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Transdermal delivery of triprolidine using TPX polymer membrane

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Abstract

Triprolidine-containing matrix was fabricated with poly(4-methyl-1-pentene) (TPX) polymer to control the release of the drug. Effect of penetration enhancer and stripping of skin on the permeation of triprolidine through the excised mouse skin was studied. Penetrating enhancers showed the increased flux probably due to the enhancing effect on the skin barrier, the stratum corneum. Among enhancers used such as glycols, fatty acids and non-ionic surfactants, polyoxyethylene-2-oleyl ether showed the best enhancement. The permeability of triprolidine was markedly increased with stripping the mouse skin to remove the stratum corneum, which acts as a barrier of skin permeation. For the controlling delivery of triprolidine, the TPX matrix containing permeation enhancer could be developed.

Keywords: Triprolidine; TPX; Transdermal; Penetration enhancer; Matrix

1. Introduction

The skin is widely recognized for its outstanding barrier properties compared other biological membranes. The low permeability of the skin relative to other biological tissues is well known and keeps the skin as a minor port of entry for drugs. To improve the permeability of drugs through the skin, penetration enhancers have been incorporated into a formulation that would reversively reduce the barrier resistance of the skin and thus allow the drug to penetrate to the viable tissues and enter the systemic circulation. In the development of a transdermal drug delivery system, it is desirable to evaluate the skin permeation characteristics of drug in vitro before conducting in vivo studies in human volunteers. It is well known that a number of factors can affect the transdermal permeation of a drug, including the formulation, penetration enhancer, partition coefficient, source of skin, and so on (Chien, 1983).

In the previous paper (Shin and Yoon, 2002), the release studies of triprolidine from the poly(4-

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methyl-1-pentene) (TPX) matrix containing various plasticizers were carried out and the triprolidine-TPX matrix system containing best plasticizer was formulated. The objective of this study were to develop the transdermal drug delivery system of triprolidine using TPX polymer known for its good mechanical strength (He and Porter, 1987) and to study its in vitro permeation characteristics through mouse skins. To enhance the permeation of triprolidine through the skin, the penetration enhancers were added to the TPX matrix system, and the permeation of triprolidine were evaluated through mouse skins. This present investigation was carried out to develope a new TPX matrix system for transdermal delivery of triprolidine

2. Materials and methods

2.1. Materials

Triprolidine was kindly supplied by Samil Pharm. Co., Ltd. (Korea). TPX (Poly (4-methyl-1-pentene)) of high molecular weight was purchased from Aldrich Chemical Co., Inc. (USA) and triethyl citrate were purchased from Morflex, Inc. (USA). Myristic acid, lauric acid, polyoxyethylene-23-lauryl ether, polyoxyethylene-2-oleyl ether, polyoxyethylene-2-stearyl ether, diethylene glycol and tetraethylene glycol were from Sigma Chemical Co., Inc. (USA). Acetonitrile was HPLC grade from J.T. Baker Inc. (USA). All other chemicals were reagent grade and used as received without further purification.

2.2. Preparation of the basic form of triprolidine

Triprolidine hydrochloride was dissolved in about 100 ml of distilled water and 100 ml of ether were added to separating funnel. Some drops of ammonia test solution was added and mechanically shaken. The ether portion was taken and dehydrated with anhydrous sodium sulfate and filtered on sintered glass before evaporation of the solvent in a rotary evaporator.

2.3. HPLC determination of triprolidine

The concentration of triprolidine was determined by HPLC. The injection volume was 0.5 ul, the column was μBondapak C_{18} (10 μm, 3.9 × 300 mm) and the mobile phases was a combination of acetonitrile: water adjusted to pH 3.0 with sodium phosphate and phosphoric acid: ethyl alcohol (1:1:1). The UV detector was operated at the wavelength of 254 nm, column temperature was maintained at ambient, and flow rate of 1.0 ml/min. Under these conditions, triprolidine peak appeared at the retention time of 4.5 min.

2.4. Determination of partition coefficient

Octanol/water partition coefficients were determined for drugs as follows. About 0.1g of drug were added to 50 ml of distilled water. After addition of an equal volume of water-saturated octanol, the separating funnel was mechanically shaken for 30 min vigorously. A 5 ml sample was taken from both the octanol and aqueous phase for drug assay. The octanol and water employed were previously saturated by high-speed mixing of both solvents. A sample of octanol phase was dehydrated using anhydrous sodium sulfate. To separate octanol and water clearly, the water phase was centrifuged at 2000 rpm for 20 min by centrifuge with refrigerator. The partition coefficients were then calculated as the ratio of the tested drug concentration in octanol to that the aqueous phase.

