DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(1), 181-191 (1987)

KINETICS OF ION-PAIR ABSORPTION

M. Boroujerdi

Northeastern University
College of Pharmacy and Allied Health Professions
Section of Pharmaceutics
Boston, MA 02115

ABSTRACT

According to the 'pH-partition' theory, drugs in their ionized form cannot readily diffuse through biological membrane. However, it is well known that the permeation of many ionized drugs can be enhanced by the presence of anionic or cationic agents. One of the explanations for this observation is that the charged molecules of drug interact with the agents and form lipophillic ion-pair species, and as a result, the absorption of ionized molecules increases. In the present paper, the kinetic relationships of the formation of the ion-pair as a function of ion-pair agent and the type of the biological membrane have been discussed and analyzed. Criteria have been developed for the distinguishing the following two cases: 1) when the absorption is the rate limiting step in the process of permeation of the ion-pair, and 2) when the ion-pair crosses the membrane as though it were a fine sieve.

INTRODUCTION

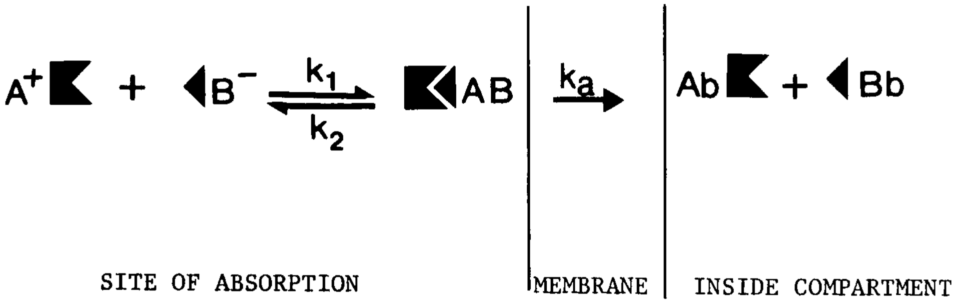
It can occur that a drug is completely ionized at the site of absorption yet is partially available to the systemic circulation; this phenomenon cannot be explained by the widely accepted 'pH-partition' hypothesis. However, it has been postulated that such absorption can be a consequence of the ion-pair formation (1). The assumption is that the interaction of drugs in the charged form with ions causes poorly permeable drugs to form a neutral and absorable complex. As a result the absorption of highly ionized drug increases. This assumption has led to studies of partitioning of such ion pairs into liquid phases and the absorption across synthetic and/or biological semipermeable membranes. For example, isopropamide-trichloroacetate ion-pair partitions greatly in octanol demonstrating the lipid solubility of the ion-pair (2). Trichloroacetate and salicylate showed significant increase in the apparent butanol water partition coefficient of an antiarrythmic quaternary ammonium compound (3). The apparent partition coefficient of tetracycline analogues increased significantly in the presence of trichloroacetate ion at acidic pH (4). In a similar study, dextromethorphan absorption from the rats stomach was shown to be dependent on anionic species but not on the trichloroacetate added to the solution (5). Transfer of warfarin across octanol impregnated membrane at pH 11 was increased by the presence of sodium ion (6). Ion pairing increased the partitioning of anionic chloramphenical succinate into the lipid phase in presence of cationic phosphonium ions (7). Addition of trichloroacetic acid to solutions containing methantheline bromide increased the lethal dose of the drug (8). Plasma levels of mixidine in rats increased when the drug was administered intraduodenally with naphthalene sulfonic acid (9).

Not all studies have supported the hypothesis. For instance, the effect of bile salts on the transport of mequitazine did not support the hypothesis that ion pairing increases the transport of ionized drugs (10). In a recent article the hypothesis was rejected on the basis of the lack of experimental data and the conceptual evaluation of the process involved (11).

