Pharmaceutical Research, Vol. 7, No. 1, 1990

Research Article

Enhancement of the *in Vitro* Skin Permeability of Azidothymidine (AZT) via Iontophoresis and Chemical Enhancer

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Received January 19, 1989; accepted July 17, 1989

Azidothymidine (AZT) was used as a model drug to study the effect of iontophoresis on the skin permeation of a neutral compound. The rate of *in vitro* permeation across hairless rat skin was low and highly variable. With iontophoresis treatment the permeation rate was two- to threefold greater than by passive diffusion. The addition of varying amounts of sodium chloride to the donor enhanced the iontophoretic permeation rate an additional two- to threefold possibly due to convective forces. The addition of *N*-decylmethyl sulfoxide (C_{10}MSO) to the donor increased the permeation rate by several hundred-fold over passive diffusion for hairless rat skin and approximately 75-fold for human skin. No additional enhancement was observed with the combination of C_{10}MSO and iontophoresis treatment at constant current or constant voltage. It may be that the presence of C_{10}MSO lowers the zeta potential of the skin, thus enhancement due to convective flow is minimized.

KEY WORDS: azidothymidine; iontophoresis; convective flow; *N*-decylmethyl sulfoxide.

INTRODUCTION

Iontophoresis has been used to enhance the permeation of charged and neutral molecules. Since no current is carried by neutral molecules, the major enhancement mechanism is due to convective flow and any alterations in skin permeability from the presence of the electric field (1–3). The combination of chemical enhancement and iontophoresis may not be strictly additive, since the chemical enhancer may alter the skin. The primary objective of this study was to use azidothymidine (AZT) as a model drug to quantitate these effects.

A secondary objective was to explore the possibility of delivering AZT transdermally. AZT, the only approved drug for the treatment of AIDS, has a half-life of approximately 1 hr (4). The bioavailability after oral administration at a dose of 5 mg/kg is 60% due to hepatic first-pass metabolism. In addition, because of the virustatic nature of the drug, it must be administered for the life of the patient (4,5). Therapeutic levels are maintained with 5 mg/kg given as a 1-hr infusion or 10 mg/kg given orally every 4 hr (assuming a typical body weight of 55 kg, this equals 1650 mg/day i.v., or 3300 mg/day orally). Peak blood levels often exceed toxic levels, with this dosing regimen producing hematological damage in the majority of patients. In some cases the hematological toxicity is severe enough to require blood transfusions or cessation of therapy (6). Therefore, controlled delivery of AZT by a route which would circumvent first-pass metabolism may offer some clinical benefits. With respect to the second objective, the current investigations are only preliminary.

THEORETICAL CONSIDERATIONS

When an ion moves through a solvent in the presence of an electric field (Fig. 1a), it carries along with it a layer of solvent (due to frictional forces). In a narrow, uncharged pore, the ion may push along solvent or less mobile molecules in its path (Fig. 1b); both of these cases represent pure convective flow (7,8). If the positive and negative ions on either side of the membrane have the same electric mobility and are present at the same concentration, the convective flow toward the positive pole will equal that in the negative direction, and the net convective flow will be zero. If, however, the mobility or concentrations are unequal, there will be a net convective flow in the direction of the more mobile, or more concentrated ion.

If the membrane is charged, there is another effect to consider (Fig. 1c). The pores of a charged membrane are lined with a diffuse double layer of opposite charge, which will move in response to the electric field and, likewise, carry along a layer of solvent; this effect is electroosmosis (9). If the ionic strength of the solution in the pores is increased, the thickness of the diffuse double layer decreases, the zeta potential (the potential difference across the diffuse double layer) decreases, and the volume flow resulting from electroosmosis lessens.

