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# TRANSDERMAL DELIVERY OF PRODRUGS

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## Introduction

It should be timely to consider the prodrug approach in controlled transdermal drug delivery. Among many drug research organizations there is evidence for an acceleration toward adopting the more "rational" approach to drug discovery and development. The more noticeable examples are the "biochemical" approach to finding new lead compounds and the consideration of sophisticated drug delivery systems in drug development. The Alza-Ciba transdermal system is an example of the latter. As part of this recent evolution, scientists should be examining and weighing all options in the area of drug delivery and, if necessary, evaluating them in the light of newly developing concepts and the improving state-of-the-art.

T. Higuchi recently pointed out (1) that the conventional prodrug approach in drug delivery is beset with the problem of what the drug regulatory agencies would require with regard to toxicity testing. He also expressed the thought, however, that the prodrug approach could be more fruitfully employed in new drug discovery or in primary delivery system design rather than in the development of second generation drugs.



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Background

During the past 10-15 years, the term "prodrug" has become rather familiar to the drug design and development people and the scope and limitations of the prodrug approach have become more and more understood and its usefulness recognized. A prodrug may be defined as a drug derivative which is converted to the drug in vivo and is able to, in one or more of various possible ways, enhance the drug delivery or efficacy characteristics and, thereby, the therapeutic value of a drug. The definition may also include better patient acceptance and compliance by minimizing taste and odor problems, pain on injection, GI irritation, etc. The conversion back to the drug may be chemical or enzymatic. As part of the prodrug concept, the prodrug itself should not be pharmacologically active; its activity is directly related to its ability to liberate the parent drug. If the prodrug itself is active, it may be considered an analog drug. In the more conventional applications, the prodrug approach has been used to improve solubility, lipophilicity (for absorption), stability (both chemical and enzymatic), taste or odor (often by reducing solubility), and improve irritation problems (pain on injection, gastric irritation).

Some recent prodrug rationales have become more sophisticated with the prodrug enzymatically converting to the active drug in the target area yielding an improved therapeutic index. An example of organ specificity is the prodrug of 2-PAM·Cl (N-methylpyridinium-2-carbaldoxine chloride) (2). 2-PAM·Cl does not penetrate the blood-brain barrier. The prodrug is a tertiary amine ($pK_a \simeq 6.3$) of moderate lipophilicity and may easily cross the blood brain barrier where it is oxidized to 2-PAM chloride which does not easily cross the blood brain barrier and therefore selectively builds up in brain tissue.

Dipivalyl epinephrine (Allergan) is another good example. Epinephrine itself would have difficulty crossing the corneal membrane barrier. Dipivalyl epinephrine, which is much more lipophilic, crosses the barrier more readily, is conveniently enzymatically converted during or after transit to the target area or chamber of the eye and epinephrine is believed to be slowly released

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to systemic circulation. Because epinephrine is rapidly metabolically disposed after systemic entry, there virtually are no systemic cardiovascular effects.

## Present Considerations and Contributions

The purpose of this presentation is to describe a methodology which combines *in vitro* diffusion cell experiments with freshly excised animal skin and theoretical techniques for describing and quantifying the transport and metabolism of prodrugs in this membrane. A quantitative model has been developed which treats the skin as a three-layer membrane (stratum corneum, epidermis and dermis). Diffusivity values are assigned to the prodrug, drug and the metabolite for each layer. Enzyme parameters are also assigned for each layer. The model with a single set of these parameter values has been shown to be in very good agreement with experimental data on the transport and metabolism of the ester prodrugs of ara-A in excised hairless mouse skin. Finally, the model parameters (the diffusivities and the enzyme parameters) have been validated by independent experiments.

This approach should prove to be valuable in evaluating the performance of and, more importantly, in the rational design of prodrugs in dermal drug delivery problems as drug fluxes, species concentration profiles and where in the skin the relevant biochemical events occur can easily be predicted or mapped out from the results of the analysis.

