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Enhanced transdermal delivery of atenolol from the ethylene–vinyl acetate matrix

Cheong-Weon Cho[a], Sang-Chul Shin[b,*]

[a] *CJ Corporation, R&D Center of Pharmaceuticals, 522-1 Dokpyongri, Ichonsi, Gyonggido 467-812, Republic of Korea*
[b] *College of Pharmacy, Chonnam National University, 300 Yongbongdong, Buggu, Gwangju 500-757, Republic of Korea*

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Abstract

To enhance transdermal delivery of atenolol, ethylene–vinyl acetate (EVA) matrix of drug containing penetration enhancer was fabricated. Effect of penetration enhancer on the permeation of atenolol through the excised rat 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. For the controlling transdermal delivery of atenolol, the application of EVA matrix containing permeation enhancer could be useful in the development of transdermal drug delivery system.

Keywords: Atenolol; Ethylene–vinyl acetate; Transdermal delivery; Penetration enhancer; Matrix

1. Introduction

Drug delivery through the transdermal route is limited due to low permeability of the skin. The stratum, the outer layer of the skin, acts as a barrier and is often rate limiting. There is a continuous search to enhance skin penetration. To increase the skin permeation of drugs, many methods such as prodrug (Waranis and Sloan, 1987), penetration enhancers (Barry, 1983), iontophoresis, phonophoresis (Brucks et al., 1989; Bhaskaran and Shree, 2000) and thermophoresis have been used. Among them, penetration enhancers are one of the most convenient methods and show relatively high 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. It is well known that a number of factors can affect the transdermal permeation of a drug, including the formulation, penetration enhancer, partition coeffi-

* Corresponding author. Tel.: +82 62 530 2924; fax: +82 62 530 2949.
E-mail address: shinsc@chonnam.ac.kr (S.-C. Shin).

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cient, source of skin, and so on (Chien, 1982; Miyazaki et al., 1983; Phillips and Michaniak, 1995; Shin and Yoon, 2002; Kim and Shin, 2004).

Atenolol is a beta-adrenergic receptor blocking agent without membrane stabilizing or intrinsic sympathomimetic activities and has been used for the treatment of hypertension, either alone or with other antihypertensives such as thiazide diuretics (Gennaro et al., 1976). It is also reported that, in case of oral administration, it can induce the side effects such as diarrhea, nausea, ischemic colitis, and mesenteric arterial thrombosis. Therefore, the development of transdermal drug delivery of the antihypertensives maintaining proper blood level for a long time without adverse effects of frequent oral administration is very important.

In the previous paper (Kim and Shin, 2004), the release study of atenolol from the EVA matrix containing various plasticizers was carried out and the atenolol-EVA matrix system containing best plasticizer was formulated. The objective of this study was to develop the transdermal drug delivery system of atenolol using EVA polymer that is known for heat-processible, flexible and inexpensive material (Miyazaki et al., 1983) and to study its in vitro permeation characteristics through rat skins. To enhance the permeation of atenolol through the skin, the penetration enhancers were added to the EVA matrix system, and the permeation of atenolol was evaluated through rat skins.

2. Materials and methods

2.1. Materials

Atenolol was kindly supplied by Hyundai Pharm. Co. Ltd. (Korea). Ethylene–vinyl acetate copolymers of 40% VA content was purchased from Aldrich Chemical Co., Inc. (USA) and triethyl citrate was purchased from Morflex, Inc. (USA). Linoleic acid, oleic acid, caprylic acid, lauric acid, polyoxyethylene-23-lauryl ether, polyoxyethylene-2-oleyl ether, polyoxyethylene-2-stearyl ether, diethylene glycol and tetraethylene glycol were obtained from Sigma Chemical Co., Inc. (USA). Acetonitrile was HPLC grade and all other chemicals of reagent grade were used as received without further purification.

2.2. HPLC determination of atenolol

The atenolol concentration was determined by HPLC methods. The column was μBondapak C_{18} (10 μm, 3.9 mm × 300 mm), the UV detector was set at the wavelength of 224 nm, and the column temperature was maintained at ambient. The mobile phase was a combination of methanol/acetonitrile/pH 3 buffer (1:1:4) at a flow rate of 1.0 ml/min. Under these conditions, atenolol peak appeared at the retention time of 6.5 min.

2.3. Drug-containing EVA matrix preparation containing penetration enhancer

The atenolol-EVA matrix containing an enhancer was fabricated by solvent casting method. Briefly, about 2.0 g of EVA polymer beads and 30 mg of atenolol were dissolved with vigorous stirring in methylene chloride and anhydrous ethanol in a beaker. About 50 mg of enhancer was dissolved in this polymer solution and 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. 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. Skin preparation

The animals used for the preparation of skin were male Sprague Dawley (220–250 g) rats obtained from Daehan Laboratory Animal Research Center Co. (Taejon, Korea). They could have a free access to food and water until used for experiments, and were sacrificed in a CO_2 chamber right before experiments. The hair of abdominal area was carefully removed with an electric clipper. The full-thickness skin was surgically removed from each rat and 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 (Durrhein et al., 1980).

