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Transdermal Delivery of Zidovudine (AZT): The Effects of Vehicles, Enhancers, and Polymer Membranes on Permeation Across Cadaver Pig Skin

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ABSTRACT

The purpose of this study was to investigate the effects of vehicles, enhancers, and polymer membranes on 3'-azido-3'-deoxythymidine (AZT) permeation across cadaver pig skin. Four binary vehicles (ethanol/water, isopropyl alcohol/water, polyethylene glycol 400/water, and ethanol/isopropyl myristate [IPM]) were tested for AZT solubility and permeability across pig skin; ethanol/IPM (50/50, vol/vol) demonstrated the highest AZT flux (185.23 μg/cm^2/h). Next, the addition of various concentrations of different enhancers (*N*-methyl-2-pyrrolidone [NMP], oleic acid, and lauric acid) to different volume ratios of ethanol/IPM was investigated for their effect on AZT solubility and permeability across pig skin. The use of 2 combinations (ethanol/IPM [20/80] plus 10% NMP and ethanol/IPM [30/70] plus 10% NMP) resulted in increased AZT solubility (42.6 and 56.27 mg/mL, respectively) and also high AZT flux values (284.92 and 460.34 μg/cm^2/h, respectively) without appreciable changes in lag times (6.25 and 7.49 hours, respectively) when compared with formulations using only ethanol/IPM at 20/80 and 30/70 volume ratios without addition of the enhancer NMP. Finally, AZT permeation across pig skin covered with a microporous polyethylene (PE) membrane was investigated. The addition of the PE membrane to the pig skin reduced AZT flux values to ~50% of that seen with pig skin alone. However, the AZT flux value attained with ethanol/IPM (30/70) plus 10% NMP was 215.31 μg/cm^2/h, which was greater than the target flux (208 μg/cm^2/h) needed to maintain the steady-state plasma concentration in humans. The results obtained from this study will be helpful in the development of an AZT transdermal drug delivery system.

KEYWORDS: Zidovudine permeation, enhancer, binary vehicles, polymer membrane, transdermal delivery system.

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INTRODUCTION

Since it was first recognized in 1981, the Acquired Immunodeficiency Syndrome (AIDS) has been a major public health problem. Zidovudine (3'-azido-3'-deoxythymidine, AZT), the first anti-HIV compound approved for clinical use, is still widely used for antiretroviral (ARV) therapy, either alone or in combination with other ARV agents. During ARV therapy, it is crucial to maintain the systemic drug concentration(s) within the therapeutic level(s) throughout the treatment course.[1] Oral AZT has a short elimination half-life and low bioavailability, and frequent high doses are required to maintain the therapeutic level. As a result, dose-dependent toxic side effects are frequently observed.[2,3] To avoid the serious toxic effects resulting from oral administration, the use of a transdermal approach for AZT delivery has been proposed.[1] However, AZT is highly hydrophilic, a characteristic that adversely affects its permeability through the stratum corneum. The use of vehicles to improve transdermal permeation of AZT has been investigated by several groups. Single vehicles were not successful in increasing transdermal permeation of AZT,[4-6] but the use of vehicle combinations appears to be promising.[4-11] Several investigators have demonstrated enhanced AZT permeation by using a mixture of hydrophilic vehicles (ie, isopropyl alcohol [IPA]/water, polyethylene glycol 400 [PEG 400]/water and ethanol/water).[7-11] A higher permeation of AZT in a mixture of hydrophilic vehicles was noted when an enhancer was added.[7,8] Good permeation, with AZT reaching therapeutic concentration, has been demonstrated in a system containing a mixture of hydrophilic and hydrophobic vehicles.[8,9] However, the effect of enhancers on the skin permeation of AZT dissolved in a binary mixture of hydrophilic and hydrophobic vehicles has not been investigated. Most studies of in vitro transdermal delivery of AZT have been conducted on rat or mouse skin.[4-11] The disadvantages of using rat or mouse skin as skin models for AZT permeation include the following: (1) the hair follicles and structure of the stratum corneum of rat or mouse skin are dissimilar to human skin, and (2) skin permeation enhancers act differently in rat or mouse skin compared with human skin.[12-14] Pig skin, however, closely resembles human skin because its histological characteristics and permeability properties are similar to

