$$Z_1 = k_1 C_\beta(0) D_\gamma + k_2 D_\alpha \qquad \text{(Eq. 15b)}$$

$$Z_2 = k_1 C_\alpha(0) D_\gamma + k_2 D_\beta \qquad \text{(Eq. 15c)}$$

The derivation of Eqs. 15*a*–15*c* is presented in Eq. 20. The computed values of θ and ΔJ_α from Eq. 14*a* are listed in Table I for the four cases. Compounding α with ω leads to reduction in the flux of the drug across the diffusion barrier by the amount 7.585×10^{-8} mole cm.$^{-2}$ sec.$^{-1}$, while complexing α with β, ϵ, and δ leads to enhancement of the transport rate compared to the flux of α across the same diffusion barrier for the same concentration gradient in the absence of the association–dissociation reaction.

Thus, to enhance the transport rate of a drug across the biological diffusion barrier, one has to choose the complexing substance β, especially when the choice is available, such that (D_β/D_α) is much less than unity. The experimental studies of some investigators (5, 6) were motivated by the observations that drug complexes having a lower lipoid–aqueous phase partition coefficient than the drug itself are more slowly absorbed across biologic membranes than the free drug. They suspected that formation of drug complexes which are more lipoid soluble than the free drug may lead to an enhancement of transport rate. This conclusion, however, was not substantiated by experimental results. It is evident from the foregoing analysis that the solubility of the drug and the complexing agent is a necessary but not sufficient condition for enhancement of flux of the drug

Table I—Computed Values of ΔJ_α and Other Parameters for Transport of α across the Diffusional Barrier, Assuming $S_0 = 0$

Parameter	β	ϵ	δ	ω
$\Delta J_\alpha \times 10^9$	+37.456	+2.1492	+2.12288	−75.8548
Diffusion coefficient	1×10^{-7}	1×10^{-6}	2×10^{-6}	1×10^{-5}
$\eta^2 h^2 \times 10^5$	354	38.3111	21.581	5.631
$-\theta \times 10^4$	0.59584	0.6544	0.7106	0.676705
$\mu \times 10^{-15}$	20.0	2.0	1.0	0.2
H	1358.75	153.55	87.896	29.86
$-X \times 10^5$	5.95	5.0	4.0	11.0
$-\theta_1^* \times 10^4$	2.3751	2.4003	2.7408	3.9638
$-\theta_2^* \times 10^4$	0.2801	0.47286	0.4226	0.2598
P	6.6666	0.6666	0.3333	6.66×10^{-2}
$Q \times 10^4$	17.7	1.9155	1.07905	0.028155
$R \times 10^9$	44.3355	6.0109	0.38615	0.6865

across the barrier. Complex formation with reactants of similar diffusion coefficients should, in general, lead to a reduction in the rate of transport of the drug, in agreement with our analysis and experimental observations.

The critical values of θ^*, which are the roots of the quadratic equation when one will observe no change in flux of α across the diffusion barrier due to an association–dissociation reaction occurring in the membrane, are also listed in Table I. For the assumed values of difference in concentrations and diffusion coefficients and membrane thickness, the flux of α in the absence of chemical reactions would be about 12×10^{-4} mole cm.$^{-2}$ sec.$^{-1}$. Thus, one may conclude, from the values listed in Table I, that the change in flux due to complex reaction is not significant. This low effect is due to the relatively high assumed values of the diffusion coefficients. If the diffusion barrier is of thickness 1×10^{-5} cm., $D_\alpha = 6 \times 10^{-9}$ cm.^{2} sec.$^{-1}$, and the difference in concentration of α under steady state equals -2.0×10^{-4} mole cm.$^{-3}$, then the observed flux of α, J_α, equals $-q_\alpha = 12 \times 10^{-8}$ mole cm.$^{-2}$ sec.$^{-1}$. Compounding α with a substance β^*, whose diffusion coefficient is 1×10^{-9}, with $C_{\beta^*}(0) = 1 \times 10^{-4}$ with rate constants $k_1 = 12 \times 10^3$ cm.^{3} mole^{-1} sec.$^{-1}$ and $k_2 = 1$ sec.$^{-1}$, will result in enhancement of flux of about 2.5% (Table II). Compounding α, on the other hand, with a substance β^{**}, with a diffusion coefficient 1×10^{-8} cm.^{2} sec.$^{-1}$, for the same rate constants and initial concentrations will reduce the flux of α by about 7.862%.