2.5. Diffusion study

The EVA matrix containing 2.5% enhancer was prepared as described in Section 2.3. Three differ-

ent types of enhancer were used to compare the enhancing effects. The enhancers used were fatty acids such as linoleic acid, oleic acid, caprylic acid, lauric acid, the non-ionic surfactants such as polyoxyethylene-23-lauryl ether, polyoxyethylene-2-oleyl ether, polyoxyethylene-2-stearyl ether, and the glycols such as diethylene glycol, tetraethylene glycol.

The freshly excised full-thickness rat skin was mounted on the Valia-Chien diffusion cell with the stratum side facing the donor compartment and the dermis side facing the receptor compartment. The drug-EVA matrix was applied on the skin, and the top cell was clamped and covered with a parafilm. The sampling port was sealed with a parafilm to prevent the evaporation of the receptor medium. The receptor medium was 0.1 M phosphate buffer (pH 7.4) which was maintained at constant temperature by a circulating water bath. The temperature was maintained at 37 °C in all diffusion studies. The samples were withdrawn from the receptor compartment at predetermined time intervals and replaced by an equal volume of fresh medium. The samples were analyzed by HPLC. Each value represents the mean and standard deviation of four determinations. Skin permeation rate was calculated by the slope of the figure (Shin et al., 2002)

The effectiveness of permeation enhancers was determined by comparing drug flux in the presence and absence of each enhancer, and their ratio was defined as the enhancement factor (EF) (Aungst et al., 1986; Kadir et al., 1988; Higuchi et al., 1982; Leopold and Lippold, 1995; Bach and Lippold, 1998).

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

3. Results and discussion

3.1. Effects of glycols on the atenolol permeation from the EVA matrix through skin

The effects of glycols such as diethylene glycol and tetraethylene glycol on the transport of atenolol through the skin were investigated at concentration of 2.5%. Fig. 1 shows the time (t) course of Q ($\mu g/cm^2$) for rat skin from the EVA matrix containing 1.5% (w/w) atenolol. The glycols (Fig. 1) increased the permeation rate of atenolol only slightly. The long-chain glycol showed a better enhancing effect than the short-chain glycol.

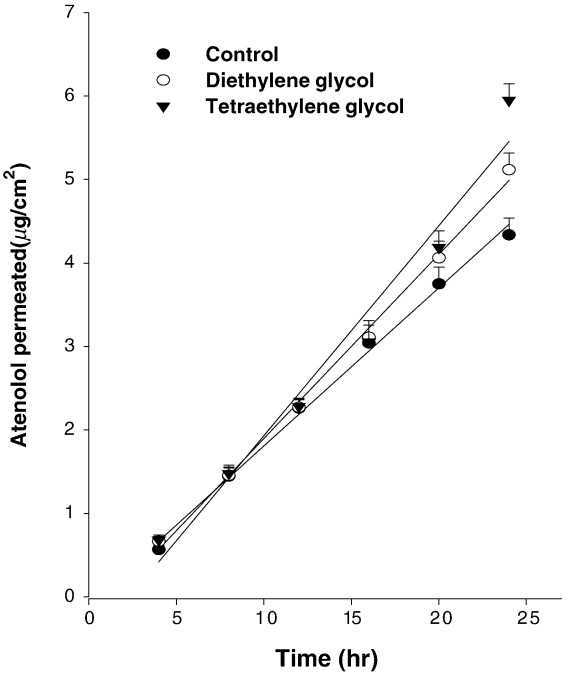

Fig. 1. Effects of glycols on the atenolol permeation from the EVA matrix through rat skin. Bars represent the standard deviation ($n = 4$).

3.2. Effects of fatty acids on the atenolol permeation from the EVA matrix through skin

The effect of fatty acids such as linoleic acid, oleic acid, caprylic acid, and lauric acid on the transport of atenolol through the skin was investigated at concentration of 2.5%. When fatty acid was added in preparation, skin permeation rate of drug increased (Aungst et al., 1990).

Fatty acids are known to have a potent skin permeation enhancing effects (Cooper, 1984; Williams and Bary, 1992). These effects appear to involve the disruption of lipid layer that are filling the fluidity of lipids in the intercellular layers of the stratum corneum because of their resemblance in structure to the lipids (Kim et al., 1996). The enhancer might affect the lipid fluidity of stratum corneum structure, thereby allowing drug to permeate easily through the rat skin.