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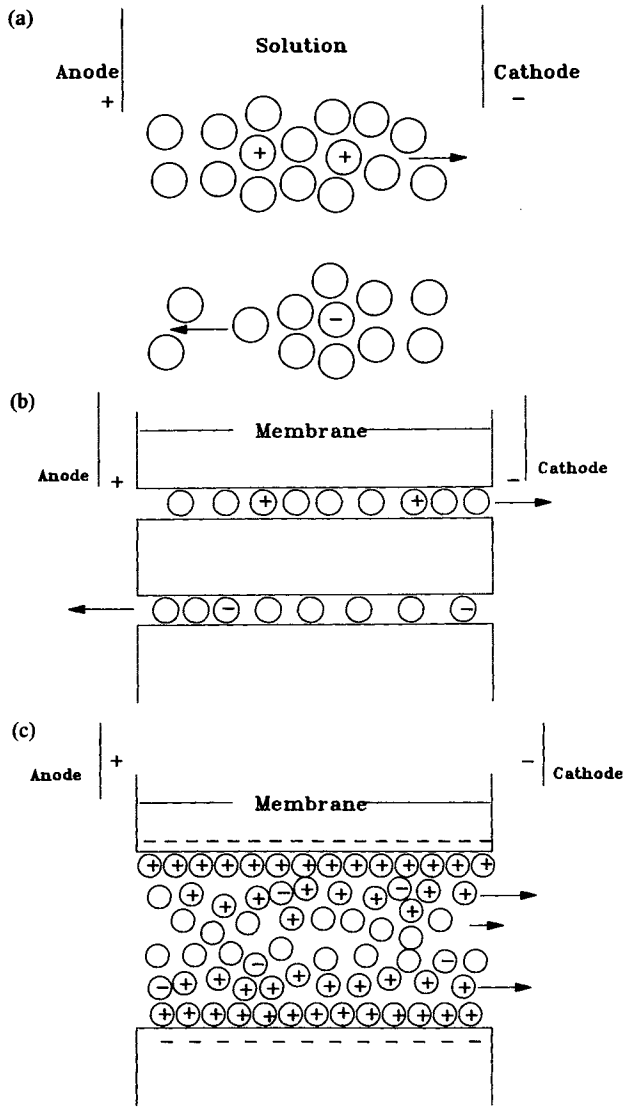

Fig. 1. (a–c) The effect of charged molecules on the flux of neutral molecules in the presence of an electric field (open circles represent solvent or uncharged solute). (a,b) Flux in a solvent and uncharged pore, respectively; (c) flux in a charged pore or electroosmosis.

Therefore, volume flow in a charged membrane, in the presence of an electric field, is the summation of both convective flow and electroosmosis. If we increase the concentration of ions on one side of a charged membrane, we may observe opposing effects; the convective flow through the membrane may increase, while the electroosmotic flow may decrease.

The coupling between ionic flux and volume flow is neglected in the Nernst Planck equation. However, the phenomenological equations of Onsager express the linear dependence of all mechanical flows on all the mechanical forces operating in a system (10). Staverman (11) gives the following useful derivation and relates the coefficients in the Onsager equation to the electrokinetic theory describing electroosmosis.

The flow, J_i, of the ith component in an n-component system is the product of a coefficient and the forces conjugate to that flow:

$$J_i = \sum_{k=1}^{n} L_{ik}(z_k F\Delta\Psi + v_k\Delta P + \Delta\mu_k) \qquad (1)$$

where L_{ik} is the coefficient, z is the charge, $\Delta\Psi$ is the potential difference across the membrane and is assumed to be constant (therefore $\Delta\Psi = E/h$, where h is the membrane thickness), v is the partial molar volume, ΔP is the pressure gradient, and $\Delta\mu$ is the chemical potential gradient across the membrane. It is useful to examine the expanded form of Eq. (1) for just one of the components (e.g., AZT) of a three-component system:

$$\begin{aligned} J_1 = {} & L_{11}z_1F\Delta\Psi + L_{12}z_2F\Delta\Psi + L_{13}z_3F\Delta\Psi \\ & + L_{11}v_1\Delta P + L_{12}v_2\Delta P + L_{13}v_3\Delta P \\ & + L_{11}\Delta\mu_1 + L_{12}\Delta\mu_2 + L_{13}\Delta\mu_3 \end{aligned} \qquad (2)$$

Note that for a neutral molecule, like AZT (where $z = 0$), the term containing z_1 would drop out. Complete solution of all the flows in the system would require that equations of the above form be written for each component and then solved simultaneously. The current flow and solvent flow can be written in terms of the solute flow:

$$I = \sum_{i=1}^{n} z_i F J_i \qquad (3)$$

$$J_v = \sum_{i=1}^{n} v_i J_i \qquad (4)$$

where I is the current flow and J_v is the solvent flow.

From these equations it becomes obvious that the flow of any one of the solute components will affect the flow of the other components. It also becomes obvious that the flow of uncharged solute can be affected by an electric field because of its coupling to the charged solute components.