COMMENTS ABOUT q_σ

Knowledge of the parameters q_σ's is needed to compute the Taylor expansion coefficients of the reaction rate profile. When one assumes that coupling between fluxes can be neglected and that local fluxes are proportional to local concentration gradients given by Fick's law, use of Eqs. 4 and 6 of *Reference 7* and Eqs. 4*a*–4*h* of this paper enables one to express concentration profiles as:

$$D_\sigma C_\sigma(x) = (K_\sigma \pm m_0) + (q_\sigma \pm m_1)x \pm \sum_{i=0} U_i x^{i+2} \quad \text{(Eq. 16a)}$$

$$U_i = T_i/(i+2) \qquad \sigma = \alpha, \beta, \text{ or } \gamma \quad \text{(Eq. 16b)}$$

In Eq. 16*a*, the plus sign is applicable when σ refers to α or β. The minus sign is valid when σ refers to γ.

Equations similar to 16*a* and 16*b* are derivable also when coupling between fluxes of different species is included and local fluxes are expressed by a generalized form of Fick's law:

$$J_\sigma(x) = -\sum_\eta D_{\sigma\eta} dC_\eta(x)/dx \quad \text{(Eq. 17)}$$

provided that the elements of the diffusion matrix, $D_{\sigma\eta}$, are constants independent of the position variable x.

From Eqs. 16*a* and 16*b*, one obtains:

$$q_\alpha - q_\beta = (D_\alpha \Delta C_\alpha - D_\beta \Delta C_\beta)/h \quad \text{(Eq. 18a)}$$

$$q_\alpha + q_\gamma = (D_\alpha \Delta C_\alpha + D_\gamma \Delta C_\gamma)/h \quad \text{(Eq. 18b)}$$

$$\Delta C_\sigma = C_\sigma(h) - C_\sigma(0) \quad \text{(Eq. 18c)}$$

When experiments are carried out with equal concentrations of, for example, species β on either side of the barrier, the reaction of Eq. 1 will be at equilibrium in the membrane region. Under these conditions, one obtains the expressions for the fluxes as:

$$J_\beta = 0 \quad \text{(Eq. 19a)}$$

$$J_\alpha = -(q_\alpha + q_\gamma)k_2 D_\alpha/[k_1 C_\beta D_\gamma + k_2 D_\alpha] \quad \text{(Eq. 19b)}$$

$$J_\gamma = -(q_\alpha + q_\gamma)k_1 C_\beta D_\gamma/[k_1 C_\beta D_\gamma + k_2 D_\alpha] \quad \text{(Eq. 19c)}$$

$$\frac{\text{[total flux of } \alpha\text{(associated + free)]}}{\text{(flux of unassociated } \alpha)} = 1 + (K D_\gamma C_\beta / D_\alpha) \quad \text{(Eq. 19d)}$$

Since all terms on the right-hand side of Eq. 19*d* are positive definite, Eq. 19*d* implies that the total flux of α will enhance with an increase in C_β in the membrane phase due to complex formation, if the reaction is at equilibrium and fluxes are given by Fick's law. Equations 16*a* and 16*b* are obtained from Eq. A13 of Appendix 2, Eqs. 19*a*–19*d*, and similar equations for J_β when $C_\alpha' = 0$, using the arguments that when $S_0 = 0$, one has:

$$\theta = \theta_1(a_1 = 0) + \Delta\theta_1(b = 0) = \theta_2(b_1 = 0) + \Delta\theta_2(a_1 = 0) \quad \text{(Eq. 20a)}$$

