Effect of Diffusional Lag Time on Multicompartmental Pharmacokinetics for Transepidermal Infusion

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Abstract □ A simple proof is given to demonstrate that the lag time to reach steady state from transepidermal infusion is the sum of the diffusional and pharmacokinetic lag times.

Keyphrases □ Diffusion—effect of lag time on multicompartmental pharmacokinetics for transepidermal infusion □ Transepidermal infusion—effect of diffusional lag time on multicompartmental pharmacokinetics □ Models, pharmacokinetic—transepidermal infusion, effect of diffusional lag time

When a compound is administered to an animal *via* constant intravenous infusion, a lag time exists before steady-state values of elimination, blood levels, *etc.*, are obtained (1). If the total amount of compound eliminated is plotted *versus* time, a linear asymptotic form obtains. The lag time is defined as the intercept of this linear asymptote. If, however, a compound is infused transepidermally, there is a lag time to reach cutaneous steady-state transport in addition to the lag time required to distribute and eliminate the compound in the body (2, 3).

Even though the nonsteady-state behavior of the blood levels and other parameters is coupled with the nonsteady-state flux of the skin transport, the total lag time is uncoupled; *i.e.*, the lag time is the sum of the diffusional and the pharmacokinetic lag times. The purpose of this report is to show that this result can be proven rather simply for multicompartmental pharmacokinetics.

MATHEMATICAL MODEL

The kinetics for absorption into a central compartment and distribution between the central compartment and other compartments can be described by:

$$\frac{dC_0}{dt} = -k_{e0}C_0 + \sum_{i=1}^{n} k_{i0}C_i - \left(\sum_{i=1}^{n} k_{0i}\right)C_0 + \frac{AJ}{V_0} \qquad \text{(Eq. 1)}$$

and:

$$\frac{dC_i}{dt} = -k_{ei}C_i - k_{i0}C_i + k_{0i}C_0 \quad i = 1, 2, \ldots, n \qquad \text{(Eq. 2)}$$

where C_j is the concentration in the jth compartment ($j = 0$ is the central compartment), k_{ej} is the elimination rate constant for the jth compartment, and k_{0j} and k_{j0} are the distribution rate constants from and into the central compartment, respectively. Here, V_0 is the central compartment volume, J is the flux of material into the central compartment, and A is the area of tissue from which transport occurs. The kinetic scheme for absorption, distribution, and elimination is given in Scheme I.

At steady state, Eqs. 1 and 2 become:

$$0 = -k_{e0}C_0^s + \sum_{i=1}^{n} k_{i0}C_i^s - \left(\sum_{i=1}^{n} k_{0i}\right)C_0^s + \frac{AJ^s}{V_0} \qquad \text{(Eq. 3)}$$

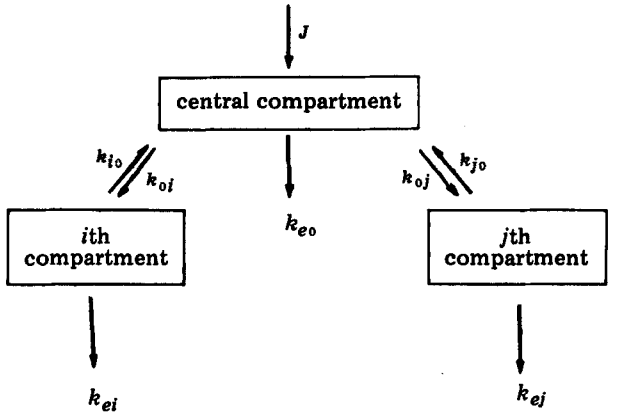
and:

$$0 = -k_{ei}C_i^s - k_{i0}C_i^s + k_{0i}C_0^s \quad i = 1, 2, \ldots, n \qquad \text{(Eq. 4)}$$

where the superscript s denotes the steady-state value of the quantity.

The long time integral (4) of Eqs. 1 and 2 gives:

$$C_0^s = -k_{e0}M_0 + \sum_{i=1}^{n} k_{i0}M_i - \left(\sum_{i=1}^{n} k_{0i}\right)M_0 + \frac{AJ^s}{V_0}(t - t_D) \qquad \text{(Eq. 5)}$$



Scheme I—Absorption, distribution, and elimination for topical infusion.

and:

$$C_i^s = -k_{ei}M_i - k_{i0}M_i + k_{0i}M_0 \quad i = 1, 2, \ldots, n \qquad \text{(Eq. 6)}$$

where t_D is the diffusional or transport lag time and:

$$M_i = \int_0^t C_i\, dt' \qquad \text{(Eq. 7)}$$

Here the integral is for t much greater than the time to reach steady state. The addition of Eq. 6 to Eq. 5 gives:

$$Q_e(t) \equiv \sum_{i=0}^{n} k_{ei}M_i = \frac{AJ^s}{V_0}(t - t_D - t_\alpha) \qquad \text{(Eq. 8)}$$

where $Q_e(t)$ is the amount eliminated as a function of time and:

$$t_\alpha = \frac{V_0 \sum_{i=0}^{n} C_i^s}{AJ^s} \qquad \text{(Eq. 9)}$$

The expression for t_α can be written as a function of the rate constants by using Eqs. 3 and 4 to obtain:

$$t_\alpha = \frac{1 + \sum_{i=1}^{n} \frac{k_{0i}}{k_{ei} + k_{i0}}}{k_{e0} + \sum_{i=1}^{n} \frac{k_{ei}k_{0i}}{k_{ei} + k_{i0}}} \qquad \text{(Eq. 10)}$$

The quantity t_α is just the pharmacokinetic lag time. Thus, the total lag time is simply the sum of the transport lag time and the pharmacokinetic lag time.

