International Journal of Pharmaceutics, 77 (1991) 221–229

IJP 02576

One-way membrane for transdermal drug delivery systems. I. Membrane preparation and characterization

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(Received 31 August 1989)
(Modified version received 17 July 1991)
(Accepted 22 July 1991)

Key words: One-way membrane; Polydimethylsiloxane copolymer; Ethanol activity; Permselectivity; Transdermal drug delivery system; Steroid permeation

Summary

A new polymeric membrane, designated as a 'one-way' membrane, was designed to be permeable to ethanol with minimal flux of drug or water. A trilaminate membrane consisting of Silastic Q7-4840, methylhydrodimethylsiloxane and cellulose acetate was designed as the one-way membrane. Membrane permeation characteristics were determined from solvent and drug diffusion experiments. The one-way membrane, which provided optimum and constant ethanol activity, may contribute a new concept in the design of transdermal delivery systems as a rate-limiting membrane.

Introduction

Several different types of transdermal drug delivery systems have been developed over the last decade (Good et al., 1985; Gale et al., 1986; Gale and Berggren, 1987; Knepp and Hadgraft, 1987; Moore and Chien, 1988). Transdermal systems for a number of drugs have proven successful at maintaining effective blood plasma levels by controlling the infusion rate of drug through the skin. A number of drugs cannot be used in transdermal systems due to low permeability through skin. Increased skin transport is of major interest; enhancers such as ethanol have been employed (Durrheim et al., 1980; Ghanem et al., 1987).

In common reservoir-type transdermal systems (Fig. 1A), the delivery of solvents and drug at saturation from a reservoir is controlled by the membrane. If solvent activity in this system is not constant, then continuous drug permeation cannot be ensured. Solvent permeation is usually fast, and this may result in the rapid depletion of solvent activity in the reservoir.

In this report, a new polymeric membrane was developed to alleviate the difficulties in reservoir-type transdermal system design. This new membrane was incorporated within the framework of a new transdermal system (Fig. 1B).

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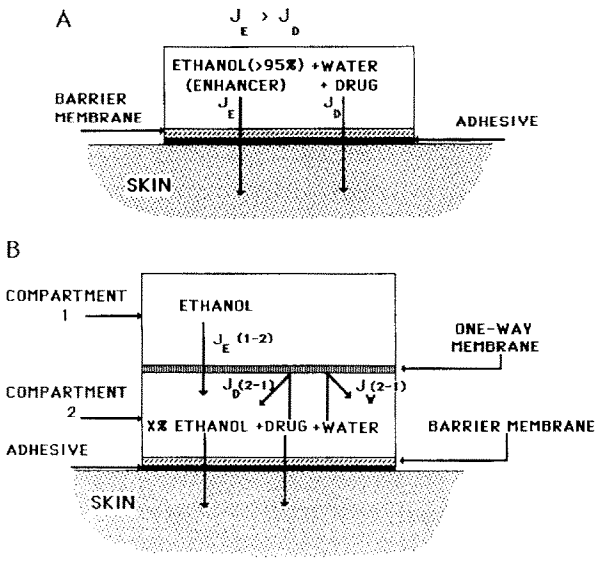


Fig. 1. Reservoir-type transdermal drug delivery systems. (A) Common system, (B) proposed system.

In this design, the solvent, ethanol, is present in the reservoir and the drug is present solely in the 'underlying compartment'. The new membrane was designed to be impermeable to drug over the storage time of the system (about 2 years or 4 orders of magnitude less permeable to drug than ethanol) and impermeable to water over the use time of the system (1–2 orders of magnitude less permeable to water than to ethanol). The membrane was freely permeable to ethanol (1.3×10^{-3} ml/cm^2 per h). This basic design was designated as a 'one-way' membrane because the only operational flux across the membrane is the permeation of ethanol.

