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Scopolamine Permation Through Human Skin *In Vitro*

The sorption and rate of permeation of scopolamine base in human skin have been measured as a function of drug concentration in aqueous solution contacting the stratum corneum surface of the skin. The sorption isotherm is nonlinear, and the apparent penetrant diffusivity computed from steady state permeation data is greater than that estimated from unsteady state (time lag) measurements.

By assuming that sorption occurs by both ordinary dissolution and binding of penetrant to immobile sites in the membrane, the experimental sorption isotherm can be predicted, and the disparity between steady state and time lag diffusivities can be reconciled.

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SCOPE

The unique molecular transport and barrier characteristics of human skin, which provide our protection against most toxic substances in the environment and have frustrated efforts to use the surface of the body as a route of entry of drugs for disease treatment, remain incompletely understood. In an earlier paper (Michaels et al., 1975), we employed the principles of membrane permeation and a simplistic two-phase representation of skin microstructure to evolve a model of the transdermal permeation process which was shown to be rational and useful for predicting the permeability of skin to various micromolecular substances.

In this paper, we examine another property of skin affecting its permeation behavior: its tendency to sorb and bind substances during the process of permeation. The extent and nature of the binding phenomenon is of great practical importance in determining the unsteady state kinetics of transdermal mass transport and the efficiency

with which a substance delivered to the skin surface will be released into the systemic circulation. Once again, we have found that a simplistic model of the sorption process, which invokes the coexistence of dissolved and mobile sorbed molecules in equilibrium with site bound and immobile molecules within the membrane, quite accurately correlates experimental sorption data and transient transport measurements.

CONCLUSIONS AND SIGNIFICANCE

The nonlinear sorption isotherm of human stratum corneum for scopolamine base from aqueous solution has been successfully correlated and predicted via a dual sorption model (initially applied with success to the sorption of gases by glassy polymers). This model postulates two populations of sorbed molecules: one comprising truly dissolved, mobile molecules, and the other, molecules which are reversibly bound to a fixed number of specific sites in the membrane and are thereby immobilized. Of perhaps greater importance is the finding that the dual sorption representation of the isotherm quite accurately predicts the experimentally observed disparity between the steady state diffusivity of the drug in skin and the unsteady state value computed from transient (time-lag) permeation measurements.

Of particular interest is the experimental finding that site bound, immobile drug is largely confined to the discontinuous protein phase of the stratum corneum, while the major drug transport resistance is encountered in the continuous lipid phase of the tissue. This is interpreted as further support for the two-phase representation of skin microstructure. The analytical treatment of skin sorption and permeation herein developed, despite its simplicity, promises to be very useful in predicting whether specific substances (drugs, toxicants, etc.) are likely to be significantly bound to and/or diffusible through human skin.

The principal resistance to permeation of drugs and other small molecules through intact human skin resides with the stratum corneum, which is comprised of dead, partially desiccated keratinized epidermal cells (Michaels et al., 1975). The stratum corneum is a heterogeneous structure containing about 40% protein (mainly keratin), 40% water, and about 15 to 20% lipids (principally, triglycerides, free fatty acids, cholesterol, and phospholipids) (Anderson and Cassidy, 1973; Katz and Poulsen, 1971). The transdermal permeation of drugs occurs principally by Fickian diffusion, with the gradient in drug concentration across the entire skin being localized within the stratum corneum (Scheuplein and Blank, 1971).

For drugs which display low permeability through skin, significant sorption of the drug by the skin may greatly delay the establishment of steady state permeation conditions. Scopolamine base has been found to possess these characteristics. The purpose of this study was to examine in some detail the concentration and time dependence of scopolamine sorption and permeation in human skin in vitro, in an effort to understand more clearly the nature of the sorption/transport processes, and ultimately to develop techniques for controlling these processes in order to achieve predictable transdermal drug delivery under clinical conditions.

THEORY

A dual sorption model has been extensively utilized to explain the equilibrium sorption data for gases in polymers (Assink, 1975; Michaels et al., 1963; Paul, 1969, 1973). The model postulates that sorption occurs by two mechanisms, the first mechanism being a simple dissolution producing mobile and freely diffusible molecules and the second being an adsorption process producing nonmobile molecules which do not participate in the diffusion process. We have attempted to use this model in the analysis of the permeation characteristics of scopolamine through human skin in vitro.

