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# THE EFFECT OF PENETRATION ENHANCERS ON THE KINETICS OF PERCUTANEOUS ABSORPTION

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*The effect of penetration enhancers on the kinetics of percutaneous absorption and transdermal drug delivery has been examined theoretically. Using a physically based pharmacokinetic description of skin absorption, the action of model promoters has been investigated as a function of the physicochemical properties of the penetrant. The kinetic simulation permits both zero- and first-order input of the drug from the delivery system; diffusion through the skin is modelled by consecutive transport steps across the stratum corneum and viable epidermis and by a partitioning process at the lipophilic–aqueous phase boundary between those two tissue layers. Two model enhancers, whose effects occur specifically in skin, are considered: the first (PE1) increases the drug diffusion coefficient ($D_s$) across the stratum corneum by an order of magnitude; the second (PE2) again increases $D_s$ ten-fold but also reduces the effective stratum corneum–viable tissue partition coefficient of the drug to 10% of its unperturbed value. The action of these promoters is shown to be sensitive to the oil–water distribution characteristics of the drug: PE1 is effective for relatively hydrophilic compounds but becomes increasingly ineffectual as a drug lipophilicity increases ($\log K(\text{octanol}/H_2O) \geqslant 2$); PE2, on the other hand, provides little additional effect over PE1 for hydrophilic substances but significantly enhances the transdermal delivery of hydrophobic moieties. It appears, therefore, that the desirable properties of a penetration enhancer may change depending upon the physico-chemical nature of the drug being delivered.*

## INTRODUCTION

The current interest in transdermal drug delivery has intensified the search for skin penetration enhancers. The reason for this activity is self-evident: a major limitation of transdermal administration is the excellent barrier function of skin and the resulting requirement of high drug potency for the route to be feasible. The development of efficient promoters will be necessary, therefore, to extend the range of pharmacologically active moieties which may be delivered via the skin.

Various criteria have been identified for the "ideal" penetration enhancer [1]. These include: (1) the ability to act specifically, reversibly and for predictable duration, (2) the absence both of local irritant and allergenic

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effect and of systemic toxicity and, (3) ease of formulation into an elegant and cosmetically appealing topical dosage form. These demands, however, do not address the molecular requirements of an enhancer nor do they speak to the mechanism of action of skin penetration promotion.

The range of molecules which have been identified as promoters of percutaneous absorption is broad and includes a variety of simple solvents (e.g. dimethylsulfoxide, ethanol, dimethyl acetamide) [1,2], a number of surfactants (e.g. decylmethylsulfoxide, oleic acid, sodium dodecyl sulfate) [1,3,4], and other miscellaneous species (e.g. 2-pyrrolidone, 1-dodecylazacycloheptan-2-one (Azone®), propylene glycol) [1,2,4–14]. Comprehension of the mechanism by which these agents induce enhanced skin absorption is limited. It is possible that the effect of the more simple solvents involves direct, limited, solubilization of skin tissue components and partial derangement of barrier function. Certain surfactants (e.g. decylmethylsulfoxide [3]) have been suggested to act more selectively on a specific trans-stratum corneum pathway. As a result, the efficacy of decylmethylsulphoxide, for example, is penetrant specific, promoting the absorption of "polar" compounds but not affecting that of more "lipophilic" moieties [3]. For other agents, however, hypotheses of mechanism of action are lacking and simple descriptions of effect have not been verified. The promoter 1-dodecylazacyloheptan-2-one (Azone®) [9–14] provides such an example. Initial investigation of this enhancer [9,10] suggested that it would affect only the penetration of specific types of molecule. More recently, however, evidence has appeared [13,14] which indicates that the action of Azone® may depend critically upon the presence of other components in the vehicle (e.g. propylene glycol) and that a degree of synergism may be involved in the promotion effect.

It should also be stated that confusion has arisen in the past because of improper distinction between perceived penetration enhancement by an agent in a vehicle and actual alteration of drug thermodynamic activity in the topically administered delivery system. The requirement that absorption be compared from vehicles in which the drug is at a constant fraction of saturation has been clearly defined in the literature [1] and the dangers of ignoring this criterion have been specified and illustrated [1,15].