The matrix of coefficients is symmetric (e.g., $L_{ik} = L_{ki}$), under certain conditions (10), substantially reducing the complexity of the system. However, it still may require many experiments to obtain values for each of the L_{ik}'s. If two of the flows are held constant, the following useful expressions may be obtained and may be related to the familiar electrokinetic terms of Helmholtz–Smoluchowski (11).

The reduced electrical transport number,

$$t_i^r = t_i/z_i = FJ_i/I \qquad (\Delta\mu = 0,\ \Delta P = 0) \qquad (5)$$

is analogous to the electrical transport number, t_i, of component i but is useful to account for the flow of uncharged molecules. Because this value is of no interest to us with $\Delta\mu = 0$, we define t_i^{r*} as the t_i^r with $\Delta\mu$ held constant. [J_i must be expressed as (mol/cm^2-sec).]

The electric permeability may be calculated when $\Delta P = 0$ and $\Delta\mu = 0$:

$$L_E = (1/\Delta\Psi)\sum_{i=1}^{n} z_i F J_i = \sum_{i=1}^{n}\sum_{k=1}^{n} L_{ik}z_i z_k = \kappa C_L \qquad (6)$$

When $\Delta\Psi = 0$, and $\Delta\mu = 0$, the mechanical permeability may be determined,

$$L_P = (1/\Delta P) \sum_{i=1}^{n} v_i J_i = \sum_{i=1}^{n} \sum_{k=1}^{n} L_{ik} v_i v_k = r^2 C_L / 8\eta \quad (7)$$

and the electroosmotic permeability may be calculated when $\Delta\mu = 0$:

$$L_{EP} = L_E \sum_{i=1}^{n} v_i F J_i / I = L_E \sum_{i=1}^{n} v_i t_i^r = \epsilon \zeta C_L / 4\eta \quad (8)$$

where κ, η, and ϵ are, respectively, the conductivity, viscosity, and dielectric constant of the liquid in the pores of the membrane. C_L is the cross-section/length ratio of the pores, ζ the zeta potential, and r, the mean radius of the pores.

The Helmhotz–Smoluchowski expressions in Eqs. (6)–(8) neglect some of the coupling terms. However, this is a useful comparison, because the importance of the conductivity and viscosity of the liquid and the zeta potential of the membrane to convective flow is easily seen. Solutes which alter these variables will have an ultimate effect on the flux of all other solutes.

It is well known that the stratum corneum has a negative charge at physiological pH, since the isoelectric point of keratin is in the range of pH 3–4 (3,12). Thus, the pores of the skin (appendageal or molecular sized) will have a negative fixed charge and a diffuse double layer of positive charge. The movement of this diffuse double layer in an electric field is, in part, responsible for volume flow (electroosmotic flow). Thus, as discussed above, diffusants which affect this double layer will also affect volume flow and the coupled flow of neutral solutes.

The increased volume flow of water into the skin resulting from convective flow of solute may result in a more rapid rate of hydration. Since hydration can increase the permeability of the skin, part of the enhancement observed with iontophoresis treatment may be due to hydration effects.

Finally, it must be noted that the presence of an electric field may change the permeability of the skin by increasing the fluidity of the lipids or polarizing the proteins of the skin (2).

EXPERIMENTAL

Apparatus

The *in vitro* apparatus was the same as previously described (1). Briefly, Ag/AgCl working electrodes and Ag/AgCl/saturated KCl reference electrodes were immersed in the donor and receptor solutions through the sampling ports of Valia–Chien skin permeation cells, which have an opening with a cross sectional area of 0.636 cm^2 between the donor and the receptor solution compartments. The anode of the working electrode was placed in the donor and the cathode in the receptor. Reference electrodes were flexible and could be placed against the skin. A pulse current with a time average value of 0.1 mA (current density equal to 0.157 mA/cm^2), frequency of 2 kHz, and 1:1 on:off ratio, square-wave form, was used for the iontophoresis treatments [this combination of frequency and duty cycle was shown to be optimum for the *in vivo* iontophoretic transdermal permeation of insulin (13) and was chosen in this investigation to be consistent with previous *in vitro* experiments (2)].