2.5. Permeation studies

2.5.1. Drug-containing TPX matrix preparation

The drug-TPX matrix was prepared using triethyl citrate chosen as a best effective plasticizer for TPX membrane in previous experiments (Shin and Yoon, 2002). TPX matrix containing 4% triprolidine and 5% triethyl citrate were prepared by solvent casting process. About 1.5 g of TPX polymer beads was dissolved in 25 ml of cyclohexane in a beaker and triethyl citrate and drug were dissolved in this polymer solution. This polymer

and drug solution was poured onto a glass plate and the solvent was allowed to evaporate off at room temperature overnight. The matrix was removed from the plate and dried for 2 days at room temperature in vaccuo. Then, a piece of matrix was cut from the membrane and weighed accurately. The drug content was calculated from the weight ratio of drug and copolymer used.

Table 1
Rate of permeation and permeability coefficient of triprolidine through mouse skin and/or TPX copolymer membrane

	Rate of permeation μg/cm^2 per h (±S.D.)	Permeability coefficient cm per h×10^3 (±S.D.)
TPX membrane	1580.98±96.44	883.72±56.35
Stripped skin	1304.63±84.81	729.25±43.63
Full skin	52.82+6.08	29.52±4.41
TPX+stripped skin	424.22±24.63	237.13±14.26
TPX+full skin	14.03±2.38	7.80±1.40

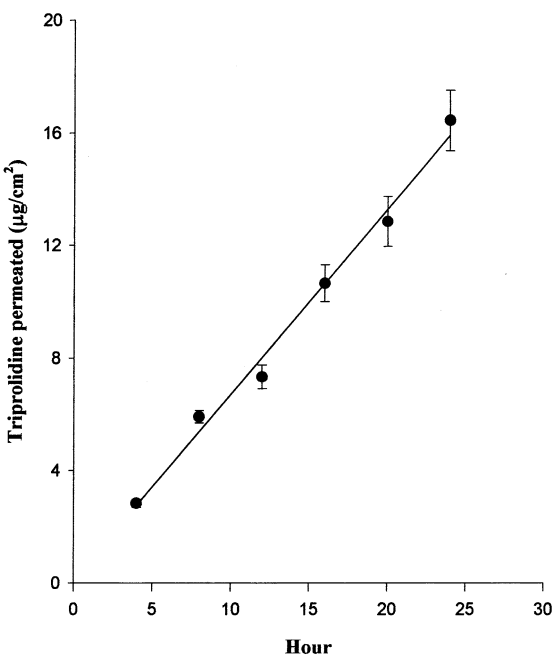

Fig. 1. Permeation of triprolidine from the TPX matrix containing 4% triprolidine and 5% triethyl citrate through skin.

2.5.2. Skin preparation

A Male mice (ICR strain) were sacrificed by snapping the spinal cord at the neck. The hair of abdominal area was carefully removed with an electric clipper. After incision the abdominal skin, the adhering fat and other visceral debris in the skin were carefully removed from the undersurface with tweezers (Durrhein et al., 1980) and used immediately. In order to prepare the stripped skin, the abdominal surface of the mouse skin was stripped with a cellophane tape for 20 times (Behl et al., 1983). It was carried out on a table by securing the abdominal skin and stripped by placing the tape on the stratum cormeun surface. A fresh piece of the tape was used for each stripping.

2.5.3. In vitro permeation of triprolidine through the excised skin

In order to determine the steady state permeation rate of triprolidine through the excised mouse skin, two-chamber diffusion cell was used. Each half-cell had a volume of about 7 ml and the effective diffusional area of 0.79 cm^2. A drug suspension of above equilibrium solubility in 40% PEG 400-saline solution was filled into the donor compartment. The 40% PEG 400-saline solution without drug was added into the receptor compartment. The diffusion cell was maintained at 37 °C with circulating water jacket and stirred constantly. Total volume of the receptor solution was removed at the predetermined intervals and replaced by 7 ml of fresh solution. The amount of drug permeated was determined by HPLC.

2.5.4. In vitro permeation of triprolidine from the drug-TPX matrix through mouse skin

The in vitro permeation of triprolidine from TPX matrix through mouse skin was examined by using the Franz diffusion cell. The matrix devices were applied to the stratum corneum side of the skin. A receptor was filled with 7 ml of PEG 400-saline solution. Other conditions were same as described above in vitro permeation experiments through the excised mouse skin.

