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Research paper

Enhanced transdermal delivery of triprolidine from the ethylene-vinyl acetate matrix

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Abstract

Triprolidine-containing matrix was fabricated with ethylene–vinyl acetate (EVA) copolymer to control the release of the drug. The permeation rate of triprolidine in the stripped skin was greatly larger than that in the whole skin. Thus it showed that the stratum corneum acts as a barrier of skin permeation. The effect of penetration enhancer and stripping of skin on the permeation of triprolidine through the excised mouse skin was studied. Penetrating enhancers showed 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 of the mouse skin to remove the stratum corneum that acts as a barrier of skin permeation. For the controlling transdermal delivery of triprolidine, the application of EVA membrane containing permeation enhancer could be useful in the development of transdermal drug delivery system. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Triprolidine; Ethylene–vinyl acetate; Transdermal delivery; Penetration enhancer; Matrix; Skin permeation

1. Introduction

The importance of skin as a site for administration of active drugs has been recognized. Several penetration enhancers [1], prodrugs [2], superfluous vehicles [3], iontophoresis, phonophoresis [4] and thermophoresis have been used as methods to increase the skin permeation of drugs. Among them, penetration enhancers are one of the most convenient methods and show relatively strong effects.

To improve the permeability of drugs through the skin, penetration enhancers have been incorporated into a formulation that would reversibly 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 [5–9].

In the previous paper [6], the release study of triprolidine from the ethylene–vinyl acetate (EVA) matrix containing various plasticizers was carried out and the triprolidine–EVA matrix system containing the best plasticizer was formulated. The objective of this study was to develop the transdermal drug delivery system of triprolidine using EVA polymer known for its heat-processable, flexible and inexpensive material [10] and to study its in vitro permeation characteristics through mouse skin. To enhance the permeation of triprolidine through the skin, the penetration enhancers were added to the EVA matrix system, and the permeation of triprolidine was evaluated through mouse skin. This present investigation was carried out to develop a new EVA matrix system for transdermal delivery of triprolidine.

2. Materials and methods

2.1. Materials

Triprolidine was kindly supplied by Samil Pharm. Co. Ltd. (Korea). Ethylene–vinyl acetate copolymers of 33% vinyl acetate content was purchased from Aldrich Chemical Co. (USA) and triethyl citrate was purchased from Morflex Inc. (USA). Myristic acid, lauric acid, polyoxyethylene-23-

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lauryl ether, polyoxyethylene-2-oleyl ether, polyoxyethylene-2-stearyl ether, diethylene glycol and tetraethylene glycol were from Sigma Chemical Co. (USA). Acetonitrile was high-performance liquid chromatography (HPLC) grade and all other chemicals of reagent grade were 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 was added to the separating funnel. Some drops of ammonia test solution were 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 column was μBondapak C18 (10 μm, 3.9 × 300 mm) and the mobile phase was a combination of acetonitrile/ethyl alcohol/pH 3 phosphate buffer (1:2:3). The UV detector was operated at the wavelength of 254 nm, column temperature was maintained at ambient, and flow rate was 1.0 ml/min. Under these conditions, the triprolidine peak appeared at the retention time of 4.5 min.

2.4. Permeation studies

2.4.1. Drug-containing EVA matrix preparation

The EVA matrix containing triprolidine was prepared by a solvent casting process. The drug–EVA matrix was prepared using tetraethyl citrate chosen as a best effective plasticizer for EVA membrane in previous experiments [6]. About 1.5 g of EVA 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 at room temperature overnight. The matrix was removed from the plate and dried for 2 days at room temperature. Then, a piece of matrix was cut from the membrane and weighed accurately. The drug content was calculated from the weight ratio of drug, plasticizer, and copolymer used.

2.4.2. Skin preparation

Male mice (ICR strain) were killed by snapping the spinal cord at the neck. The hair of the abdominal area was carefully removed with an electric clipper. A square section of the abdominal skin was excised. After incision, the adhering fat and other visceral debris in the skin were carefully removed from the undersurface with tweezers. The excised skin was used immediately [11]. The abdominal surface of the mouse skin was stripped with cellophane tape 20 times [12]. The procedure was carried out by securing the animal skin on a table after which the abdominal skin was stripped by placing the tape on the stratum corneum surface. A fresh piece of the tape was used for each stripping.