Materials

AZT (a gift from Burroughs–Wellcome Co., Research Triangle, NC), decylmethyl sulfoxide (Proctor & Gamble, Cincinnati, OH), sodium chloride (reagent grade), and methanol (HPLC grade) were used as obtained. The distilled water used was purified by a Nanopure water purification system (Sybron/Barnstead, Boston, Ma.) and had a resistivity of 14 MΩ or greater.

Analytical Methods

The amount of AZT in donor and receptor solutions was quantitated by HPLC. The method utilized a Waters μBondapak C_{18} column (15 cm × 4 mm) with a precolumn of the same material and a mobile phase of methanol:water at a ratio of 20:80. At a flow of approximately 2 ml/min, the retention times of AZT and thymine, the major degradation product, were approximately 4 and 2 min, respectively. Detection was by UV at 270 nm.

In Vitro Skin Permeation Studies

For the *in vitro* studies (except where noted), freshly excised abdominal skin of male hairless rat was mounted on the modified skin permeation cells with a saturated solution of AZT (approximately 25 mg/ml) in water as the donor solution and normal saline as the receptor solution. The donor solution was sampled before and after the permeation study and additional drug was added to the donor as needed to keep the solution saturated. The receptor solution was sampled periodically for a minimum of 8 hr; an equal volume of normal saline was added after each sample was withdrawn.

The effect of duration of iontophoresis treatment was studied with the same donor and receptor solutions as described above. Pulse current of 0.1 mA was applied for durations of 4, 8, 24, 48, and 72 min, and samples of the receptor solution were taken at predetermined intervals.

In order to study the effect of increasing ionic strength on the flux of AZT with iontophoresis, varying amounts of NaCl (0 to 1 *M*) were added to the donor solution (which contained 10 mg/ml of AZT in water). Pulse current of 0.1 mA was applied for 6 hr and the receptor solution was sampled periodically.

The effect of a chemical enhancer, C_{10}MSO, on the skin permeation rate of AZT was also studied. This substance has been reported to be a very potent enhancer which increases the skin permeation rate of polar compounds to levels equivalent to that observed with stripped skin (14–16). Initially the concentration of C_{10}MSO in the donor solution was varied from 0.2 to 10% to determine the optimum concentration for enhancement. Then the combination of chemical enhancement and iontophoretic enhancement was studied in two separate experiments. In the first study (a constant-current experiment), 0.1 mA of pulse current was applied across hairless rat skin for 5 hr with a 10% C_{10}MSO solution saturated with drug or a 10% C_{10}MSO/0.1 *M* NaCl solution saturated with drug as the donor solution and receptor solution of normal saline. In the second study (a constant-voltage

experiment), the membrane potential was held at approximately 1 V for 1 hr and the current was allowed to vary (the current in this experiment varied from 2 to 10 mA, which is above the level recommended for *in vivo* use when the skin impedance is normal; however, these levels were necessary to explore the enhancing effect when the skin impedance was lowered by C_{10}MSO). In trial experiments under these conditions, the current flow was high enough to cause water decomposition at the Ag/AgCl electrodes. Therefore, buffer (0.1 *M* sodium acetate, pH 5) was added to the donor and receptor solutions to prevent pH shifts due to the electrode reaction. Because the 10% solution of C_{10}MSO is quite viscous, [which could decrease convective flow, according to Eqs. (7) and Eq. (8)], the effect of pretreating with C_{10}MSO was also studied. C_{10}MSO (10% solution in acetate buffer) was added to the donor half-cell in contact with the stratum corneum. After 1 hr, this solution was removed, the skin was rinsed three times with buffer, and then the saturated solution of AZT in acetate buffer was added to the donor with 0.1 *M* sodium acetate buffer (pH 5) as the receptor solution. It was necessary to use fuzzy rat skin for the latter study, because of the extermination of the hairless rat colony by disease. However, comparisons were made only within the experiment.

A study was also conducted to evaluate the enhancing effect of C_{10}MSO on the permeation of AZT across human skin. White, male cadaver skin excised from the thigh region was microtomed to a thickness of approximately 200 μm and then frozen until use. Before the permeation study, it was thawed in approximately 500 ml of normal saline and then mounted in the skin permeation cell. One set of skin specimens (four cells) was pretreated with a 10% solution of C_{10}MSO for 1 h in the same manner as described above for the hairless rat skin, and a second set was left untreated as the controls. The donor compartment contained a saturated solution of AZT in water, while the receptor compartment was filled with normal saline.