Note that compartment 2 of Fig. 1B contains both ethanol and water. In a practical system, this entire section, ethanol/water/drug chamber, barrier membrane, and medical grade adhesive, could be replaced by a hydrophilic pressure-sensitive adhesive. However, for the purpose of the research concept reported here, aqueous ethanol is a simpler system and will be utilized throughout the report.

To accomplish the high ethanol selectivity required with this new membrane, it is useful to examine the ethanol-water selectivity ratio of existing polymeric materials as a reference point. For example, ethanol flux through low density polyethylene film (600 μm thick) is approx. 2.4×10^{-6} ml/cm^2 per h and the ethanol-water selectivity ratio is 24. Silicone rubber was expected to provide adequate flux and selectivity and was used for this study.

Copolymers of polydimethylsiloxane were synthesized, characterized, and investigated for ethanol and water transport properties. To allow for high ethanol flux, silicone rubber was combined with high ethanol swelling epoxide. Water flux was kept to a minimum with the use of a second hydrophobic Silastic copolymer membrane. To exclude drug solutes of varying hydrophobicity, laminate systems were examined to identify an appropriate one-way membrane.

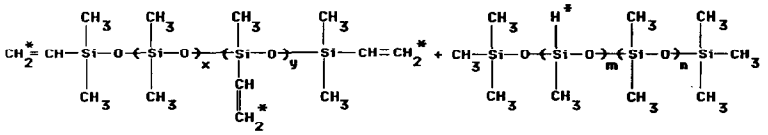
Materials and Methods

Materials

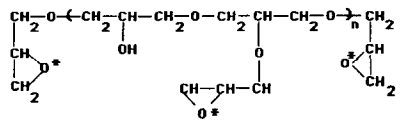
Liquid silicone rubber (Medical grade Silastic elastomers, Silastic Q7-4840) was generously donated by Dow Corning Corp. (Midland, MI). Methylhydrodimethylsiloxane (30 : 70 w/w) copolymer was purchased from Petrarch Systems (Bristol, PA). Polyglycerol-polyglycidyl ethers (Denacol 512 and 521) were obtained from Nagase Chemical Ltd (Japan). Cellulose acetate and acetone (spectroscopic grade) were obtained from Aldrich (Milwaukee, WI). Tritiated estradiol, testosterone, hydrocortisone, water and ethanol from NEN-Dupont (Boston, MA) were used as radiotracers in the permeation experiments.

Membrane preparation

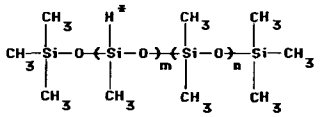
The membranes used were either single layers, bilaminates, or trilaminates. Three different types of single layer membranes were fabricated. Copolymer membranes of Silastic Q7–4840 with 0, 1, 2 or 5% Denacol 512 will be referred to as membrane I-n where n was the w% of Denacol 512 used. Membrane A was a copolymer of Silastic Q7-4840 and 5w% Denacol 521. Membrane B was a copolymer of Silastic Q7-4840 and 5w% methylhydrodimethylsiloxane. Monomer structures and membrane composition are given in Fig. 2. The bilaminate membrane II was com-



SILASTIC Q7-4840



n=2 DENACOL 512
n=3 DENACOL 521



(30/70 w/w) METHYLHYDRO-
DIMETHYLSILOXANE COPOLYMER

SILASTIC Q7-4840 + DENACOL ⟶ MEMBRANE I-n & A

SILASTIC Q7-4840
+
(30/70 w/w) METHYLHYDRO-
DIMETHYL SILOXANE COPOLYMER
⟶ MEMBRANE B

Fig. 2. Membranes used for the investigation of one-way membranes.

posed of a 0.4 mm layer of membrane A with a second layer of 0.2 mm thick membrane B. For all of the above membranes, the total membrane thickness was 0.6 mm. The trilaminate (membrane III) had the same composition as membrane II with an additional center layer of cellulose acetate (10–40 μm thickness).