## The Model and Equations for the Transport/Metabolism of the 5'-Monoesters of ara-A in the Hairless Mouse Skin

Figure 1 schematically illustrates the hairless mouse skin which is comprised of the stratum corneum ($h \simeq 40$ to 50 $\mu$), the epidermis ($h \simeq 10$ to 20 $\mu$) and the dermis ($h \simeq 250$ $\mu$). In the skin we have the following scheme for the enzymatic reactions:

$$\text{A (prodrug)} \xrightarrow{\text{esterase}} \text{B (drug)} \xrightarrow{\text{deaminase}} \text{(metabolite)}$$

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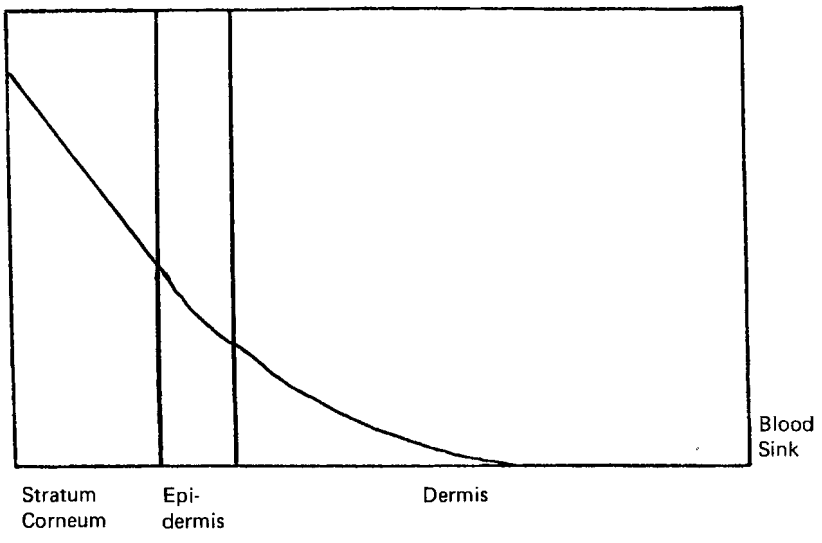


Figure 1 The multilayer model for simultaneous diffusion and metabolism of drug in the skin.

In the quasi-steady-state, we may write the following equations which describe the (one-dimensional) simultaneous enzymatic reactions and diffusion:

$$D_{A,i} \frac{d^2[A]}{dX^2} - \frac{V_{m,i}[A]}{K_m + [A]} = 0 \qquad \text{(Eq. 1)}$$

$$D_{B,i} \frac{d^2[B]}{dX^2} + \frac{V_{m,i}[A]}{K_m + [A]} - \frac{V'_{m,i}[B]}{\left(1 + \frac{[A]}{k_I}\right) K'_m + [B]} = 0 \qquad \text{(Eq. 2)}$$

$$D_{C,i} \frac{d^2[C]}{dX^2} + \frac{V'_{m,i}[B]}{\left(1 + \frac{[A]}{k_I}\right) K'_m + [B]} = 0 \qquad \text{(Eq. 3)}$$

The D's are the diffusivities. The subscripts A, B and C refer to the three species and i refers to the ith component, or stratum, of the membrane. The coordinate X is the perpendicular depth in the membrane. $V_m$ and $K_m$ are the Michaelis-Menten kinetics parameters for the esterase and $V'_m$ and $K'_m$ are those for the deaminase. $k_I$ is the deaminase inhibition constant for

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the prodrug (3). For the general case, the D's, $K_m$'s, $V_m$'s and the $k_I$'s may all be functions of X. It is however shown that, although the parameter values may be different for the different components of a membrane (e.g., epidermis, dermis and stratum corneum) they may be assumed to be constant within a particular membrane component.