$$\Delta\theta_1 = -\Delta\theta_2 = -X \quad \text{(Eq. 20b)}$$

CARRIER TRANSPORT MODEL

Unlike the case of drug transport, in the carrier-facilitated transport model it is assumed that the permeant molecule α reacts with species β present in the membrane and that no discernible chemical reaction occurs in the surrounding solutions. Both the carrier β and the complex γ are thus assumed to be confined to the membrane region (9). A good example of this system is the physical system of Scholander (10). Since β is found in the biological membranes, one cannot *a priori* state that θ is negative definite. If the concentration of permeant C_α at location $x = 0$ is greater than its concentration at location $x = h$, it is reasonable to assume that the flux of α has a direction from left to right. Stein (12) summarized the information on the properties of carriers revealed by kinetic analysis—*viz.*, that carrier molecules β present in limited amounts in cell membranes combine with permeant molecules α, that the carrier–permeant complex can cross the membranes from one side to the other, and that the rate of transit of free carrier and carrier–permeant complex γ can differ. *A priori*, one may state that assumed circulation suggests that the flux of carrier β and permeant α will be opposite in

Table II—Computed Values of ΔJ_α and Other Parameters for Transport of α across the Diffusional Barrier, Assuming $S_0 = 0$, $K = 12$ l. mole^{-1}, and $D_\alpha = 6 \times 10^{-9}$

Parameter	β^*	β^{**}
$\Delta J_\alpha \times 10^9$	+2.9906	−9.4333
Diffusion coefficient	1×10^{-9}	1×10^{-8}
$P \times 10^{-5}$	7.3052	0.666
Q	0.19836	2.8155×10^{-2}
$R \times 10^9$	6.233	11.13
$-\theta \times 10^8$	5.95707	7.28185
H	157.99	222.74
$-X \times 10^8$	5.0	1.0
$\eta^2 h^2$	0.38311	5.6311×10^{-2}

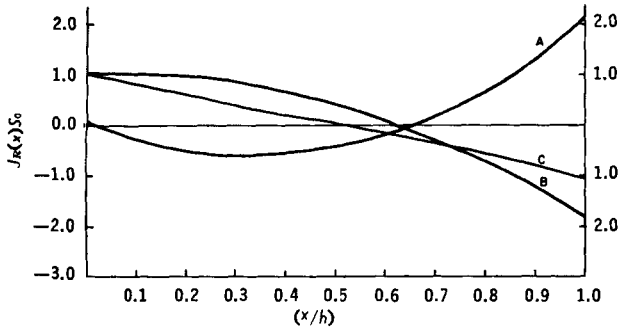

Figure 1—*Reaction rate profiles in barrier phase for the illustrative example. Curves A and B are obtained from Eqs. 3 and 4 and the values listed in the second and third rows, respectively, of Table III. Curve C is the result of solution of a linearized differential equation (Eq. 7 of* Reference 7*) of Blumenthal and Katchalsky (9) with* $\eta = \lambda^{-1}$.

direction in the membrane region. The sign and magnitude of θ are determined by the magnitudes of fluxes of the permeant and carrier at a location close to $x = 0$. However, one may state that the ratio (a_1/b_1) will be negative.

In addition to a detailed analysis of the carrier transport model, the method of calculation of the reaction rate profile as well as concentration and flux profiles is presented in this section. The inputs for the calculations are assumed values of rate constants, diffusion coefficients, $(q_\alpha - q_\beta)$, and concentrations of the three species at location $x = 0$. The condition expressed by Eq. 8 is utilized to evaluate θ, a_1, and b_1. The use of the boundary condition equation, Eq. 8, in conjunction with the expressions of Eqs. 4*a*–4*h*, neglecting terms of the order of x^5 in the expression for the reaction rate profile, yields a quadratic expression for θ with constant coefficients:

$$\theta^2 P_n + \theta Q_n + R_n = 0 \qquad n = 2,3,4 \qquad \text{(Eq. 21)}$$

The subscript n of P, Q, and R of Eq. 21 denotes that terms of the order x^{n+1} have been neglected in the expression for the reaction rate profile in computing the integral of Eq. 8. P_n, Q_n, and R_n can be expressed in terms of experimentally available quantities as