The total concentration of scopolamine in the skin is thus assumed to be composed of two parts

$$C_T = C_D + C_I \tag{1}$$

The mobile solute concentration C_D can be adequately expressed in the proportionality

$$C_D = K_D C \tag{2}$$

On the other hand, the concentration of immobilized solute C_I can be represented adequately by an adsorption isotherm of the Langmuir form:

$$C_I = \frac{C_I^* bC}{1 + bC} \tag{3}$$

Substitution of Equations (2) and (3) into Equation (1) gives

$$C_T = K_D C + \frac{C_I^* bC}{1 + bC} \tag{4}$$

The steady state flux J is given by

$$J = -D \frac{\partial C_D}{\partial x} \tag{5}$$

In the transient time period we have

$$\frac{\partial C_T}{\partial t} = \frac{-\partial J}{\partial x} = D \frac{\partial^2 C_D}{\partial x^2} \tag{6}$$

where

$$\frac{\partial C_T}{\partial t} = \frac{\partial C_D}{\partial t} + \frac{\partial C_I}{\partial t} \tag{7}$$

Assuming that exchange between mobile and immobile species is rapid compared with the diffusion process, and thus that local equilibrium exists between the mobile and immobilized species, Equation (6) can be rewritten as

$$\left[1 + \frac{C_I^* b/K_D}{(1 + C_D b/K_D)^2} \right] \frac{\partial C_D}{\partial t} = D \frac{\partial^2 C_D}{\partial x^2} \tag{8}$$

where the additional term on the left-hand side arises as a consequence of drug immobilization.

A steady state diffusion coefficient D_{SS} can now be written as

$$D_{SS} = D \left[1 + \frac{C_I^* b/K_D}{(1 + C_D b/K_D)^2} \right] \tag{9}$$

Following the procedure of Frisch (1957) and Paul (1969), and assuming that infinite source and sink condi-

tions exist on two sides of the skin, we can obtain the diffusion time lag θ for the transient Equation (8):

$$\theta = \frac{l^2}{6D}\left\{ 1 + 6C_I^* a \left[\frac{\tfrac{1}{2}(aC_D)^2 + aC_D - (1 + aC_D)\ln(1 + aC_D)}{(aC_D)^3} \right] \right\} \quad (10)$$

where $a = b/K_D$, and l is the thickness of the membrane.

Eliminating D from Equations (9) and (10), we have

$$\frac{D_{SS}}{D_{TL}} = \frac{\left\{ 1 + 6C_I^* a \left[\frac{\tfrac{1}{2}(bC)^2 + bC - (1 + bC)\ln(1 + bC)}{(bC)^3} \right] \right\}}{\left[1 + \frac{C_I^* a}{(1 + bC)^2} \right]} \quad (11)$$

where the apparent time lag diffusion coefficient $D_{TL} = l^2/6\theta$.

It is now apparent that the ratio of the steady state to the time lag diffusion coefficients is only a function of C, the concentration of solute in the solution phase contacting the skin.

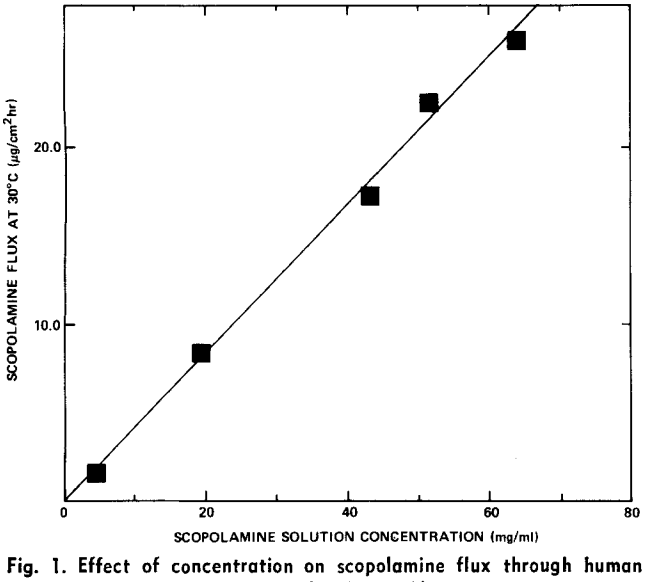

Fig. 1. Effect of concentration on scopolamine flux through human epidermis (epidermis A).

