EFFECT OF COSOLVENTS ON ETHYL ACETATE ENHANCED PERCUTANEOUS ABSORPTION OF LEVONORGESTREL*

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(Received May 25, 1989; accepted in revised form October 12, 1989)

Key words: penetration enhancers; levonorgestrel; hairless mouse skin

The effect of various cosolvents on ethyl acetate (EtAc) enhanced percutaneous absorption of levonorgestrel (LN) was studied using excised hairless mouse skin. The steady-state flux of LN through hairless mouse skin was increased when mixtures of EtAc and ethanol (EtOH) were used as donor phase solvents relative to that when neat EtAc was used. For example, the flux of LN was increased about 2 fold (4.5 to 10 μg/cm² h) when EtOH was added to EtAc at a volume fraction of 0.5 relative to neat EtAc. In contrast, the flux of LN from water was measured at 0.02 μg/cm² h. Adding oleic acid or isopropyl myristate at a volume fraction of 0.5 in EtAc lowered the flux to approximately 1.0 μg/cm² h. In contrast, when oleic acid was added to EtAc/EtOH (1:1) or EtOH, both at a volume fraction of 0.05, the transdermal flux of LN was found to be 9 and 7 μg/cm² h, respectively. Apparent diffusion coefficients and partition coefficients were calculated and it was found that EtAc and EtOH increased the diffusivity of LN relative to water while skin/vehicle partition coefficients correlated roughly with the observed flux of LN from the saturated solutions, with the exception of the water vehicle.

INTRODUCTION

Penetration enhancers are often used to reduce the problem of low skin permeability as well as to reduce the inherent biological variability of skin [1-5]. Ethyl acetate (EtAc) is an effective penetration enhancer for the contraceptive agent levonorgestrel (LN), as well as a variety of other drugs [6-8]. Certain mixtures of EtAc and ethanol (EtOH) are known to increase the percutaneous absorption of LN through rodent skins to a greater extent than neat EtAc from solutions saturated with drug [6,8]. It is also known that small amounts of long chain fatty acids (e.g., oleic acid) added to a hydrophilic vehicle can increase the percutaneous absorption of some coapplied drugs [9-11]. Another chemical found to increase the percutaneous absorption of certain drugs is isopropyl myristate [12]. We therefore tested various mixtures of EtAc, EtOH, and hydrophobic cosolvents (oleic acid and isopropyl myristate) as penetration enhancing solvent systems on hairless mouse skin in vitro using the drug LN. The percutaneous absorption of the solvents EtAc and EtOH through the rodent skins was also characterized. The relationship between drug flux and solvent flux is discussed in terms of possible mechanisms by which EtAc and var-
ious cosolvent systems increase the percutaneous absorption of LN.

MATERIALS AND METHODS

Materials

LN (micronized) was a gift from the World Health Organization. EtAc (U.S.P./N.F.), absolute EtOH (U.S.P./N.F.), and isopropyl myristate (U.S.P./N.F.) were obtained from Spectrum Manufacturing Corp. (Gardena, CA). Oleic acid (U.S.P./N.F.) was purchased from Mallinckrodt, Inc., Paris, KT. All solvents were used as received. The hairless mice (male HRS/J strain; 8 to 10 weeks old; 20 to 25 g) were obtained from Jackson Labs, Bar Harbor, ME.

Permeability experiments

A system employing nine glass Franz diffusion cells was used for the permeability experiments. The Franz cells were modified with inlet and outlet receiver phase ports to allow continuous flow through the cell.

The rodents were sacrificed in a CO₂ chamber, and an approximately 3 to 4 cm² area of full-thickness skin was excised from the abdomen. After removal of the subcutaneous fat, the skin were washed with physiological saline and used in the permeability experiment within one hour. The skin was mounted and clamped between the cell body and the cell cap with the epidermal side facing upward (donor side). The surface area exposed to the donor phase was 2.0 cm². The donor phase (ca. 3 mL) was prepared by suspending excess solid LN in the appropriate solvent system. The donor phase suspension was applied directly on the skin through the cell cap, which was then sealed with a glass stopper. The receptor phase, in contact with the underside of the skin, was isotonic saline at 37°C with 0.05% sodium azide added to prevent bacterial growth. The cells were maintained at 37°C by thermostatically controlled water which was circulated through a jacket surrounding the cell body. The donor phase temperature was measured at 32°C.