$$P_4 = (\mu h^3/3)\{1 + (\eta^2 h^2/4)\} \qquad \text{(Eq. 22a)}$$

$$Q_4 = (\eta^2 h^2/2)\{1 + (\eta^2 h^2/12)\} + (\mu h^4/60)[4Hh + 15S_0] \qquad \text{(Eq. 22b)}$$

$$R_4 = S_0 h\{1 + (\eta^2 h^2/3!) + (\eta^4 h^4/5!)\} + (\mu S_0 h^5/20) + (Hh^2/2)\{1 + (\eta^2 h^2/12)\} - (\mu h^3/12) \times (q\alpha - q_\beta)^2\{1 + (\eta^2 h^2/20)\} \qquad \text{(Eq. 22c)}$$

Since one has knowledge of (ηh), S_0, H, and $(q_\alpha - q_\beta)$ from experimental information, one can compute easily P_4, Q_4, and R_4 and solve Eq. 21 for θ. Unless (ηh) is a significant fraction of unity, the values of P_n, Q_n, R_n, and θ_n with $n = 2,3$ will not be significantly different from P_4, Q_4, R_4, and θ_4. For example, θ_2 may be computed as:

$$\theta_2 = -(3\eta^2/4\mu h) \pm (3\eta^2/4\mu h)[1 - (4\mu T/9\eta^4)]^{1/2} \qquad \text{(Eq. 23a)}$$

$$T = 2S_0(6 + \eta^2 h^2) + 6Hh - \mu h^2 (q_\alpha - q_\beta)^2 \qquad \text{(Eq. 23b)}$$

Table III—Computed Values of S_i's and a_i's, Using the Values of θ, Utilizing Eqs. 8 and 4*a*–4*h*, Assuming $S_0 = 1.52 \times 10^{-4}$ mole cm.$^{-3}$ sec.$^{-1}$ and Diffusion Coefficients to be of the Order of 10^{-9} cm.^{2} sec.$^{-1}$

	$\theta = -2.8 \times 10^{-7}$	$\theta = 1.3 \times 10^{-10}$
θ	-2.8147×10^{-7}	1.3×10^{-10}
S_1	-1.0732×10^{3}	5.49804
S_2	1.53743×10^{8}	-4.70885×10^{6}
S_3	-7.70843×10^{11}	3.54992×10^{9}
a_1	−5.5245	−0.81166
a_2	1.266×10^{4}	1.266×10^{4}
a_3	-2.9136×10^{10}	$+15.2723 \times 10^{7}$
a_4	2.13525×10^{15}	-6.540×10^{13}
b_1	−23.147	5.135

One will obtain two values for θ, which may have the same signs or opposite signs, depending on the assumed order of magnitude of $(q_\alpha - q_\beta)$. For example, when $(q_\alpha - q_\beta)$ is assumed to be of the order of -14×10^{-8} and $\eta h = 0.61896$, computed values of θ are both negative. When $(q_\alpha - q_\beta)$ is assumed to be of the order of -14×10^{-7}, the computed values of θ are -6.9775×10^{-7} or 3.8229×10^{-7}. The sign of (a_1/b_1) can be determined from the values of θ, using the relations:

$$(a_1/b_1) = (D_\beta/D_\alpha)[(\theta + X)/(\theta - X)] \qquad \text{(Eq. 24a)}$$

$$X = (q_\alpha - q_\beta)/2 \qquad \text{(Eq. 24b)}$$

Substitution of the obtained values of θ in Eqs. 4*a*–4*h* enables one to compute the Taylor expansion coefficients of the reaction rate profile. If one has reasonable grounds to suspect that (a_1/b_1) is negative, then one should prefer the negative value of θ. It is now a simple matter to compute the Taylor expansion coefficients of concentration profiles of permeant species, using the relations:

$$+D_\alpha(k + 2)(k + 1)a_{k+2} = S_k \qquad k = 0,1,2\ldots \qquad \text{(Eq. 25)}$$