Single-layer membranes were cast on a Teflon plate with the thickness controlled by the use of a film casting knife and vulcanized at 70°C for 30 min. The casting system was based on the Gardner film casting knife (Pacific Scientific Gardner/Neotec Instrument Division, Silver Spring, MD).

To fabricate the bilaminate (membrane II), membrane A was synthesized as described above and a 0.2 mm film of membrane B was cast and cured on its surface. Membrane III was prepared by first casting cellulose acetate in 50 ml acetone on a 400 cm^2 glass plate and evaporating the acetone in a closed system. The film thickness was controlled by the amount of cellulose acetate, (2 and 4.5 g cellulose acetate for 10 and 40 μm films, respectively). Membranes A and B were then cast on either side of the cellulose acetate film to give membrane III (see Fig. 3). To ensure good contact between the cellulose acetate and silicone layers, the cellulose acetate membrane must be embedded into the silicone matrix.

Swelling measurements and solvent uptake

Membrane swelling was measured as a function of ethanol solution composition. membrane I-*n* and membrane A were selected as reference membranes for the swelling behavior of silicone

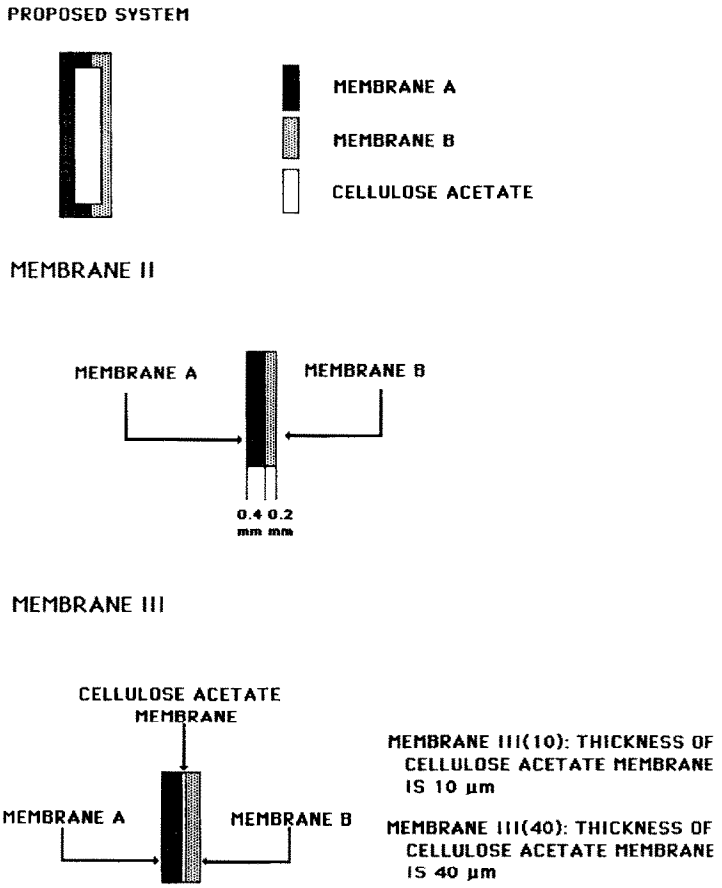


Fig. 3. Membrane fabrication.

rubber. Swelling was measured by the following equation:

$$\text{Swelling} = (W_s - W_o)/W_o \times 100 \quad (1)$$

where W_s is the weight of swollen polymer and W_o is the weight of dehydrated polymer.

The solvent composition inside membrane I-0 and membrane A was analyzed by a sorption-desorption method. The polymers were fabricated as discs (0.5 cm diameter and 0.1 cm thickness) and immersed in aqueous ethanol containing [^{14}C]ethanol and ^3H_2O. After sorption occurred, the discs were placed in pure water for 3 days. The amount of [^{14}C]ethanol and ^3H_2O released from the membranes was quantitated by liquid scintillation counting.

