# Pharmacokinetics of Skin Penetration

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**Abstract** □ A model for estimating *in vivo* skin permeability coefficients is presented. Explicit expressions are derived for the permeability coefficient in terms of excretion rates and tissue absorption. The excretion rate has a linear asymptotic limit from which the permeability coefficient can be determined. The usefulness of the model is demonstrated with existing literature data.

**Keyphrases** □ Pharmacokinetics—model for estimating *in vivo* skin permeability coefficients in terms of excretion rates and tissue absorption □ Permeability coefficients, skin—estimated using pharmacokinetic models, in terms of excretion rates and tissue absorption □ Skin permeability coefficients—estimated using pharmacokinetic models, in terms of excretion rates and tissue absorption □ Excretion rate—data used in deriving pharmacokinetic models for estimating *in vivo* skin permeability coefficients

Quantitative studies of skin penetration have been conducted primarily with *in vitro* systems, *i.e.*, with epidermis obtained at autopsy, and Scheuplein and Blank (1) pioneered much of this important work. However, little effort has been directed toward a quantitative understanding of skin penetration *in vivo*, and it is very difficult to extract permeability coefficients from existing *in vivo* data. Thus, accurate comparisons of *in vivo* and *in vitro* skin penetration are sparse.

The *in vitro* and *in vivo* transport of alkyl methyl sulfoxides across rabbit skin was studied, and the steady-state urinary elimination rate was about one-half of the *in vitro* steady-state flux (2). Since only one-half of the sulfoxide was eliminated *via* the urinary pathway, this result is evidence for reasonable agreement between *in vivo* and *in vitro* skin penetration.

The *in vivo* skin penetration of three esters of salicylic acid was measured using urinary excretion rates in humans (3). The system (3) was somewhat more ideal than that of Sekura and Scala (2), since 90% of the intravenously injected salicylate was recovered in the urine. That is, the urinary excretion at steady state should closely reflect the diffusion rate across the skin.

The purpose of this report is to show quantitatively how permeability coefficients can be extracted from excretion data. Diffusion theory is coupled with simple elimination kinetics to derive mathematical expressions for the amount of material excreted as a function of time. The excretion rate is shown to have a linear (in time) asymptotic limit, with a lag time that is the sum of the diffusional and excretion lag times.

## MATHEMATICAL MODEL

It is assumed that a drug is applied to the skin surface over an area, $A$, and that the diffusion across the skin into the body fluids can be represented by diffusion theory. That is, it is assumed that the concentration of material in the skin (the membrane) is governed by:

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} \qquad \text{(Eq. 1)}$$

where $c$ is the concentration, $D$ is the diffusion coefficient, $t$ is time, and $x$ is the position inside the membrane. The flux of material into the body fluids is given by:

$$J = -D\left(\frac{\partial c}{\partial x}\right)_{x=l} = D\left[\frac{c_0}{l} + \frac{2c_0}{l}\sum_{n=1}^{\infty}(-1)^n e^{-\alpha_n t}\right] \qquad \text{(Eq. 2)}$$

where $c(x,t)$ is the solution (4) of Eq. 1 for a membrane of thickness $l$ and boundary conditions $c(0,t) = c_0$ and $c(l,t) \ll c_0$. Here $\alpha_n = (n^2\pi^2/6)k_D$ and $k_D = 6D/l^2$, which is just the reciprocal of the diffusional lag time. The constant concentration, $c_0$, is related to the vehicle concentration *via* the partition coefficient, and $c(l,t)$ is related to the concentration in the body fluids.

As the drug diffuses across the stratum corneum, it is assumed to be carried away into the body fluids, where it is either in solution or bound. Furthermore, it is assumed that the drug is eliminated by parallel first-order routes of metabolism, biliary excretion, and urinary excretion and that distribution between body fluids and tissue is rapid. Thus, one can employ conservation of mass to obtain the time rate of change of drug in solution in the body fluids:

$$V_l\frac{dC_l}{dt} = AJ - V_b\frac{d\theta_b}{dt} - V_tK\frac{dC_l}{dt} - (k_M + k_B + k_U)C_lV_l \qquad \text{(Eq. 3)}$$

where $C_l$ is the drug concentration in solution in the liquid portion of the body fluids; $V_l$ is the volume of the liquid; $\theta_b(C_l)$ is the amount (per unit volume) of material bound to a volume, $V_b$, of substrate in the body fluids; and $k_M$, $k_B$, and $k_U$ are metabolism, biliary excretion, and urinary elimination coefficients, respectively. Here, $K$ is the distribution coefficient between the body fluids and the tissue of volume $V_t$. Equation 3 can now be written as:

$$\left(1 + \frac{V_b}{V_l}\frac{d\theta_b}{dC_l} + \frac{V_tK}{V_l}\right)\frac{dS}{dt} = -kS + Q\left[1 + 2\sum_{n=1}^{\infty}(-1)^n e^{-\alpha_n t}\right] \qquad \text{(Eq. 4)}$$