2.4.3. In vitro permeation of triprolidine through the excised skin

For the determination of steady-state permeation of triprolidine through the mouse skin, a two-chamber diffusion cell was used. Each half-cell has a volume of about 7 ml and an effective diffusional area of 0.79 cm^2. A piece of mouse skin was clamped between the two halves of the cell and the assembled cell was placed in a shaking incubator at 37 °C. A drug saturated suspension of above solubility in a given concentration of PEG 400–saline solution was poured into the donor compartment, and a same concentration of PEG 400–saline solution (without the drug) was added to the receptor compartment. The cell was shaken horizontally at the rate of 120 rpm to minimize the boundary effect. The total volume of the receptor solution was removed at predetermined intervals and replaced by 7 ml of fresh solution. The amount of drug permeated was determined by HPLC.

2.4.4. Effects of an enhancer on the permeation of triprolidine from EVA matrix through mouse skin

The EVA matrix containing 10% enhancer was prepared as in Section 2.4.1. 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, and polyoxyethylene-23-lauryl ether. The enhancer was used to affect the lipid fluidity of the stratum corneum structure and the drug could then permeate easily through the mouse skin, defined as the enhancement factor (EF) [9,13–18].

$$\mathrm{EF} = \frac{\text{Drug flux from EVA matrix containing enhancer}}{\text{Drug flux from EVA matrix without enhancer}}$$

3. Results and discussion

3.1. Skin permeation of triprolidine through a mouse skin

The effect of the stratum corneum on skin permeability of triprolidine was evaluated by studying the skin permeation

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

	Flux ($\mu g/cm^2/h \pm SD$)	Permeability coefficient ($m/h \times 10^3 \pm SD$)
EVA membrane	3139.30 ± 191.50	1754.78 ± 107.04
Stripped skin	1304.63 ± 84.81	729.25 ± 47.41
Full skin	52.82 ± 6.08	29.52 ± 3.40
EVA + stripped skin	635.52 ± 87.33	356.63 ± 42.11
EVA + full skin	23.67 ± 4.01	13.15 ± 1.97

Table 2
Effects of enhancers on drug permeation from the triprolidine–EVA matrix through mouse skin

	Enhancer	Rate of permeation ($\mu g/cm^2/h \pm SD$)	Enhancement factor
Glycols	Diethylene glycol	3.20 ± 0.38	1.47
	Tetraethylene glycol	3.90 ± 0.41	1.80
Fatty acids	Lauric acid	2.22 ± 0.28	1.02
	Myristic acid	2.91 ± 0.32	1.34
	Capric acid	3.79 ± 0.42	1.75
Non-ionic surfactants	Polyoxyethylene 2-oleyl ether	5.10 ± 0.45	2.35
	Polyoxyethylene 23-lauryl ether	3.48 ± 0.35	1.60
	Polyoxyethylene 2-stearyl ether	3.22 ± 0.28	1.48
Control	No enhancer	2.17 ± 0.20	1.00

through a stripped mouse skin using a 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 intact (full thickness) or damaged (stripped) skin was measured. EVA membrane of 40% VA content was selected as a rate-controlling layer because of its relatively high permeability. Table 1 shows the time course of Q through a piled layer of the EVA 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 show that the 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 to the permeation of triprolidine through the skin. The fact that there is little difference between the intact skin or the damaged skin when plied with EVA membrane shows that the permeation of triprolidine through the mouse skin is highly controlled by the controlling membrane.

3.2. Effect of enhancers on the permeation of triprolidine through the mouse skin

The effect of 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 were evaluated by an enhancement factor (Table 2). Figs. 1–3 show the time (t) course of Q ($\mu g/cm^2$) for mouse skin from the EVA matrix containing