At low concentrations of the prodrug, Eqs. 1-3 reduce to:

$$D_{A,i} \frac{d^2[A]}{dX^2} - k_i [A] \qquad \text{(Eq. 4)}$$

$$D_{B,i} \frac{d^2[B]}{dX^2} + k_i [A] - k_i' [B] = 0 \qquad \text{(Eq. 5)}$$

$$D_{C,i} \frac{d^2[C]}{dX^2} + k_i' [B] = 0 \qquad \text{(Eq. 5)}$$

Much of the model development studies and model validation studies were conducted using tracer levels of substrates and Eqs. 4-6.

## Analysis of Model with Experimental Data

Diffusion cell experiments (4,5) using full thickness hairless mouse skin, stripped (Scotch$^R$ tape removal of stratum corneum) and dermis skin yielded permeability coefficients. Table 1 shows the permeability coefficients of ara-A and its three monoesters for full thickness skin. Moderate increases in permeability coefficients are seen with increases in lipophilicity of the prodrug. Stripped skin permeabilities are listed in Table 2. Permeability coefficients are around 100 times larger when the stratum corneum is removed. The moderate influence of lipophilicity upon the permeability coefficient is still present when the stratum corneum is removed. The diffusivity (D) values may be calculated from the relation $D = P \cdot h$, where P is the permeability coefficient and h is the thickness for the membrane component in question.

Model validation studies were conducted for tracer levels of all three ester prodrugs. Equations 4-6 were solved numerically using experimental D

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Table 1. Permeability Coefficients of ara-A, A-ara-A, V-ara-A and O-ara-A Through Whole Skin.

| Mouse Number | Permeability Coefficient x $10^8$, cm/sec | | | | |
|---|---|---|---|---|---|
| | ara-A | A-ara-A | V-ara-A | O-ara-A | Ester/ara-A |
| 0621797 | 0.74 | 0.90 | -- | -- | 1.21 |
| 0621798 | 0.93 | 1.18 | -- | -- | 1.26 |
| 0714802 | 0.81 | 0.97 | -- | -- | 1.20 |
| 0714803 | 0.65 | 0.84 | -- | -- | 1.30 |
| 0621797 | 0.74 | -- | 1.39 | -- | 1.87 |
| 0621798 | 0.93 | -- | 1.92 | -- | 2.06 |
| 0714802 | 0.81 | -- | 1.47 | -- | 1.81 |
| 0714803 | 0.65 | -- | 1.34 | -- | 2.07 |
| 0621797 | 0.74 | -- | -- | 3.22 | 4.33 |
| 0621798 | 0.93 | -- | -- | 3.37 | 3.61 |
| 0714802 | 0.81 | -- | -- | 3.42 | 4.22 |
| 0714803 | 0.65 | -- | -- | 3.01 | 4.65 |

Table 2. Permeability Coefficients of ara-A, A-ara-A, V-ara-A and O-ara-A in Stripped Skin.

| Mouse Number | Permeability Coefficient x $10^6$ cm/sec | | | | |
|---|---|---|---|---|---|
| | ara-A | A-ara-A | V-ara-A | O-ara-A | Ester/ara-A |
| 0405802 | 1.25 | 1.90 | -- | -- | 1.52 |
| 0417802 | 1.19 | 0.82 | -- | -- | 1.53 |
| 0405802 | 1.25 | -- | 3.78 | -- | 3.02 |
| 0417802 | 1.19 | -- | 3.67 | -- | 3.08 |
| 0405802 | 1.25 | -- | -- | 8.11 | 6.49 |
| 0417802 | 1.19 | -- | -- | 7.98 | 6.71 |

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Table 3. Observed Fluxes in Go-Through Experiment with A-ara-A → V-ara-A → O-ara-A Using Stripped Skin from a 12-Week-Old Mouse (#0417804A, Skin was Soaked and Rinsed for 2 Hours Before the First Run).

| Order of Run[a] | Direction[b] | Prodrug | Flux/Initial Donor Conc. x $10^6$ (cm/sec) | | | |
|---|---|---|---|---|---|---|
| | | | Donor | | Receiver | |
| | | | Prodrug | ara-A | Prodrug | ara-A |
| 1 | epidermis → dermis | A-ara-A | -- | 1.12 | 1.37 | 0.77 |
| 2 | epidermis → dermis | V-ara-A | -- | 3.64 | 1.24 | 2.26 |
| 3 | epidermis → dermis | O-ara-A | -- | 16.70 | 1.55 | 6.86 |

[a]Indicates the 1st, 2nd, or 3rd run with the given skin preparation.

