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Pharmacokinetics of Drug Permeation through Human Skin

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Abstract □ Based on sorption and permeation characteristics of scopolamine in human skin *in vitro* and drug elimination kinetics obtained from pharmacokinetic studies, a mathematical model was developed for estimating and optimizing the temporal pattern of scopolamine delivery from a transdermal therapeutic system through human skin *in vivo*. Experimentally measured scopolamine delivery *in vivo* conformed to this model.

Keyphrases □ Permeation, cutaneous—scopolamine, mathematical model for pharmacokinetics in human skin □ Scopolamine—cutaneous permeation, mathematical model for pharmacokinetics in human skin □ Pharmacokinetics—cutaneous permeation of scopolamine, mathematical model for human skin □ Dosage forms—transdermal therapeutic system for scopolamine delivery, mathematical model for pharmacokinetics □ Anticholinergics—scopolamine, cutaneous permeation, mathematical model for pharmacokinetics in human skin

Considerable attention has been focused on drug permeation through skin *in vitro* (1–3). The principal resistance to drug permeation through intact human skin resides within the stratum corneum, which is comprised of dead, partially desiccated, keratinized epidermal cells (3). Transdermal permeation of drugs occurs by Fickian diffusion, with most of the gradient in drug concentration across the entire skin being localized within the stratum corneum (3). There is an 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. This discrepancy can be reconciled using the dual-sorption model, which invokes the coexistence of dissolved and mobile sorbed molecules in equilibrium with site-bound and immobile molecules within the skin (4).

Little effort has been directed to a quantitative understanding of drug permeation through skin *in vivo*, correlation with *in vitro* skin permeation, and a quantitatively understood application of transdermal drug permeation principles to systemic drug administration. The purpose of this study was to examine the kinetics of scopolamine sorption and permeation in human skin to achieve predictable transdermal drug delivery under clinical conditions.

THEORY

***In Vitro* Skin Permeation**—Previously (4), the basic validity of the dual-mode sorption model was demonstrated in the analysis of the permeation characteristics of scopolamine through human skin *in vitro*. 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 that do not participate in the diffusion process. If it is assumed that exchange between mobile and immobile species is rapid compared with the diffusion process and, thus, that a local equilibrium exists between the mobile and immobilized species, the drug concentration in the skin is governed by (4):

$$\left[1 + \frac{C_1^* b^*/k_D}{(1 + C_D b^*/k_D)^2}\right] \frac{\partial C_D}{\partial t} = D \frac{\partial^2 C_D}{\partial x^2} \qquad \text{(Eq. 1)}$$

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

Pharmacokinetics—*Oral*—For scopolamine administered orally, the plasma concentration can be represented adequately by a two-compartment pharmacokinetic model after the completion of absorption (5):

$$C_p = Ae^{-at} + Be^{-bt} \qquad \text{(Eq. 2)}$$

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The urinary excretion rate is given by:

$$R_o = k_E C_p V \qquad \text{(Eq. 3)}$$

where V is the volume of distribution given by:

$$V = \frac{T}{A + B} \qquad \text{(Eq. 4)}$$

and k_E is the elimination rate constant given by:

$$k_E = \frac{ab(A + B)}{Ab + Ba} \qquad \text{(Eq. 5)}$$

Intravenous—During a constant rate intravenous infusion of scopolamine in a two-compartment pharmacokinetic model, the drug excretion rate can be represented by (6):

$$R_I = I\left[1 + \left(\frac{k_E - a}{a - b}\right)e^{-bt} - \left(\frac{k_E - b}{a - b}\right)e^{-at}\right] \qquad \text{(Eq. 6)}$$

After the constant rate infusion, the drug excretion rate is given by:

$$R_I^* = I\left[\left(\frac{k_E - b}{a - b}\right)\left(1 - e^{-at^*}\right)e^{-a(t-t^*)} - \left(\frac{k_E - a}{a - b}\right)(1 - e^{-bt^*})e^{-b(t-t^*)}\right] \qquad \text{(Eq. 7)}$$

where t^* is the termination time of the infusion.