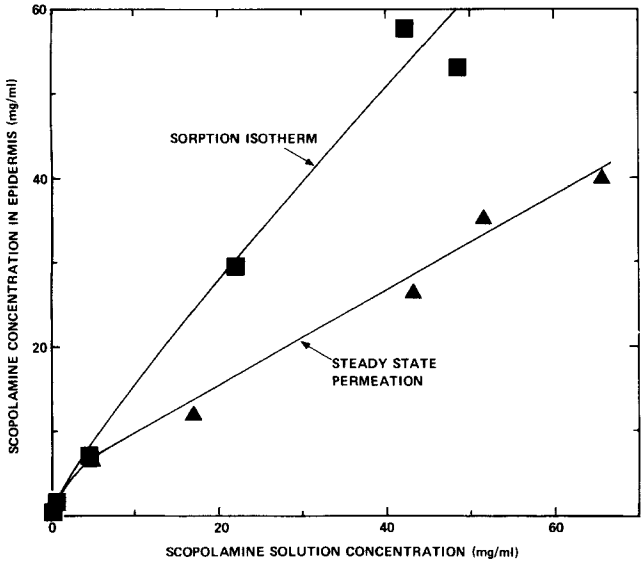

Fig. 2. Variation of drug concentration in epidermis with aqueous solution concentration (epidermis A).

EXPERIMENTAL

Details of the experimental apparatus and technique have been previously described by Michaels et al. (1975). Skin was obtained from Caucasian cadavers, in most instances excised from the inner surface of the thigh; samples were preserved in heat sealed plastic bags, stored at 4°C prior to use. The epidermis was separated from the remaining layers of tissue by stirring the skin for 45 to 60 s in water at 60°C. For scopolamine, skin permeability is strongly pH dependent in that the nonionic (more lipophilic) form of the drug is decidedly more skin permeable compared to the ionic form. On this basis, only scopolamine base was used in the permeation and sorption experiments.

Scopolamine base permeation rates through intact human cadaver epidermis were measured (at 30° ± 0.1°C) in glass permeation cells, concentrated aqueous radiolabeled drug solution being confined in one compartment in contact with the stratum corneum surface of the skin sample, with drug free Ringer's solution in the other compartment. Periodic sampling of the downstream solution and assay of drug content by scintillation counting permitted determination of the amount and rate of drug permeation as a function of time.

Equilibrium sorption isotherms were determined by equilibration of a measured weight of isolated epidermis in a relatively large volume of radiolabeled drug solution of known concentration for about 24 hr at 30° ± 0.1°C, removing the tissue from the solution, digesting it in a proteolytic solvent, and subsequently scintillation counting the resulting solution for total drug present in the tissue.

RESULTS

The transdermal steady state flux of scopolamine as a function of concentration of the aqueous drug solution contacting the stratum corneum surface of the skin is shown in Figure 1. The in vitro flux of scopolamine shows a linear increase with increasing concentration, with the flux approximating 26 μg/cm² hr at a concentration of 64 mg/ml. The concentration of scopolamine in the skin at the termination of the steady state permeation experiments was determined by the technique previously described. The results of these measurements together with the equilibrium sorption isotherm for the same epidermis are shown in Figure 2. For scopolamine solution concentrations greater than about 20 mg/ml, the concentration of scopolamine in the epidermis during the steady state permeation experiment is almost one half of that present in the sorption isotherm, suggesting the attainment of a linear concentration gradient during the permeation process.

The two components of the equilibrium sorption isotherm are shown in Figure 3. The values of the constants K_D, C_I^*, and b are, respectively, 1.1, 5.0 mg/ml, and 0.56 ml/mg. The steady state diffusivity was now determined by dividing the measured steady state in vitro transdermal flux by the computed gradient in the epidermis of dissolved drug. The apparent time lag diffusivity was determined in the usual manner from the plot of cumulative drug permeating the skin vs. time after exposure to the drug containing solution. The results of these computations are presented in Table 1. The steady state diffusivity is essentially independent of drug concentration in the solution

