Significance of Coupling Terms in Passive Transport of Drugs Affected by Complex Formation Reactions

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Abstract □ Fluxes of drugs across membranes are affected by the presence of a reactant in the membrane phase with which the drug can associate to form a complex. When the reaction is at equilibrium, the use of the simple form of Fick's law leads to prediction of enhancement of total flux. It is shown that inclusion of coupling terms by a generalized form of Fick's law leads to an adequate explanation of the possibility of the total flux increasing, decreasing, or remaining unaffected by the complex formation reaction.

Keyphrases □ Passive transport—significance of coupling terms, complex formation reactions, Fick's law, equations □ Complex formation reactions—significance of coupling terms in passive transport, Fick's law, equations □ Flux—significance of coupling terms for drugs affected by complex formation reactions, simplified Fick's law, equations

The subject of diffusion is one of great practical and theoretical importance in biological sciences (1). Diffusion is one of the chief means by which (in accordance with the second law of thermodynamics) materials are transported from one side of the membrane to the other. Fick's law assumes that the rate of diffusion across a plane normal to the direction of transport is proportional to the concentration gradient, the proportionality constant being defined as the diffusion coefficient. According to Fick's law, one writes the flux of species σ, J_σ, as equal to (one-dimensional transport):

$$J_\sigma = -D_\sigma(dC_\sigma/dx) \qquad \text{(Eq. 1)}$$

where the flux is given in moles per unit area per unit time, concentrations are expressed in moles per unit volume, x is the position variable, and (dC_σ/dx) is the concentration gradient denoted in the following by C_σ'. The negative sign of Eq. 1 signifies that the materials transport in a direction of decreasing concentrations. Equation 1 has been very widely used in many simple considerations of the transport of molecules across membranes with the well-known assumption that the diffusion coefficients are constants (2). In principle, the diffusion coefficients are not constants since the frictional resistance that a molecule suffers is determined by interactions of all molecules present in the system. In addition, principles of irreversible thermodynamics (3) recognize existence of coupling between fluxes of different species, which may be included to modify Eq. 1 as (4):

$$J_\sigma = -\sum_\eta D_{\sigma\eta}C_\eta' \qquad \text{(Eq. 2)}$$

where the flux of species σ is made up of contributions from concentration gradients of all species η present in the system, the proportionality constants being $D_{\sigma\eta}$. The summation sign in Eq. 2 runs over all species with nonvanishing concentration gradients present in the system. In principle, the elements of the diffusion coefficient matrix are dependent on concentration profiles and, for lack of better knowledge and to avoid messy mathematical equations, one adopts the simplifying assumption that $D_{\sigma\eta}$'s can be regarded as constants independent of x.

While Eq. 1 is widely used in biological fields, only recently have the contributions of irreversible thermodynamics and their importance begun to be appreciated. Equation 2 is less familiar than Eq. 1 since all of us prefer simple expressions and are skeptical of the fruitfulness of undertaking the construction of rational theoretical foundations, especially when the utility of refined attempts are not obvious.

The objective of this paper is to illustrate the importance of Eq. 2 in drug transport problems as influenced by complex formation and off-diagonal elements. Numerous examples of experimental observations are available in which the presence of a complexing agent in the membrane phase sometimes leads to the enhancement or to the reduction or to no apparent change in the total flux of a substance (both in unassociated and in associated complex forms) across a diffusion barrier.

In a separate publication (5), the effect of diffusion coefficients and rate constants on the flux of specified species was presented. The analysis was confined to the unassociated flux of a reactant—not to the total flux. In the next section, it is shown that use of Eq. 1 leads to results which agree with possibly limited sets of observations, while the use of Eq. 2 leads to results that are not predicted by Eq. 1. Specifically, use of Eq. 1 along with the assumption that the reaction is at equilibrium in the diffusion barrier predicts the enhancement of total flux by the complex formation reaction in the presence of a complexing agent. In addition, Eq. 1 predicts that the amount of enhancement is proportional to the concentration of the complexing agent present in the membrane phase. Use of Eq. 2 along with the assumption that the reaction is at equilibrium predicts a more reasonable result: that the total flux can increase or decrease or remain unaffected by the complex formation reaction. In addition, Eq. 2 puts an upper limit on enhancement by an increase in the concentration of the complexing agent in the membrane phase.