Clear understanding of the unperturbed mechanism of drug transport through stratum corneum (and whether the transport pathway is dependent upon drug physico-chemical properties) remains elusive. This uncertainty is in part responsible for the wide range of molecular characteristics associated with present putative penetration enhancers. If one does not know where to direct the action of the promoter, then rational design of an adjuvant will continue to be a difficult task.

In previous work [16–19], a kinetic model of percutaneous absorption and transdermal drug delivery has been developed, refined and validated. Rate constants characterizing delivery system input, stratum corneum and viable epidermis diffusion, and partitioning between these skin layers have been identified. The basis of the simple model has been tested against human *in vivo* penetration data for a wide range of molecules [16] and was then extended to the interpretation of drug plasma levels following transdermal delivery [17–19]. In this paper, the effects of model absorption promoters on the predictions of the simulation are examined as a function of penetrant physical properties. The objective of the work, therefore, is to identify and illustrate how topical adjuvants must exert their action in order to enhance a specific transdermal drug delivery candidate.

## EXPERIMENTAL

The kinetic model is shown in Fig. 1 and has been fully described elsewhere [16–19]. Both zero-order and first-order delivery system input

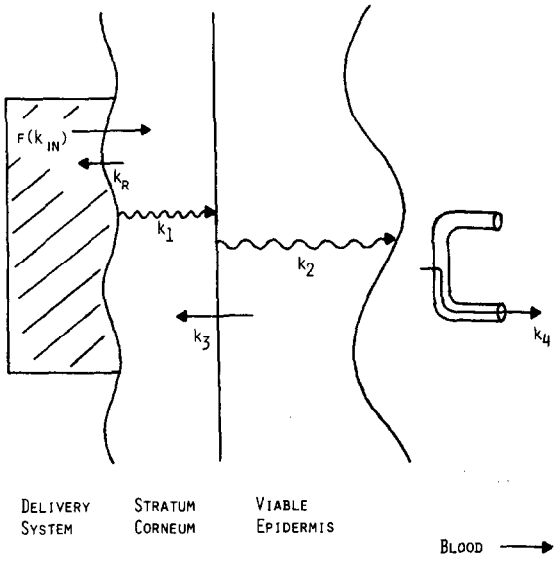


Fig. 1. Schematic representation of the physically based kinetic model for percutaneous absorption. Input kinetics from the delivery system, $f(k_{IN})$, are considered to be zero- or first-order; all other kinetics are first-order. The competition for drug between delivery system and stratum corneum is described by $k_r$; $k_1$ and $k_2$ characterize drug diffusion through stratum corneum and viable epidermis, respectively, and are drug molecular weight ($M_w$) dependent; $k_3$ allows for slow drug partitioning between stratum corneum and viable epidermis; $k_3/k_2$, an effective stratum corneum–viable tissue partition coefficient, may be equated with $K/5$, where $K$ is the drug's distribution coefficient between octanol and pH 7.4 aqueous buffer [16]; $k_4 = \ln 2/t_{0.5}$, where $t_{0.5}$ is the plasma elimination half-life of the drug.

kinetics are considered here and the action of model adjuvants on the predicted plasma concentration-time profiles is examined for a range of representative drugs. For the model as illustrated, eqns. (1) and (2) describe the plasma concentration ($C_p$) versus time relationships following zero-order and first-order input, respectively

$$C_p^0 = \frac{Ak^0 k_1 k_2}{V}\left[\frac{1}{\alpha\beta\epsilon} - \frac{\exp(-\alpha t)}{\alpha(\alpha-\beta)(\alpha-\epsilon)} - \frac{\exp(-\beta t)}{\beta(\beta-\alpha)(\beta-\epsilon)} - \frac{\exp(-\epsilon t)}{\epsilon(\epsilon-\alpha)(\epsilon-\beta)}\right] \quad (1)$$

$$C_p^I = \frac{AMk^I k_1 k_2}{V}\left[\frac{\exp(-\alpha t)}{(\beta-\alpha)(\alpha-\omega)(\alpha-\mu)} + \frac{\exp(-\beta t)}{(\alpha-\beta)(\beta-\omega)(\beta-\mu)} + \frac{\exp(-\omega t)}{(\alpha-\omega)(\omega-\beta)(\omega-\mu)} + \frac{\exp(-\mu t)}{(\alpha-\mu)(\mu-\beta)(\mu-\omega)}\right] \quad (2)$$