[b]Indicates the permeation direction, i.e., the donor side to the receiver side.

Table 4. Observed Fluxes in Go-Through Experiment with A-ara-A → V-ara-A → O-ara-A Using Stripped Skin from a 12-Week-Old Mouse (#0417804B, Skin was Soaked and Rinsed for 2 Hours Before the First Run).

| Order of Run[a] | Direction[b] | Prodrug | Flux/Initial Donor Conc. x $10^6$ (cm/sec) | | | |
|---|---|---|---|---|---|---|
| | | | Donor | | Receiver | |
| | | | Prodrug | ara-A | Prodrug | ara-A |
| 1 | dermis → epidermis | A-ara-A | -- | 7.05 | 1.17 | 0.69 |
| 2 | dermis → epidermis | V-ara-A | -- | 22.30 | 1.16 | 2.15 |
| 3 | dermis → epidermis | O-ara-A | -- | 59.00 | 1.14 | 5.03 |

[a]Indicates the 1st, 2nd, or 3rd run with the given skin preparation.

[b]Indicates the permeation direction, i.e., the donor side to the receiver side.

values and thicknesses for each of the membrane components. Data were obtained in a two-chamber diffusion cell for the simultaneous transport and bioconversion as described previously (4,5). Tables 3 and 4 give the back diffusion fluxes and forward fluxes of prodrug and drug for ara-A-acetate, ara-A-valerate and ara-A-octanoate. Tables 5, 6 and 7 show the best fit of

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Table 5. Least Squares Fitting of the Calculated Fluxes to the Experimental Data for the Determination of the Esterase Rate Constants (Based on Data in Tables 3 and 4).

| | Flux/Initial Donor Conc. x $10^6$ (cm/sec) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Epidermis → Dermis[a] (1st Run) | | | | Dermis → Epidermis[a] (2nd Run) | | | |
| | Donor | | Receiver | | Donor | | Receiver | |
| | A-ara-A | ara-A | A-ara-A | ara-A | A-ara-A | ara-A | A-ara-A | ara-A |
| Expt. data | -- | 1.12 | 1.37 | 0.77 | -- | 7.05 | 1.17 | 0.69 |
| Best fit[b] | -- | 0.98 | 1.39 | 0.67 | -- | 6.95 | 1.27 | 0.68 |

[a]Indicates the permeation direction, i.e., the donor side to the receiver side

[b]Iteration parameters:

$k_{epi} = 2.52 \times 10^{-3}$ sec$^{-1}$
$D_{PDepi} = 3.22 \times 10^{-9}$ cm$^2$/sec
$h_{epi} = 1.0 \times 10^{-3}$ cm
$D_{dermis} = 5.3 \times 10^{-7}$ cm$^2$/sec
$k_{dermis} = 2.96 \times 10^{-4}$ sec$^{-1}$
$D_{Depi} = 2.61 \times 10^{-9}$ cm$^2$/sec
$h_{dermis} = 2.5 \times 10^{-2}$ cm

Table 6. Least Squares Fitting of the Calculated Fluxes to the Experimental Data for the Determination of the Esterase Rate Constants (Based on the Data in Tables 3 and 4).

| | Flux/Initial Donor Conc. x $10^6$ (cm/sec) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Epidermis Dermis[a] (1st Run) | | | | Dermis Epidermis[a] (2nd Run) | | | |
| | Donor | | Receiver | | Donor | | Receiver | |
| | V-ara-A | ara-A | V-ara-A | ara-A | V-ara-A | ara-A | V-ara-A | ara-A |
| Expt. data | -- | 3.64 | 1.24 | 2.26 | -- | 22.3 | 1.16 | 2.15 |
| Best fit[b] | -- | 3.96 | 1.18 | 2.63 | -- | 23.7 | 1.18 | 2.21 |

[a]Indicates the permeation direction, i.e., the donor side to the receiver side.