EQUILIBRIUM CONSIDERATIONS

Consider the simple case of transport of a substance α across a diffusion barrier in the presence of a substance β of concentration C_β. The substance β is so chosen that it associates with α to form a complex γ as indicated by the reaction:

$$\alpha + \beta \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \gamma \qquad \text{(Eq. 3)}$$

where k_1 and k_2 are the position-independent rate constants. If the concentration of the reactant β is maintained equal on both sides

of the barrier (membrane), the usual assumption that the reaction is at equilibrium at all locations is valid under stationary-state conditions (6). In addition, the concentration profiles of α, β, and γ are linear, given by the relations:

$$C_\alpha(x) = C_\alpha(0) + a_1 x \quad \text{(Eq. 4a)}$$

$$C_\beta(x) = C_\beta(0) \quad \text{(Eq. 4b)}$$

$$C_\gamma(x) = C_\gamma(0) + c_1 x \quad \text{(Eq. 4c)}$$

where a_1 and c_1 are constants; $C_\sigma(x)$ denotes the concentration of species σ at location x. The barrier extends from $x = 0$ to $x = h$. Equation 3 follows from the basic assumption that the reaction is at equilibrium everywhere in the diffusion barrier, which leads to the conditions:

$$J_R(x) = k_1 C_\alpha(x) C_\beta(x) - k_2 C_\gamma(x) = 0 \quad \text{(Eq. 5a)}$$

$$J_R'(x) = k_1[C_\alpha(x) C_\beta' + C_\beta(x) C_\alpha'] - k_2 C_\gamma' = 0 \quad \text{(Eq. 5b)}$$

$$J_R'' = k_1[C_\alpha C_\beta'' + C_\beta C_\alpha'' + 2C_\alpha' C_\beta'] - k_2 C_\gamma'' = 0 \quad \text{(Eq. 5c)}$$

$$J_R(x) = J_\gamma'(x) = -J_\alpha'(x) = -J_\beta'(x) \quad \text{(Eq. 5d)}$$

If the fluxes are given by Eq. 1, so that Eq. 5*d* is satisfied, the second derivatives of concentration profiles of the species vanish when diffusion coefficients are constants. Thus, concentration profiles are linear in the diffusion barrier. Satisfying the requirements of Eq. 5*c* when the reaction is at equilibrium requires the concentration gradient of one of the reactants to vanish; thus it is adopted that $C_\beta' = 0$ in Eq. 4. With these relations, it follows that the ratio of fluxes of complex γ and reactant α in the presence of β, when the reaction is at equilibrium, is given by the expression:

$$J_\gamma/J_\alpha = K(D_\gamma/D_\alpha) C_\beta \quad \text{(Eq. 6)}$$

where K is the equilibrium constant equal to (k_1/k_2) of the reaction; and D_α and D_γ are the diffusion coefficients of α and γ, respectively, in the membrane phase. Equation 6 is in agreement with the result of Eq. 29 of a previous paper (6) obtained by a different method. Equation 6 has the correct limiting property that as C_β tends to zero, the flux of complex γ vanishes. However, it has the property that as C_β tends to infinity, the ratio of flux of α transported in complexed form to the flux of unassociated form of α also tends to infinity. In addition, if one considers the total flux of α transported both as free and as complex as given by the differential equation:

$$J_\alpha^* = J_\alpha + J_\gamma = -D_\alpha C_\alpha' - D_\gamma C_\gamma' \quad \text{(Eq. 7)}$$

one obtains:

$$J_\alpha^* = J_\alpha\{1 + K(D_\gamma/D_\alpha) C_\beta\} \quad \text{(Eq. 8)}$$