Transdermal Therapeutic System—This system is a multilayer laminate comprised of a drug reservoir, containing scopolamine in a polymeric gel, sandwiched between an impermeable backing membrane and a rate-controlling microporous membrane. On the dermal side of the rate-controlling membrane is an adhesive gel containing scopolamine; this gel layer serves both as an adhesive to secure the system on the skin surface and as an additional drug reservoir to provide an initial priming dose of drug prior to the controlled input of drug to the skin surface (7).

The transport characteristics of scopolamine from the system are determined by molecular diffusion through the various elements of the multilayer laminate. During the priming dose period, drug diffusion from the contact adhesive layer dominates the temporal pattern of drug release. However, during steady-state delivery, rate limitation or control is resident in the microporous membrane.

The scopolamine delivery rate from the system can be adequately approximated by (7):

$$R_S = G + He^{-ht} \qquad \text{(Eq. 8)}$$

where G, h, and H are constants. The first term on the right-hand side represents the steady-state delivery rate; the second term represents the temporal pattern of drug release during the priming dose period.

Mathematical Model—The delivery of scopolamine from a transdermal therapeutic system into and across human skin *in vivo* has been modeled, assuming that drug transport occurs by normal Fickian diffusion, with partition equilibrium of penetrant being maintained at the interlayer boundaries.

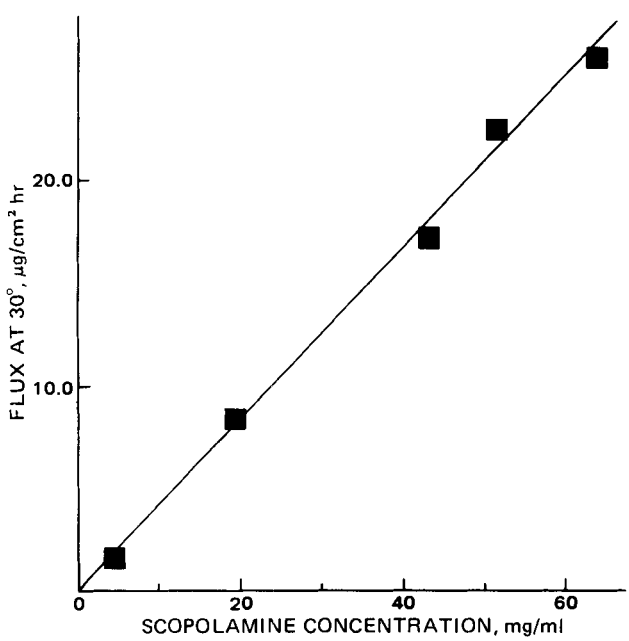
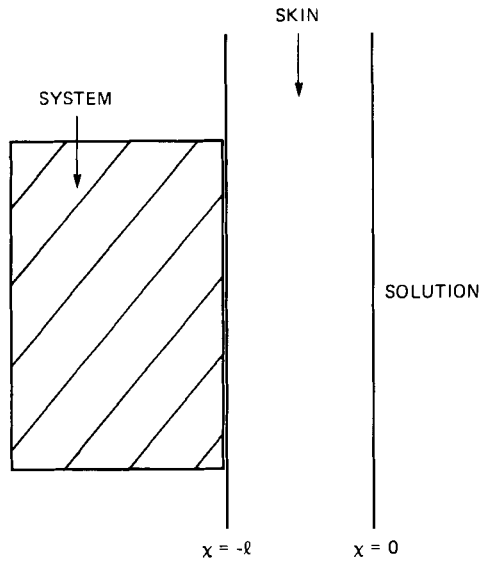


Figure 1—*Effect of concentration on scopolamine flux through human epidermis (epidermis A).*



Scheme I—Diagram of system placed on skin.