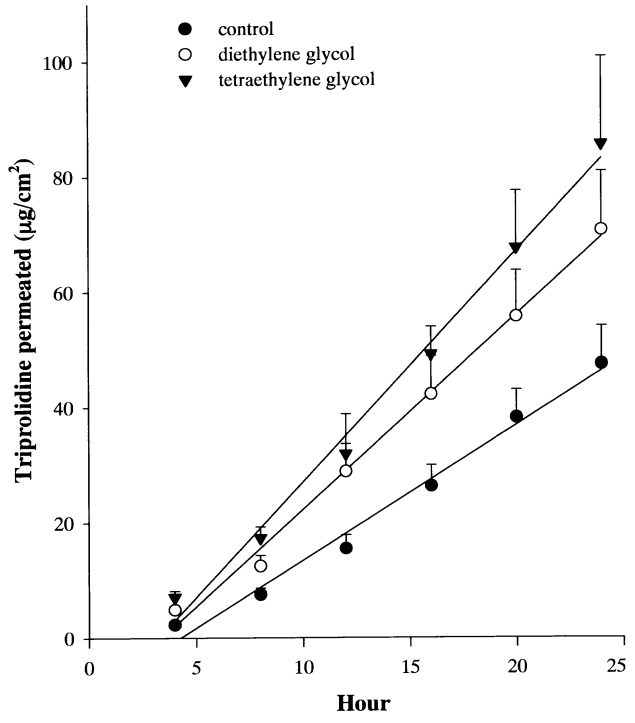

Fig. 1. Effects of glycols on the triprolidine permeation from the EVA matrix through skin.

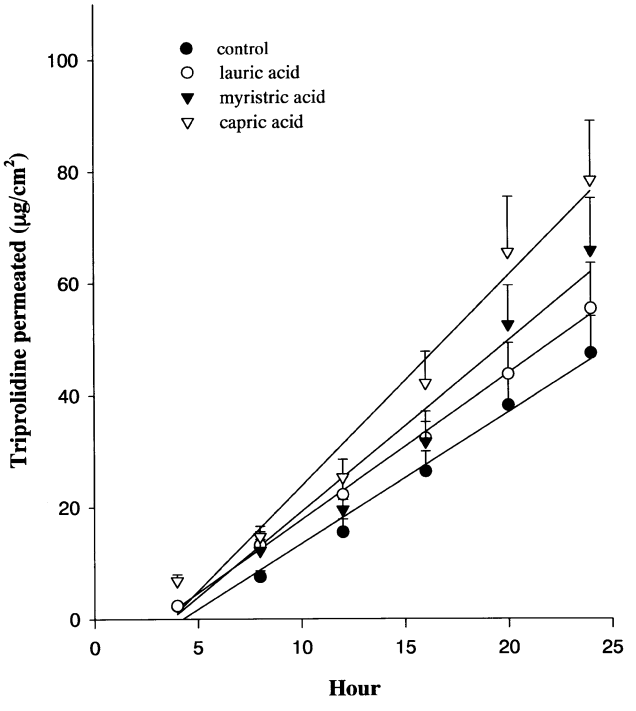

Fig. 2. Effects of fatty acids on the triprolidine permeation from the EVA matrix through skin.

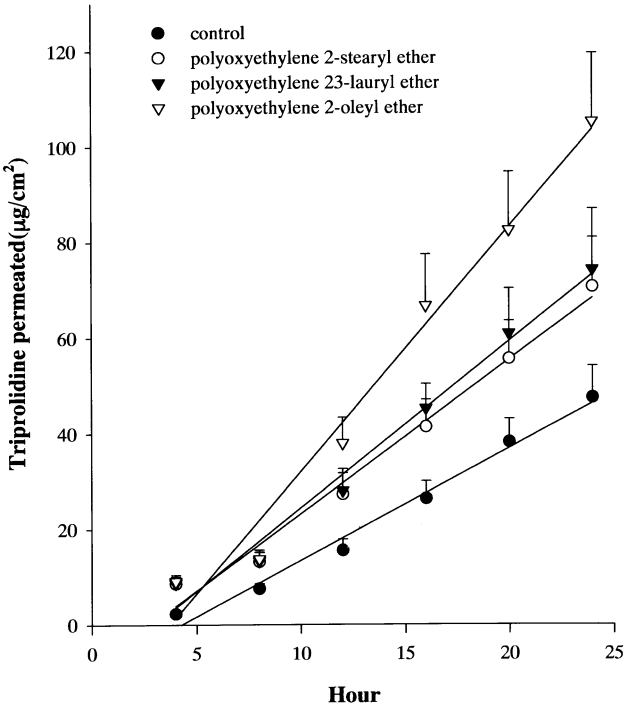

Fig. 3. Effects of non-ionic surfactants on the triprolidine permeation from the EVA matrix through skin.

4% (w/w) triprolidine. The glycols (Fig. 1), fatty acids (Fig. 2) and non-ionic surfactants (Fig. 3) showed good enhancement. Table 2 shows the permeation data of triprolidine with and without enhancers. The permeation of drug from the EVA matrix containing enhancers through mouse skin showed a better enhancing effect. Among enhancers used, polyoxyethylene 2-oleyl ether showed the best enhancement.

For controlling the delivery of triprolidine, the EVA matrix containing permeation enhancer would be a favorable development.

Acknowledgements

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