Equation 8 implies that it is always possible to enhance the total flux of drug α by complexing it with substance β. Except for the limitation imposed by the solubility of β in the membrane phase, according to Eq. 8 one can enhance J_α^* to any desired extent by a corresponding increase in C_β. It also follows from Eq. 8 that (dJ_α^*/dC_β) will be positive definite unless (dJ_α/dC_β) is negative and has a magnitude greater than $J_\alpha K(D_\gamma/D_\alpha)[1 + K(D_\gamma/D_\alpha)C_\beta]^{-1}$.

Utilization of Eq. 2 in place of Eq. 1 for the fluxes leads, however, to the result, in place of Eq. 6, that:

$$J_\gamma/J_\alpha = [D_{\alpha\gamma} + KC_\beta D_{\gamma\gamma}]/[D_{\alpha\alpha} + KC_\beta D_{\alpha\gamma}] \quad \text{(Eq. 9)}$$

The derivation of Eq. 9 is presented in the *Appendix*. Unlike Eq. 6, Eq. 9 has the limiting properties that:

$$\text{limit } C_\beta \to 0, \quad J_\gamma/J_\alpha = D_{\alpha\gamma}/D_{\alpha\alpha} \quad \text{(Eq. 10a)}$$

$$\text{limit } C_\beta \to \infty, \quad J_\gamma/J_\alpha = D_{\gamma\gamma}/D_{\alpha\gamma} \quad \text{(Eq. 10b)}$$

In addition, when:

$$C_\beta = (1/K)[D_{\alpha\alpha} - D_{\alpha\gamma}]/(D_{\gamma\gamma} - D_{\alpha\gamma}) \quad \text{(Eq. 11a)}$$

$$J_\gamma/J_\alpha = 1 \quad \text{(Eq. 11b)}$$

One may recall that the principle of minimum entropy production requires that the diagonal elements of the diffusion matrix be positive definite and that the off-diagonal elements may be either positive or negative. The positive-definite character of KC_β is preserved in Eq. 11*a*.

If one defines the dimensionless quantities, x, y, and r, by the relations:

$$x = (D_{\alpha\gamma}/D_{\alpha\alpha}) \quad \text{(Eq. 12a)}$$

$$y = (D_{\gamma\gamma}/D_{\alpha\gamma}) \quad \text{(Eq. 12b)}$$

$$r = J_\gamma/J_\alpha \quad \text{(Eq. 12c)}$$

from Eq. 9, one obtains:

$$dr/dC = K(y - x)/(1 + KC_\beta x)^2 \quad \text{(Eq. 13)}$$

Equation 13 admits (dr/dC_β) assuming positive, null, and negative values, depending on the relative magnitudes of x and y. Thus, unlike Eq. 6, Eq. 9 contains an upper bound value for r. namely y, and states that the total flux of drug cannot be enhanced to infinity by an increase in concentration of the reactant β in the membrane phase.

APPARENT FIRST-ORDER RATE CONSTANTS

Similar arguments can also be advanced to the familiar evaluation of apparent first-order rate constants for the flux of α in the presence of β of concentration C_β, k_α^* and in the absence of β, k_α. As presented in the *Appendix*, following the method of Northrop and Anson (7), the ratio of the two rate constants may be evaluated as:

$$k_\alpha^*/k_\alpha = 1 + K(D_\gamma/D_\alpha) C_\beta \quad \text{(Eq. 14)}$$

when Eq. 1 is used for the flux expressions. Equation 14, which is obtained for quasistationary-state conditions, bears close similarity to Eq. 6.