By assuming values of $(q_\alpha - q_\beta) = -10 \times 10^{-8}$ mole cm.$^{-2}$ sec.$^{-1}$, $D_\alpha = 6 \times 10^{-9}$, $D_\beta = 1 \times 10^{-9}$, and $D_\gamma = 0.9 \times 10^{-9}$ cm.^{2} sec.$^{-1}$ and concentrations $C_\alpha(0) = 2.1 \times 10^{-4}$ and $C_\beta(0) = C_\gamma(0) = 1 \times 10^{-4}$ mole cm.$^{-3}$, $\eta^2 h^2$ is computed as equal to 0.38311, when stability constant K is assumed to equal 12 l./mole. By using these values and $S_0 = 1.52 \times 10^{-4}$ mole cm.$^{-3}$ sec.$^{-1}$ in Eqs. 22*a*–22*c*, P_4, Q_4, and R_4 are computed as 7.2828×10^5, 0.205086, and 1.8756×10^{-9}, respectively. Equation 21 is now solved to yield θ as equal to either -2.8147×10^{-7} or 1.3×10^{-10}. In Table III are listed the computed values of S_i's of the reaction rate profile and a_i's of the concentration profile of permeant species α. In Fig. 1 are plotted the two resultant reaction rate profiles as a function of the fraction of membrane thickness (curves A and B). In the same figure is plotted the profile obtained by using Blumenthal and Katchalsky's (9) Eq. 19. Curve C of Fig. 1 represents the reaction rate profile predicted by solution of linearized differential Eq. 7 of *Reference 7* with $\lambda^{-1} = \eta$. Curve C is almost linear, with the reaction being at equilibrium at midplane of the membrane. Curve B is the result predicted when one does not neglect the nonlinear terms, with $\theta = 1.3 \times 10^{-10}$. Inclusion of nonlinear terms results in an unsymmetrical reaction rate profile. The condition expressed by Eqs. 16*a* and 16*b* does not require a symmetrical reaction rate profile. Curve A represents the reaction rate profile predicted using the value $\theta = -2.8147 \times 10^{-7}$, which is markedly different from curves B and C, and exhibits a minimum at about $(x/h) = 0.3$ with a value $J_R(x/h = 0.3)/S_0 = -11.08$. (In Fig. 1, the y-coordinates for curve A are different from that of curves B and C; $J_R(0)/S_0 = 1$ and $J_R(h)/S_0 = 42.79$.) This illustrative calculation of reaction rate profiles for carrier transport substantiates the conclusion (13) that inclusion of neglected nonlinear terms in the differential equation will have a profound effect on the reaction rate profile.

DISCUSSION

One may conclude from the results presented in this paper that calculation of reaction rate profiles and flux and concentration profiles of permeant molecules in the diffusion barrier is a tractable problem. Provided that the molecules undergoing transport can participate in a chemical reaction of the type presented in Eq. 1, provided that local fluxes are described by a Fick's law with constant diffusion coefficients, and provided that coupling between fluxes of different species can be neglected, one can quantitatively compute the influence of complexing a drug α with another substance β (either present or absent in the biological membrane) on the rate of transport across a biological diffusion barrier. (Certain questions of a mathematical nature, which are not of general interest, are discussed in Appendix 1.)

It is shown that the rate of transport of a drug α will decrease by complexing it with a substance β not normally found in biological systems, when (D_α/D_β) in the membrane phase is of the order of unity. *A priori* calculation of the rate of drug transport is possible by the methods presented in this paper, provided one has even approximate knowledge of (D_α/D_β), rate constants, and dosage composition. To enhance the transport rate of drug α by complexation, one has to choose β, when choice is available, such that (D_α/D_β) is

much greater than unity. An additional prerequisite is that both α and β are lipid soluble.