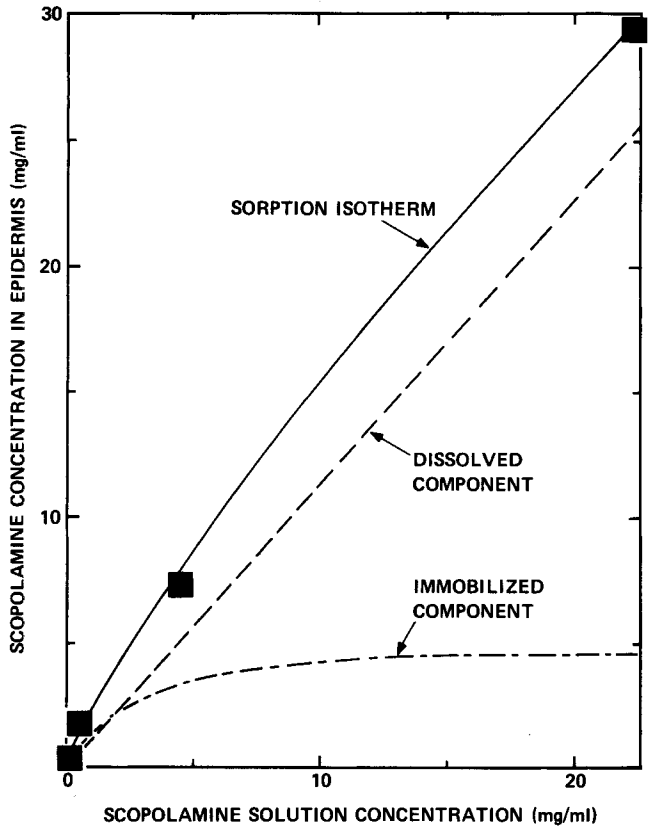

Fig. 3. Scopolamine sorption isotherm in human epidermis in vitro (epidermis A).

TABLE 1. SCOPALAMINE DIFFUSION COEFFICIENTS

(Epidermis A)

Scopolamine solution concentration C, mg/ml	Steady state diffusion coefficient, D_{SS} $cm^2/s \times 10^{10}$	Apparent time lag diffusion coefficient, D_{TL} $cm^2/s \times 10^{10}$	Ratio $\frac{D_{SS}}{D_{TL}}$
64.0	5.0	3.6	1.4
51.4	5.2	—	—
43.1	4.8	—	—
19.5	5.0	2.5	2.0
4.4	4.6	1.5	3.1

TABLE 2. EFFECT OF DELIPIDIZATION ON SCOPOLAMINE DIFFUSION COEFFICIENTS

(Epidermis B)

Tissue	Avg. steady state diffusion coefficient D_{SS}, cm^2/s
Control epidermis	4×10^{-10}
Delipidized epidermis	2×10^{-7}

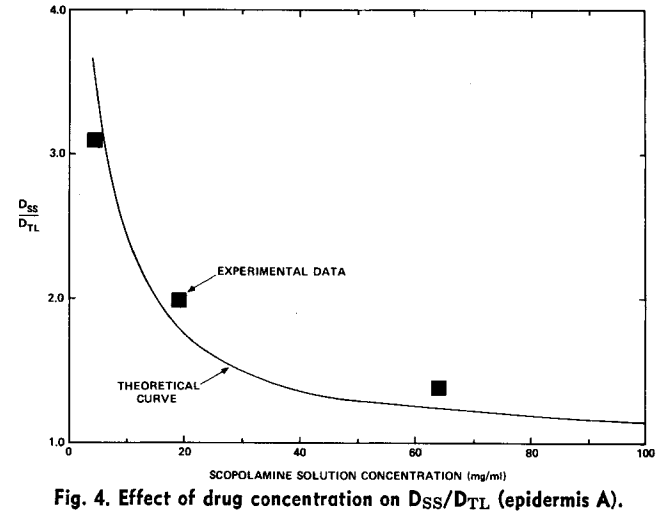

Fig. 4. Effect of drug concentration on D_{SS}/D_{TL} (epidermis A).

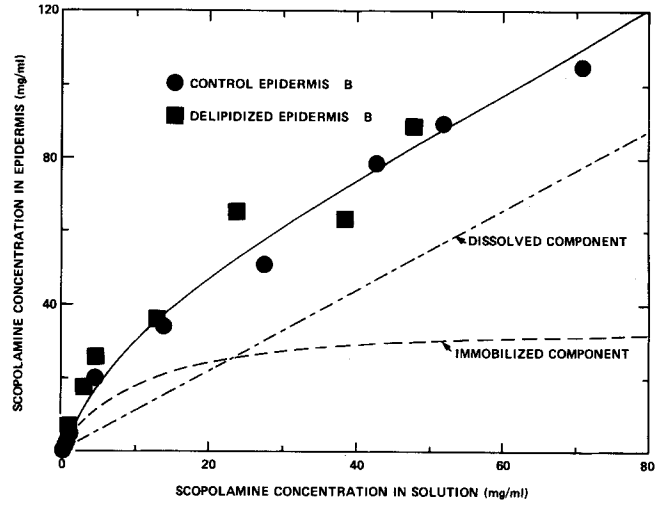

Fig. 5. Effect of delipidization on scopolamine sorption isotherm.