Table 1. Formulation of AZT*

	Vehicles (volume ratio)					Enhancers (% vol/vol)								
						NMP			Oleic acid			Lauric acid		
Formulation	**Ethanol**	**Water**	**IPA**	**PEG 400**	**IPM**	**1**	**5**	**10**	**1**	**5**	**10**	**1**	**5**	**10**
F1†	50	50												
F2†		50	50											
F3†		50		50										
F4†	50				50									
F5	20				80									
F6	30				70									
F7	40				60									
F8	20				80	√								
F9	20				80		√							
F10	20				80			√						
F11	20				80				√					
F12	20				80					√				
F13	20				80						√			
F14	20				80							√		
F15	20				80								√	
F16	20				80									√
F17	30				70	√								
F18	30				70		√							
F19	30				70			√						

*AZT indicates 3′-azido-3′-deoxythymidine; IPA, isopropyl alcohol; PEG 400, polyethylene glycol 400; IPM, isopropyl myristate; and NMP, N-methyl-2-pyrrolidone.

†Seventy percent of saturated AZT in each binary vehicle.

human skin.[15-18] In this study, pig skin was selected to investigate the effects of binary vehicles (hydrophilic as well as a combination of hydrophilic and hydrophobic vehicles) with and without enhancers on transdermal delivery of AZT. The effect of polymer membranes, an essential element of the transdermal delivery patch, on AZT permeation was also investigated.

Materials and Methods

Materials

AZT was purchased from Brantford Chemical (Ontario, Canada). Isopropyl myristate (IPM) was supplied by Fluka Chemie (Buchs, Switzerland). Polyethylene glycol 400 (PEG 400, commercial grade) was obtained from Srichand United Dispensary Co, Ltd (Bangkok, Thailand). *N*-methyl-2-pyrrolidone (NMP) was purchased from ISP Pharmaceutical (Texas City, Texas). Oleic acid was supplied by Sigma (Buchs, Switzerland) and lauric acid was obtained from Uniqema (Emmarich, Germany). Isopropyl alcohol (IPA) and high-performance liquid chromatography (HPLC)-grade methanol were purchased from Labscan Asia, Ltd (Bangkok, Thailand). All other chemicals were reagent grade.

Methods

Determination of AZT Solubility[19]

An excess amount of AZT was added into a screw-capped test tube containing 5 mL of various combinations of binary vehicles (Table 1). The test tube was continuously rotated for 24 hours using a top to bottom rotator[20] at 33°C. The sample was then centrifuged at 5200*g* for 10 minutes. The clear supernatant was transferred into a vial for HPLC analysis of AZT.

HPLC Analysis of AZT

The HPLC system (Thermo Separation Product, San Jose, CA) consisted of a Spectra SYSTEM P1000 pump, an AS 3000 autosampler, and a UV spectra SYSTEM P1000 absorption detector. Data acquisition was performed on a PC1000 system software integrator. The column, a Spherisorb ODS column (5 μm, 250 × 4.6 mm inner diameter, Waters Corporation, Milford, MA) was equilibrated with a mixture of methanol and water (60/40, vol/vol) at a flow rate of 1.0 mL/min. A 20-μL sample was injected into the column, and the eluent was monitored at a wavelength of 267 nm using methyl paraben as an internal standard. AZT and methyl paraben were eluted at 3.2 and 4.9 minutes, respectively.

AZT Formulation

The saturated solutions of AZT in various vehicles obtained from the solubility study were used to prepare AZT formulations F1 to F19 (Table 1). Apart from formulations F1 to F4, which contained 70% saturated AZT in various vehicle combinations at a volume ratio of 1:1, the rest of the formulations were prepared using saturated AZT. Formulations F5 to F7 were prepared using ethanol and IPM as the binary vehicles at volume ratios of 20/80, 30/70, and 40/60, respectively. Formulations F8 to F19 containing mixtures of ethanol and IPM (20/80 for F8 to F16 and 30/70 for F17 to F19) were supplemented with different types (NMP, oleic acid, and lauric acid) and concentrations (1%, 5%, 10%) of enhancers.