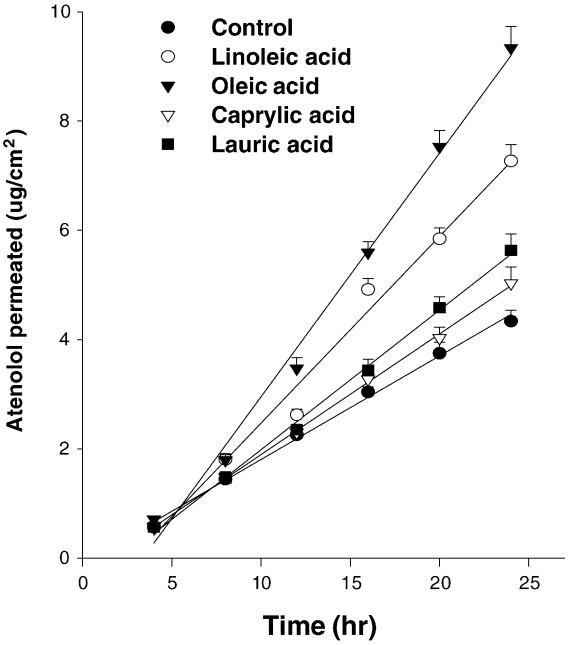

Fig. 2. Effects of non-ionic surfactants on the atenolol permeation from the EVA matrix through rat skin. Bars represent the standard deviation ($n = 4$).

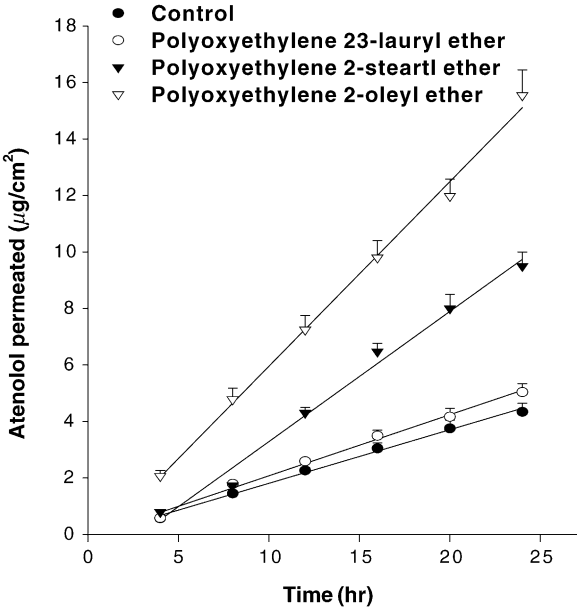

Fig. 3. Effects of fatty acids on the atenolol permeation from the EVA matrix through rat skin. Bars represent the standard deviation ($n = 4$).

Among the fatty acids tested, oleic acid, having a double bond, showed the best enhancement (Fig. 2). The result revealed that oleic acid increased the diffusion of drug through the skin that agrees with the reported mechanism by which oleic acid enhanced the permeability of drug (Kandimalia et al., 1999). Oleic acid was reported to function by partitioning into the lipid regions of stratum corneum, disrupting the structure and lipid fluidity of the stratum corneum (Kim et al., 1993). In this study, oleic acid was the most effective enhancer among the fatty acids tested in this study.

3.3. Effects of non-ionic surfactants on the atenolol permeation from the EVA matrix through skin

The effect of non-ionic surfactants such as polyoxyethylene 2-oleyl ether, polyoxyethylene 2-stearyl

Table 1
Effects of enhancers on drug permeation from the atenolol-EVA matrix through rat skin

	Enhancer	Rate of permeation μg/cm^2/h	Enhancement factor
Glycols	Diethylene glycol	0.221	1.17
	Tetraethylene glycol	0.251	1.33
Fatty acids	Oleic acid	0.446	2.36
	Linoleic acid	0.341	1.80
	Lauric acid	0.255	1.35
	Caprylic acid	0.220	1.16
Non-ionic surfactants	Polyoxyethylene 2-oleyl ether	0.641	3.39
	Polyoxyethylene 23-lauryl ether	0.216	1.14
	Polyoxyethylene 2-stearyl ether	0.454	2.40
Control	No-enhancer	0.189	1.00

ether, and polyoxyethylene 23-lauryl ether on the transport of atenolol through the skin was investigated at concentration of 2.5%.

Table 1 represents the permeation data of atenolol with/without enhancers showing the enhancement factor. The permeation of drug from EVA matrix containing non-ionic surfactants through rat skin showed better enhancing effect (Fig. 3). Among the non-ionic surfactants, polyoxyethylene 2-oleyl ether, derivatives of oleic acid having a double bond, showed the best enhancement, with an enhancement ratio of 3.39. The result revealed that polyoxyethylene-2-oleyl ether, one of derivatives of oleic acid, increased the diffusion of drug through the skin that agrees with the reported mechanism by which oleic acid enhanced the permeability of a drug (Kandimalia et al., 1999).

4. Conclusions

Among enhancers used such as glycols, fatty acids and non-ionic surfactants, polyoxyethylene-2-oleyl ether showed the best enhancement. For the controlling transdermal delivery of atenolol, the application of EVA membrane containing permeation enhancer could be useful in the development of transdermal drug delivery system.

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