With reference to Scheme I and the assumption that infinite sink conditions are maintained on the dermal side of the skin, the scopolamine concentration in the skin is given by (4):

$$\frac{\partial C_D}{\partial t} = \frac{D}{\left[1 + \frac{C_I^* b^*/k_D}{(1 + C_D b^*/k_D)^2}\right]}\frac{\partial^2 C_D}{\partial x^2} \qquad \text{(Eq. 9)}$$

with boundary conditions:

$$C_D = 0 \qquad \text{at } x \text{ and } t = 0$$

$$C_D = 0 \qquad \text{at } x = 0 \text{ and } t$$

$$\frac{-D}{\left[1 + \frac{C_I^* b^*/k_D}{(1 + C_D b^*/k_D)^2}\right]}\left.\frac{dC_D}{dx}\right|_{x=-l} = f(t) \qquad \text{at } x = -l \text{ and } t > 0$$

where $f(t) = G + He^{-ht}$.

To provide mathematical simplicity to obtain an analytical solution, it is assumed that, based on experimental data:

$$\frac{C_I^* b^*/k_D}{(1 + C_D b^*/k_D)^2} \simeq \text{constant} = R \qquad \text{(Eq. 10)}$$

Under these conditions, the analytical solution of Eq. 9 is:

$$C_D = \frac{2}{l}\sum_{n=1}^{\infty}(-1)^{n-1}e^{-\alpha(2n-1)^2 t} \sin\frac{(2n-1)\pi x}{2l}\left[\frac{G}{\alpha(2n-1)^2}(e^{(2n-1)^2\alpha t} - 1) + \frac{H}{(2n-1)^2\alpha - h}(e^{[(2n-1)^2\alpha - h]t} - 1)\right] \qquad \text{(Eq. 11)}$$

where $\alpha = \pi^2 D/[4l^2(R + 1)]$.

From mass balance considerations, the drug accumulation in the systemic circulation equals the input of drug *in vivo* minus the excretion of drug *in vivo* and is given by:

$$\frac{dC_p V}{dt} = \frac{D}{R + 1}\left.\frac{dC_D}{dx}\right|_{x=0} - k_E C_p V \qquad \text{(Eq. 12)}$$

where dC_D/dx is the derivative of Eq. 1 with respect to x.

Therefore:

$$\frac{dC_p V}{dt} = k_E C_p V = \frac{4}{\pi}\alpha\sum_{n=1}^{\infty}(-1)^{n-1}(2n-1)e^{-\alpha(2n-1)^2 t} \times\left[\frac{G}{\alpha(2n-1)^2}(e^{(2n-1)^2\alpha t} - 1) + \frac{H}{(2n-1)^2\alpha - h}(e^{[(2n-1)^2\alpha - h]t} - 1)\right] \qquad \text{(Eq. 13)}$$

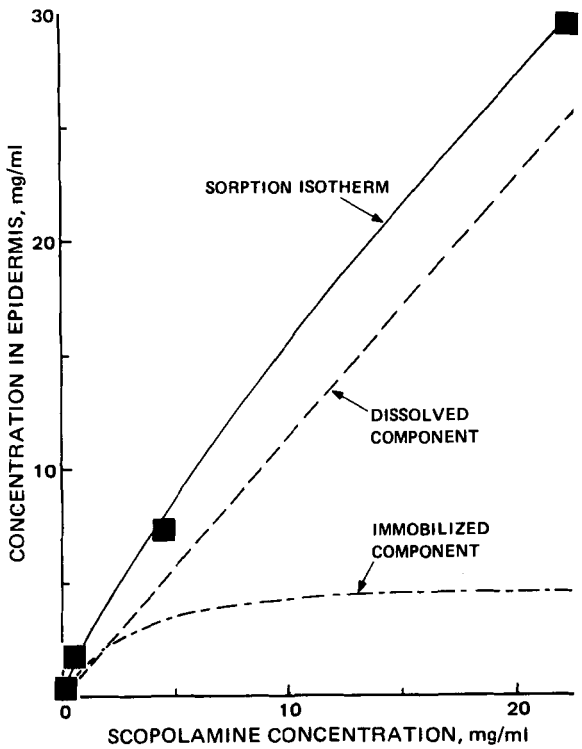


Figure 2—*Scopolamine sorption isotherm in human epidermis* in vitro.