Receiver phase solution was pumped through the diffusion cells by means of a Manostat Cassette Pump drive unit. A fraction collector was used to collect the cell effluent. The flow rate was set so that the drug concentration in the receptor phase remained below about 10% of saturation; a typical flow rate was 10 mL/h. Uniform mixing of the drug in the receiver phase was achieved by a small magnetic stirring bar driven by an external 600 rpm motor. The donor suspensions were changed at certain times during the permeability experiments to reduce the possibility of dilution with water, which might enter the donor phase by reverse flux (back diffusion) from the receptor phase. Fractions were collected every 2 h in test tubes.

The donor phases tested were neat EtAc, neat EtOH, neat H₂O, and mixtures (0.3, 0.5, and 0.7 volume fractions) of EtAc in EtOH; EtAc/isopropyl myristate (0.5:0.5); EtAc/oleic acid (0.5:0.5); EtAc/EtOH/oleic acid (0.475:0.475:0.05); and EtOH/oleic acid (0.95:0.05). All vehicles were tested in triplicate.

Chromatographic analysis

LN concentration in the receptor phase was measured using HPLC. No sample pretreatment was required. The HPLC analyses were performed on a Waters 840 system consisting of two Model 510 pumps, a Model 481 UV detector, a Model 710B WISP (sample processor), and a Digital Computer Model 350 microprocessor/programmer. The column used to separate LN was a 4.6 mm × 25 cm, 10 μm, Whatman ODS-3 Partisil C-18. LN was measured with a mobile phase of acetonitrile/H₂O (50:50; v/v) at a flow rate of 2.0 mL/min with absorbance monitoring at 243 nm. The retention time of LN was 6.0 min.

EtOH and EtAc were measured in the receptor phase with a Waters Fast Fruit Juice Col-
umn (7.8 mm x 15 cm). The mobile phase used was 0.05% \( \text{H}_3\text{PO}_4 \) in \( \text{H}_2\text{O} \) (v/v) at a flow rate of 1.5 mL/min. EtAc and EtOH were detected with a Waters R-400 Differential Refractometer. The retention time of EtOH was 4.2 min while that of EtAc was 6.6 min. Standards of EtAc and EtOH were used to correct for the loss of these two volatile solvents from the effluent collected in the test tubes on the fraction collector prior to analysis by HPLC.

**Solubility of levonorgestrel in vehicles**

The solubility of LN in the donor vehicles tested were determined as follows. An excess of LN was suspended in the appropriate solvent system at 32°C (the temperature of the donor vehicle in the permeability cells). These suspensions were stirred for 48 h at which time the samples were centrifuged (5000 g, 10 min, 32°C). The concentration of LN in the supernatant was measured using HPLC as described above and is expressed as mg/mL of solvent.

**Determination of diffusion coefficients and partition coefficients**

Apparent diffusion coefficients \( (D_s) \) of LN in HM skin from the various solvent vehicles was determined using the following equation [13]:

\[
D_s = \frac{\delta^2}{6t_L}
\]  

where \( \delta \) is the thickness of the skin and \( t_L \) is the lag time estimated by extrapolation of the linear portion of the cumulative release curve to the axis where drug release = 0. The thickness of the skin (0.026 cm) was measured with a Van Keuren light wave micrometer (L.S. Sarrett Co., Athol, MA). Skin thickness measurements were averaged from 6 different animals at a minimum of three locations on each abdominal skin. The skin/vehicle partition coefficients \( (K_m) \) were determined using the following relationship:

\[
J_s = \frac{D_sK_mC_v}{\delta}
\]

where \( J_s \) is the drug flux (\( \mu \text{g/cm}^2 \text{h} \)), and \( C_v \) is the saturation concentration of LN in the vehicle. Sink conditions were assumed as the concentration of LN in the receptor solution was kept below 10% of saturation (the water solubility of LN at room temperature is about 1 ppm).