RESULTS AND DISCUSSION

The permeation rate of AZT across hairless rat skin by passive diffusion was low and highly variable (ranging from 0.49 to 19 μg/cm^2-hr), with a mean rate (±SD) of 4.9 ± 4.13 μg/cm^2-hr for n = 12. However, the within-animal (and thus within-experiment) variation was much smaller, and for most experiments the passive permeation was thus conducted and used as the reference.

Figure 2 shows that as the duration of iontophoresis treatment increases, the skin permeation rate of AZT also increases linearly up to about 25 min and then gradually levels off. The same trend was previously reported for the iontophoretic permeation of verapamil-HCl, which is charged at physiological pH (1). Since AZT is uncharged, the mechanism of enhancement under these conditions could be attributed to (1) electroosmotic flow caused by the movement of ions in the electric double layer of the skin in the presence of the applied electric field, (2) an increase in the rate of hydration due to the movement of water into the skin, and (3) permeability changes in the skin in the presence of an electric field.

With the addition of an electrolyte, like NaCl, the skin

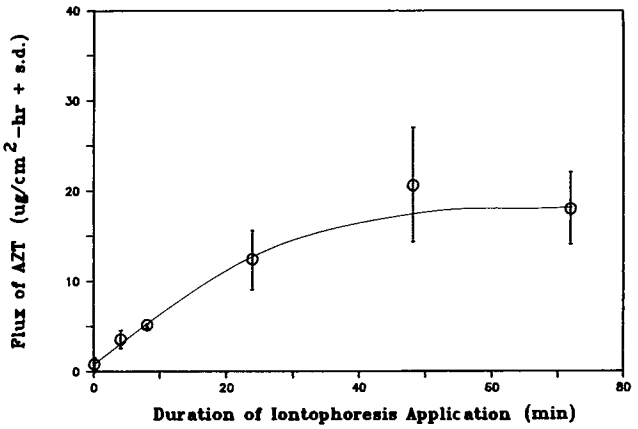

Fig. 2. Effect of duration of iontophoresis treatment on the skin permeation of AZT.

permeation rate of AZT was observed to increase. The results in Fig. 3 indicate that as the NaCl concentration increases, the skin permeation rate and the reduced electrical transport number, t^{r*}, first increase proportionally up to 0.1 *M* NaCl and then reach a plateau. The mechanism attributed to this enhancement in skin permeation rate (below 0.1 *M*) may be due to the convective flow of Na^+ ions added. As the concentration of Na^+ ions increases, the convective flow may increase [as indicated by Eqs. (2) and (4)] and thus the permation flux of AZT. The maximum enhancement achieved with 0.1 *M* NaCl was approximately sixfold greater than the passive diffusion of AZT. The effect of NaCl on the skin permeation rate profile for the neutral AZT molecule is in contrast to that reported earlier for the charged verapamil ion (1). In the latter case, the iontophoretic permeation rate of verapamil ions was noted to decrease at low concentrations of NaCl, due to the decrease in the electrical transference number of verapamil; after the minimum value (equal to the passive diffusion rate of verapamil) was reached the skin permeation rate of verapamil was observed to increase, possibly due to the convective flow of Na^+ ions.

The plateau in the AZT iontophoretic permeation rate and t^{r*} at NaCl concentrations greater than 0.1 *M* could be attributed to the effects of Na^+ ions on the zeta potential of the skin. As the ionic strength of the solution in the negatively charged pores of the skin increases, the thickness of

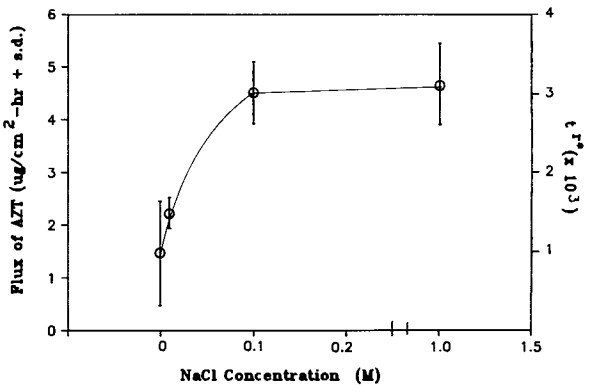

Fig. 3. Effect of increasing NaCl concentration on the skin permeation flux and reduced electrical transport number, t^{r*}, of AZT.