The solution of Eq. 13 is given by:

$$C_pV = \frac{4}{\pi}\alpha e^{-k_E t}\sum_{n=1}^{\infty}(-1)^{n-1}(2n-1) \times\left[\frac{G}{\alpha(2n-1)^2}\left(\frac{e^{k_E t}}{k_E}-\frac{e^{[k_E-\alpha(2n-1)^2]t}}{k_E-\alpha(2n-1)^2}-\frac{1}{k_E}+\frac{1}{k_E-\alpha(2n-1)^2}\right)+\frac{H}{(2n-1)^2\alpha-h}\left(\frac{e^{(k_E-h)t}}{k_E-h}-\frac{e^{[k_E-\alpha(2n-1)^2]t}}{k_E-\alpha(2n-1)^2}-\frac{1}{k_E-h}+\frac{1}{k_E-\alpha(2n-1)^2}\right)\right] \quad \text{(Eq. 14)}$$

From Eqs. 3 and 14, under transdermal drug administration, the model predicts that the urinary drug excretion rate is given by:

$$R_E = \frac{4\alpha}{\pi}k_E\sum_{n=1}^{\infty}(-1)^{n-1}(2n-1) \left[\frac{G}{\alpha(2n-1)^2}\left(\frac{1}{k_E}-\frac{e^{-\alpha(2n-1)^2t}}{k_E-\alpha(2n-1)^2}-\frac{e^{-k_E t}}{k_E}+\frac{e^{-k_E t}}{k_E-\alpha(2n-1)^2}\right)+\frac{H}{(2n-1)^2\alpha-h}\left(\frac{e^{-ht}}{k_E-h}-\frac{e^{-\alpha(2n-1)^2t}}{k_E-\alpha(2n-1)^2}-\frac{e^{-k_E t}}{k_E-h}+\frac{e^{-k_E t}}{k_E-\alpha(2n-1)^2}\right)\right] \quad \text{(Eq. 15)}$$

In the unit of large values for time t:

$$R_E = \frac{4\alpha}{\pi}k_E\sum_{n=1}^{\infty}(-1)^{n-1}\frac{G}{(2n-1)\alpha k_E} = G \quad \text{(Eq. 16)}$$

which implies that, under steady-state conditions, the urinary drug excretion rate will be constant and equal to the steady-state drug input rate.