$A$ is the area of the delivery system. $V$ is the volume of distribution of the drug. $M$ is the amount per unit area of drug available to be released with first-order kinetics, $k^I$. For zero-order input ($k^0$ ($\mu$g/cm$^2$/h)), it is assumed that sufficient drug is present within the delivery system to maintain a constant supply for the entire application period; $\alpha$ and $\beta$ are functions of $k_2$, $k_3$ and $k_4$; and $\omega$ and $\mu$ are defined by $k^I$, $k_r$ and $k_1$ [17–19].

The effects of two "model" penetration enhancers, PE1 and PE2, have been examined on four "representative" drug molecules, D0, D1, and D2 and D3. The enhancers elicit the following actions on the transdermal process:

(a) PE1 causes a ten-fold increase in the diffusion coefficient ($D_s$) of drugs across the stratum corneum, i.e. PE1 leads to an order of magnitude increase in $k_1$.

(b) PE2 also increases $k_1$ by a factor of 10 but induces, in addition, a reduction in the ratio of $k_3/k_2$ by the same factor. In other words, PE2 reduces the effective stratum corneum–viable epidermis partition coefficient of the penetrant to 10% of its unperturbed value.

The four drug molecules are designed to have identical properties *except* for their octanol–water partitioning characteristics. For D0, log $K=0$; D1, log $K=1$; D2, log $K=2$, D3, log $K=3$, where $K$ is the octanol–water partition coefficient. The four compounds all have a molecular weight ($M_w$) of 250 Da, a biological

half-life ($t_{0.5}$) of 30 min and a volume of distribution of 100 l in a 70 kg adult (corresponding to a clearance ($Cl$) of 2.32 l/min).

Transdermal input of the model drugs is considered, in the presence and absence of PE1 and PE2, from two delivery systems:

A: a 10-cm$^2$ device, releasing the drug at a constant rate ($k^0$) of 20 $\mu$g/cm$^2$/h;

B: an identical device which includes a priming dose of 2 mg (located in the patch adhesive) which is released with first-order kinetics ($k^I = 1.3\ h^{-1}$) [20].

The clearance and hypothetical target steady-state plasma concentration ($C_{ss}$) for the four drugs determines the product of the zero-order input rate constant ($k^0$) and the delivery system area ($A$) chosen:

$$A \cdot k^0 = Cl \cdot C_{ss} \quad (3)$$

Hence, devices A and B are designed to produce a desired $C_{ss}$ of between 1.4 and 1.5 ng/ml.

## RESULTS

Figures 2–5 show the predicted plasma concentration versus time profiles for drugs D0–D3, respectively, following transdermal delivery from device A. Figures 6–9 show the corresponding profiles when the drugs are administered in device B. Each of the figures contains three curves: (i) the control profile (C) in the absence of enhancer, (ii) the profile (I) obtained when drug is delivered in the presence of PE1, and (iii) the profile (II) predicted when drug is delivered in conjunction with PE2.

The physico-chemical and pharmacokinetic data characteristic of the drug–enhancer–delivery system combination, and the derived rate parameters used to determine the profiles in Figs. 2–9, are summarized in Tables 1 and 2.