Table 2
Effects of enhancers on drug permeation from the triprolidine-TPX matrix through mouse skin

	Enhancer	Permeation rate μg/cm^2 per h	Enhancement factor
Glycols	Diethylene glycol	0.90	1.52
	Tetraethylene glycol	1.18	2.00
Fatty acids	Lauric acid	0.61	1.03
	Myristic acid	0.81	1.37
	Capric acid	1.10	1.86
Non-ionic surfactants	Polyoxyethylene 2-oleyl ether	1.51	2.55
	Polyoxyethylene 23-lauryl ether	1.40	2.37
	Polyoxyethylene 2-stearyl ether	1.23	2.08
Control	No-enhancer	0.59	1.00

2.5.5. Effect of an enhancer on the permeation of triprolidine from TPX matrix through mouse skin

The TPX matrix containing 10%(w/w) enhancer was prepared as experimental method 5.1. Three different types of enhancer were used to compare the enhancing effects.

The enhancers used were fatty acids such as myristic acid(sodium salt), lauric acid(sodium salt), glycols such as diethylene glycol, tetraethylene glycol and non-ionic surfactants such as polyoxyethylene-2-oleyl ether, polyoxyethylene-2-stearyl ether, polyoxyethylene-23-lauryl ether. The enhancer might effect the lipid fluidity of stratum corneum structure and drugs could be permeated easily through the mouse skin. It was defined as the enhancement factor(EF).

$$\mathrm{EF} = \frac{\text{drug flux from TPX matrix containing enhancer}}{\text{drug flux from TPX matrix without enhancer}}$$

3. Results and discussion

3.1. Partitionc cefficient

Despite several advantages over conventional routes of drug administration. Transdermal delivery of pharmaceutically active agents is greatly limited. Regardless of the different mechanisms implicated in percutaneous absorption, the relative impermeability of the stratum corneum with its intercellular lipid multilayers provides the principal resistance to skin penetration, especially for hydrophilic compound (Coderch et al., 1994; Ho et al., 1994). In contrast, for highly lipophilic drugs, the diffusion through the hydrophilic domain of viable skin (viable epidermis and dermis) can represent the rate-limiting step of skin absorption (Diez-Salez et al., 1993). In percutaneous absorption it is generally accepted that first cross the lipid-rich stratum corneum and then the more hydrophilic region (the viable skin), and, therefore, the penetrant must have balanced lipophilic–hydrophilic properties (Guy and Hadgraft, 1989; Calpena et al., 1994). Determination of the octanol/water partition coefficient is a useful approach to evaluate the lipophilicity of a drug and, therefore, its suitability for transdermal delivery (Takahashi et al., 1993)

In our study, the partition coefficient values (K_p) determined for the salt and base form of triprolidine were 0.069 ($\log K_p = -0.914$), 80.103 ($\log K_p = 1.91$), respectively. Studies on groups of chemically related compounds have implied that flux measurements through skin show a characteristic parabolic shape with an optimal value for the partition coefficient. Many authors have reported a similar relationship between permeability of biological barriers and lipophilicity of a drug, with a maximum occurring in the same range of $\log K_p$ range of 2–3 (Lee et al., 1994; Rim et al., 1986). The large difference in lipophilicity between the two compounds suggests that the base form of triprolidine could be an excellent candidate for transdermal delivery.

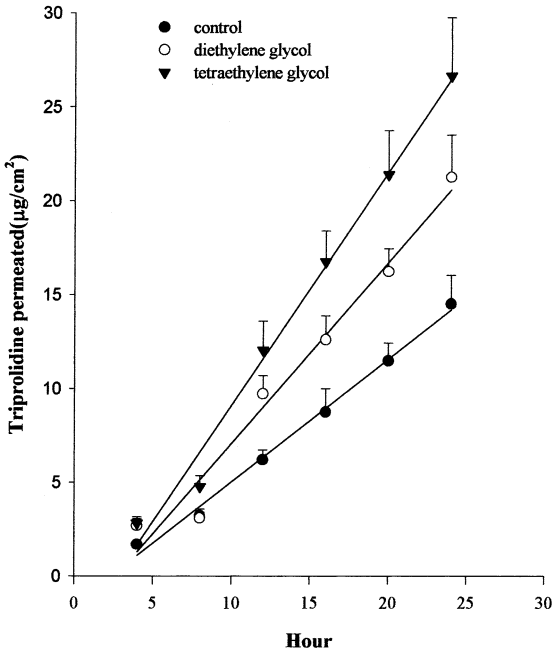

Fig. 2. Effects of glycols on the triprolidine permeation from TPX matrix through skin.