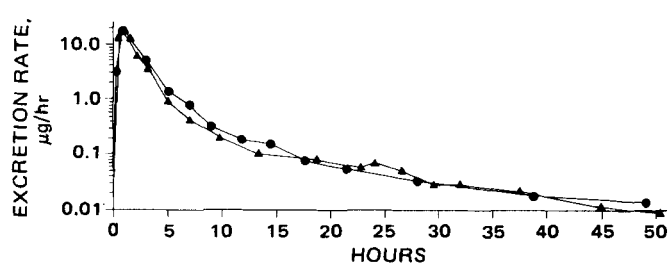


Figure 3—*Urinary excretion rates for scopolamine.*

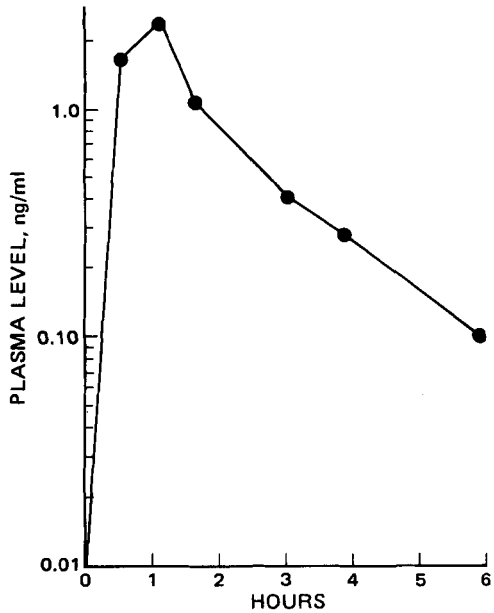


Figure 4—*Plasma levels following oral dose of 906 μg of scopolamine (base).*

After the termination of transdermal scopolamine administration, assuming a linear drug concentration gradient in the skin, the urinary drug excretion rate is given by (8, 9):

$$R_E^* = \alpha\beta k_E\sum_{n=0}^{\infty}\frac{1}{(2n+1)}\sin\left(\frac{2n+1}{2}\right) \times\pi\left[\frac{e^{-(2n+1)^2\alpha t}-e^{-k_E t}}{k_E-(2n+1)^2\alpha}\right] \quad \text{(Eq. 17)}$$

where $\beta = (16lC_D^*)/\pi^3$.

EXPERIMENTAL

***In Vitro* Skin Permeation**—Details of the experimental apparatus and technique were described previously (1, 4). Skin from Caucasian cadavers was in most instances excised from the inner surface of the thigh; samples were preserved in heat-sealed plastic bags, stored at 4° prior to use. Permeation experiments were conducted in glass permeation cells, with concentrated radiolabeled drug confined in one compartment in contact with the stratum corneum surface of the tissue and drug-free solution in the other compartment. Periodic sampling of the downstream solution and assay of drug content by liquid scintillation counting permitted determination of the amount and rate of drug permeation as a function of time.

Equilibrium sorption isotherms were determined by equilibrating a measured weight of isolated epidermis in a relatively large volume of radiolabeled drug solution of known concentration for about 24 hr at 30

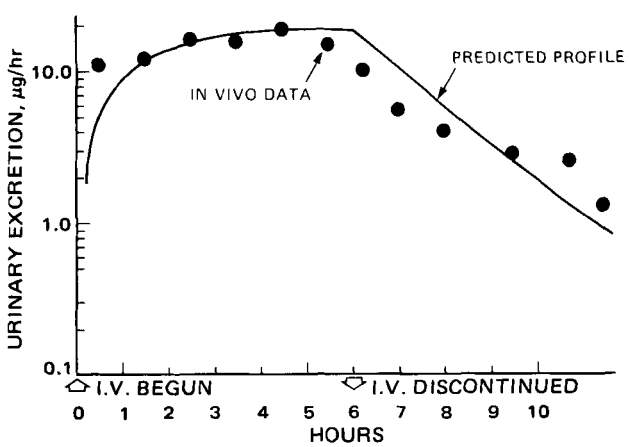


Figure 5—*Urinary excretion of scopolamine base during and following an intravenous infusion.*

Table I—Scopolamine Diffusion Coefficients (Epidermis A)

Scopolamine Solution Concentration, C, mg/ml	Steady-State Diffusion Coefficient, D_{SS}, $cm^2/sec \times 10^{10}$	Time-Lag Diffusion Coefficient, D_{TL}, $cm^2/sec \times 10^{10}$
64.0	5.0	3.6
51.4	5.2	—
43.1	4.8	—
19.5	5.0	2.5
4.4	4.6	1.5

± 0.1°, 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.

Pharmacokinetics—A sensitive and specific assay for scopolamine in plasma and urine was developed to follow the drug input rate into the systemic circulation (5). The assay utilized a stable isotope-substituted internal standard in conjunction with GLC–mass spectrometry and involved monitoring a fragment produced under electron-impact ionization of the heptafluorobutyryl derivative of scopolamine formed from the base-catalyzed hydrolysis of scopolamine.