## DISCUSSION

The results in Figures 2–5 show that the efficacy of a percutaneous penetration enhancer depends significantly upon the oil–water partitioning properties of the drug to be delivered. It is observed that PE1, which promotes the speed of drug diffusion across the stratum corneum, can markedly improve the plasma concentration versus time profile for relatively hydrophilic drugs (D0 and D1; log $K = 0$ (Fig. 2) and log $K = 1$ (Fig. 3), respectively). Enhancer PE2, though, which, in addition, reduces (by ten-fold) the partition coefficient of the drug between stratum corneum and viable tissue, induces little additional effect on the absorption of D0 and D1 over that effected by PE1.

On the other hand, while PE1 does not particularly improve the transdermal delivery of the more hydrophobic agents D2 and D3 (log $K = 2$ (Fig. 4) and log $K = 3$ (Fig. 5), respectively), PE2 causes a large effect. The interpretation is straightforward: for drugs of reasonably balanced partitioning behavior (e.g. D0 and D1), slow diffusion across the stratum corneum is the rate-limiting step in percutaneous absorption; a promoter which acts specifically to reduce the diffusional resistance, therefore, will be efficacious. For drugs of greater lipophilicity (e.g. D2 and D3), however, the rate of stratum corneum to viable epidermis transfer is slowed. These compounds find the environment of the stratum corneum sympathetic and do not, as a result, partition readily into the more aqueous viable epidermis. This transport step assumes progressively greater significance as log $K$ increases and ultimately dominates the absorption process for materials of high hydrophobicity. Hence, reduction of the diffusional barrier of the stratum corneum may not be sufficient for skin penetration enhancement. A more subtle action involving alteration of the relative stratum corneum–viable epidermis affinity of the drug may be an additional essential requirement.

Comparing the control curves (C) in Figs. 6–9 with their counterparts in Figs. 2–5 reveals the utility of a priming dose in the delivery system (device B versus device A). The difference

TABLE 1

Physicochemical and pharmacokinetic parameters common to drugs D0–D3[a]

| Parameter | Device A | Value | Device B |
|---|---|---|---|
| Molecular weight, $M_w$ (Da) | | 250 | |
| Half-life, $t_{0.5}$ (h) | | 0.5 | |
| Volume of distribution, $V$ (l) | | 100 | |
| Delivery system area, $A$ ($cm^2$) | | 10 | |
| $k^0$ ($\mu g/cm^2/h$) | 20 | | 20 |
| Adhesive priming dose ($mg/cm^2$) | – | | 0.1 |
| $k^I$ ($h^{-1}$) | – | | 1.3 |
| $k_r$ ($h^{-1}$)[b] | $10^{-4}$ | | $10^{-4}$ |

[a]D0, D1, D2 and D3 differ only in their oil–water distribution behavior as defined by their octanol–water partition coefficients ($K$): D0, log $K=0$; D1, log $K=1$; D2, log $K=2$; D3, log $K=3$.
[b]A very small value is assigned to $k_r$, thereby ensuring the essentially unidirectional passage of drug from delivery system into skin (a property desirable in a well-designed formulation).

TABLE 2

Rate constants[a] of the pharmacokinetic model (Fig. 1) used to evaluate the plasma concentration versus time profiles in Figs. 2–9

| Drug/enhancer | $k_1$ ($h^{-1}$) | $k_3$ ($h^{-1}$) | Device A (figure, curve) | Device B (figure, curve) |
|---|---|---|---|---|
| D0, control | 0.145 | 0.457 | 2,C | 6,C |
| D0 & PE1 | 1.45 | 0.457 | 2,I | 6,I |
| D0 & PE2 | 1.45 | 0.046 | 2,II | 6,II |
| D1, control | 0.145 | 4.57 | 3,C | 7,C |
| D1 & PE1 | 1.45 | 4.57 | 3,I | 7,I |
| D1 & PE2 | 1.45 | 0.457 | 3,II | 7,II |
| D2, control | 0.145 | 45.7 | 4,C | 8,C |
| D2 & PE1 | 1.45 | 45.7 | 4,I | 8,I |
| D2 & PE2 | 1.45 | 4.57 | 4,II | 8,II |
| D3, control | 0.145 | 457 | 5,C | 9,C |
| D3 & PE1 | 1.45 | 457 | 5,I | 9,I |
| D3 & PE2 | 1.45 | 45.7 | 5,II | 9,II |