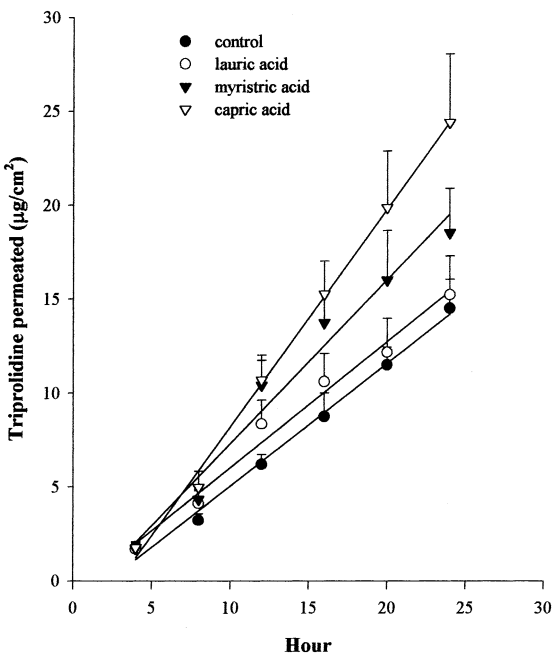

Fig. 3. Effects of fatty acids on the triprolidine permeation from TPX matrix through skin.

3.2. Skin permeation of triprolidine through a mouse skin

The effect of stratum corneum on the skin permeability of triprolidine was evaluated by studying the skin permeation through a stripped mouse skin using side by side diffusion cell. The effect of the rate controlling membrane on the permeation of triprolidine from suspension in 40% (v/v) PEG 400-saline solution through stripped skin was evaluated. Table 1 shows the time course of Q through a piled layer of the TPX membrane and intact or stripped skin.

The skin permeation profiles of triprolidine through the stripped skin (no stratum corneum) or full skin also followed the same linear relationship (Table 1). The triprolidine permeation through the stripped skin was about 24.7 times larger than that through the intact skin. The results shows that stripping process appears to promote substantially the skin permeability of the rather impermeable triprolidine by elimination of the rate-limiting stratum corneum. The results demonstrate that the stratum corneum acts as the major barrier on the permeation of triprolidine through the skin.

3.3. In vitro permeation of triprolidine from the TPX matrix containing triethyl citrate through mouse skin

In the previous paper (Shin and Yoon, 2002), the release study of triprolidine from the TPX matrix containing various plasticizers was carried out and the triprolidine-TPX matrix system containing triethyl citrate as a best plasticizer was formulated. The permeation of triprolidine from the TPX matrix containing 4% triprolidine, 5% triethyl citrate through mouse skin was studied using Franz diffusion cell. From this plot (Fig. 1), the slope, the steady state permeation rate (μg/cm^2 per h), could be calculated. The steady state permeation rate of triprolidine from the TPX matrix through mouse skin was 26.3 μg/cm^2 per h.

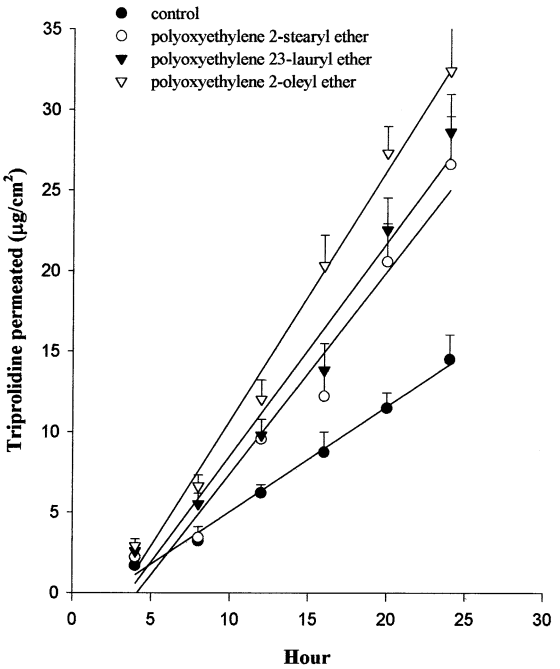

Fig. 4. Effects of non-ionic surfactants on the triprolidine permeation from TPX matrix through skin.

3.4. Effect of an enhancers on the permeation of triprolidine through the mouse skin

The effect of an enhancers such as fatty acids, glycols, and non-ionic surfactants on the transport of triprolidine through the skin was investigated at a concentration of 10%. Permeation enhancing effects was evaluated by an enhancement factor (Table 2). Figs. 2–4 show the time (t) course of Q ($\mu g/cm^2$) for mouse skin from the TPX matrix containing 4%(w/w) triprolidine. The glycols (Fig. 2), fatty acids (Fig. 3) and non-ion surfactants (Fig. 4) showed good enhancement. Table 2 represents the permeation data of triprolidine with/without enhancers. The permeation of drug from TPX matrix containing enhancers through mouse skin showed better enhancing effect. Among enhancers used, polyoxyethylene 2-oleyl ether showed the best enhancement.

For the controlling delivery of triprolidine, the TPX matrix containing permeation enhancer could be developed.

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