**RESULTS**

**Skin permeability experiments**

The cumulative amount of LN permeating through hairless mouse (HM) skin from neat EtAc, neat EtOH, and neat \( \text{H}_2\text{O} \) donor vehicles, all saturated with excess LN, is shown in Fig. 1. By using saturated solutions, the thermodynamic activity (driving force) is equal (all have unit activity) regardless of the solvent. Hence, changes in flux are the result of specific solvent/skin/drug interactions [14]. This assumes that flux of LN is limited by the skin and that dissolution is not rate limiting. The delivery of LN from EtAc increased rapidly to reach a maximum of about 4.5 \( \mu \text{g/cm}^2 \text{h} \) after which it fell to about 2 \( \mu \text{g/cm}^2 \text{h} \) until the experiment was completed (48 h). The donor phase was replaced at 42 h without a significant change in the flux of LN. The lag time \( (t_L) \) for delivery of

![Fig. 1. Cumulative amount of LN permeated through HM skin over time from LN saturated solutions of EtAc, EtOH, and \( \text{H}_2\text{O} \) as donor vehicles.](image-url)
LN from EtAc, EtOH, and H₂O were 2 h, 2 h, and 16 h respectively. The steady-state flux of LN used to determine \( t_L \) was estimated from the initial linear portion of the cumulative plots in those instances where the flux diminished during the later time points.

The cumulative amount of EtAc and EtOH permeating across the HM skin from the donor vehicles used in the example above is shown in Fig. 2. The delivery of both EtAc and EtOH was nearly constant over the course of the experiment. The lag times for delivery of both solvents were very short (1 h). The steady-state flux for LN and solvents and the corresponding lag times for all the permeation experiments are summarized in Table 1.

The cumulative amounts of LN permeating through the skin from three mixtures of EtAc and EtOH are shown in Fig. 3. The donor vehicles tested were 0.3:0.7, 0.5:0.5, and 0.7:0.3 volume fractions of EtAc in EtOH. The flux of LN was relatively high from the EtAc/EtOH (0.5:0.5) vehicle (ca. 10 \( \mu \)g/cm² h), while delivery of LN was lower from the other two vehicles (ca. 4 \( \mu \)g/cm² h). The lag time for permeation of LN through HM skin in these experiments was the same (2 h) for all three donor vehicles. The cumulative amounts of EtAc permeating through the HM skin from these three donor vehicles is shown in Fig. 4.

The delivery of EtAc was greatest from the 0.7:0.3 EtAc/EtOH vehicle; however, the delivery of EtAc from the 0.7:0.3 EtAc/EtOH vehicle was only about half that observed from neat EtAc (see Table 1). The delivery of EtOH through HM skin from the EtAc/EtOH mixtures is shown in Fig. 5. The steady-state flux of EtOH from all three solvent systems was about the same over the first 24 h (16 to 17 mg/cm² h) and the lag times were very short (about 1 h). A plot of the steady-state flux of LN versus the volume fraction of EtAc in EtOH (0 to 1) is shown in Fig. 6. The flux of LN through HM was highest from an equal volume of EtAc in EtOH.
TABLE 1

Vehicles, lag times, and steady-state fluxes from the in vitro skin permeability experiments with hairless mouse skin

<table>
<thead>
<tr>
<th>Vehicle</th>
<th>Lag time (h)</th>
<th>Steady-state flux*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LN</td>
<td>EtAc</td>
</tr>
<tr>
<td>H₂O</td>
<td>16</td>
<td>NA</td>
</tr>
<tr>
<td>EtOH</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td>EtAc/EtOH (0.3:0.7)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>EtAc/EtOH (0.5:0.5)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>EtAc/EtOH (0.7:0.3)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>EtAc</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>EtAc/OA (0.5:0.5)</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>EtAc/IPM (0.5:0.5)</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>EtAc/EtOH/OA (0.475:0.475:0.05)</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>EtOH/OA (0.95:0.05)</td>
<td>10</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Steady-state flux of LN expressed as µg/cm² h; steady-state flux of EtAc and EtOH expressed as mg/cm² h.

bNA = not applicable.

Fig. 5. Cumulative amount of EtOH permeated through HM skin over time from EtAc/EtOH (0.3:0.7), EtAc/EtOH (0.5:0.5), and EtAc/EtOH (0.7:0.3) as donor vehicles.