[a]For all drug–enhancer–device combinations, $k_2=2.28\ h^{-1}$ and $k_4=1.39\ h^{-1}$.

is amplified further when penetration enhancers are present. For D0, D1 and D2, one or both of the promoters cause(s) overshoot of the steady-state plasma concentration (by almost a factor of 4 in some cases). The significance of this effect will, of course, depend upon the narrowness of the drug's therapeutic index; given that most candidates for transdermal delivery will be in a high potency category, indiscriminate use of promoters may lead to undesirable side-effects and/or toxicity.

The approach described in this paper has focussed specifically on the putative effect of penetration enhancers within skin tissue. Actions associated with alterations in the thermodynamic activity of the drug in the applied

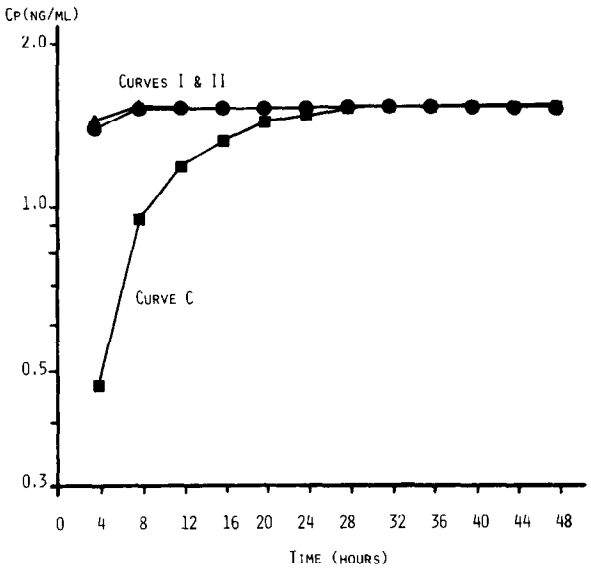


Fig. 2. Predicted plasma concentration ($C_p$) versus time ($t$) profiles for drug D0 delivered from device A in the absence of enhancer (curve C) and in the presence of PE1 (curve I) and PE2 (curve II).

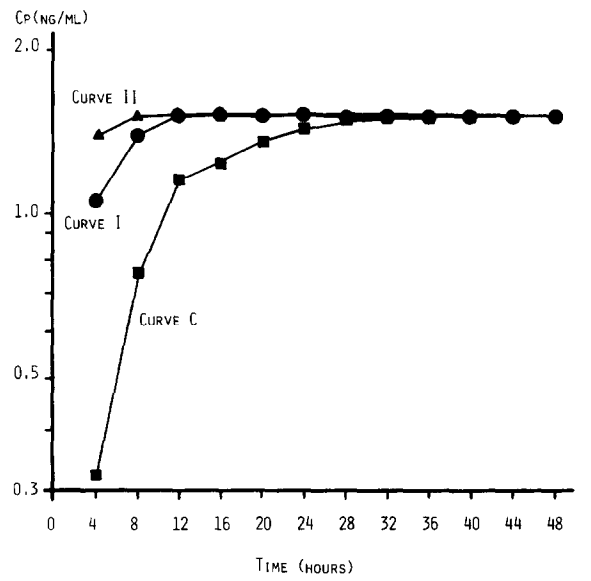


Fig. 3. Predicted $C_p$ versus $t$ profile for D1 delivered from device A; without enhancer (curve C), with PE1 (curve I), and with PE2 (curve II).