where $S = V_lC_l$ is the total amount of drug in solution and:

$$Q = AC_0D/l \qquad \text{(Eq. 5)}$$

$$k = k_M + k_B + k_U \qquad \text{(Eq. 6)}$$

Evaluation of Eq. 4 depends on a knowledge of $\theta_b$. If one assumes that the body fluids contain a low concentration of drug, then one can approximate $\theta_b$ by:

$$\theta_b = \beta C_l \qquad \text{(Eq. 7)}$$

This approximation allows Eq. 4 to be written as:

$$\frac{dS}{dt} = -k_aS + Q_a\left[1 + 2\sum_{n=1}^{\infty}(-1)^n e^{-\alpha_n t}\right] \qquad \text{(Eq. 8)}$$

where $k_a = k/\delta$, $Q_a = Q/\delta$, and $\delta = 1 + \beta(V_b/V_l) + K(V_t/V_l)$.

The solution of Eq. 8 is:

$$S = \frac{Q_a}{k_a}(1 - e^{-k_at}) + 2Q_a\sum_{n=1}^{\infty}\frac{(-1)^n}{(k_a - \alpha_n)}(e^{-\alpha_n t} - e^{-k_at}) \qquad \text{(Eq. 9)}$$

from which one can obtain the urinary excretion rate, $k_US$, or the total excretory rate, $kS$. Equation 9 has a simplifying limit for $k_D \gg k$, *i.e.*, when the diffusional lag time is small with respect to the excretory time scale. In this limit:

$$\lim_{k_D \gg k} S = \frac{Q_a}{k_a}(1 - e^{-k_at}) \qquad \text{(Eq. 10)}$$

which says that the excretion rate rises exponentially.

A more useful parameter is the total amount excreted as a function of time, since it has a linear asymptotic solution from which $Q_a$ and $k_a$ can be estimated more easily. The total amount excreted is obtained by multiplying the appropriate excretion constant by $M$, where:

$$M = \int_0^t dtS = \frac{Q_a}{k_a}\left[t - \frac{1}{k_a}(1 - e^{-k_at})\right] + 2Q_a\sum_{n=1}^{\infty}\frac{(-1)^n}{k_a - \alpha_n}\left[\frac{1}{\alpha_n}(1 - e^{-\alpha_n t}) - \frac{1}{k_a}(1 - e^{-k_at})\right] \qquad \text{(Eq. 11)}$$

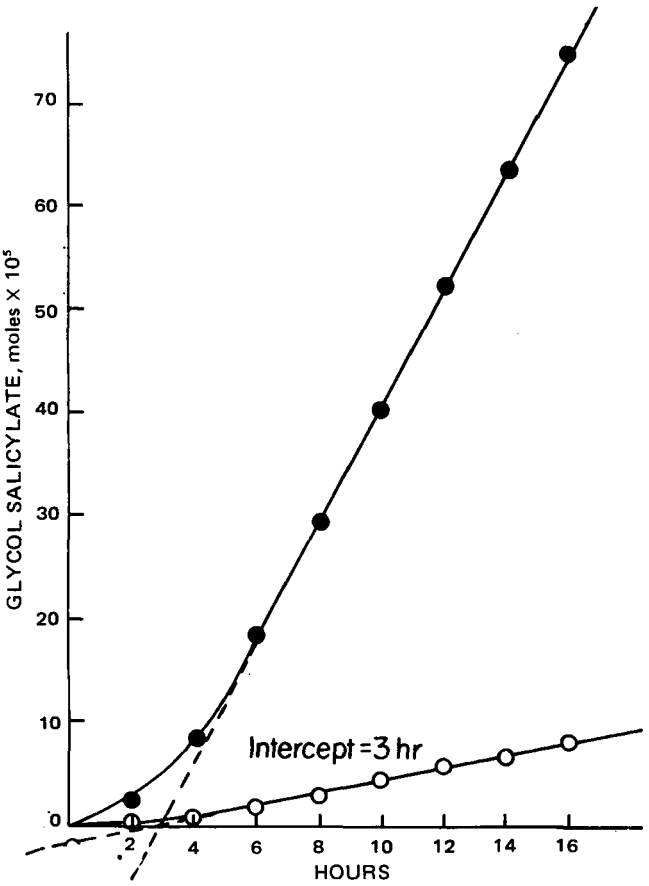


**Figure 1**—*Accumulative urinary salicylate data showing influence of moisture on percutaneous absorption rate of glycol salicylate. Key: ●, hydrous system rate, 11.7; and ○, anhydrous system rate, 1.3. (Reproduced, with permission, from Fig. 7 of Ref. 3.)*

which has the asymptotic limit:

$$M_A = \lim_{\substack{k_a t \gg 1 \\ k_D t \gg 1}} M = \frac{Q_a}{k_a}\left(t - \frac{1}{k_a} - \frac{1}{k_D}\right) \qquad \text{(Eq. 12)}$$

Thus, $M$ is linear at long times and has an intercept or lag time of:

$$t_L = \frac{1}{k_a} + \frac{1}{k_D} \qquad \text{(Eq. 13)}$$

and a slope of $Q_a/k_a$.