The present study is an attempt to analyze, theoretically, changes in concentration of the ion-pair as a function of the ion-pair agent and the time required to establish the maximum concentration of the ion-pair at the site of absorption for the following two cases: 1) When the absorption is the rate limiting barrier in the process of permeation, wherein the ion-pair would be in equilibrium with the ionized molecules: 2) When the ion-pair crosses the membrane as though it were a five sieve, wherein the ion-pair formation would be an intermediate step in the consecutive processes of the ion-pair formation and absorption.

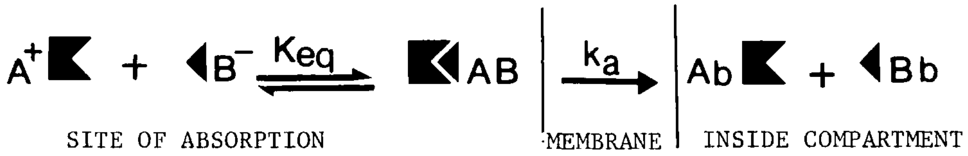
THEORETICAL

The formation and subsequent absorption of the ion-pair may be characterized by the following schematic diagram.



(Model I)

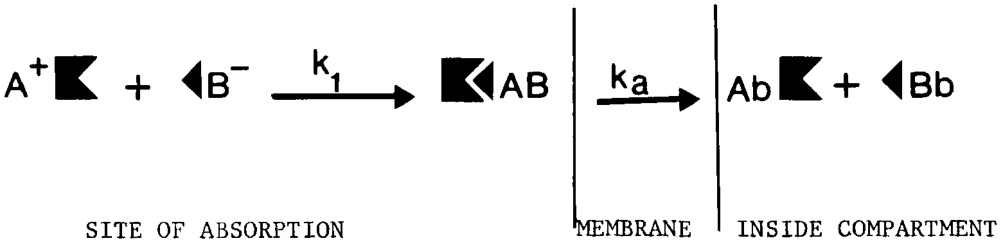
Where A^+ and B^- are drug ion and counter ion (ion-pair agent), respectively. (A-B) is the ion-pair, Ab and Bb represent the drug and the ion-pair agent in the inside compartment, k_1 and k_2 are chemical rate constants and k_a is the absorption rate constant. In quantitative analysis, it is important to establish which of the processes (i.e., reversible ion-pairing or irreversible absorption) determines the concentrations of the ion-pair at early times. If the absorption is the rate limiting step, $k_2 >> k_a$ and it can be assumed that the drug ion, counter ion and the ion-pair are at a steady state of chemical equilibrium that is:



(Model II)

where Keq is the equilibrium constant. At the equilibrium the concentrations of the reactants and the product is determined by the mass-action equations for the two opposing reactions.

If $k_2 << k_a$, no equilibrium can be established and the ion-pairing would be an intermediate step in the process of absorption. In this case, the following scheme would be more appropriate.



(Model III)

METHOD

For the general Model I, the following differential equations hold:

$$\frac{d[A\text{-}B]}{dt} = k_1[B^-]_0[A^+]_f - (k_2 + k_a)\,[A\text{-}B] \tag{1}$$

$$\frac{d[A^+]_f}{dt} = -k_1[B^-]_0[A^+]_f + k_2[A\text{-}B] \tag{2}$$

where $[B^-]_0$ is the amount of the ion-pair agent at time zero, $[A^+]_f$ is the amount of the free ionized drug at time t, and $[A\text{-}B]$ is the amount of the absorbable ion-pair. In terms of material balance, $[A^+]_f$ may be defined as:

$$[A^+]_f = [A^+]_0 - [A\text{-}B] - [Ab]_t$$

where $[A^+]_0$ is the total amount of drug introduced at the site of absorption at time zero, and $[Ab]_t$ amount of drug in the body at time t. When the amount of the ion-pair agent is present in large excess relative to the ionized drug, as is the case for *in situ* investigations (3), the ion-pairing may be regarded as a pseudo-first order process. The general solutions of the system of differential equations with the initial conditions of $[A\text{-}B]_{t=0}=0$ and $[A^+]_{f(t=0)} = [A^+]_0$ are as follows