[b]Iteration parameters:

$k_{epi} = 1.21 \times 10^{-2}$ sec$^{-1}$
$D_{PDepi} = 4.90 \times 10^{-9}$ cm$^2$/sec
$h_{epi} = 1.0 \times 10^{-3}$ cm
$D_{dermis} = 5.3 \times 10^{-7}$ cm$^2$/sec
$k_{dermis} = 1.63 \times 10^{-3}$ sec$^{-1}$
$D_{Depi} = 3.10 \times 10^{-9}$ cm$^2$/sec
$h_{dermis} = 2.5 \times 10^{-2}$ cm

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Table 7. Least Squares Fitting of the Calculated Fluxes to the Experimental Data for the Determination of the Esterase Rate Constants (Based on the Data in Tables 3 and 4).

| | Flux/Initial Donor Conc. x $10^6$ (cm/sec) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Epidermis → Dermis[a] (1st Run) | | | | Dermis → Epidermis[a] (2nd Run) | | | |
| | Donor | | Receiver | | Donor | | Receiver | |
| | O-ara-A | ara-A | O-ara-A | ara-A | O-ara-A | ara-A | O-ara-A | ara-A |
| Expt. data | -- | 16.7 | 1.55 | 6.86 | -- | 59.0 | 1.14 | 5.03 |
| Best fit[b] | -- | 14.8 | 1.43 | 8.02 | -- | 49.8 | 1.16 | 5.18 |

[a]Indicates the permeation direction, i.e., the donor side to the receiver side.

[b]Iteration parameters:

$k_{epi} = 5.03 \times 10^{-2}$ sec$^{-1}$ $k_{dermis} = 4.87 \times 10^{-3}$ sec$^{-1}$

$D_{PDepi} = 1.61 \times 10^{-8}$ cm$^2$/sec $D_{Depi} = 3.79 \times 10^{-9}$ cm$^2$/sec

$h_{epi} = 1.0 \times 10^{-3}$ cm $h_{dermis} = 2.5 \times 10^{-2}$ cm

$D_{dermis} = 5.3 \times 10^{-7}$ cm$^2$/sec

the calculated data to the experimental fluxes for ara-A-acetate, ara-A-valerate and ara-A-octanoate, respectively. The fitting involved deducing the best set of $k_i$ and $k_i'$ values.

Direct experimental values for $k_i$ and $k_i'$ in the epidermis and dermis were obtained by the use of trypsin to separate the dermis from the epidermis. Tissue homogenization of the separated components yielded $k_i$ and $k_i'$ in the epidermis and dermis for ara-A and its three monoesters (Table 8). Examining Table 9, it can be seen that for all three monoesters the rate constants in the epidermis are 8-10 times higher than in the dermis. This is in agreement with the results previously obtained (4) for ara-A-valerate.

The good agreement between the directly obtained experimental homogenate values and the model deduced values in the epidermis is seen in Table 9. Table 10 shows the good agreement between experimental and model-deduced enzyme constants in the dermis.

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Table 8. Comparison of Esterase and Adenosine Deaminase Activities in the Epidermis and Dermis of the Hairless Mouse Skin.

| Mouse Number | Fraction of Membrane | Specific Enzymatic Activity x $10^3$ $sec^{-1}$/gm of Tissue | | | |
|---|---|---|---|---|---|
| | | Deaminase | Esterase | | |
| | | ara-A | A-ara-A | V-ara-A | O-ara-A |
| 1027806 | Epidermis | 9.62 | 2.33 | 13.30 | 43.10 |
| | Dermis | 1.54 | 0.25 | 1.41 | 5.20 |
| 1201802 | Epidermis | 7.75 | 2.60 | 11.20 | 47.00 |
| | Dermis | 1.20 | 0.32 | 1.51 | 5.90 |
| 1201804 | Epidermis | 7.62 | 2.71 | 15.50 | 56.60 |
| | Dermis | 1.41 | 0.31 | 1.77 | 4.15 |