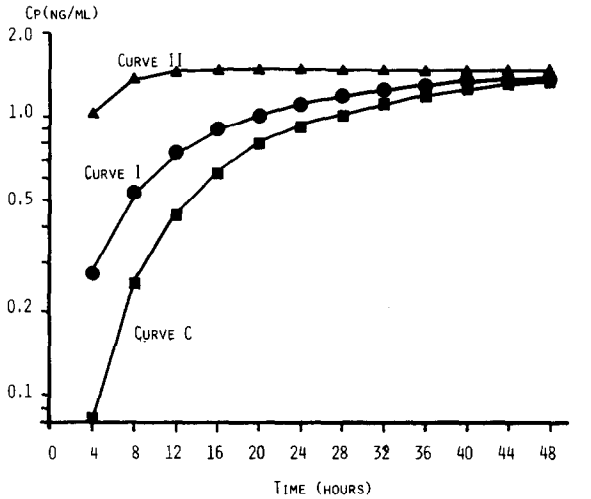


Fig. 4. Predicted $C_p$ versus $t$ profile for D2 delivered from device A; without enhancer (curve C), with PE1 (curve I), and with PE2 (curve II).

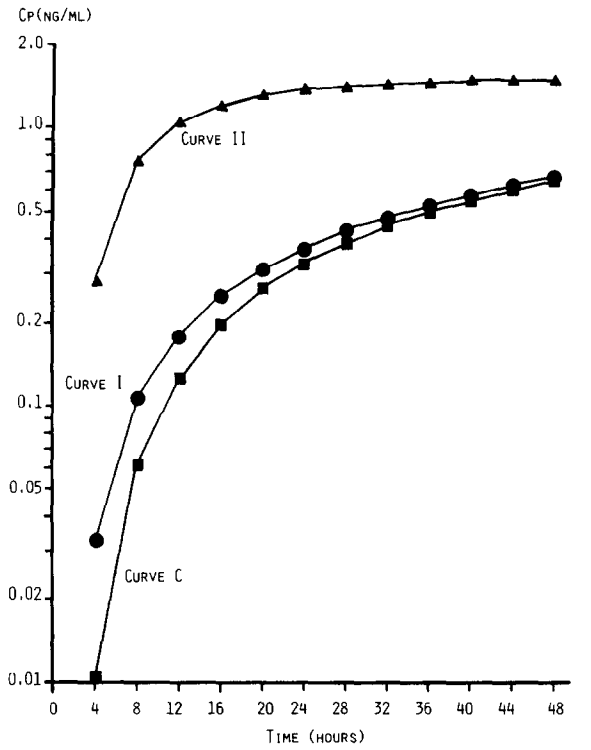


Fig. 5. Predicted $C_p$ versus $t$ profile for D3 delivered from device A; without enhancer (curve C), with PE1 (curve I), and with PE2 (curve II).

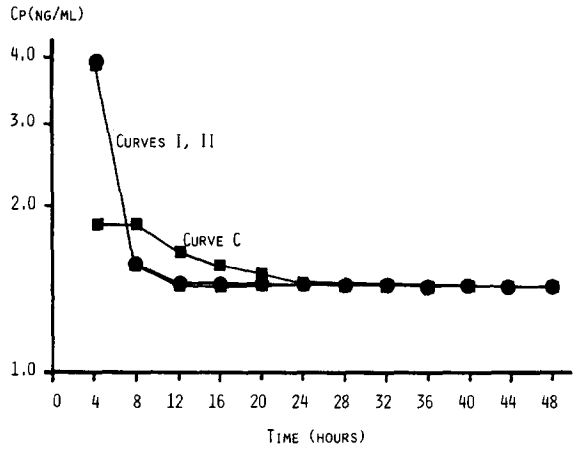


Fig. 6. Predicted plasma concentration ($C_p$) versus time ($t$) profiles for drug D0 delivered from device B in the absence of enhancer (curve C) and in the presence of PE1 (curve I) and PE2 (curve II).

formulation have not been considered. The model enhancers proposed, PE1 and PE2, have been shown to have promoting characteristics specific to the physico-chemical nature of the drug being delivered. With respect to experimental observations of penetration enhancement, PE1 may be illustrated by those simple organic solvents which fluidize lipids of the stratum corneum [1]. Definite assignment of a