On the other hand, if one utilizes Eq. 2, in the presence of β in the barrier, when the reaction is at equilibrium, one has the differential equation:

$$dQ_\alpha^*/dt = -(A/h)S[C_\alpha(0) - C_\alpha(h)] \quad \text{(Eq. 15a)}$$

$$S = [D_{\alpha\alpha} + D_{\alpha\gamma} + KC_\beta(D_{\alpha\gamma} + D_{\gamma\gamma})] \quad \text{(Eq. 15b)}$$

Following the procedure of Northrop and Anson, one has the expressions for the apparent first-order rate constants as:

$$K_\alpha = \{(V_1 + V_2)A/hV_1V_2\}[D_{\alpha\alpha} + KD_{\alpha\gamma}C_\beta] \quad \text{(Eq. 16a)}$$

$$K_\alpha^* = \{(V_1 + V_2)A/hV_1V_2\}[D_{\alpha\alpha} + D_{\alpha\gamma} + KC_\beta(D_{\alpha\gamma} + D_{\gamma\gamma})] \quad \text{(Eq. 16b)}$$

The ratio of (K_α^*/K_α) now remains finite for large values of C_β. This ratio can increase, decrease, or remain unaltered, depending on the sign and relative magnitude of $D_{\alpha\gamma}$ in comparison with other terms. In Eqs. 15 and 16, A is the surface area of the diffusion barrier, and V_1 and V_2 are the volumes of solutions on the two sides of the barrier; $Q_\alpha^*(t)$ is the amount of substance α transported at time t, both as unassociated and as complex γ.

CONCLUSIONS

In theoretical studies of drug absorption and transport as influenced by a complex forming agent, it is probably important to include terms to represent coupling between fluxes of different species as given in Eq. 2. The simple form of Fick's law is inadequate to explain the possibility of the total flux of a drug α increasing, decreasing, or remaining unaffected by the presence of a complexing substance in the membrane phase. An alternative explanation involving distinct equilibrium constants for the reaction in aqueous and membrane phase was suggested by Hayton *et al.* (8).

APPENDIX

In a previous paper (6), a nonlinear differential equation for a function $G(x)$ was derived, and its solution was obtained (Eqs. 18 and 41 of *Reference* 6) when coupling between fluxes of different

species was ignored. Inclusion of coupling terms by the use of Eq. 2 in place of Eq. 1 also leads to a similar differential equation for the function $G(x)$ related to the reaction rate profile $J_R(x)$—*viz.*:

$$G'' = N^2G + MG^2 + SGx + F_1x^2 + F_2x + F_3 = J_R(x) \quad \text{(Eq. 17a)}$$

$$N^2 = k_1(P_\alpha H_\beta + P_\beta H_\alpha) + k_2P_\gamma \quad \text{(Eq. 17b)}$$

$$M = k_1P_\alpha P_\beta \quad \text{(Eq. 17c)}$$

$$S = k_1(P_\alpha T_\beta + P_\beta T_\alpha) \quad \text{(Eq. 17d)}$$

$$F_1 = k_1T_\alpha T_\beta \quad \text{(Eq. 17e)}$$

$$F_2 = k_1(H_\beta T_\alpha + H_\alpha T_\beta) - k_2T_\gamma \quad \text{(Eq. 17f)}$$

$$F_3 = k_1H_\alpha H_\beta - k_2H_\gamma \quad \text{(Eq. 17g)}$$

$$P_\sigma = R_{\sigma\alpha} + R_{\sigma\beta} - R_{\sigma\gamma} \quad \text{(Eq. 17h)}$$

$$T_\sigma = R_{\sigma\alpha}Q_\alpha + R_{\sigma\beta}Q_\beta + R_{\sigma\gamma}Q_\gamma \quad \text{(Eq. 17i)}$$

$$G'(x) = I(x);\ I'(x) = J_R(x);\ |R_{\sigma\eta}| = |D_{\sigma\eta}|^{-1} \quad \text{(Eq. 17j)}$$