Table 9. Comparison of Epidermis Esterase Rate Constant Obtained from Model Fitting to Those Obtained from Trypsin Treatment.

| Prodrug | Trypsin x $10^3$ $K_{sec^{-1}}$/gm of Tissue | Model x $10^3$ $K_{sec^{-1}}$/gm of Tissue | $\frac{K_{trypsin}}{K_{e\ acetate}}$ | $\frac{K_{model}}{K_{e\ acetate}}$ |
|---|---|---|---|---|
| A-ara-A | 2.3 - 2.7 | 2.5 - 3.5 | 1 | 1 |
| V-ara-A | 11.2 - 15.5 | 10.6 - 13.5 | 4.3 - 5.7 | 3.8 - 4.3 |
| O-ara-A | 43.1 - 56.6 | 46.3 - 56.8 | 17.1 - 20.8 | 16.1 - 18.6 |
| ara-A | 7.6 - 9.6* | 6.5 - 9.3* | -- | -- |

*Deaminase constants.

After completing the model validation studies for tracer levels (Eqs. 4-6), the validity of the model when prodrug levels were near saturated solution concentrations (Eqs. 1-3) was established. The results of saturated go-through experiments are presented in Tables 11, 12 and 13 for ara-A-acetate, ara-A-valerate and ara-A-octanoate, respectively. In these experiments

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Table 10. Comparison of Dermis Esterase Rate Constant Obtained from Model Fitting to Those Obtained from Trypsin Treatment.

| Prodrug | Trypsin x $10^4$ $K_{sec}^{-1}$/gm of Tissue | Model x $10^4$ $K_{sec}^{-1}$/gm of Tissue | $\frac{K_{trypsin}}{K_{d\ acetate}}$ | $\frac{K_{model}}{K_{d\ acetate}}$ |
|---|---|---|---|---|
| A-ara-A | 2.5 - 3.1 | 2.8 - 3.1 | 1 | 1 |
| V-ara-A | 14.1 - 17.7 | 11.3 - 15.2 | 4.5 - 7.0 | 4.8 - 5.4 |
| O-ara-A | 41.5 - 59.0 | 41.9 - 45.7 | 13.2 - 23.4 | 13.3 - 16.4 |
| ara-A | 1.2 - 1.5* | 1.4 - 1.6* | -- | -- |

*Deaminase constants.

Table 11. Go-Through Experiment with Saturated A-ara-A Solution (#0418811).

| Order of Runs[a] | Flux/Initial Donor Conc. x $10^6$ (cm/sec) | | | | | |
|---|---|---|---|---|---|---|
| | Donor | | | Receiver | | |
| | A-ara-A | ara-A | ara-H | A-ara-A | ara-A | ara-H |
| 1st[b] | -- | 0.82 | 0.24 | 1.72 | 0.19 | 0.57 |
| 2nd[c] | -- | 0.59 | 0.08 | 1.55 | 0.37 | 0.23 |
| 3rd[b] | -- | 0.82 | 0.25 | 1.77 | 0.19 | 0.58 |

[a]All runs were conducted with epidermis facing the donor chamber.

[b]Only trace amounts of $^3$H-A-ara-A were used in these two runs.

[c]Saturated A-ara-A solution (2.69 x $10^{-2}$M) spiked with trace amount of $^3$H-A-ara-A was used in this run.

the first and third runs were always tracer levels with the second run having saturated or near saturated drug concentrations. The above sequence of runs allowed for direct comparison of the effect, if any, of using saturated drug concentrations.