Permeation experiments

Two-compartment glass permeation cells (Fig. 4) were used for solvent and solute permeation studies. The volume of each compartment was 8.0 ml and the area for diffusion was 1.77 cm^2. Com-

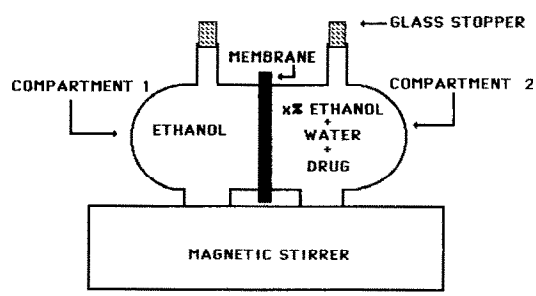


Fig. 4. Two-compartment glass permeation cells.

partment 1 was filled with [^{14}C]ethanol in neat ethanol and compartment 2 contained $^{3}H_2O$ in aqueous ethanol. To study drug permeation, tritiated testosterone, estradiol or hydrocortisone were placed in compartment 2. Samples (100 μl) were withdrawn at fixed time intervals from both compartments and assayed by liquid scintillation counting. Both estradiol and testosterone are insoluble in water, consequently, drug permeation studies were performed as a function of ethanol content in compartment 2.

Results and Discussion

Swelling and solvent uptake

Prior to the permeation experiments, one-way membrane permselectivity for ethanol over water was examined by swelling and solvent uptake experiments. Permselectivity, which originates from the ability of a given solvent to partition into the membrane, is an important parameter in allowing ethanol flux with a minimum of water flux.

The swelling of the membrane I-*n* series and membrane A is shown in Fig. 5 as a function of ethanol concentration. Poly(2-hydroxyethyl methacrylate) (HEMA) showed a maximum in swelling with a change in ethanol composition (Good and Mueller, 1980). The solubility parameter of

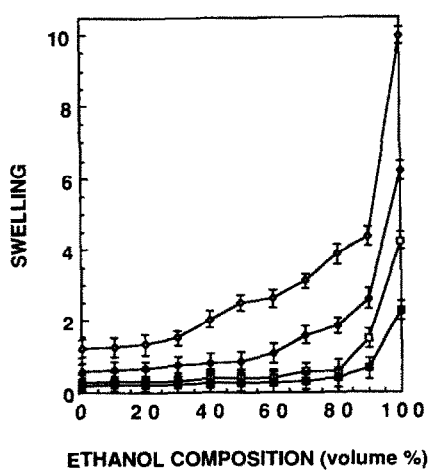


Fig. 5. Swelling behavior of membrane I-*n* ($n = 4$). (◇) membrane A, (◆) membrane I-5, (□) membrane I-2, (■) membrane I-0.

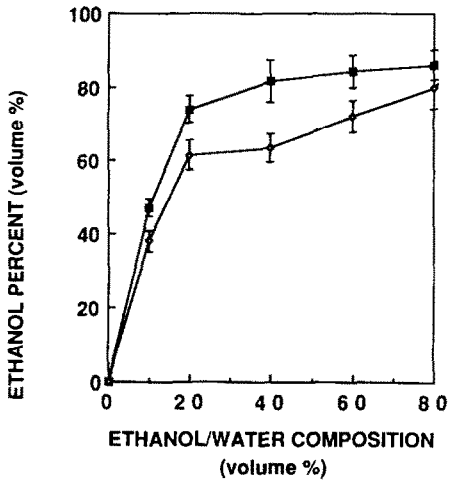


Fig. 6. Solvent composition ($n = 4$) inside: (◇) membrane A, (■) membrane I-0.

poly(HEMA) falls between those of ethanol and water, therefore, exhibiting poor permselectivity to ethanol vs water. In contrast, the swelling of the silicone membranes increases monotonically with ethanol concentration. This is consistent with the solubility parameter of polydimethylsiloxane (7.35) being less than that of either ethanol (12.92) or water (23.5), but closest to ethanol (Burrell, 1975; Fig. 5). This suggests that silicone rubber would be permselective for ethanol over water.