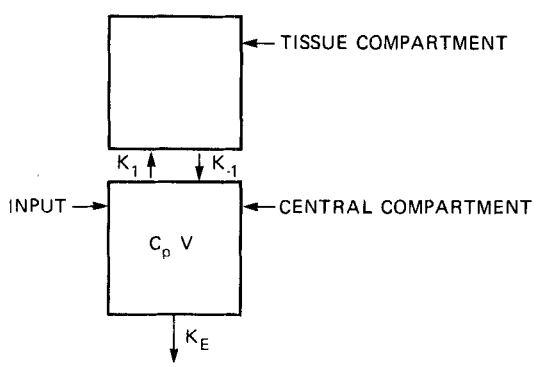
RESULTS

***In Vitro* Skin Permeation**—The transdermal steady-state flux of scopolamine as a function of concentration of the aqueous solution contacting the stratum corneum surface of the skin is shown in Fig. 1. The *in vitro* flux of scopolamine showed a linear increase with increasing concentration, with the flux approximating 26 $\mu g/cm^2$ hr at a concentration of 64 mg/ml. The two components of the equilibrium sorption isotherm are shown in Fig. 2. The values of the constants k_D, C_I^*, and b^* were 1.1 and 5.0 μg/ml and 0.56 ml/mg, respectively.

The steady-state diffusivity was then 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 *versus* time after exposure to the drug-containing solution. The results of these computations are presented in Table I.

Pharmacokinetics—Pharmacokinetic studies were performed to establish the absorption, metabolism, and excretion of scopolamine following oral administration of ~900 μg of free base, intramuscular administration of 200 μg of scopolamine hydrobromide, and intravenous infusion at 20.6 μg/hr. The urinary excretion profiles for two subjects and the plasma scopolamine levels for one of these subjects following oral administration of scopolamine are presented in Figs. 3 and 4. The computed instantaneous clearance for scopolamine is about 120 ml/min, indicating that glomerular filtration is the prime mode of clearance. The total amount of scopolamine excreted from both subjects was 4–5% of the orally administered dose. With a nonlinear regression analysis, the urinary excretion profile can be related to a two-compartment pharmacokinetic model (Scheme II) (5) and Eq. 2, where A = 35.0 μg/hr, B = 0.3 μg/hr, a = 0.67 hr^{-1}, and b = 0.07 hr^{-1}.

Following intramuscular or intravenous administration of scopolamine, the total amount of scopolamine excreted was about 10% of the administered dose; the clearance of drug from the plasma again approximated the glomerular filtration rate. With the two-compartment pharmacokinetic model constants computed following oral administration, good agreement was obtained between the predicted urinary excretion profile



Scheme II—Two-compartment pharmacokinetic model for scopolamine.

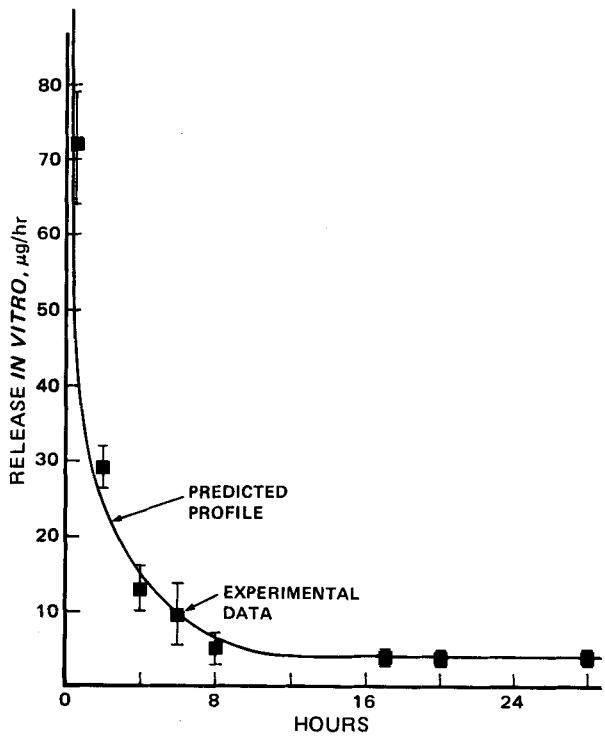


Figure 6—*Scopolamine release rate profile (average ± SD, n = 10): comparison of theory and experiment.*