Oleic acid (OA) and isopropyl myristate (IPM) were tested along with EtAc and EtOH to observe the penetration enhancing effect of these cosolvents. Figure 7 shows the effect of adding IPM or OA at a volume fraction of 0.5 in EtAc to the donor vehicle. The steady-state flux of LN was much lower from these two donor vehicles, and the lag times (about 4 h) were slightly longer than from EtOH, EtAc, and various mixtures thereof (see Table 1). The addition of OA at a 0.05 volume fraction to EtOH and at a 0.05 volume fraction to EtAc/EtOH (0.475:0.475) were also tested as a donor vehicle. The amount of LN permeated through HM from these two donor vehicles is also shown in Fig. 7. The delivery of LN was enhanced about 4 fold by the addition of OA to EtOH at a 0.05 volume fraction relative to that from neat EtOH; however, the lag time for LN was increased to about 10 h. The addition of a 0.05 volume fraction of OA to EtAc/EtOH (0.475:0.475) did not result in any increase in flux of LN across the HM skin relative to that from the EtAc/EtOH (0.5:0.5) vehicle.

The cumulative amounts of EtAc permeated through HM skin from the EtAc/OA (0.5:0.5), EtAc/IPM (0.5:0.5), and the EtAc/EtOH/OA (0.475:0.475:0.05) donor vehicles are shown in

Fig. 6. Steady-state flux (µg/cm² h) of LN through HM skin from various volume fractions (0 to 1.0) of EtAc in EtOH.
Fig. 7. Cumulative amount of LN permeated through HM skin over time from LN saturated solutions of EtOH/OA (0.95:0.05), EtAc/OA (0.5:0.5), EtAc/IPM (0.5:0.5), and EtAc/EtOH/OA (0.475:0.475:0.05) as donor vehicles.

Fig. 8. The delivery of EtOH from the 0.05 OA in EtOH and the EtAc/EtOH/OA (0.475:0.475:0.05) donor mixtures is shown in Fig. 9 along with the cumulative amount of EtOH collected in the receptor fluid from the EtAc/OA (0.5:0.5) experiment. The EtOH in the receptor solution was probably produced by hydrolysis of EtAc in the skin by esterases [15,16] or by esterases leached into the receptor phase [17,18]. EtAc is stable in the donor chamber over the course of the experiment. The cumulative amounts of EtAc and EtOH permeated through the HM skin over time are uncorrected for metabolism.

TABLE 2

<table>
<thead>
<tr>
<th>Vehicle</th>
<th>LN solubility* (mg/mL)</th>
<th>$D_s$ ($cm^2/h \times 10^5$)</th>
<th>$K_m$</th>
</tr>
</thead>
<tbody>
<tr>
<td>H$_2$O</td>
<td>0.001</td>
<td>0.70</td>
<td>74</td>
</tr>
<tr>
<td>EtOH</td>
<td>8.8</td>
<td>5.6</td>
<td>0.085</td>
</tr>
<tr>
<td>EtAc/EtOH (0.3:0.7)</td>
<td>13.7</td>
<td>5.6</td>
<td>0.18</td>
</tr>
<tr>
<td>EtAc/EtOH (0.5:0.5)</td>
<td>15.7</td>
<td>5.6</td>
<td>0.35</td>
</tr>
<tr>
<td>EtAc/EtOH (0.7:0.3)</td>
<td>15.8</td>
<td>5.6</td>
<td>0.14</td>
</tr>
<tr>
<td>EtAc</td>
<td>8.0</td>
<td>5.6</td>
<td>0.29</td>
</tr>
<tr>
<td>EtAc/OA (0.5:0.5)</td>
<td>6.9</td>
<td>2.8</td>
<td>0.18</td>
</tr>
<tr>
<td>EtAc/IPM (0.5:0.5)</td>
<td>4.7</td>
<td>2.8</td>
<td>0.23</td>
</tr>
<tr>
<td>EtAc/EtOH/OA (0.475:0.475:0.05)</td>
<td>15.3</td>
<td>3.8</td>
<td>0.45</td>
</tr>
<tr>
<td>EtOH/OA (0.95:0.05)</td>
<td>8.5</td>
<td>1.1</td>
<td>2.4</td>
</tr>
</tbody>
</table>

* Determined at 32°C.