Model validation studies with high concentrations of the prodrugs entailed determining the $K_m$, $k_m'$ and $k_I$ vlaues for all three prodrugs with the

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Table 12. Go-Through Experiment with Saturated V-ara-A Solution (#0418812).

| Order of Runs[a] | Flux/Initial Donor Conc. x $10^6$ (cm/sec) | | | | | |
|---|---|---|---|---|---|---|
| | Donor | | | Receiver | | |
| | V-ara-A | ara-A | ara-H | V-ara-A | ara-A | ara-H |
| 1st[b] | -- | 2.28 | 0.87 | 1.13 | 0.54 | 1.62 |
| 2nd[c] | -- | 0.84 | 0.21 | 1.19 | 0.59 | 0.83 |
| 3rd[b] | -- | 2.31 | 0.87 | 1.12 | 0.55 | 1.66 |

[a]All runs were conducted with epidermis facing the donor chamber.

[b]Only trace amounts of $^3$H-V-ara-A were used in these two runs.

[c]Saturated V-ara-A solution (2.39 x $10^{-2}$M) spiked with trace amount of $^3$H-V-ara-A was used in this run.

Table 13. Go-Through Experiment with Saturated O-ara-A Solution (#0418813).

| Order of Runs[a] | Flux/Initial Donor Conc. x $10^6$ (cm/sec) | | | | | |
|---|---|---|---|---|---|---|
| | Donor | | | Receiver | | |
| | O-ara-A | ara-A | ara-H | O-ara-A | ara-A | ara-H |
| 1st[b] | -- | 6.68 | 10.20 | 1.08 | 1.15 | 4.65 |
| 2nd[c] | -- | 10.20 | 5.88 | 1.18 | 1.77 | 3.37 |
| 3rd[b] | -- | 6.70 | 10.20 | 1.13 | 1.17 | 4.71 |

[a]All runs were conducted with epidermis facing the donor chamber.

[b]Only trace amounts of $^3$H-O-ara-A were used in these two runs.

[c]Saturated O-ara-A solution (5.85 x $10^{-4}$M) spiked with trace amount of $^3$H-O-ara-A was used in this run.

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Table 14. Fitting of Experimental Fluxes from Go-Through Experiment Using the Modified Physical Model (#0418811)

| | Flux/Initial Donor Conc. x $10^6$ (cm/sec) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Donor | | | | Receiver | | | |
| | A-ara-A | ara-A + ara-H | ara-A | ara-H | A-ara-A | ara-A + ara-H | ara-A | ara-H |
| Expt. data | -- | 0.67 | 0.59 | 0.08 | 1.55 | 0.60 | 0.37 | 0.23 |
| Calc. data[a] | -- | 0.71 | 0.62 | 0.09 | 1.54 | 0.63 | 0.39 | 0.24 |

[a]Parameters used in the calculations:

$D_{epi} = 1.1 \times 10^{-9}$ cm$^2$/sec

$V_{m,epi}$ (esterase) $= 3.5 \times 10^{-5}$ mole/sec

$V_{m,dermis}$ (esterase) $= 5.0 \times 10^{-6}$ mole/sec

$h_{epi} = 1.0 \times 10^{-3}$ cm

$K_m$ (esterase) $= 3.3 \times 10^{-2}$M

$k_I = 2.3 \times 10^{-4}$M

$D_{dermis} = 5.0 \times 10^{-7}$ cm$^2$/sec

$V'_{m,epi}$ (deaminase) $= 1.0 \times 10^{-5}$ mole/sec

$V'_{m,dermis}$ (deaminase) $= 1.5 \times 10^{-6}$ mole/sec

$h_{dermis} = 2.5 \times 10^{-2}$ cm

$K'_m$ (deaminase) $= 3.3 \times 10^{-4}$M

homogenates. $V_{m,i}$ and $V'_{m,i}$ values were then calculated from $(V_{m,i}/K_m) = k_i$ and $(V'_{m,i}/K'_m) = k'_i$. These parameter values were then used in Eqs. 1-3 and fluxes were numerically calculated for the two-chamber diffusion cell experiments. It should be noted that all variables except diffusivities were determined independently, the diffusivities being obtained directly from permeability experiments. Tables 14, 15 and 16 show the reasonably good

