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One-way membrane for transdermal drug delivery systems. II. System optimization

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Summary

Effective flux of steroid solute through skin can be achieved by the use of ethanol as a co-solvent and penetration enhancer. To maintain constant drug release from a reservoir-type transdermal device and permeation through the skin, the composition of ethanol in the reservoir must remain constant. Ethanol permeability is much higher than that of either drug or water; any decrease in ethanol content may result in decreased drug flux. In an attempt to design a transdermal delivery device with constant ethanol enhancing activity, a model system was designed with separate ethanol reservoir, drug/solvent reservoir and receiver compartments. The ethanol and drug/solvent reservoir compartments were separated by a polydimethylsiloxane copolymer laminate membrane. This 'one-way' rate-controlling membrane (Yuk et al., *Int. J. Pharm.*, 77 (1991) 221–229) optimized ethanol flux while preventing drug and water back flux. Permeation studies with model steroid solutes in this system demonstrated consistent ethanol enhancing activity with constant solute flux across the skin.

Introduction

There have been a number of reports concerning transdermal drug delivery systems aiming to provide a continuous infusion of drug across the skin (Ebert et al., 1987; Friend et al., 1988; Guy and Hadgraft, 1987; Chien et al., 1988; Patel and Vasavada, 1988). Due to the diffusion-resistant nature of the skin, the use of an enhancer in the transdermal drug delivery system is often required to provide a reasonable drug flux across the skin (Durrheim et al., 1980; Barry, 1987). When solvent is used as the enhancer, solvent flux is usually more rapid than drug flux. In this case, a loss in enhancing activity may be caused by a rapid depletion of enhancer in the reservoir.

In the preceding report (Yuk et al., 1991), a 'one-way' membrane was designed to overcome these difficulties for a reservoir-type transdermal drug delivery device (see Fig. 1). Polydimethylsiloxane copolymer laminate membranes with a

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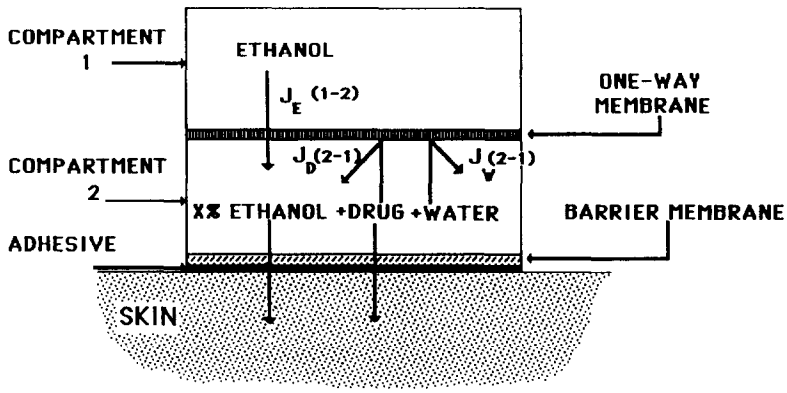

Fig. 1. Proposed transdermal drug delivery system.

central layer of cellulose acetate were studied for their ability to be permselective for ethanol over water. The membranes were designed to allow ethanol to diffuse through easily while retarding the diffusion of solute or water. In a reservoir-type transdermal device, the major advantage of the one-way membrane is the maintenance of constant ethanol concentration and activity in the drug reservoir compartment and the prevention of drug and water back flux into the ethanol reservoir compartment.

In this paper, a three-compartment system was developed as a model transdermal drug delivery system to obtain the precise analysis of drug and solvent flux in an in vitro environment. The system was composed of an ethanol reservoir (compartment 1) separated from a drug/solvent reservoir (compartment 2) by the one-way membrane and a receiver chamber (compartment 3) separated from compartment 2 by a porous barrier membrane.