using Eqs. 6 and 7 and the experimentally measured profile following intravenous infusion (Fig. 5). The results indicate the validity of the pharmacokinetic model and the consistency in the parameters obtained for different routes of scopolamine administration.

Transdermal Therapeutic System–Scopolamine *In Vitro*—A typical *in vitro* release rate–time profile of scopolamine from a transdermal therapeutic system into an infinite sink at isotonic and isothermal conditions is shown in Fig. 6. The data points represent values experimentally measured, and the solid line represents the profile predicted by theory (7). When the release rate–time profile was approximated using Eq. 8, the values of the constants G, H, and h were found to be 3.8 and 150 $\mu g/cm^2$ hr and 1.3 hr^{-1}, respectively.

Transdermal Therapeutic System–Scopolamine *In Vivo*—For the prediction of scopolamine permeation through human skin *in vivo* on the basis of *in vitro* permeation measurements, it was assumed that the stratum corneum thickness was 40 μm and that the average steady-state scopolamine diffusivity was 5 × 10^{-10} cm^2/sec (1, 4). From the two-compartment pharmacokinetic model, the elimination rate constant was estimated using Eq. 5 to be 0.62 hr^{-1}. The predicted urinary excretion rate profile for a single 24-hr application of the transdermal therapeutic system is shown in Fig. 7.

To follow the drug input rate to the systemic circulation *in vivo*, the urinary excretion rate of scopolamine was monitored. Since only 10% of the drug is recovered in the urine in the free form following intramuscular

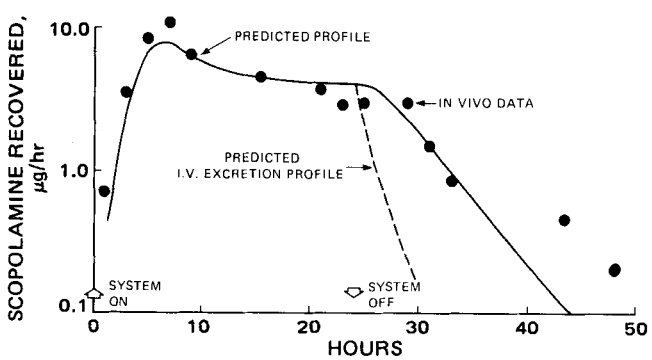


Figure 7—*Scopolamine excretion rate: comparison of theory and* in vivo *data.*

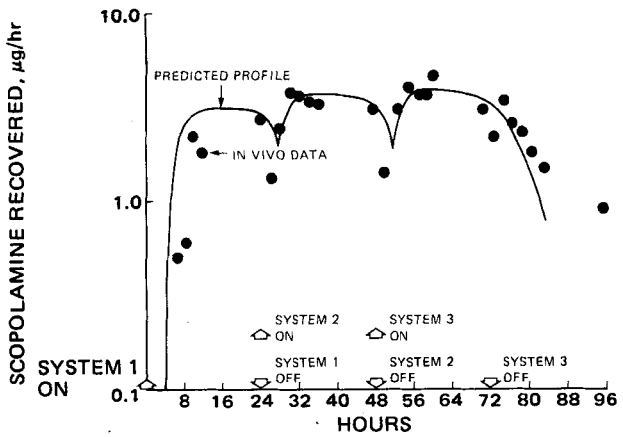


Figure 8—*Scopolamine excretion rate after multiple applications: comparison of theory and* in vivo *data.*

or intravenous administration of scopolamine, it was assumed that a similar recovery would be obtained during transdermal administration. The measured urinary excretion rate of scopolamine for a single 24-hr application of the transdermal system is also shown in Fig. 7.