DISCUSSION

Another way to determine the lag time for transepidermal infusion is to solve Eqs. 1 and 2 *via* a LaPlace transform technique. A quick look for just two compartments reveals that some unwieldly infinite sums must be evaluated and that the lag time could contain cross-terms. However, all of these sums cancel appropriately to give the results of Eq. 8, which demonstrates that the lag times are additive. That is, the time to reach steady state does not contain cross-terms as it does in transport across more than one membrane (5), and one does not have to be concerned with any unexpected delays in the establishment of steady state.

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COMMUNICATIONS

Micellar Catalysis of an Analytical Reaction: Spectrophotometric Determination of Amino Acids and Peptides after Cetrimonium Bromide-Catalyzed Reaction with 1-Fluoro-2,4-dinitrobenzene

Keyphrases □ Surfactants—cetrimonium bromide, micelle formation, catalysis of amino acid and peptide derivatization, spectrophotometry of derivatives □ Amino acids—spectrophotometric determination following derivatization, catalysis by surfactant micelles □ Peptides—spectrophotometric determination following derivatization, catalysis by surfactant micelles

To the Editor:

Surfactants can alter chemical reaction rates through their micelle-forming capabilities. During the past decade, intensive study of this phenomenon has been stimulated by the hope that micellar catalysis of organic reactions might be a useful model of enzyme catalysis. Although the dynamic and fluid structure of micelles limits their utility as enzyme models, micelle-induced alterations in reaction rates are worth studying on their own account (1, 2). It was suggested (3, 4) that micellar catalysis might be exploited for organic analytical purposes, but no such experimental studies have been reported. We describe the use of micellar catalysis to increase the derivative formation rate prior to spectrophotometric measurement of a product.

1-Fluoro-2,4-dinitrobenzene undergoes aromatic nucleophilic substitution by amines to give arylated amines. This reaction was employed to study the amino acid sequence of insulin (5), and it has since been adapted to the analysis of other amines and polyamines (6–8). The reaction is carried out in an alkaline medium, and the product is measured spectrophotometrically. For the determination of many amines and amino acids, the reaction was essentially complete (within 5% of its maximum) for most samples in 10 min at 65°; some compounds required ≥20 min at this temperature (8).

Several surfactants, notably the cation cetrimonium bromide (cetyltrimethylammonium bromide), catalyze substitution reactions between fluorodinitrobenzene and amine nucleophiles (9); rate enhancements of ~five- to 30-fold were found. Therefore, this reaction appeared to provide an appropriate system for testing the proposal (3, 4) that micellar catalysis may be analytically useful.

Rates were measured for the substitution reaction between fluorodinitrobenzene and some amino compounds in the presence and absence of cetrimonium bromide. In these reactions, the fluorodinitrobenzene was in excess, as it would be in an analytical system; samples were withdrawn and examined spectrophotometrically by a literature method (8). The kinetics were apparent first order over at least two half-lives. Table I gives the half-lives and conditions for these reactions. (Tyrosine showed a slow secondary reaction, resulting in a small absorbance decrease.) All compounds gave slightly higher absorbances (~10%) in the presence of the surfactant compared with the final absorbance in its absence.

Table I—Micellar Catalysis of Amine–Fluorodinitrobenzene Reactions by Cetrimonium Bromide

Amine	Half-Life, min[a]	
	No Surfactant	0.035 *M* Surfactant[b]
Glycine	37.2	2.0
Alanine	85.0	4.7
Phenylalanine	32.0	0.5
Tyrosine	22.0	<0.5
Glycylglycine	63.5	5.4
Glycylglycylglycine	94	7.5

[a] Using 5×10^{-4} *M* amine, 3.5×10^{-3} *M* fluorodinitrobenzene, pH 9.2, 23°. [b] About twice the concentration recommended in the analytical procedure.

The following analytical procedure was developed. To a 25-ml volumetric flask were added 0.12 g of cetrimonium bromide, 1.0 ml of 1.3% (v/v) 1-fluoro-2,4-dinitrobenzene in acetone, 9.0 ml of 2.5% sodium borate in water, and 10.0 ml of an aqueous amine solution (1×10^{-4}–1×10^{-3} *M*). After about five half-lives (Table I) at room temperature, 1.0 ml of the solution was pipetted into 9.0 ml of a 1:100 dilution of concentrated hydrochloric acid in dioxane. The absorbance was read in a 1-cm cell at the absorption maximum against a reagent blank carried through the same procedure.

The absorption maximum was at 340 nm for the tyrosine derivative and at 350 nm for the other samples in Table I. Calibration plots were linear over the sample concentration range.

According to Table I, the more hydrophobic reactants (the aromatic amino acids) gave much larger relative rate enhancements, as expected for micellar catalysis. All rate enhancements are analytically useful, and this method can be applied with the reaction carried out at room temperature. This work provides the scope for further study of this analytical system and of the potential applications of micellar catalysis to other analytical reactions.

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