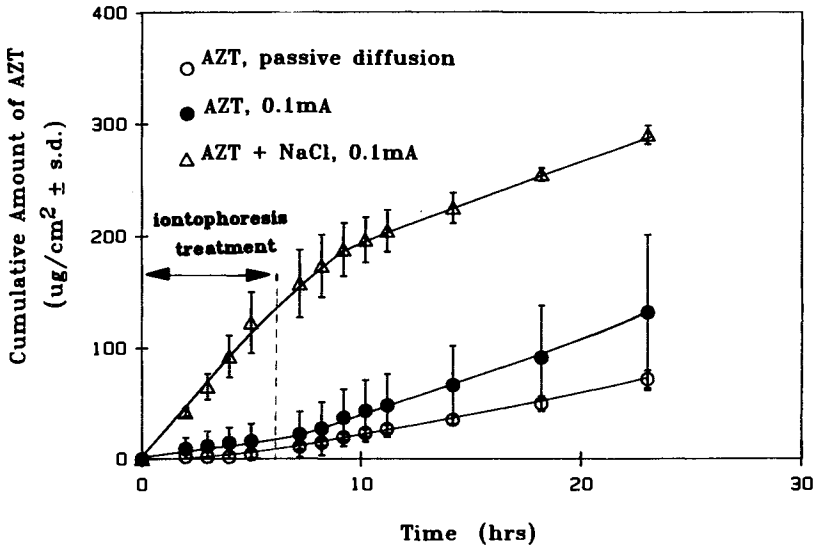

Fig. 4. Passive and iontophoresis-facilitated skin permeation profiles of AZT. Iontophoresis treatment was 0.1 mA of pulse current for 6 hr.

the diffuse double layer (and thus the zeta potential) decreases (9). At concentrations greater than 0.1 *M* the effect on the zeta potential may dominate and this decrease in the zeta potential may decrease the flux of AZT according to Eq. (8).

Figure 4 shows the permeation profiles for AZT under passive diffusion conditions, with iontophoresis treatment (0.1 mA for 6 hr, no NaCl in donor) and with iontophoresis treatment (0.1 mA for 6 hr) and 0.1 *M* NaCl in the donor solution. Note that for the latter profiles, the permeation rate after the cessation of iontophoresis treatment gradually decreases to a rate equal to that resulting from iontophoresis alone. As discussed above, hydration or permeability changes in the skin may account for the difference between the passive permeation rate and the rate observed after treatment.

Figure 5 shows the relationship between AZT skin permeation rate and concentration of C_{10}MSO in the donor solution. It is interesting to note that even at low concentrations C_{10}MSO is effective in promoting the skin permeation rate of AZT quite significantly. As the concentration is increased from 2 to 10% there is very little difference in the enhancement.

In Fig. 6 the effect of C_{10}MSO on the skin permeation profiles of AZT under passive diffusion and iontophoresis is compared. The iontophoretic profile with 0.1 *M* NaCl in the donor solution is redrawn from Fig. 4 for comparison. There is no significant difference among the AZT permeation profiles when C_{10}MSO is present in the donor solution. The enhancement due to C_{10}MSO alone is significantly greater than the maximum achieved with iontophoresis and 0.1 *M* NaCl.

One of the reasons for the insignificant increase in enhancement when iontophoresis is coupled with the effects of C_{10}MSO become clear from Fig. 7. The top curve is the potential difference measured with normal saline in the donor and the receptor compartment during a 0.1-mA iontophoresis treatment. The lower profile was obtained with 10% C_{10}MSO in the donor solution with the same iontophoresis

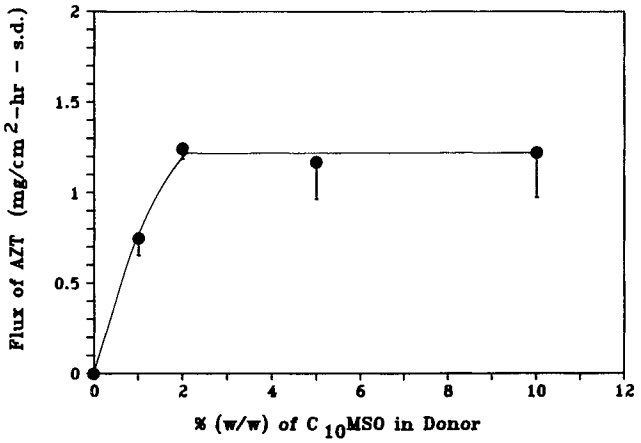

Fig. 5. Effect of increasing C_{10}MSO concentration in donor on the permeation rate of AZT.