Materials and Methods

Glass permeation cell

A three-compartment glass permeation cell was designed and is shown in Fig. 2A. Compartment 1 was the ethanol reservoir, compartment 2 was the drug/solvent reservoir and compartment 3 served as a receiving compartment. The volume of each compartment was 6.5 ml with a cross-sectional area of 1.77 cm^2.

Membranes

A one-way membrane and three different types of barrier membranes (membranes 1–3) were used in this study. The synthesis, characterization and fabrication method of the polydimethylsiloxane copolymer one-way membrane have been described in the previous paper (Yuk et al., 1991). Membrane 1 was a Celgard membrane (porous polypropylene with a 0.1 μm pore size, Celanese fiber Co., Summit, NJ). Adhesive laminated membrane 1 (membrane 2) was prepared to observe the effect of an adhesive layer on ethanol and drug permeation. Membrane 2 (thickness: 0.1 mm) was prepared by casting Dow Corning 355 medical grade adhesive, generously donated by the Dow Corning Corp. (Midland, MI), on the surface of a Celgard membrane. Membrane 3 consisted of hairless mouse abdominal skin (male, 6 weeks old) attached to membrane 2 with the epidermal layer towards membrane 2 and the dermal side in contact with compartment 3. Membrane 3 was designed for the measurement of ethanol and drug permeation from the transdermal device through skin in an in vitro environment. The hairless mouse was killed prior to an in vitro permeation experiment by cervical dislocation. A square arc of full-thickness abdominal

skin was surgically removed and its dermal surface carefully cleaned to remove excess fatty acid (Chien et al., 1988).

Solvent uptake measurement

Solvent uptake by the membranes was measured as a function of ethanol composition using the following equation:

$$\text{Solvent uptake} = (W_s - W_o)/W_o \times 100$$

where W_s is the weight of solvent taken up by the polymer and W_o is the weight of dried polymer.

Permeation experiments

The three-compartment glass permeation cell was used for all permeation experiments. The parameters indicated in Fig. 2A were measured. $P_E(1-2)$ and $P_E(2-3)$ represent the amount of ethanol permeation from compartment 1 to 2 and from compartment 2 to 3, respectively. $P_W(2-1)$