With Denacol copolymers (membranes I-*n* and A), total ethanol swelling increases dramatically with Denacol content while the ethanol:water swelling ratio remains nearly constant at approx. 12. Denacol has a solubility parameter approximately equal to that of propylene glycol (14.8), close to that of ethanol. It might be expected to improve the permeability of ethanol without significant change in permselectivity. The use of epoxide copolymers can control total ethanol and water flux.

Denacol 521 has an extra molecular segment when compared to Denacol 512, therefore, membrane A exhibited even greater swelling in ethanol than membrane I–5. However, membrane A did not show improvement in permselectivity.

The preferential uptake of ethanol by these polymers is shown in Fig. 6. The preference for ethanol is reflected by the ratio of the concentra-

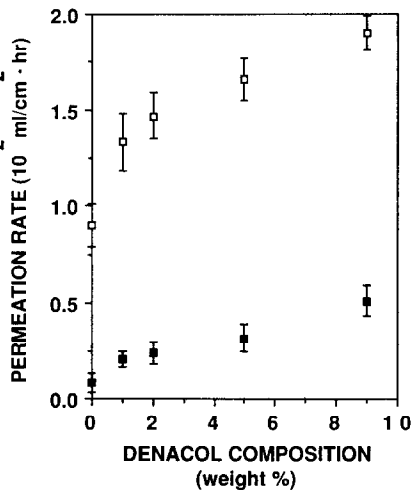


Fig. 7. Ethanol/water counter permeation ($n = 3$) through membrane I-n and membrane A (9 w% Denacol). (□) Ethanol, (■) water.

tion of ethanol in the polymer phase to that in the surrounding aqueous ethanol. Even at 20 v% ethanol in solution, ethanol predominates in these polymers. This phenomenon is a result of the relevant solubility parameters and should be indicative of the permselectivity for ethanol. The uptake of ethanol into the polymers significantly increased with increasing ethanol composition at low ethanol concentrations and leveled off at high ethanol concentrations. Membrane I-0 demonstrated higher ethanol uptake than membrane A; the use of Denacol 521 may decrease permselectivity.

Ethanol and water permeation studies

Based on the swelling and solvent uptake experiments, ethanol and water permeation studies to investigate the permselectivity and permeability of the one-way membranes were conducted.

In Fig. 7, the fluxes of ethanol and water through membranes I-n and A are presented as a function of Denacol content. The ethanol flux increased with increased Denacol content (double with 5% Denacol 512) while a decrease in selectivity was observed. Membrane A (Fig. 7) exhibits an increased ethanol flux of 1.9×10^{-2} ml/cm^2 per h, which is comparable to membrane I-5, while its selectivity decreased. The addition of Denacol can be used to regulate ethanol flux allowing small changes in permselectivity.

To determine the optimum composition in compartment 2 for ethanol flux from compartment 1 to 2, ethanol and water permeation were studied as a function of ethanol composition in compartment 2.

As shown in Fig. 8, ethanol permeation increased with ethanol concentration and plateaued above 40 v% ethanol. This reflects the ethanol swelling and preference of the membrane discussed previously. Ethanol flux from compartment 1 was controlled in part by the ethanol composition of compartment 2. However, membrane A showed poor permselectivity as high water back flux into compartment 1 was seen (Fig. 9).

An improvement in permselectivity was obtained with a laminate of membrane A:membrane B in a 2:1 thickness ratio (membrane II). Membrane A maintained the high ethanol flux; membrane B provided the permselectivity. membrane B, a copolymer of Silastic Q7–4840 with methylhydrodimethylsiloxane, was water repellent due to its hydrophobic crosslinked network (Figs 8 and 9). For membrane III, the addition of the cellulose acetate layer gave a membrane which allowed appreciable ethanol flux, but negligible permeation of either water or solute.