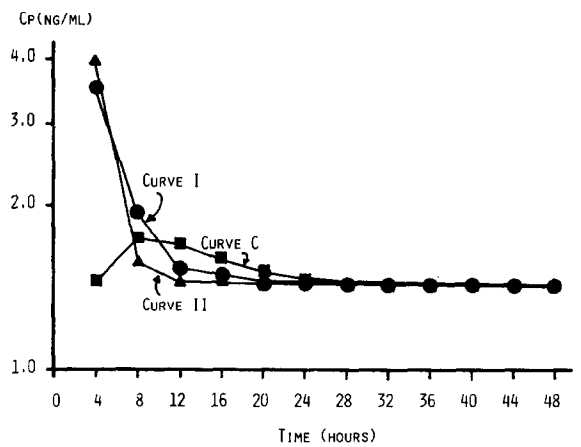


Fig. 7. Predicted $C_p$ versus $t$ profile for D1 delivered from device B; without enhancer (curve C), with PE1 (curve I), and with PE2 (curve II).

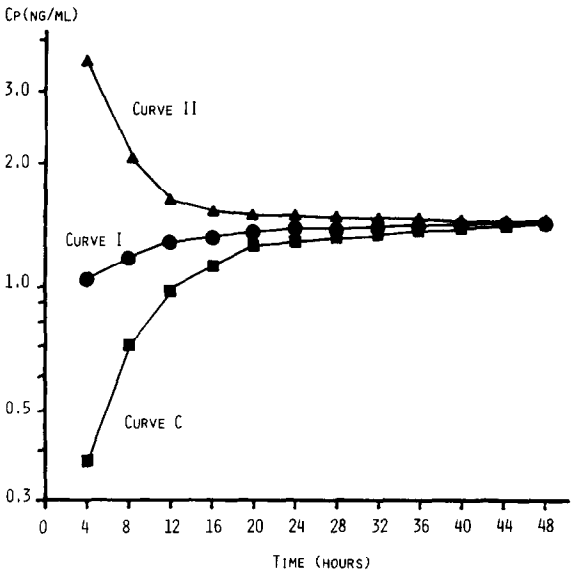


Fig. 8. Predicted $C_p$ versus $t$ profile for D2 delivered from device B; without enhancer (curve C), with PE1 (curve I), and with PE2 (curve II).

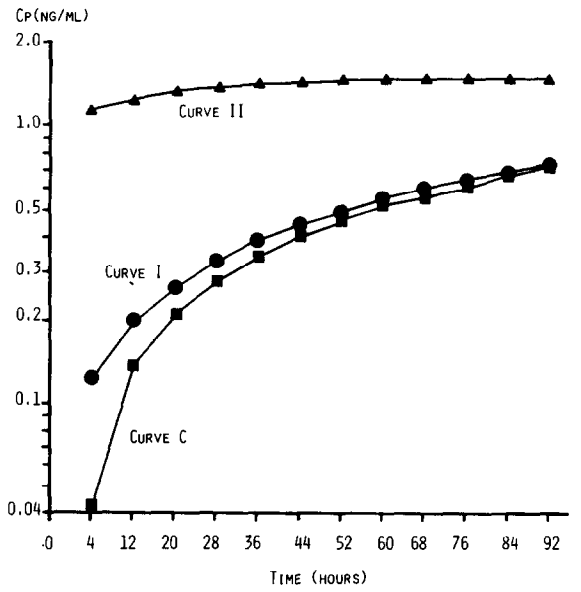


Fig. 9. Predicted $C_p$ versus $t$ profile for D3 delivered from device B; without enhancer (curve C), with PE1 (curve I), and with PE2 (curve II).

PE2-like action is more difficult. It is possible that the differential effect of decylmethylsulfoxide and other surfactants on penetrants of different polarity reflects an example of this type of specificity. Also, recent publications [13,14,21], indicating a synergistic action between propylene glycol and 1-dodecylazacycloheptan-2-one or 2-pyrrolidone, imply a modification of stratum corneum environment which reduces its lipophilic character. The validity of these hypotheses and conclusions awaits further experimental work in both *in vitro* and *in vivo* test systems.

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