In Vitro Permeation of AZT Across Cadaver Pig Skin

Cadaver pigs aged less than a week were collected and kept at 0°C within 12 hours after death. Abdominal skins of cadaver pigs were carefully excised within 1 week of collection. Subcutaneous fat and other extraneous tissue adhering to the dermis were completely removed and trimmed, if necessary, using forceps and scissors. The skins were cleaned with phosphate buffered saline (PBS) pH 7.4 before being cut into 2 × 2 cm^2 pieces. Individual pig skins were wrapped with aluminum foil and put into plastic bags prior to storage at –20°C. The prepared pig skins were used within 1 week.[21-22] Skin samples were checked for barrier integrity by the Trans Epidermal Water Loss (TEWL) method.[23]

For the permeation study, the frozen pig skin was thawed at room temperature before mounting on the modified Franz diffusion cell (vertical type) between the donor and receptor compartments. The diffusion area was ~1.81 ± 0.01 cm^2. The receptor compartment (in contact with the dermis side of the skin) was filled with 12 mL of PBS (37°C ± 1°C). Since the temperature of the donor solution was maintained at 32°C to 33°C, the saturated AZT formulations were prepared at the same temperature. A 1.5-mL aliquot of AZT preparation was introduced into the donor compartment, which was in contact with the stratum corneum side of the pig skin. The donor compartment was then covered with an occlusive polyester laminate film (Scotchpak 3M, St Paul, MN) and aluminum foil to prevent evaporation. At predetermined times, 2.0-mL samples were taken from the receptor compartment and kept frozen for subsequent analysis of AZT by HPLC. The sink condition of the receptor compartment was maintained with freshly prepared PBS (37°C ± 1°C).

Determination of Permeation Parameters

The amount of permeated AZT was calculated by multiplying AZT concentration with the receptor volume. For each skin specimen, the drug permeated per unit area was calculated and plotted against time. The steady-state flux (J_{ss}) and lag time (L) were calculated from the slope and x-intercept of the linear portion fitted through the regression analysis.

The permeability coefficient (K_p, cm/h) of AZT was calculated according to Equation 1,

$$K_p = \frac{J_{ss}}{C_d} , \quad (1)$$

where C_d is the saturated solubility of AZT in the binary vehicles (mg/mL) and J_{ss} is the steady-state flux (μg/cm^2/h).

For the prediction of AZT permeation through human skin, the target flux (J_{target}) of AZT can be calculated using Equation 2. The target flux can be used to predict the ability of the formulation to maintain the steady-state plasma concentration of AZT in human.

$$J_{target} = \frac{C_{ss} Cl_t BW}{A} \quad (2)$$

A represents the maximum surface area of the transdermal patch (ie, 100 cm^2); BW, the standard human body weight of 60 Kg; C_{ss}, the AZT concentration at the therapeutic level of 0.2672 μg/mL;[24] and Cl_t the total clearance of AZT in humans (ie, 1.30 L/Kg/h).[24] The calculated target flux value for AZT was 208 μg/cm^2/h.

The Effect of Polymer Membrane on AZT Permeation Across Cadaver Pig Skin

Two types of rate-controlling polymer membranes (microporous; ie, polyethylene [PE, 3M, 0.2 μm average pore size] and nonporous; ie, 9% ethyl vinyl acetate [EVA, 3M]) were used in this study to compare the rate controlling qualities of the 2 membranes on AZT flux. AZT flux through the microporous PE or nonporous EVA membrane was determined by mounting the membrane between the donor and receptor compartments and conducting the experiment using the conditions described previously.

The effect of a polymer membrane and pig skin (ie, PE placed on top of the pig skin) on AZT flux was also investigated using the method described above. The polymer membranes were equilibrated overnight by soaking in blank formulation before use.

Statistics

Data are mostly expressed as means with standard error (SE). For statistical analysis, the 1-way analysis of variance (ANOVA) was performed using the SPSS program version 9.0 (SPSS Inc, Chicago, Illinois).

Table 2. The Solubility of AZT in Various Binary Vehicles at 33°C*

Binary Vehicles Volume Ratio (50/50)	AZT Solubility† (mg/mL)
Ethanol/Water	158.64 ± 0.58
IPA/Water	208.28 ± 0.22
PEG 400/Water	52.55 ± 0.29
Ethanol/IPM	40.09 ± 0.44

*Abbreviations are explained in the first footnote to Table 1.