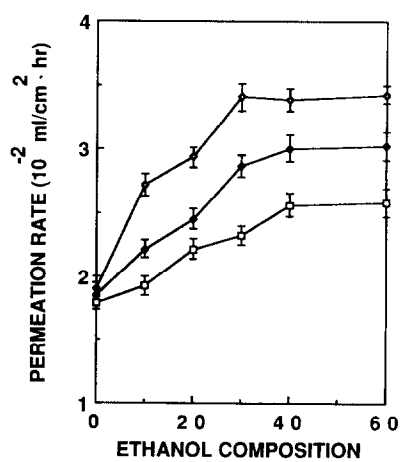


Fig. 8. Ethanol flux ($n = 3$) at various ethanol/water compositions to compartment 2 through: (◇) membrane A, (◆) membrane II, (□) membrane III with 40 μm cellulose acetate layer.

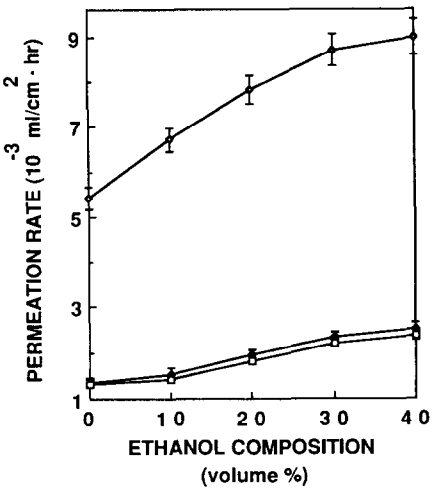


Fig. 9. Water flux ($n = 3$) at various ethanol/water compositions to compartment 1 through: (◇) membrane A, (◆) membrane II, (□) membrane III with 40 μm cellulose acetate layer.

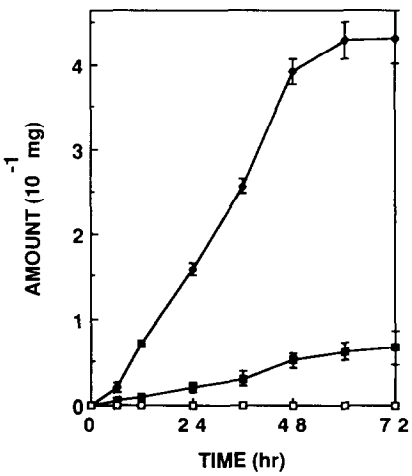


Fig. 11. Amount of estradiol permeated ($n = 3$) through: (◆) membrane II, (■) membrane III with 10 μm cellulose acetate layer, (□) membrane III with 40 μm cellulose acetate layer.

Solute permeation

Solute permeation properties of membrane A were evaluated using estradiol and hydrocortisone. The ratio of C_{re} (drug concentration in compartment 1 after 5 days) to C_{di} (initial drug concentration in compartment 2) as a function of compartment 2 ethanol composition is shown in Fig. 10. Permeation of estradiol did not increase monotonically with ethanol content. Polymer-solute interactions (partitioning through hydrophobic polymer phase) dominated estradiol transport, as opposed to permeation through the ethanol phase of the matrix (pore diffusion mechanism). For the more hydrophilic steroid hydrocortisone, permeation through membrane A was minimal. This result confirmed that solute permeation was independent of solvent permeation for a hydrophobic solute. The one-way membrane may provide dual control of both solute and solvent permeation.