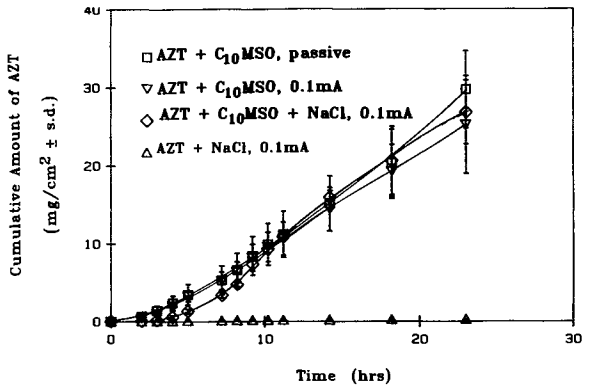

Fig. 6. Effect of C_{10}MSO on the skin permeation profiles for AZT. The permeation profile for AZT with 0.1 mA of pulse current and 0.1 *M* NaCl is redrawn here for comparison.

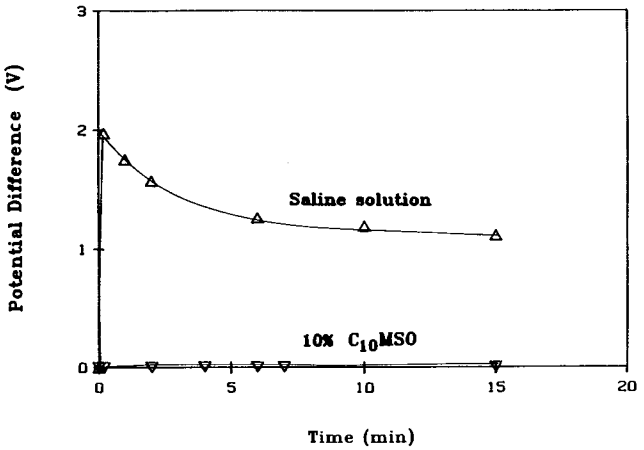

Fig. 7. Effect of C_{10}MSO on the potential difference across the skin during a 0.1-mA iontophoresis treatment.

treatment conditions. The potential difference is in the millivolt range, the same order of magnitude obtained for stripped skin (1). C_{10}MSO significantly lowers the resistance of the stratum corneum. The result is a significant increase in the passive permeability of AZT across the skin [the $L_{ik}\Delta\mu_k$ term in Eqs. (1) and (2) increases], accompanied by a significant decrease in the potential difference [the $L_{ik}zF\Delta\Psi$ term in Eqs. (1) and (2) decreases, for all terms where z is not zero]. Therefore, for the same amount of current flowing, the enhancement due to iontophoresis either alone or by convective flow is negligible.

The effect of iontophoresis treatment under constant voltage on the C_{10}MSO-facilitated skin permeation rate of AZT is summarized in Fig. 8. Pretreatment with C_{10}MSO decreased the lag time relative to that observed when C_{10}MSO was applied simultaneously with AZT, however, the steady-state flux was approximately the same. The application of iontophoresis with constant voltage did not improve the skin permeation profile of AZT enhanced by C_{10}MSO alone. These results are in direct contrast to those reported by Srinivasan *et al.*, who found that the effects of ethanol and constant voltage iontophoresis in enhancing the permeability of a charged permeant, insulin, were additive

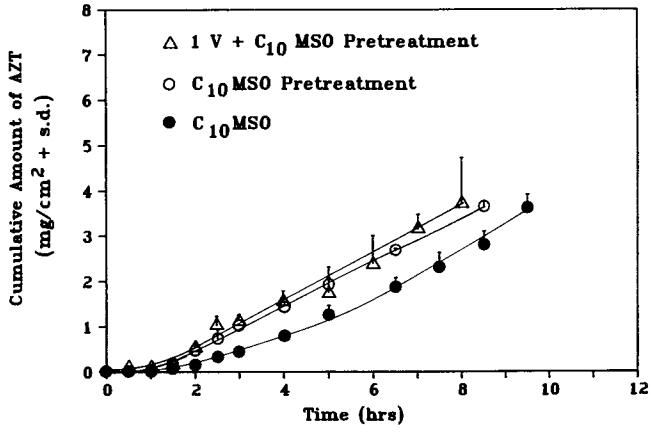

Fig. 8. Skin permeation profiles of AZT after C_{10}MSO pretreatment followed by constant-voltage iontophoresis.