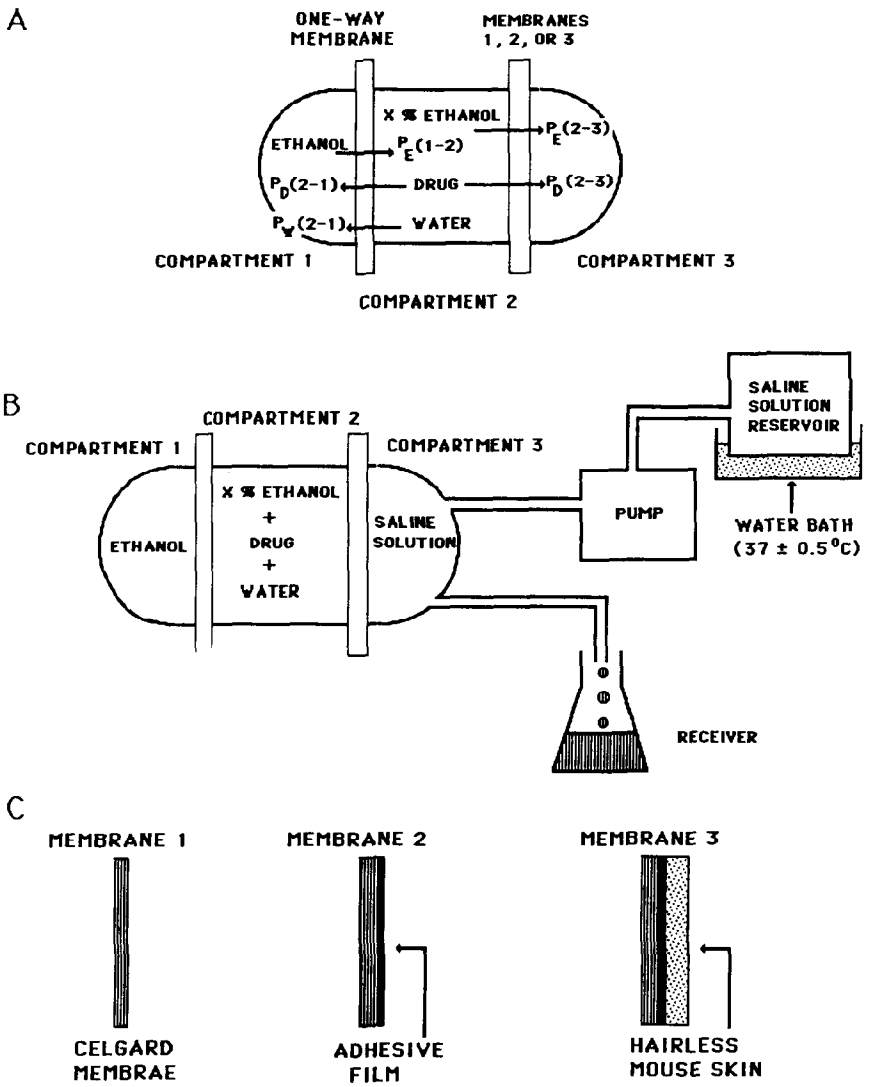

Fig. 2. Experimental set-up: (A) indicated parameters measured in permeation experiment, (B) three-compartment glass permeation cells, (C) membranes 1–3.

is the amount of water permeation from compartment 2 to 1. $P_D(2-1)$ and $P_D(2-3)$ denote the drug permeation from compartment 2 to 1 and from compartment 2 to 3, respectively.

Permeation experiments were performed using two different methods to measure the parameters indicated in Fig. 2A. One method used the condition that compartment 1 was filled with [^{14}C]ethanol (200 dpm/μl) and compartment 2 was filled with x vol% of an ethanol/water binary solvent mixture containing ^{3}H-labelled drug (300 dpm/μg estradiol, testosterone or hydrocortisone). By this method $P_E(1-2)$, $P_D(2-1)$ and $P_D(2-3)$ were determined. The other method used the condition that compartment 1 was filled with [^{14}C]ethanol (200 dpm/μl) and compartment 2 was filled with x vol% of a [^{14}C]ethanol/[^{3}H]water binary solvent mixture. By this method, $P_E(2-3)$ and $P_W(2-1)$ were obtained. In all experiments, compartment 3 was filled with saline solution. The radiochemicals [^{14}C]ethanol, [^{3}H]-water, [^{3}H]estradiol, [^{3}H]testosterone and [^{3}H]hydrocortisone were purchased from NEN-Dupont (Boston, MA). To prevent bacterial degradation of hairless mouse skin, sodium azide was used (0.1 wt% in both compartments 2 and 3). Since estradiol and testosterone are practically water-insoluble, sink conditions were maintained in compartment 3 to prevent solute saturation in compartment 3, as shown in Fig. 2B. The temperature of the saline solution reservoir was maintained at 37 ± 0.5°C and the flow rate of saline solution through compartment 3 was 0.1 ml/min.

Results and Discussion

Solvent permeation

The major advantage of the proposed transdermal drug delivery system is to keep ethanol and water activity constant at the skin surface (constant ethanol enhancing activity) for a prolonged period of time. This can best be accomplished by exactly matching ethanol depletion in the ethanol reservoir [$P_E(1-2)$] to ethanol efflux from the drug/solvent reservoir to the receiving compartment [$P_E(2-3)$]. To do this, precise analysis of solvent and solute flux was required.