In Fig. 8, the predicted urinary excretion rate profile of scopolamine for three successive 24-hr applications of the transdermal system in different skin sites is compared with *in vivo* data. Again, the agreement between theory and experiment is good. After system removal, the predicted profile underestimates the rate experimentally measured at the lower values of the urinary excretion rate. These deviations are most likely caused by the permeation of immobilized drug occurring at these late time periods.

CONCLUSIONS

A mathematical model was developed for estimating the temporal pattern of scopolamine delivery from a transdermal therapeutic system through human skin *in vivo*. The model, in turn, was useful in optimizing the design of the therapeutic system, especially in regard to the provision of the priming dose of drug that serves to saturate the immobilization sites for scopolamine within the stratum corneum and, hence, permits rapid establishment of a steady state in the urinary excretion rate of the drug (Fig. 9).

The present transdermal therapeutic system is 2.5 cm^2 in area, and its strength is specified by its temporal pattern of drug release: 200 μg priming dose, 10 μg/hr for 72 hr. Results of large-scale clinical studies indicated that the system is a safe and effective dosage form for systemic administration of scopolamine for prevention of motion-induced nausea (10). The temporal pattern of systemic delivery permits the antiemetic activity of scopolamine to be realized, with minimal incidence of other parasympatholytic effects of the drug.

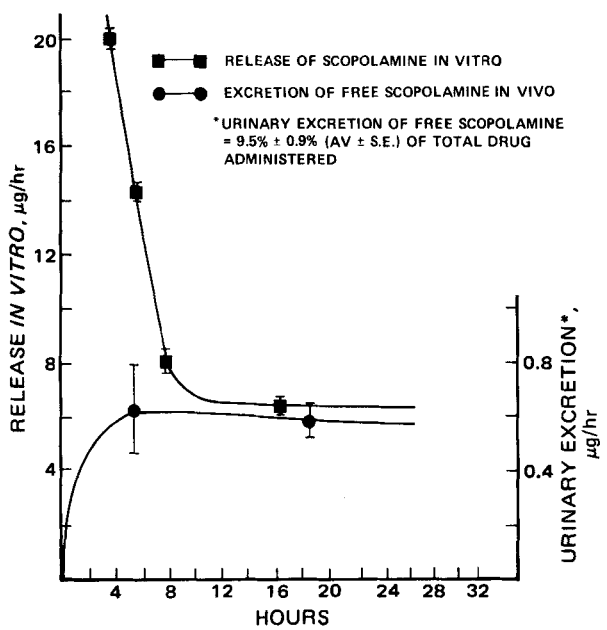


Figure 9—*Functionality of transdermal therapeutic system-scopolamine* in vitro *(average ± SE, n = 6) and* in vivo *(average ± SE, n = 15).*

SYMBOLS

A = constant
a = constant
B = constant
b = constant
b^* = Langmuir's affinity constant
C = concentration
C_D = mobile concentration
C_D^* = mobile concentration at termination of transdermal administration
C_I = immobilized concentration
C_I^* = Langmuir's saturation constant
C_p = plasma concentration
D = diffusion coefficient
D_{SS} = steady-state diffusion coefficient
D_{TL} = time-lag diffusion coefficient
G = constant
h = constant
H = constant
I = infusion rate
k_D = partition coefficient
k_E = elimination rate constant
l = thickness
R = constant
R_E = urinary excretion rate after transdermal administration
R_I = urinary excretion rate after intravenous administration
R_o = urinary excretion rates after oral administration
R_S = transdermal therapeutic system release rate
t = time
T = oral dose
V = volume of distribution
x = distance
$\alpha = [\pi^2 D/4l^2(R+1)]$
$\beta = (16lC_D^*/\pi^3)$

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