† Saturated AZT in each binary vehicle. Data are given as mean ± SD (n = 3).

Results and Discussion

Preliminary Experiment to Determine the Choice of Binary Vehicles for AZT Formulation

Four binary combinations of various solvent systems consisting of water, ethanol, IPA, PEG 400, and IPM were initially investigated for their effects on the in vitro permeation of AZT across pig skin. Table 2 shows the compositions of various formulations and their abilities to dissolve AZT. A combination of a hydrophilic (ethanol) and a hydrophobic (IPM) vehicle demonstrated the lowest AZT solubility when compared with the other formulations prepared in hydrophilic binary vehicles.

The permeation parameters of formulations F1, F2, F3, and F4 across pig skin are shown in Table 3. Formulation F4 demonstrated a long lag time (8.64 hours), and since the steady-state flux could not be obtained within the 12-hour period of the study, only the initial flux value was calculated. Although the solubility of AZT in F4 was the lowest compared with the other 3 formulations, the high AZT flux and permeability coefficient (K_p) for AZT attained with F4 indicated that ethanol/IPM was the best vehicle combination. This finding is in accord with those of other investigators who have demonstrated that the in vitro permeation of AZT and probenecid through rat skin was significantly enhanced by using the ethanol/IPM mixed system.[9,10] The combination of a polar (ie, ethanol) and a nonpolar (ie, IPM) vehicle has also been used to enhance transdermal delivery of other drugs.[25]

Ethanol is the most commonly used alcohol as a transdermal penetration enhancer.[26] Although maximum AZT flux has been reported with 66.6% ethanol among ethanol/water solvents across rat skin,[11] one possible drawback could be skin irritation induced by high dose ethanol.[9] Thus, ethanol/IPM vehicle combinations with volume ratios of 20/80, 30/70, and 40/60 were chosen for further study.

Ethanol/IPM Binary Vehicle Systems

Permeation profiles of AZT from the ethanol/IPM mixed system (containing volume ratios of 20/80, 30/70, and 40/60 (ie, formulations F5, F6, and F7, respectively) across pig skin are shown in Figure 1. The corresponding values for AZT solubility, lag times, steady-state permeation rates (ie, flux), and permeability coefficients are summarized in Table 4.

AZT solubility and flux values increased as the volume fraction of ethanol in the donor solution increased and the maximum flux was achieved with F7. Lag times also increased with further increases in the volume ratio of ethanol. However, there was no significant difference in permeability coefficients among the vehicles.

Both ethanol and IPM act as permeation enhancers on the skin. Many researchers have investigated the mechanism of the enhancing effect of ethanol on skin permeability. Some have demonstrated an ethanol concentration dependent enhancement mechanism: low concentrations of ethanol affect only the lipid pathway, while the polar pathway is also affected at higher concentrations.[8,11] However, the mechanism of action of IPM is poorly understood despite its well established use in pharmaceutics.[25] Kim and Chien[8] investigated the effects of vehicles and enhancers on the skin permeation of AZT using rat skin. The skin permeation rate of AZT from the ethanol/water cosolvent system increased as the volume fraction of ethanol was increased (ie, from 0%-50%), but there was no significant difference in lag times among the vehicles. This is in contrast to our findings since the increase in volume ratio of ethanol was associated with an increase in both AZT flux values and lag times. We can only speculate that this is due to some unknown effect of

Table 3. Permeation of 70% Saturated AZT in Various Binary Vehicles Across Pig Skin*

Binary Vehicles (50/50 vol/vol)	AZT Concentration (mg/mL)	Lag Time (hours)†	Flux (μg/cm²)/h†	Permeability (K_p) × 10^3 (cm/h)†
Ethanol/Water (F1)	111.04	2.86 ± 0.29	9.96 ± 0.63‡	0.09 ± 0.01
IPA/Water (F2)	145.81	3.90 ± 0.09	10.35 ± 0.67‡	0.07 ± 0.08
PEG 400/Water (F3)	36.80	3.29 ± 0.13	15.52 ± 0.60‡	0.42 ± 0.02
Ethanol/IPM (F4)	25.05	8.64 ± 0.11	185.23 ± 10.05§	6.60 ± 0.33

*Abbreviations are explained in the first footnote to Table 1. Permeation study time was 0 to 12 hours.