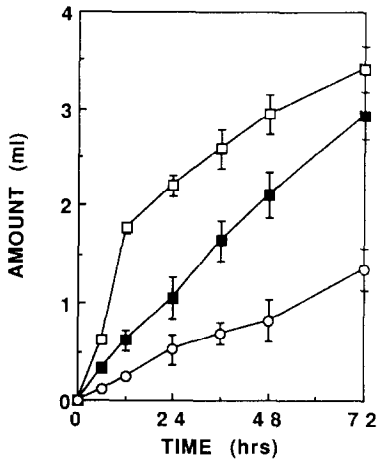

Fig. 3. Amount of ethanol permeation ($n = 3$) through membranes at 40% ethanol composition in compartment 2. (□) Membrane 1, (■) membrane 2, (○) membrane 3.

Fig. 3 shows $P_E(2-3)$ through membranes 1–3 at 40% ethanol composition in compartment 2 (drug/solvent reservoir). In the case of membrane 1, $P_E(2-3)$ levelled off after 18 h because $P_E(2-3)$ through Celgard was greater than $P_E(1-2)$ through the one-way membrane. Although $P_E(2-3)$ through membranes 2 and 3 decreased due to the barrier effect of the adhesive layer and the skin, the permeation rate became constant. This indicated that $P_E(1-2)$ became almost equivalent to $P_E(2-3)$ Therefore, the constant permeation rate of ethanol (constant ethanol activity) could be obtained using membranes 2 and 3.

To determine the optimum conditions when $P_E(1-2)$ is equal to $P_E(2-3)$, $P_E(2-3)$ through membrane 3 was measured as a function of ethanol composition in compartment 2 as shown in Fig. 4A. Fig. 4A shows that $P_E(2-3)$ through membrane 3 can be regulated by controlling the ethanol composition in compartment 2. $P_E(1-2)$ and $P_W(2-1)$ through the one-way membrane were measured using the same conditions as measuring $P_E(2-3)$ through membrane 3. $P_W(2-1)$ was marginal at all ethanol concentrations. $P_E(1-2)$ at 40 and 50% ethanol concentration was almost the same and larger than that at 30% (Fig. 4B). Based on the results in Fig. 4A and B, ethanol permeation could be controlled by vary-

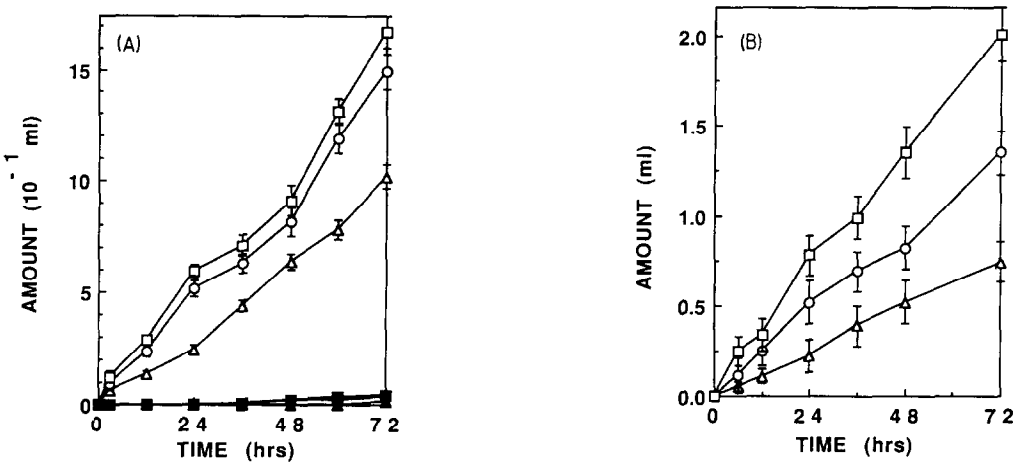

Fig. 4. (A) Amount of ethanol permeation through membrane 3 at various ethanol compositions in compartment 2 ($n = 3$). (□) 50%, (○) 40%, (△) 30%. (B) Ethanol/water counter permeation through one-way permeation membrane at various ethanol compositions in compartment 2 ($n = 3$). (□) 50%, (○) 40%, (△) 30%. Open symbols are for ethanol; closed symbols are for water.