$$[A\text{-}B] = \frac{k_1[B^-]_0[A^+]_0}{(m_1-m_2)}(\exp(m_1t)-\exp(m_2t)) \tag{3}$$

$$[A^+]_f = \frac{[A^+]_0}{(m_1-m_2)}[m_1 + k_2 + k_a)\exp(m_1t)-(m_2 + k_2 + k_a)\exp(m_2t)] \tag{4}$$

where $[A\text{-}B]$ is the amount of the ion-pair at time t; $[A^+]_f$ is the amount of free ionized drug at time t; m_1 and m_2 are the roots of a quadratic equation set up from the determinant of the system of differential equations (Appendix).

DISCUSSION

(a) When the absorption of the ion-pair proceeds far more slowly than the reversible step into the drug ion and counter ion, this means that the chemical rate constant, k_2, is greater than the absorption rate constant, ka, and Model II would be appropriate model. The equations are reported in Appendix, Eqs. (A6)-(A10). The absorbable fraction of dose, $F = ([A\text{-}B]/[A^+]_0)$, may then be approximated by the following two equations for different intervales of time. We may treat the early times, before any substantial absorption has occurred as though an equilibrium were being established, (e.g., at $t = 0$ or $\frac{1}{K_s}$, where $K_s = [B^-] + k_2 + k_a$, or when $t \ll \frac{1}{k_a}$. Hence,

$$F = F_{eq}(1-\exp[-k_1[B^-]_0 + k_2)t]) \tag{5}$$

where

$$F_{eq} = 1/(1 + \gamma_1) \tag{6}$$

$$1/\gamma_1 = Ke[B^-] \text{ and } Ke = \frac{k_1}{k_2}$$

and

$$[A^+]_f/[A^+]_0 = \gamma_1/(1 + \gamma_1) \tag{7}$$

The equilibrium concentrations are determined by the initial concentrations of the drug ion and the ion-pair agent and are maximum for Model II. The time required to establish equilibrium is determined by the sum of the rate constants of the forward and reverse reactions, and can be as small as desired if these constants are sufficiently large:

$$T_{eq} \cong \frac{\ell n 1/(1-F/Feq)}{k_1[B^-]_0 + k_2} \cong \frac{2.3}{k_1[B^-]_0 + k_2} \text{ (for } F/F_{eq} = 0.90) \qquad (8)$$

At times substantially greater than the time to establish equilibrium (e.g., when $t \cong 1/ka >> T_{eq}$), the equation for F can be represented in the following form

$$F = F_{eq} \exp(-k_e t) \qquad (9)$$

and $F = \exp(-k_a t)$ (as $\gamma_1 \rightarrow 0$ $F_{eq} \rightarrow 1$) (10)

where $k_e = k_a/(1 + \gamma_1)$ is the effective absorption rate constant for the ion-pair. The characteristic time constant of the ion-pair in the process of its irreversible absorpiton is

$$T_c \cong 1/k_e \rightarrow 1/ka \text{ (as } \gamma_1 \rightarrow 0) \qquad (11)$$

From this analysis it is evident that the characteristic indicator of Model II is a substantially shorter time to establish equilibrium in comparison with the characteristic time constant of ion-pair absorbption, i.e., $T_{eq} << T_c$.

(b) The irreversible absorption of the ion-pair proceeds far more rapidly than the reversible breakdown into the drug ion and the counter ion and hence Model III with the equations listed in Appendix, (A11)-(A14) would be appropriate. In the case of a sequence of processes, such as Model III, the concentration of the intermediate product passes through a maximum (F_{max}) at time T_{max}:

$$F_{max} + (\gamma_2)^{(\gamma_2/(1-\gamma_2))} \qquad (12)$$

where $1/\gamma_2 = k_1[B^-]_0/ka$, and

$$T_{max} = \frac{\ell n(1/F_{max})}{k_a} \tag{13}$$

With a sufficiently large excess of the ion-pair, the irreversible absorption of the ion-pair is described by the equation F = exp(-kat), as $\gamma_2 \to 0$, when $F_{max} \to 1$. The condition for fulfillment of Model III is that the time T_{max} and T_c are similar in value, since each of them is determined by the magnitude of the rate constant for the irreversible absorption of the ion-pair.