†Data are given as mean ± SE (n = 5).

‡Steady-state flux

§Initial flux

Table 4. Permeation of Saturated AZT in Different Volume Ratios of Ethanol/IPM Across Pig Skin*

Ethanol/IPM Ratio (vol/vol) (Formulation)	AZT Concentration (mg/mL)†	Lag Time (hours)‡	$Flux^{ss}$ ($\mu g/cm^2$)/h‡	Permeability (K_p) $\times 10^3$ (cm/h)‡
20/80 (F5)	9.61 ± 0.14	6.10 ± 0.40	120.69 ± 12.71	12.64 ± 1.33
30/70 (F6)	19.85 ± 0.25	8.23 ± 0.44§	246.16 ± 14.64§	12.53 ± 0.74
40/60 (F7)	26.22 ± 0.24	13.11 ± 0.64§,‖	348.02 ± 9.05§,‖	12.68 ± 0.33

*AZT indicates 3′-azido-3′-deoxythymidine; IPM, isopropyl myristate; and $Flux^{ss}$, steady-state flux. Permeation study time was 0 to 24 hours.
†Data are given as mean ± SD (n = 3).
‡Data are given as mean ± SE (n = 5).
§Significantly different from (F5) ($P < .05$).
‖Significantly different from (F6) ($P < .05$).

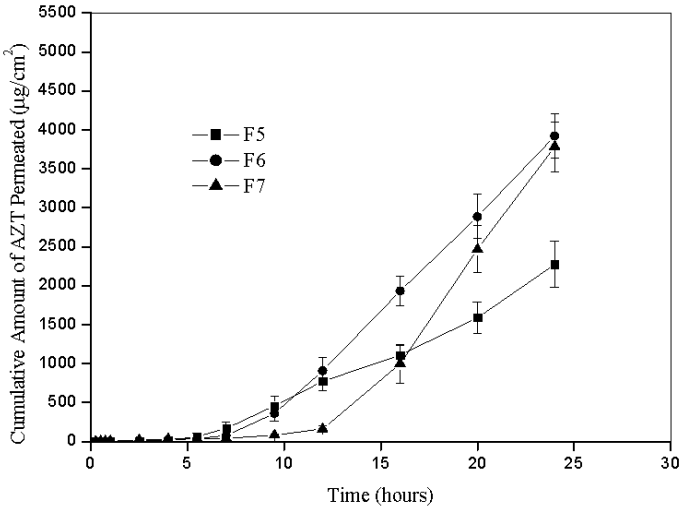

Figure 1. Permeation profiles of AZT across pig skin at 37°C ± 1°C. Donor solutions contained saturated solution of AZT in different compositions of ethanol/IPM binary vehicles. Each point represents the mean ± SE of 5 determinations.

IPM acting either alone or in combination with ethanol on the pig skin. According to the Higuchi model of percutaneous penetration, the flux of drug from the saturated solution should be the same regardless of the composition of solvents unless vehicle components alter the barrier functions of the skin.[8] By definition, permeability coefficient (K_p), diffusion coefficient (D), and skin/vehicle partition coefficient (K) can be expressed with the following equations:

$$K_p = \frac{KD}{h} \tag{3}$$

$$D = \frac{h^2}{6L}\ , \tag{4}$$

where h and L are the skin thickness and lag time, respectively.

Since the lag times (L) were significantly ($P < .05$) increased among the vehicles (Table 4), diffusivity (D) across the skin would be decreased by increasing the volume fraction of ethanol in the ethanol/IPM system. Thus, according to Equation 3, there will be increased partitioning of drug into the skin if skin thickness is unchanged since diffusibility is decreased and permeability was not significantly different among the vehicles (Table 4). Therefore, it can be speculated that the ethanol/IPM system increased the drug solubility in the stratum corneum by increasing the partitioning of the drug. The increased AZT flux can also be explained using the following equation:

$$J_{ss} = K_p C_d\ , \tag{5}$$

where J_{ss}, K_p, and C_d represent steady-state flux, permeability coefficient, and saturated solubility of AZT in the donor solution, respectively. The solubility of AZT was increased when the volume ratio of ethanol was increased. This increase in drug content associated with the increased ethanol fraction means that more of the drug is available to be partitioned with the vehicle system into the skin leading to the higher AZT flux values seen with increased volume ratios of ethanol.