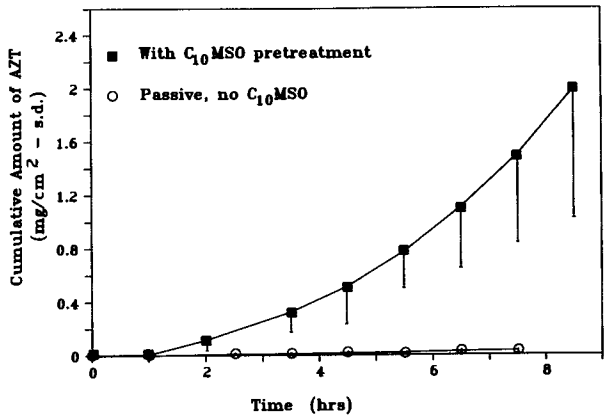

Fig. 9. Permeation profiles of AZT across human cadaver skin with and without C_{10}MSO pretreatment.

(17). It may be that the enhancement due to C_{10}MSO is so large that the enhancement due to convective flow is negligible in comparison. Alternatively, the surface active properties of C_{10}MSO may be decreasing the zeta potential of the skin such that convective flow is minimized [according to Eq. (8)]. The long alkyl chain of the C_{10}MSO molecule may shield the fixed charges of the skin, eliminating the diffuse double layer and thus the movement of this layer in the presence of electric field.

Figure 9 shows the permeation profiles of AZT across human cadaver skin with and without C_{10}MSO pretreatment and Table I summarizes the permeation rate values obtained for human cadaver skin, hairless rat skin and fuzzy rat skin with and without C_{10}MSO treatment. The enhancement with C_{10}MSO was lower for human skin than for rat skin. These results are not unexpected, since differences in skin permeability and variability in the effects of chemical enhancers between species have been reported by a number of investigators (18–20).

CONCLUSION

The *in vitro* permeation rate of AZT across hairless rat skin is low and quite variable (4.9 ± 4.1 μg/cm²-hr). This rate can be enhanced by approximately sixfold with the addition of 0.1 *M* NaCl to the donor solution and iontophoretic treatment of 0.1-mA pulse current. With C_{10}MSO incorporated into the donor solution, the skin permeation rate was enhanced by several hundred-fold for hairless rat skin and approximately 75-fold for human skin. No additional enhancement was noted with the combination of C_{10}MSO and either constant-current or constant-voltage iontophoresis. Skin

Table I. Passive AZT Permeation Rate Values (Standard Deviation) With and Without C_{10}MSO Treatment

Skin species	Permeation rate (mg/cm² − hr) Without C_{10}MSO	With C_{10}MSO	Enhancement ratio
Hairless rat	0.0018 (0.00055)	1.24 (0.255)	688.9
Fuzzy rat	0.00047 (0.000057)	0.42 (0.076)	893.6
Human cadaver	0.0052 (0.0025)	0.40 (0.22)	76.9

permeation enhancers which are less likely to alter the zeta potential of the skin may be a better choice to achieve an additive enhancement of skin permeation of uncharged molecules with iontophoresis.

ACKNOWLEDGMENTS

The authors with to express their appreciation to Burroughs Wellcome for the donation of azidothymidine for this investigation and to TBS Laboratories, Inc., for providing a nonrestricting research grant to this Research Center; both have made this research investigation possible.

NOMENCLATURE

J_i	Flux of *i*th solute
L_{ik}	Coefficient of conjugate force
I	Current flow
z	Charge
v	Partial molar volume
J_v	Solvent flow
t^r	Reduced electrical transport number ($\Delta\mu = 0$, $\Delta P = 0$)
t^{r*}	Reduced electrical transport number ($\Delta\mu$ = constant, $\Delta P = 0$)
L_E	Electric permeability
L_P	Mechanical permeability
L_{EP}	Electroosmotic permeability
ϵ	Dielectric constant
η	Viscosity
κ	Conductivity
C_L	Crosssection/length of the pores
ζ	Zeta potential
Ψ	Electrical potential
r	Mean radius of the pore

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