Olander (14) considered the problem of mass transfer and chemical reactions of various types, including the reaction of the type of Eq. 1, when these reactions are at equilibrium. Thus the results of this paper are more general in nature. From Eqs. 16*a* and 16*b*, one may derive Eqs. 5–7 and 30–38 of Olander's paper. One may identify Olander's notations $a_1 = (q_\alpha + q_\gamma)$, $a_2 = K_\alpha + K_\gamma$, $a_3 = (q_\beta + q_\gamma)$, $a_4 = K_\beta + K_\gamma$, and $C_t = (K_\alpha D_\gamma + K_\gamma D_\alpha)/(D_\alpha D_\gamma)$. The conclusions of Olander that concentration profiles are necessarily linear when the reaction is at equilibrium everywhere is in agreement with our conclusions. However, the terms within the parentheses of Eqs. 41, 42, and 49 of *Reference 14* cannot be distinct from unity in agreement with his Eq. 40, since the condition that $J_R(x) = 0$ for all x demands $J_R(0) = k_1a_0b_0 - k_2c_0 = 0$, $J_R' = 0$, and $k_1a_1b_1 = 0$ (a_1, b_1, and c_1 are the concentration gradients of the species α, β, and γ, respectively). Thus, either a_1 or b_1 must necessarily vanish in the barrier, and we have chosen $C_\beta(0) = C_\beta(h)$.

The roadmap for calculation of enhancement or reduction of flux of α may be summarized as follows. For artificial lipoid barriers, the difference in concentrations of α and β on either side of the membrane is known. For biological membranes, one may assume that these concentrations on one side are essentially zero. Assume one has approximate knowledge of diffusion coefficients and rate constants. Compute η^2, μ, H, and X, using Eqs. 4*f*–4*h*. If the reaction can be considered to be at equilibrium at $x = 0$, $S_0 = 0$, and θ can be computed using Eqs. 15*a*–15*c*. P, Q, and R can be computed using Eqs. 14*b*–14*d*; insertion of the above value of θ in Eq. 14*a* yields ΔJ_α. Since ΔJ_R can be computed using Eq. 9, θ can be computed when the reaction is not at equilibrium at the boundaries as the solution of the quadratic equations:

$$\theta^2 A + \theta B + C = 0 \qquad \text{(Eq. 26}a\text{)}$$

$$A = (\mu h^2)\{1 + (5/12)\eta^2 h^2\} \qquad \text{(Eq. 26}b\text{)}$$

$$B = \eta^2 h\{1 + (\eta^2 h^2/6)\} + (\mu h^3/3)(3S_0 + Hh) \qquad \text{(Eq. 26}c\text{)}$$

$$C = Hh\{1 + (\eta^2 h^2/6)\} - (\mu h^2 X^2)\{1 + (\eta^2 h^2/12)\} + (S_0/4)[\eta^2 h^2\{1 + (\eta^2 h^2/6)\} + \mu h^4 S_0] - \Delta J_R \qquad \text{(Eq. 26}d\text{)}$$

Insertion of this value in Eqs. 4*a*–4*h* yields the Taylor expansion coefficients of reaction rate profile, and in Eq. 14*a* it yields ΔJ_α. The Taylor expansion coefficients of concentration profiles are computed using Eq. 25 and computed values of S_k. Flux profiles can be computed using Eqs. 16*a* and 16*b* and Fick's law.

APPENDIX 1

The basic approach of expansion of reaction rate profile in a Taylor series (Eq. 13*a*) raises the question whether the series is convergent or not. Since concentrations are positive definite and it is assumed that $C_\alpha(0) > C_\alpha(h)$, the series expansion:

$$C_\alpha(x) = \sum_{k=0}^{\infty} a_k x^k \qquad \text{(Eq. A1)}$$

is evidently convergent for positive values of x. From Eq. 6 of *Reference 7*, one has:

$$J_R(x) = \sum_{i=0}^{\infty} S_i x^i \qquad \text{(Eq. A2}a\text{)}$$

$$= \sum_{k=2}^{\infty} D_\alpha k(k-1) a_k x^{k-2} \qquad \text{(Eq. A2}b\text{)}$$

Since the series of Eq. A2*b* is convergent, it follows that the series of Eq. 3*a* is convergent.