Although F7 (ethanol/IPM [40/60]) demonstrated the highest AZT flux value across pig skin, it was not considered for further study due to its long lag time of 13.11 hours. F5 and F6 containing ethanol/IPM (20/80) and ethanol/IPM (30/70), respectively, were selected to determine whether the addition of various enhancers would further increase AZT flux across pig skin.

Effect of Skin Permeation Enhancers

Hydrophobic (oleic acid and lauric acid) and hydrophilic (NMP) enhancers at concentrations of 1%, 5%, and 10% were added to ethanol/IPM (20/80) to produce formulations F8 to F16 (Table 1). The permeation parameters of saturated AZT in ethanol/IPM (20/80) (with and without enhancers), across pig skin are shown in Table 5. Of the hydrophobic enhancers (oleic acid and lauric acid), only 5% oleic acid increased the AZT flux value, but the change was not significant when compared with the control formulation F5. With the hydrophilic enhancer NMP, however, a concentration of 10% NMP (F10) significantly increased ($P < .05$) the AZT flux value by more than 2-fold when compared with F5.

Table 5. Permeation Parameters of Saturated AZT in Ethanol/IPM (20/80) or Ethanol/IPM (30/70) Binary Vehicles With and Without Enhancers Across Pig Skin*

Binary Vehicles + Enhancer (Formulation)	AZT Concentration (mg/mL)†	Lag Time (hours)‡	$Flux^{ss}$ § (μg/cm²)/h‡	Permeability (K_p) × 10^3 (cm/h)‡
Ethanol/IPM (20/80) no enhancer added (F5)	9.61 ± 0.14	6.10 ± 0.40	120.69 ± 12.7	12.64 ± 1.33
+ NMP				
1% (F8)	14.07 ± 0.46	6.59 ± 0.35	84.76 ± 5.62	6.04 ± 0.40
5% (F9)	27.50 ± 0.45	6.97 ± 0.30	128.34 ± 5.94	4.65 ± 0.21
10% (F10)	42.60 ± 0.49	6.25 ± 0.45	284.92 ± 18.34‖	6.74 ± 0.43
+ Oleic acid				
1% (F11)	10.35 ± 0.47	4.24 ± 0.43	69.12 ± 3.41	6.71 ± 0.33
5% (F12)	15.33 ± 0.29	6.11 ± 0.32	130.60 ± 6.04	8.50 ± 0.39
10% (F13)	9.58 ± 0.49	5.37 ± 0.71	88.60 ± 10.65	9.16 ± 1.10
+Lauric acid				
1% (F14)	10.25 ± 0.23	3.32 ± 0.46	54.78 ± 5.42	5.32 ± 0.53
5% (F15)	13.24 ± 0.34	7.40 ± 0.61	106.28 ± 13.60	8.01 ± 1.15
10% (F16)	9.38 ± 0.55	5.48 ± 0.78	93.11 ± 8.70	9.99 ± 0.93
Ethanol/IPM (30/70) no enhancer added (F6)	19.85 ± 0.25	8.23 ± 0.44	246.16 ± 14.64	12.53 ± 0.74
+ NMP				
1% (F17)	23.44 ± 0.43	7.91 ± 0.55	262.60 ± 9.99	11.20 ± 0.43
5% (F18)	33.37 ± 0.28	7.80 ± 0.13	348.84 ± 9.30¶	10.46 ± 0.27
10% (F19)	56.27 ± 0.19	7.49 ± 0.59	460.34 ± 18.72¶	8.16 ± 0.33

*Abbreviations are explained in the first footnote to Table 1. Permeation study time was 0 to 24 hours.

†Data are given as mean ± SD (n = 3).

‡Data are given as mean ± SE (n = 5).

§$Flux^{ss}$ indicates steady-state flux.