Diffusion and partition coefficients

The diffusion coefficients ($D_s$) and partition coefficients ($K_m$) for the absorption of LN through HM skin under the influence of the various donor solvents was calculated as described under Materials and Methods. The results are summarized in Table 2. The diffusion coefficient for the water vehicle was the lowest obtained ($7.0 \times 10^{-6} cm^2/h$); the largest $D_s$ observed were those for the EtOH, EtAc/EtOH
mixtures, and EtAc. Addition of OA or IPM to EtAc at 0.5 volume fractions lowered \( D_r \) relative to the EtOH/EtAc vehicles as did the addition of OA at a volume fraction of 0.05 in EtAc/EtOH and EtOH.

The skin/vehicle partition coefficients \( (K_m) \) were calculated using the apparent \( D_r \) values and the observed flux of LN at steady state obtained from the initial portion of the cumulative drug permeated over time curves using eqn. (2). The calculated \( K_m \) values are reported in Table 2. The saturated concentrations of LN in the various vehicles used to calculate \( K_m \) are also found in Table 2. The largest \( K_m \) observed was from the water vehicle (74) and the lowest from the neat EtOH vehicle (0.085). There were small differences in the calculated \( K_m \) values for the EtAc/EtOH mixtures and neat EtAc. Addition of OA and IPM to the vehicles at 0.5 volume fractions did not alter the \( K_m \) values significantly. However, addition of OA at a 0.05 volume fraction to an equal volume mixture of EtAc/EtOH did lead to a modest increase in \( K_m \) while addition of OA at a 0.05 volume fraction to EtOH increased \( K_m \) to 2.4.

**DISCUSSION**

Development of a small (5- to 10-cm\(^2\)), once-a-day transdermal delivery system for LN requires an effective penetration enhancer. EtAc, either alone or in combination with EtOH, meets this requirement. Other chemicals effective at increasing the skin permeability of LN and other hydrophobic progestational and estrogenic compounds include L-\( \alpha \)-amino acids [19], trichloroethanol/trifluoroethanol [20], various monolaurate and monooleates (e.g., sucrose monolaurate) [21,22], and tocopherol [23]. Small amounts of long-chain fatty acids (e.g., oleic acid) in a hydrophilic cosolvent (e.g., propylene glycol) have also been found to enhance the percutaneous absorption of hydrophobic drugs [9,24].

The results presented herein indicate that a significant increase in the flux of LN through HM skin results when EtOH, EtAc/EtOH mixtures, or EtAc are used as penetration enhancers *in vitro* relative to a water vehicle. The maximum LN flux (about 10 \( \mu\)g/cm\(^2\) h) was obtained from a 0.5:0.5 mixture of EtAc/EtOH. Similar results have been observed with rat skin and hairless guinea pig skin *in vitro* where EtAc/EtOH cosolvents gave higher fluxes than did neat EtAc [6,8]. Interestingly, maximum flux of LN through human cadaver skin *in vitro* was obtained from neat EtAc rather than a mixture of EtAc/EtOH [8].

The two primary factors governing the permeation of drugs through the skin are diffusivity within the skin and partitioning from the vehicle into the skin [25]. If the drug is very hydrophobic, partitioning from the stratum corneum into the viable epidermis may be important as well. LN is a very hydrophobic drug (log octanol/water partition coefficient = 3.7 [26]), suggesting that partitioning of LN from the lipid-rich stratum corneum into the aqueous viable tissues could limit overall permeation through the skin. The apparent \( D_r \) and \( K_m \) values can be used to help describe the relative effect of the enhancers tested. However, they cannot be used to identify specific effects of the solvents within various components of the skin (viz., the stratum corneum, viable epidermis, and dermis) and the vehicles. Also, the absolute values for \( D_r \) and \( K_m \) are apparent values and probably do not reflect the precise diffusion and partition coefficients, which require rigorous techniques to determine precisely [27]. It should be noted that the skin thickness was used to calculate the apparent diffusion coefficients, which were then used to calculate the apparent partition coefficients. Changes in the diffusion coefficients under the influence of the various solvent systems tested may be due in part to changes in the diffusional pathway the drug molecules are taking through the skin. Because the actual pathway a molecule follows when it passes through the skin cannot be measured directly, it is assumed in this discussion...
that the pathways are unchanged by the penetration enhancers. The apparent $D_s$ for permeation of LN through full-thickness HM skin (260 μm) indicates that EtOH and EtAc increased the diffusivity of LN within the skin relative to water. Therefore, these solvents are in some way altering the physical nature of the barrier by either extracting lipids from the stratum corneum, increasing the fluidity of the lipids, or by disrupting the structure of the keratin fibrils within the corneocytes. Differential scanning calorimetry studies as well as Fourier transform infrared spectroscopic studies indicate that EtAc is capable of extracting measurable amounts of lipid from HM stratum corneum [28]. EtAc has been used to solubilize sebum in human subjects demonstrating its ability to remove lipids from skin [29]. Other work suggests that EtOH also extracts lipids from HM stratum corneum as assessed by attenuated total reflectance infrared spectroscopy [30].