The second point is that one obtains two values for θ by retention of terms up to the order of x^4 in Eqs. 26*a*–26*d* and is thus faced with the choice between two reaction rate profiles. In addition, if one retained higher order terms, the resultant nth-order polynomial would have given n values for θ and thus n reaction rate profiles. What criteria should be used to determine the correct reaction rate profile? Under stationary state, θ has a unique value and sign. For reasonable values of diffusion coefficients, concentrations, and thickness of diffusion barrier, the value of (ηh) is a very small fraction of unity, which assures rapid convergence of the series of Eq. A2*a*. The value of θ is given approximately by the expression:

$$\theta_1 = -(2S_0 + Hh)/(\eta^2 h^2) \qquad \text{(Eq. A3)}$$

obtained by inserting the expression $J_R(x) = S_0 + S_1 x$ in Eqs. 16*a* and 16*b*. One obtains, by successive inclusions of additional terms, that $\theta_1 = -3.237 \times 10^{-7}$, $\theta_2 = -2.8629 \times 10^{-7}$, $\theta_3 = -2.966 \times 10^{-7}$, and $\theta_4 = -2.7054 \times 10^{-7}$ for the illustrative example considered in the paper as one of the roots. The sign and approximate magnitude of θ are given uniquely by the sign and relative magnitudes of S_0 and H used in Eq. A3. For the assumed value of $(q_\alpha - q_\beta) = -10 \times 10^{-7}$, the value of θ_1 yields $(D_\alpha a_1/D_\beta b_1) = -1.8291$, whose negative sign assures for the carrier model that the flux of carrier in the membrane phase has a direction opposite to that of the permeant flux.

APPENDIX 2

The derivation of Eqs. 4*a*–4*h* is as follows. Since the fluxes are related to the reaction rate at every location under conditions of stationary states by the relations:

$$J_\alpha' = J_\beta' = -J_R(x) = -J_\gamma' \qquad \text{(Eq. A4)}$$

and fluxes are assumed given by $J_\sigma = -D_\sigma C_\sigma'$, $(\sigma = \alpha, \beta, \gamma)$, one has:

$$D_\sigma C_\sigma'(x) = \pm I(x) + q_\sigma \qquad \text{(Eq. A5}a\text{)}$$

$$I' = J_R(x) \qquad \text{(Eq. A5}b\text{)}$$

In Eqs. 16*a*, 16*b*, and A5, the plus sign is applicable when $\sigma = \alpha, \beta$. The negative sign is applicable when $\sigma = \gamma$. Fluxes of species at location x are constrained by the relations:

$$J_\alpha(x) - J_\beta(x) = (q_\beta - q_\alpha), \qquad J\alpha(x) + J_\gamma(x) = -(q_\alpha + q_\gamma) \qquad \text{(Eq. A6)}$$

In addition, one has:

$$\lim_{x \to 0} I(x) = m_1 = D_\alpha a_1 - q_\alpha = D_\beta b_1 - q_\beta = q_\gamma - D_\gamma c_1 \qquad \text{(Eq. A7)}$$

Defining the parameter θ by Eq. 5, one has:

$$m_1 = -(q_\alpha + q_\beta)/2 + \theta \qquad \text{(Eq. A8}a\text{)}$$

$$D_\alpha a_1 = (\theta + X); \quad D_\beta b_1 = (\theta - X) \qquad \text{(Eq. A8}b\text{)}$$

Since the kth Taylor expansion coefficient of the reaction rate profile is given by:

$$S_k = k_1 \left\{ C_\alpha(0) b_k + C_\beta(0) a_k + \sum_{\substack{i,j=1 \\ i+j=k}}^{k-1} a_i b_j \right\} - k_2 c_k \qquad \text{(Eq. A9)}$$

one has:

$$k_1 a_1 b_1 = \mu(\theta^2 - X^2) = S_2 - (\eta^2 S_0/2) \qquad \text{(Eq. A10)}$$

$$S_0 = J_R(0) = k_1 K_\alpha K_\beta - k_2 K_\gamma \qquad \text{(Eq. A11}a\text{)}$$

$$= k_1 C_\alpha(0) C_\beta(0) - k_2 C_\gamma(0) \qquad \text{(Eq. A11}b\text{)}$$

The equivalence of Eqs. A11*a* and A11*b* follows from Eqs. 41*a*, 42, and 43 of *Reference 7*. Equations 4*a*–4*h* follow from Eqs. 41*a*–41*e* of *Reference 7* and Eqs. A9 and A10.