‖Significantly different from (F5) ($P < .05$).

¶Significantly different from (F6) ($P < .05$).

Formulations F17, F18, and F19 consisting of ethanol/IPM (30/70) and containing NMP 1%, 5%, and 10%, respectively, were also investigated to determine the transdermal enhancement effect of NMP. F19, a formulation containing 10% NMP significantly increased ($P < .05$) AZT flux value by 1.8-fold when compared with the control formulation F6. These results indicate that 10% NMP is an effective enhancer for AZT when compared with the other enhancers used in this study (Figure 2). AZT solubility was increased when increasing concentrations of NMP (1%, 5%, 10%) were added to the ethanol/IPM mixed systems (ie, 20/80 and 30/70). However, the AZT solubility was greater in the ethanol/IPM (30/70) mixed system at all concentrations of NMP (Table 5). The AZT flux attained with F19 was greater than that attained with F10. We have previously shown that the ethanol/IPM binary vehicle increased drug solubility in the stratum corneum by increasing the partitioning of AZT. Since the AZT concentration in F19 is greater than that attained in F10, more of the AZT would be available for partitioning with the vehicle/enhancer system into the skin leading to the higher AZT flux value seen with F19.

Effect of Polymer Membrane on AZT Permeation Across Pig Skin

Two polymer membranes (a microporous PE membrane and a nonporous EVA membrane) were tested for their suitability for use as a rate-controlling membrane in a transdermal delivery system. The permeation profiles of AZT in F10 across the 2 membranes are shown in Figure 3. AZT readily permeated through the microporous membrane, whereas the AZT flux through the nonporous membrane was negligible.

The permeation profiles of AZT from F10 and F19 across pig skin alone and across pig skin covered with the microporous PE membrane are shown in Figure 4. For both formulations, there was a reduction in lag times, AZT flux, and permeability coefficient values when the pig skin was covered with microporous PE membrane (Table 6). Although the AZT flux values for both F10 and F19 were decreased by more than 50% when the microporous PE membrane was applied to the pig skin, the AZT flux value of F19, at 215.31 μg/cm²/h was still greater than the target flux value of 208 μg/cm²/h, which is required to maintain a therapeutic level in the blood. The

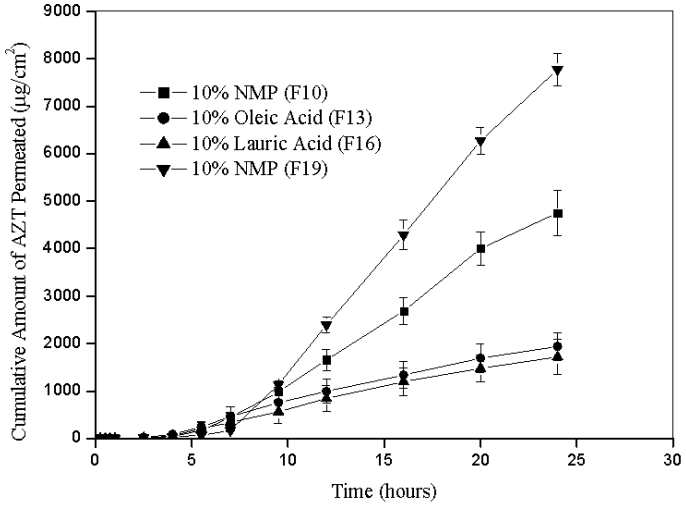

Figure 2. Permeation profiles of saturated AZT in ethanol/IPM (20/80) plus 10% NMP (F10) or 10% oleic acid (F13) or 10% lauric acid (F16), and in ethanol/IPM (30/70) plus 10% NMP (F19) across pig skin at 37°C ± 1°C. Each point represents the mean ± SE of 5 determinations.