For $k_a \gg k_D$, $t_L$ is just the diffusional lag time; for $k_D \gg k_a$, the intercept is just the reciprocal of the adjusted excretion rate constant, $k_a$. The slope, $Q_a/k_a = Q/k$, is not affected by binding in the body fluids or by tissue absorption, whereas the lag time is increased by fluid binding and tissue absorption.

## APPLICATIONS

To illustrate the usefulness of the results derived in the previous section, the model is applied to interpret the data of Wurster and Kramer (3). Figure 1 is a graph of the amount of salicylate excreted in the urine as a function of time for a topical application of glycol salicylate[1]. The amount excreted does indeed become linear after 6 hr, and the lag time is about 3 hr. The slope of the linear portion of the curve should be given by:

$$\text{slope} = k_U\left(\frac{Q}{k}\right) = \frac{Q}{1+\Delta} \qquad \text{(Eq. 14)}$$

where $\Delta = (k_M + k_B)/k_U$ ($k_M$ refers to the rate constant for metabolism to a compound other than salicylic acid).

[1] Since the data do not distinguish between salicylic acid and glycol salicylate in the urine, it is assumed that glycol salicylate is rapidly converted to salicylic acid or that both species have the same elimination kinetics. Both of these possibilities are consistent with the lag time equal to $k_a^{-1} = 3.45$ hr.

If $\Delta \ll 1$, then the slope is a direct measure of the *in vivo* steady-state flux, and the permeability coefficient is just:

$$k_{per} \simeq \frac{\text{slope}}{AC_{GS}} \qquad \text{(Eq. 15)}$$

where $C_{GS}$ is the concentration of glycol salicylate applied to the skin. From Eq. 14, one observes that the permeability coefficient is underestimated by the factor $1 + \Delta$. Thus, if the urinary excretion rate is not large with respect to the other elimination rates, the permeability coefficient is significantly underestimated.

The parameter $\Delta$ can be approximated from the urinary recovery after intravenous injection. The elimination is governed by:

$$\frac{dS}{dt} = -k_a S \qquad \text{(Eq. 16)}$$

which has the solution:

$$S = S_0 e^{-k_a t} \qquad \text{(Eq. 17)}$$

where $S_0$ is the initial amount in solution, and $S_0\delta$ is the total amount injected. Since Wurster and Kramer (3) determined the elimination rate constant from the slope of the logarithm of the urinary excretion rate, $k_U S$, *versus* time, they essentially measured $k_a$. The total amount excreted in the urine is:

$$\int_0^t dt k_U S = \frac{S_0\delta}{1+\Delta}(1 - e^{-k_a t}) \qquad \text{(Eq. 18)}$$

so that the 90% recovery of Wurster and Kramer estimates $\Delta = 0.11$. Thus, the *in vivo* permeability coefficient is given by:

$$k_{per} = 1.11\left(\frac{\text{slope}}{AC_{GS}}\right) \qquad \text{(Eq. 19)}$$

The diffusional lag time is small, since $k_a^{-1}$ is almost identical with the excretion lag time of Fig. 1. Thus, a knowledge of the excretion rate constant and the urinary excretion lag time permits one to estimate the diffusional lag time.

## DISCUSSION

Permeability coefficients for skin can be measured *in vivo* from excretion data, provided that the excretion rate is proportional to the drug concentration in the body fluids. The asymptotic limit for the amount of material excreted is linear in time. The slope of the asymptotic limit is dependent upon the particular excretion path, but the lag time is identical for all paths of elimination. Tissue absorption and binding to proteins in the body fluids do not alter the asymptotic slope but do increase the lag time contribution from the excretion process.

Accurate determination of the skin permeability coefficient requires a knowledge of all rates of elimination. However, the percent recovery in the urine following intravenous injection provides an estimate of the magnitude of the error involved in computing the permeability coefficient from the urinary excretion rate. Thus, one can obtain reasonable estimates of skin permeability coefficients *in vivo* by measuring urinary excretion.

If the skin metabolizes the drug to some degree before it enters the body fluids, the preceding arguments have to be modified. A term has to be added to the diffusion equation to account for the kinetics of the reaction taking place in the skin. *In vivo* permeability coefficients determined by ignoring skin metabolism would clearly be significantly smaller than those measured *in vitro* if skin metabolism is an important process.

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