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Table 15. Fitting of Experimental Fluxes from Go-Through Experiment Using the Modified Physical Model (#0418812).

| | Flux/Initial Donor Conc. x $10^6$ (cm/sec) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Donor | | | | Receiver | | | |
| | V-ara-A | ara-A + ara-H | ara-A | ara-H | V-ara-A | ara-A + ara-H | ara-A | ara-H |
| Expt. data | -- | 1.05 | 0.84 | 0.21 | 1.19 | 1.42 | 0.59 | 0.83 |
| Calc. data[a] | -- | 1.02 | 0.83 | 0.19 | 1.16 | 1.37 | 0.57 | 0.79 |

[a]Parameters used in the calculations:

$D_{epi} = 2.2 \times 10^{-9}$ cm$^2$/sec

$V_{m,epi}$ (esterase) $= 2.9 \times 10^{-5}$ mole/sec

$V_{m,dermis}$ (esterase) $= 2.6 \times 10^{-6}$ mole/sec

$h_{epi} = 1.0 \times 10^{-3}$ cm

$K_m$ (esterase) $= 1.08 \times 10^{-3}$M

$k_I = 1.2 \times 10^{-5}$M

$D_{dermis} = 5.0 \times 10^{-7}$ cm$^2$/sec

$V'_{m,epi}$ (deaminase) $= 1.0 \times 10^{-5}$ mole/sec

$V'_{m,dermis}$ (deaminase) $= 1.5 \times 10^{-6}$ mole/sec

$h_{dermis} = 2.5 \times 10^{-2}$ cm

$K'_m$ (deaminase) $= 3.3 \times 10^{-4}$M

agreement obtained between the calculated and experimentally determined fluxes for ara-A-acetate, ara-A-valerate and ara-A-octanoate.

It can be concluded that both esterase and deaminase enzymes are quantitatively accounted for by the model with the diffusivities obtained in the permeability experiments.

## Summary

A quantitative methodology has been presented for analyzing the transport and metabolism of prodrugs in skin. The example presented here is

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Table 16. Fitting of Experimental Fluxes from Go-Through Experiment Using the Modified Physical Model (#0418813).

| | Flux/Initial Donor Conc. x $10^6$ (cm/sec) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Donor | | | | Receiver | | | |
| | O-ara-A | ara-A + ara-H | ara-A | ara-H | O-ara-A | ara-A + ara-H | ara-A | ara-H |
| Expt. data | -- | 16.0 | 10.2 | 5.88 | 1.18 | 5.14 | 1.77 | 3.37 |
| Calc. data[a] | -- | 16.1 | 10.1 | 6.03 | 1.15 | 5.05 | 1.72 | 3.33 |

[a]Parameters used in the calculations:

$D_{epi} = 5.8 \times 10^{-9}$ cm$^2$/sec

$V_{m,epi}$ (esterase) $= 1.3 \times 10^{-5}$ mole/sec

$V_{m,dermis}$ (esterase) $= 1.0 \times 10^{-6}$ mole/sec

$h_{epi} = 1.0 \times 10^{-3}$ cm

$K_m$ (esterase) $= 1.51 \times 10^{-4}$M

$k_I = 8.8 \times 10^{-7}$M

$D_{dermis} = 5.0 \times 10^{-7}$ cm$^2$/sec

$V'_{m,epi}$ (deaminase) $= 1.0 \times 10^{-5}$ mole/sec

$V'_{m,dermis}$ (deaminase) $= 1.5 \times 10^{-6}$ mole/sec

$h_{dermis} = 2.5 \times 10^{-2}$ cm

$K'_m$ (deaminase) $= 3.3 \times 10^{-4}$M

that for the transport, deacylation and deactivation of the ester prodrugs of ara-A in hairless mouse skin. The quantitative self-consistency between experimental results and a proposed model demonstrate that this approach should be considered part of the armamentaria in dermal drug delivery research.

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