ing ethanol composition in compartment 2. A concentration of 40% ethanol was the optimal composition for keeping ethanol activity constant. A second rationale for using 40% ethanol was based on the solvent uptake behavior of Celgard membrane (Fig. 5). As ethanol composition increased, solvent uptake increased. Minimal solvent uptake occurred below 30% ethanol composition; maximum solvent uptake was obtained above 50% ethanol composition. A 40% ethanol composition was within a controllable range based on ethanol's permeation properties. The hydrophobic pores in Celgard membrane allowed for preferential ethanol flux. Solvent flux was hindered at low ethanol composition of the binary solvent mixture. Based on this, the ethanol composition in compartment 2 was fixed at 40%.

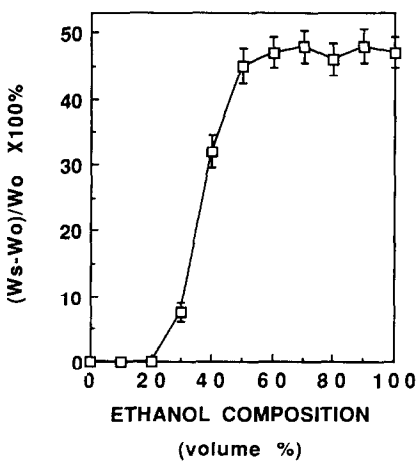

Fig. 5. Solvent uptake by Celgard membrane in ethanol/water binary solvent mixtures ($n = 3$).

Solute permeation

It was hypothesized that drug permeation could be controlled by ethanol permeation and the constant rate for drug permeation into the skin could be accomplished by keeping the permeation rate of ethanol constant. Based on this hypothesis, solute permeation experiments through barrier membranes were performed using three model drugs (estradiol, testosterone and hydrocortisone), as shown in Fig. 6A–C. The amount of drug permeation through membrane 1 depended on the solubility of the drug in ethanol. The solubilities of testosterone, estradiol and hydrocortisone in ethanol are 0.167, 0.036 and 0.025 g/ml, respectively. Therefore, the permeated amount of testosterone is highest and hydrocortisone lowest among the three drugs. The drug permeation pattern paralleled ethanol permeation. The permeation of the three drugs through membrane 1 levelled off due to ethanol depletion.

The barrier effect of the adhesive layer on ethanol permeation through membrane 2 also affected drug permeation through membrane 2.

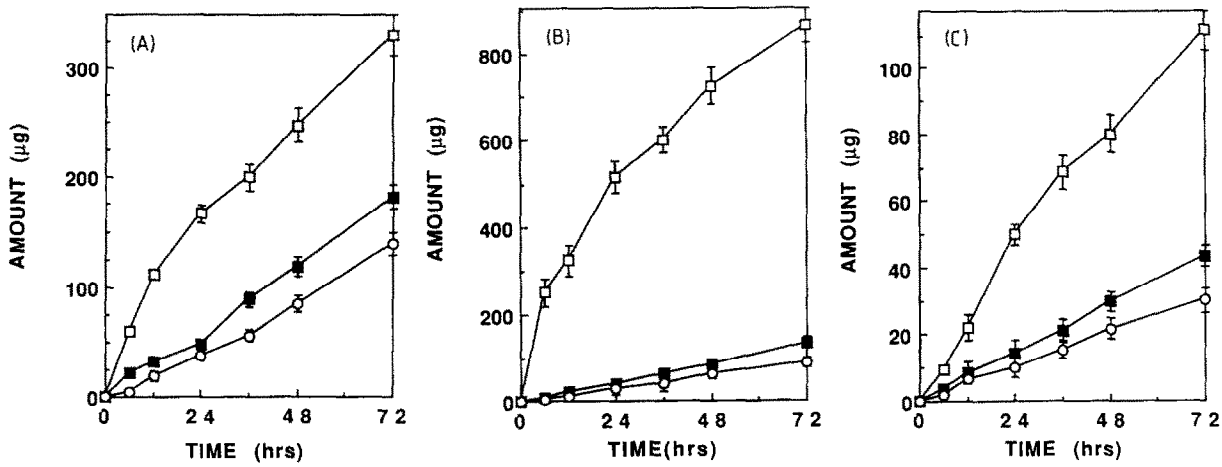

Fig. 6. Amount of drug permeation through membranes ($n = 3$). (A) Estradiol, (B) testosterone, (C) hydrocortisone; (□) membrane 1, (■) membrane 2, (○) membrane 3.