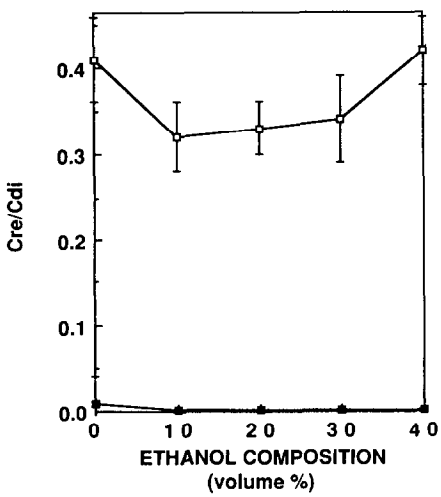


Fig. 10. Ratio of amount of drug in compartment 1 after 5 days (C_{re}) to initial amount of drug in compartment 2 (C_{di}). $n = 3$. (□) Estradiol, (■) hydrocortisone.

One requirement for a one-way membrane is the absence of solute back flux. For hydrophilic solutes, either membrane A or B may be appropriate as one-way membranes (see Fig. 10). To exclude more hydrophobic solutes, such as estradiol or testosterone, additional hydrophilicity may be required. This additional membrane hydrophilicity could not be provided by the existing layers, because the permselectivity for ethanol would decrease. An additional hydrophilic layer, cellulose acetate, was then added.

As shown in Figs 11 and 12, estradiol permeation was markedly reduced by the presence of a 10 μm cellulose acetate membrane. The perme-

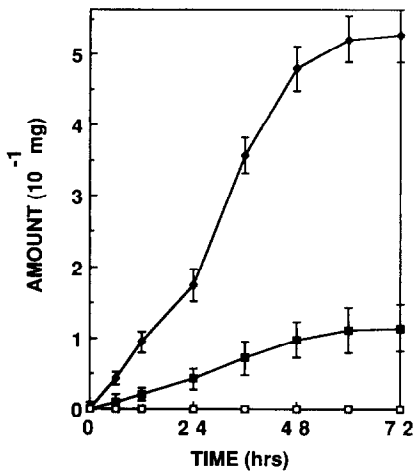


Fig. 12. Amount of testosterone permeated ($n = 3$) through: (♦) membrane II, (■) membrane III with 10 μm cellulose acetate layer, (□) membrane III with 40 μm cellulose acetate layer.

ation of an additional hydrophobic model drug, testosterone, was also investigated. The 40 μm cellulose acetate layer reduced estradiol and testosterone permeation to undetectable levels (Figs 11 and 12). This drastic reduction was unexpected from a series resistance viewpoint and solvent gradient effects cannot explain the discrepancy in this simple model. Since lag time can become excessively long, estradiol was measured through a trilaminate with a 40 μm cellulose acetate layer for 1 month. No permeation of estradiol was observed. Testosterone permeation was also not detected. This trilaminate structure appeared to be suitable as a one-way membrane for hydrophobic solutes such as estradiol and testosterone.

In summary, the use of membrane B, a copolymer with a dense hydrophobic crosslinked network, allowed for large ethanol flux while minimizing water flux. The use of laminate structures of appropriate hydrophilicity permitted the design of one-way membranes for solutes of varying hydrophobicity. The use of a one-way membrane in a transdermal system may lead to optimization of enhancement with hydration and effectively deliver the drug through the skin.

Conclusions

A common problem in transdermal delivery systems that utilize solvent as solubilizer and penetration enhancer is inconsistent permeation rates and rapid depletion of solvent and solvent activity. To alleviate these deficiencies, a new polymeric membrane, termed a one-way membrane, was designed and fabricated. The requirements for a one-way membrane were found to be: (A) high ethanol flux from compartment 1 to 2, (B) minimal water flux from compartment 2 to 1, and (C) no drug flux from compartment 2 to 1. These objectives were accomplished using a trilaminate membrane composed of Silastic Q7-4840, methylhydrodimethylsiloxane and cellulose acetate layers.

Acknowledgements

The authors wish to thank Dr Eric Mack for assistance in the preparation of the manuscript. This work was supported by the CIBA-GEIGY Corporation.

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