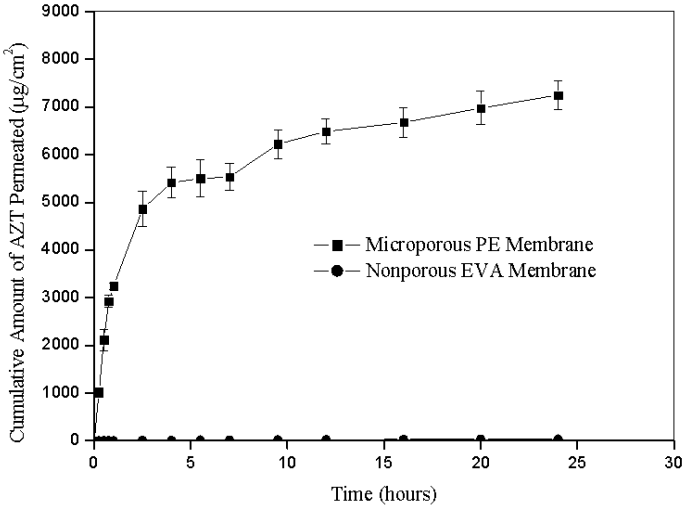

Figure 3. Permeation profile of AZT saturate in ethanol/IPM (20/80) with 10% NMP (F10) across microporous PE membrane and nonporous EVA membrane at 37°C ± 1°C. Each point represents the mean ± SE of 3 determinations.

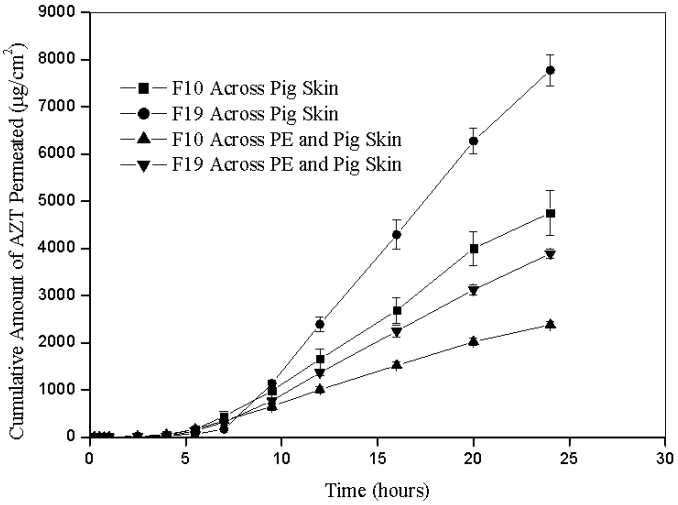

Figure 4. Permeation profile of AZT from F10 and F19 across pig skin alone and across pig skin covered with microporous PE membrane at 37°C ± 1°C. Each point represents the mean ± SE of 5 determinations.

shorter lag times for F10 and F19 could be due to the improvement in skin hydration resulting from the occlusion effect by the microporous PE membrane.[27] A reduction in lag time should theoretically result in increased flux and permeability coefficient values. However, in this study, the shorter lag times were associated with decreased flux and permeability coefficient values, which probably reflect the rate-controlling properties of the microporous PE membrane.

CONCLUSION

Although the use of a polymer membrane for its rate-controlling properties can reduce the AZT flux by half as shown in this study, a careful selection of binary vehicles plus the addition of enhancers can still permit adequate permeation of AZT across both polymer membrane and pig skin, such as to maintain a therapeutic systemic level. The results indicate that the mutual enhancement effect of ethanol/IPM and NMP may make transdermal delivery of AZT feasible.

Table 6. Permeation Parameters of AZT from F10 and F19 Across Pig Skin Alone and Across Pig Skin Covered With Microporous PE Membranes*

	Lag Time (hours)†	$Flux^{ss}$ (µg/cm²)/h‡	Permeability (K_p) ×10³ (cm/h)‡
F10 Across			
Pig skin alone	6.25 ± 0.45	284.92 ± 18.34	6.74 ± 0.43
PE and pig skin	3.89 ± 0.56	121.99 ± 3.28	2.85 ± 0.08
F19 Across			
Pig skin alone	7.49 ± 0.59	460.34 ± 18.72	8.16 ± 0.33
PE and pig skin	5.71 ± 0.29	215.31 ± 5.20	3.22 ± 0.56

*AZT indicates 3′-azido-3′-deoxythymidine; PE, polyethylene; and $Flux^{ss}$, steady-state flux. Permeation study time was 0 to 24 hours.
†Data are given as mean ± SD (n = 3).
‡Data are given as mean ± SE (n = 5).

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