The permeation experiments for solutes through membrane 3 were performed to measure the amount of the drug that could, theoretically, cross the skin. As shown in Fig. 6A–C, a constant permeation rate of drug through membrane 3 was obtained for 72 h. This indicated constant activity for both ethanol and drug in the model transdermal drug delivery system.

To verify that the constant activity of ethanol provided constant solute permeation, estradiol permeation experiments through membrane 3 were performed with and without compartment 1. As shown in Fig. 7, a constant permeation rate for estradiol was obtained using the proposed system (with the ethanol reservoir). In the absence of the ethanol reservoir, the permeation rate plateaued after 40 h. These results indicated that the drug activity (solute permeation rate) could be maintained constant with constant ethanol activity in compartment 2.

Good et al. (1985) reported that an estradiol permeation rate of 0.25 $\mu g/cm^2$ per h was re-

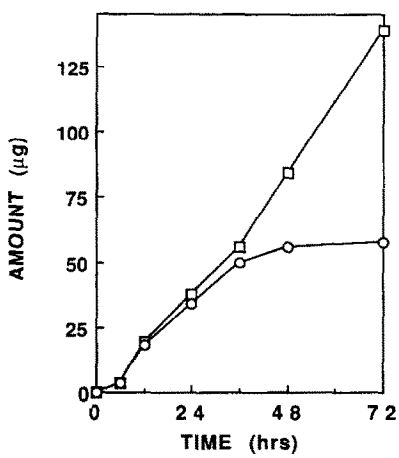

Fig. 7. Amount of estradiol permeation through membrane 3. (□) With, (○) without ethanol reservoir.

TABLE 1

Conditions for solute permeation experiments

	Estradiol	Testosterone	Hydrocortisone
Initial amount of drug in compartment 2 (a) [a]	1074	1074	1170
Amount of drug permeated through [a,b]			
Membrane 1	331.5	867.5	111.5
Membrane 2	182.3	133.5	43.4
Membrane 3 (b)	138.8	88.3	30.2
b/a [c]	12	8	2.6
Permeation rate through membrane 3 [d]	1.14	0.73	0.25

[a] μg.
[b] after 72 h.
[c] %.
[d] $\mu g/cm^2$ per h.

quired for effective transdermal delivery. As shown in Table 1, the observed flux for each drug was sufficient to provide this rate. Table 1 shows that 12% or less of the initial amount of drug in compartment 2 permeated through membrane 3.

Based on these results, it is expected that a constant delivery of drug for a prolonged period of time can be accomplished transdermally by the design of an improved device using a one-way membrane.

Conclusions

A three compartment model transdermal drug delivery system was developed and tested in vitro. A one-way membrane was used to separate the ethanol reservoir from the drug/solvent reservoir. Three rate-controlling barrier membranes were used between the drug/solvent reservoir and the receiver chamber to simulate transdermal diffusion: (1) porous polypropylene membrane; (2) the membrane laminated with an adhesive layer; and (3) the laminated membrane in intimate contact with hairless mouse skin. Ethanol permeation through barrier membranes was regulated by the ethanol composition of the drug/solvent reservoir. A constant permeation rate of ethanol through the barrier/adhesive/skin membrane was achieved. Constant ethanol enhancing activity was obtained by precise analysis of both one-way membrane and rate-controlling barrier membrane ethanol permeation rates. Based on the constant permeation rate of ethanol, constant delivery of steroid drug for a prolonged period of time with a constant permeation rate was accomplished.

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