The solution of the nonlinear differential Eq. 18 of *Reference 7* reduces for the case when reaction is at equilibrium as:

$$G(x) = m_0 + m_1 x \qquad \text{(Eq. A12)}$$

When $b_1 = 0$, $m_1 =$ can be evaluated in this case as equal to:

$$m_1 = [q_\gamma k_2 D_\alpha - q_\alpha k_1 C_\beta(0) D_\gamma]/[k_1 C_\beta(0) D_\gamma + k_2 D_\alpha] \qquad \text{(Eq. A13)}$$

GLOSSARY OF SYMBOLS

D_σ = diffusion constant of species σ in membrane phase
C_σ = concentration of species σ
ΔC_σ = difference in concentration across the barrier of species σ
ΔJ_R = difference in reaction rate at barrier boundaries
η = reciprocal of relaxation length characteristic of system
k_1 = rate constant for association reaction
k_2 = rate constant for dissociation reaction
K = equilibrium constant of the reaction
J_σ = matter flux of species σ expressed in moles cm.$^{-2}$ sec.$^{-1}$

P, Q, R, A, B, and C are constants computed and utilized for calculation of θ.

a_1, b_1, and c_1 are concentration gradients at $x = 0$, respectively, of species α, β, and γ.

All other parameters are combinations of these quantities, whose algebraic relations are defined by equations in the paper.

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Blood Levels of Sulfamethizole in Dogs following Administration of Timed-Release Tablets Employing Lipase–Lipid–Drug Systems

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Abstract □ Blood levels of sulfamethizole in dogs following the administration of timed-release tablets are reported. Tablet formulations containing 5% glyceryl monostearate were employed for *in vivo* studies because the *in vitro* release from this formulation extended more than 12 hr. The formulations employed a pancreatic lipase-glyceryl trilaurate and glyceryl tristearate system, with enzyme-substrate combinations serving as a release-controlling vehicle to produce a timed-release effect. The main portion of the drug was released through the lipolytic digestion of the substrate by the lipase in addition to some release due to leaching and surface dissolution. A timed-release effect and uniform blood levels were observed over 12 hr. from tablets made from lipase–lipid–drug granules. Blood levels from tablets containing lipase were significantly higher and more consistent than blood levels obtained from tablets without lipase. The variations in blood levels observed in dogs receiving tablets with lipase were much less than variations observed in dogs receiving tablets without lipase.

Keyphrases □ Timed-release lipase–lipid–sulfamethizole tablets—effect of lipase, blood levels, dogs □ Lipase effect—blood levels of dogs following administration of timed-release lipase–lipid–sulfamethizole tablets □ Drug-release rates—effect of lipase on timed-release lipase–lipid–sulfamethizole tablets, blood levels, dogs

Enzymes play an important role in the breakdown and digestion of nutrient materials in the GI tract. This concept was utilized to control the drug release from a substrate system containing sulfamethizole incorporated in a lipase–lipid matrix. Lipase causes a controlled digestion of the substrate through the hydrolysis of the ester substrate controlling the release of the drug to produce a timed-release effect.

The concentration of lipase in the intestinal tract varies considerably with time (1) and from person to person. The range of lipase activity of 169 persons with normal pancreatic functions, in terms of the amount of acid liberated by the action of lipase on olive oil, was 110–1360 μeq. acid/min./ml. of duodenal fluid (2). The incorporation of lipase in the system, in addition to its release-controlling mechanism, would help minimize the wide range of variations in the concentration of lipase in the intestinal tract.

The purpose of this investigation was to study the blood levels of sulfamethizole following the oral administration of timed-release tablets during *in vivo* studies in dogs after *in vitro* dissolution patterns were established. The results of *in vitro* dissolution studies conducted on timed-release tablets employing lipase–lipid–sulfamethizole systems were reported previously (3).

EXPERIMENTAL

Composition of Spray-Congealed Granules—The manufacture of spray-congealed granules of lipase-lipid-sulfamethizole systems and the composition of initial-release granules were described pre-