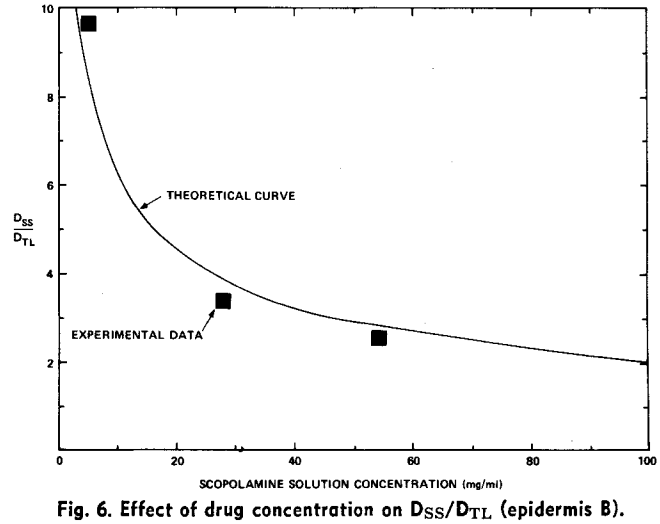

Fig. 6. Effect of drug concentration on D_{SS}/D_{TL} (epidermis B).

contacting the stratum corneum, whereas the time lag diffusivity increases with increasing drug concentration. As a consequence, the ratio of the steady state to time lag diffusion coefficients decreases with increasing drug concentration, and these results are plotted in Figure 4. Also plotted in Figure 4 is the theoretical curve generated by Equation (11) by using the obtained values of the constants K_D, C_I^*, and b. It is apparent that the agreement between theory and experiment is good, suggesting the validity of the dual sorption model in the analysis of scopolamine permeation through human skin.

The effect of lipid extraction on the permeation and sorption characteristics of scopolamine base was studied by using skin from a second cadaver. Prior to experimentation, the tissue was extracted for 3 hr with a chloroform/methanol mixture and subsequently rehydrated without de-

tectable mechanical or morphological alterations. The equilibrium sorption isotherm for both the control and lipid extracted epidermis is shown in Figure 5. The selective removal of the lipid components of the epidermis appears to have no effect on the equilibrium sorption characteristics of the skin. Furthermore, the sorption isotherm can be similarly split into the dissolved and immobilized components as shown in Figure 5. In this case, the values of the constants K_D, C_I^*, and b are, respectively, 1.1, 36.0 mg/ml and 0.11 ml/mg.

The average steady state diffusion coefficients determined by dividing the measured steady state flux by the computed gradient of dissolved drug are shown in Table 2. Lipid extraction of the skin prior to permeation measurements results in a 500 fold increase in the steady state diffusivity. Similarly, a comparison is made between the ratio of the steady state to time lag diffusion coefficients measured experimentally as a function of concentration, and the ratio predicted by using Equation (11), and is shown in Figure 6. Again, the agreement between theory and experiment is good.

CONCLUSIONS

We have been able to demonstrate the basic validity of the dual mode sorption model and its usefulness in the analysis of the permeation characteristics of scopolamine through human skin in vitro. The interstitial lipid phase of the stratum corneum is the cause for the exceedingly low apparent diffusivity of scopolamine and in this regard acts as the principal permeation barrier. Selective removal of the lipid phase of the stratum corneum enhances the transdermal permeation rate of scopolamine by orders of magnitude without causing any change in the equilibrium sorption isotherm, suggesting that scopolamine sorbed by the skin is localized predominantly within the protein phase of the tissue.

NOTATION

a = b/K_D = constant
b = Langmuir's isotherm constant
C = concentration
C_D = mobile concentration
C_I = immobilized concentration
C_I^* = Langmuir's isotherm constant
C_T = total concentration
D = diffusion coefficient
D_{SS} = steady state diffusion coefficient
D_{TL} = time lag diffusion coefficient
J = flux
K_D = partition coefficient
l = membrane thickness
t = time
x = distance
θ = diffusion time lag

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Shear Viscosity of Native and Enzyme Hydrolyzed Amioca Starch Pastes

Shear viscosity of an Amioca starch paste undergoing hydrolysis by immobilized α-amylase is shown to follow a power law behavior. The power law constants are uniquely related in a way which reduces the power law to a dimensionless form, a result previously reported only for retrograding starch and coagulating milk. The concept of a total hydrodynamic volume [Amioca starch molecules (amylopectin) plus associated immobilized liquid] is extended to concentrations above the dilute solution regime. A molecular interpretation is proposed for the shear viscosity behavior of Amioca starch pastes vs. extent of starch hydrolysis.

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SCOPE

For viscous media such as those commonly encountered in the food, textile, and paper industries, useful immobilized enzyme catalyst configurations are notably lacking. This paper presents a novel, monolithic enzyme mesh, supported on a rotating or reciprocating agitator, which is shown to be active in moderately viscous media (1 to 5 poise).

The pseudoplastic fluids examined are 1.0 to 4.7% wt/