The partitioning of LN between HM skin and the vehicles showed considerable variation depending on the vehicle. Water, for which LN has very little affinity, gave a relatively large $K_m$ value of 74. This indicates that LN is more soluble in the skin (probably the lipid regions of the stratum corneum) than in water. The overall flux of LN is very low from water because the $D_s$ for the water/HM system is relatively small. Replacing water with EtOH as the donor vehicle dramatically decreased the apparent $K_m$. At the same time, the diffusivity of LN in the skin was greater due to specific skin/solvent/drug interactions. Addition of EtAc to EtOH increased the $K_m$ while not affecting $D_s$, suggesting that the increase in flux observed by the addition of EtAc to EtOH was due to increased partitioning (increased solubility) of LN into the skin. Relatively large amounts of solvent (EtAc and EtOH) are present in the skin that can influence the solubility of LN in the stratum corneum, viable epidermis, and dermis.

The addition of OA or IPM to EtAc at a volume fraction of 0.5 lowered the apparent $D_s$ while not significantly changing $K_m$. Addition of OA at a 0.05 volume fraction to EtAc/EtOH gave a lower $D_s$, but a slightly increased $K_m$. The increase in $K_m$ may have been due to the increased amount of EtAc and EtOH permeating through the skin (see Table 1). The effect of OA on solvent flux was more pronounced when OA was added to EtOH at a volume fraction of 0.05. The calculated $K_m$ for this system was 2.4 (about 10 times greater than any of the other vehicles tested except water). As shown in Table 1, the total amount of EtOH permeating through the HM skin was greatest from the EtOH/OA (0.95 : 0.05) vehicle. Thus, it appears that OA is increasing the amount of EtOH in the skin that might be leading to increased solubility (partitioning) of LN in the skin. This type of behavior has been observed in similar cosolvent systems [12,24].

HM skin has been criticized as a model for human skin in skin permeability experiments in vitro [31,32]. In our own work, we have found that HM skin considerably over-estimates drug flux under the influence of EtAc and EtOH [8]. Therefore, the data presented herein are unique to HM skin and the results should be used with caution when extrapolating the absolute values to human skin. A specific problem with HM skin is its susceptibility to the effects of long-term hydration [31,33]. However, the results from these experiments were derived primarily from the data collected over the first 24 h of the experiment. Hydration effects are generally observed when HM skin is mounted in diffusion cells longer than 48 h [31]. When EtAc was used in the vehicles, LN flux generally increased to a maximum after which time it diminished. One reason for this may be that water entered the donor chamber through back-diffusion. This has been suggested to occur in at least several cases with the penetration enhancers dimethyl sulfoxide [34-36] and laurocapram (Azone)/EtOH [37]. The donor vehicles were replaced with fresh, drug-saturated solutions at various times in these experiments without a signifi-
cant change in drug flux. Because water entering the donor chamber should not affect the thermodynamic activity of LN (LN would remain at saturation), and the fact that solvent flux was constant once it reached steady state, the drop in flux was probably due to changes in the barrier properties of the skin over time. It has been suggested that water can cause aggregation of certain drugs in the donor chamber leading to a decrease in the free drug concentration available for permeation across the skin [36]. Replacing the donor solvent system with fresh, drug saturated solvent should restore the driving force and hence restore drug flux to its initial steady-state level. As noted, this did not occur in the present experiments.

ACKNOWLEDGEMENT

This work was funded in part by the Contraceptive Development Branch of the National Institute of Child Health and Human Development under Contract No. N01-HD-5-2911.

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