The solution of Eqs. 17*a*–17*j* enables one to compute the reaction rate profile from a knowledge of rate constants, elements of the diffusion matrix, and concentrations at boundaries when coupling between fluxes is to be included in a manner similar to that outlined in *Reference 5*. In Eqs. 17*a*–17*j*, the index σ can refer to α, β, or γ. H_σ and Q_σ are integration constants independent of the position variable. N is the reciprocal of relaxation length, characteristic of the system (analogous to η of *References 5* and *6*) when coupling between fluxes is included. $R_{\sigma\eta}$'s are the elements of the resistance coefficient matrix which is the inverse of the matrix of diffusion coefficients. The constants F_1, F_2, and F_3 have similar meanings to A, B, and $J_R(0)$ of Eq. 18 of *Reference 6*. H_α, H_β, and H_γ have dimensions of concentrations. M and S play the roles of μ and σ. Thus, when the elements of the diffusion coefficient matrix are constants and independent of the position variable, computation of the function $G(x)$ and the reaction rate profile, as well as concentration profiles, from a knowledge of boundary concentrations and rate constants in the inhomogeneous membrane phase is feasible, except for more computation tediousness than that presented in *Reference 5*. Thus, use of Eq. 2 in place of Eq. 1 also leads to solution of the problem and, in particular, requires linear concentration profiles for the species α, β, and γ participating in the reaction when the reaction is at equilibrium. When the reaction is at equilibrium, the solution of Eq. 17*a* is of the simple form:

$$G(x) = M_0 + M_1x \quad \text{(Eq. 18a)}$$

$$M_1 = -(T_\alpha/P_\alpha) \text{ or } -(T_\beta/P_\beta). \quad \text{(Eq. 18b)}$$

This result is similar to the result of Eq. 24*b* of *Reference 6*. When one chooses that M_1 equals $-(T_\beta/P_\beta)$, one has:

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

$$C_\alpha' = (P_\beta T_\alpha - P_\alpha T_\beta)/P_\beta \quad \text{(Eq. 19b)}$$

$$C_\gamma' = (P_\beta T_\gamma - P_\gamma T_\beta)/P_\beta \quad \text{(Eq. 19c)}$$

Therefore, from Eq. 19 it follows that when Eq. 2 is utilized for fluxes and reaction is at equilibrium in the membrane phase, validity of Eq. 5 leads to Eq. 4.

Equation 9 results from the equations:

$$J_\alpha = -D_{\alpha\alpha}a_1 - D_{\alpha\gamma}c_1 \quad \text{(Eq. 20a)}$$

$$J_\gamma = -D_{\alpha\gamma}a_1 - D_{\gamma\gamma}c_1 \quad \text{(Eq. 20b)}$$

$$c_1 = KC_\beta a_1 \quad \text{(Eq. 20c)}$$

As long as concentration profiles are linear, $a_1 = [C_\alpha(0) - C_\alpha(h)]/h$. To obtain k_α^*, for example, one integrates the expression (1):

$$(dQ_\alpha^*/dt) = -(D_\alpha A/h)[1 + K(D_\gamma/D_\alpha)C_\beta] \times [\{Q_\alpha^{I} - Q_\alpha(t)\}/V_1 - \{Q_\alpha^{II} - Q_\alpha(t)\}/V_2] \quad \text{(Eq. 21)}$$

with the condition that $Q_\alpha(t) = 0$ when $t = 0$. Q_α^{I} and Q_α^{II} are time-independent initial amounts of α in solutions I and II, respectively, sandwiching the membrane. If one desires to introduce partition coefficients, one obtains:

$$k_\alpha^* = \{(V_1 + V_2)/V_1V_2\}(D_\alpha AE_\alpha/h) \times [1 + K(D_\gamma/D_\alpha)E_\beta C_\beta] \quad \text{(Eq. 22a)}$$

$$E_\alpha C_\alpha(0) = C_\alpha^{I} = (Q_\alpha^{I}/V_1) \quad \text{(Eq. 22b)}$$

$$E_\beta C_\beta(0) = C_\beta^{I} \quad \text{(Eq. 22c)}$$

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