The function of F_{eq} and F_{max} have exactly the same limit: $F_{eq} \to 1$ as $\gamma_1 \to 0$, and $F_{max} \to 1$ as $\gamma_2 \to 0$. This means that theoretically, with any ratio of the rate constants k_2 and k_a, under conditions of a sufficiently large excess of one of the components, a limiting concentration of the ion-pair will be reached that will be equal to the concentration of the ionized drug at time zero, i.e., $[A\text{-}B]_\infty = [A^+]_0$. Obviously, this can be true only when all drug ions covert to ion-pair. The function of F_{eq} can be plotted on coordinates of $1/F_{eq}$ vs γ_1; in this case, the slope of the line can be used to determine the equilibrium constant. An analogous linear relationship can also be found for F_{max} on coordinates of $1/F_{max}$ vs γ_2. In this case, the slope can be determined by the ratio of the rate constants for the formation and irreversible absorption of the ion-pair. The two cases can be distinguished by analysis of the characteristic times for passage of the concentration through the maximum T_{eq} and T_{max} as defined in equations (8) and (13). From the kinetic curve of log[A-B] vs time the half-life of absorption can be estimated. We can then estimate the effective rate constant for irreversible absorption of the ion-pair. If $T_{eq} << T_c$; i.e., equilibrium is established rapidly, and the absorption of the ion-pair is the rate limiting step. If no equilibrium were established, the time required to reach the maximum concentration of the ion-pair may be estimated by equation 13.

ACKNOWLEDGEMENT

The author wishes to thank Mrs. Bernadette Roche who typed the manuscript.

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Appendix A

1. The roots of the quadratic equation set up from the determinant of the system of differential equations

$$m_{1,2} = -K_s(1 \pm \sqrt{1-4\gamma_2/(1+\gamma_1+\gamma_2)^2})/2 \qquad \text{(A1)}$$

where

$K_s = k_1[B^-] + k_2 + ka$ is the sum of the constants; (A2)

$K_e = k_1/k_2$ is the equilibrium constant; (A3)

$1/\gamma_1 = K_e[B^-]_0$ and (A4)

$1/\gamma_2 = k_1[B^-]_0/k_a$ are dimensionless ion-pair agent (A5)

concentrations.

2. When $k_2 > k_a$

$$K_s = k_1[B^-]_0 + k_2; \qquad \text{(A6)}$$

$$m_1 = k_3/(1+\gamma_1); \qquad \text{(A7)}$$

$$m_1 = -k_1[B^-](1+\gamma_1), \qquad \text{(A8)}$$

and the general solution assumes the form

$$[A\text{-}B] = \frac{[A^+]}{(1+\gamma_1)}(\exp(-k_a t/(1+\gamma_1)) - \exp(-k_1[B^-]_0 + k_2)t) \qquad \text{(A9)}$$

$$[A^+]_f/[A^+]_0 = \gamma_1 \frac{[A\text{-}B]}{[A^+]_0} \qquad \text{(A10)}$$

3. When $k_a > k_2$

$$K_s = (k_1[B^-]_0 + ka) \qquad \text{(A11)}$$

$$m_1 = -ka \tag{A12}$$

$$m_2 = -k_1[B^-]_0 \tag{A13}$$

and general solution assumes the form

$$[A\text{-}B] = \frac{[A^+]_0}{(1-\gamma_2)}(\exp(-k_a t)-\exp(-k_1[B^-]_0 t)) \tag{A14}$$