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Antihistamine Effects of Triprolidine from the Transdermal Administration of the TPX Matrix in Rats

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The antihistamine effects of the triprolidine were studied in rats to determine the feasibility of their enhanced transdermal delivery from the poly (4-methyl-1-pentene) (TPX) matrix system containing penetration enhancer and plasticizer. The antihistamine effects were determined by the Evans blue dye procedure by comparing the changes in vascular permeability increase following the transdermal administration. The vascular permeability increase was significantly reduced by transdermal administration of the triprolidine-TPX system containing triethyl citrate (TEC) and polyoxyethylene-2-oleyl ether (POE). Both the plasticizer and penetration enhancer played an important role in the skin permeation of triprolidine and increased the antihistamine effects. These results showed that the triprolidine-TPX matrix system containing plasticizer and penetration enhancer could be a transdermal delivery system providing the increased antihistamine effects.

Key words: Triprolidine, TPX, Antihistamine effects, Vascular permeability increase, Evans blue

INTRODUCTION

In the last decades, transdermal dosage forms have been introduced for providing a controlled delivery via the skin into the circulation system (Hadgraft, 1987; Ocak and Agabeyoglu, 1999; Chien, 1987; Morimoto *et al.*, 1988)

Antihistamines diminish or abolish the main actions of histamine in the body by its competitive action, and reversible blockade of the histamine receptor sites on tissues. Histamine H_1 receptor are responsible for vasodilation, increased capillary permeability, flare and itch reactions on the skin, and to some extent the contraction of smooth muscles in the bronchi and gastro-intestinal tract. Triprolidine, an anti-histamine drug, has been orally administered, 7.5 mg, three or four times a day. After taking the drug, many adverse effects such as sedation, varying from slight drowsiness to sleep, dizziness, dry mouth occurred due to transient blood concentration (Gennaro, 1995) have been reported.

Therefore, the development of a transdermal delivery system of antihistamine without adverse effects associated with frequent oral administration is very important. In my previous paper (Shin and Yoon, 2002; Shin *et al.*, 2002), a triprolidine-TPX matrix system containing polyoxyethylene-2-oleyl ether (POE) as an enhancer and triethyl citrate (TEC) as a plasticizer was formulated. When the triprolidine-TPX matrix system containing the enhancer and plasticizer was administered to some rabbits *via* the transdermal routes, the relative bioavailability increased by about 2.13 fold compared to the control group. That result provides a relatively constant and sustained blood concentration with minimal fluctuation (Shin and Choi, 2002).

The present study was carried out to determine the feasibility of the transdermal delivery of triprolidine by studying its *in vivo* antihistamine effects and to develop a triprolidine-TPX matrix system containing a penetration enhancer and a plasticizer.

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MATERIALS AND METHODS

Materials

Triprolidine, polyoxyethylene-2-oleyl ether, Evans blue, histamine dihydrochloride were purchased from Sigma Chemical Co., Inc. (USA). The TPX of high molecular weight was obtained from Aldrich Chemical Co., Inc. (USA), and the triethyl citrate was from Morflex, Inc. (USA).

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 *via* a separating funnel. Then, some drops of ammonia 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.

Drug-containing TPX matrix preparation

The triprolidine-TPX matrix containing an enhancer and a plasticizer was prepared by the solvent casting process using polyoxyethylene-2-oleyl ether chosen as the best enhancer and triethyl citrate chosen as the best plasticizer for TPX matrix in previous experiments (Shin *et al.*, 2002).

About 1.5 g of TPX polymer beads was dissolved in 25 mL of cyclohexane in a beaker. Then, the drugs, polyoxyethylene-2-oleyl ether and triethyl citrate were dissolved in that polymer solution. The mixed 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 *in vacuo*. Then, a piece of the matrix was cut from the membrane and weighed accurately. The drug content was calculated from the weight ratio of the drug and copolymer used.

Determination of the vascular permeability increase induced by histamine in rats

The changes in vascular permeability increased following the transdermal application were determined by the Inagaki methods (Inagaki, *et al.*, 1988). One day before the experiment, the hair of the abdominal area was carefully removed with an electric clipper. In a previous TPX formulation study (Shin and Choi, 2002), the highest drug blood concentration appeared at eight hour after abdominal administration of the triprolidine-TPX matrix. Consequently, eight hours after abdominal application of the triprolidine-TPX matrix, 0.1 mL of histamine solutions (0.05 mg/mL) or the same volumes of saline were injected intradermally into different sites of the rat dorsal skin.

At the appropriate times thereafter, 1 mL of Evans blue solution in saline was injected into the rat-tail vein. After 30 min, the rats were killed and the dye amounts of the Evans blue on the excised circle section of the dorsal skin were determined by the Katayama method (Katayama *et al.*, 1978). Each skin fragment was taken into glass-stoppered test tubes and incubated with 1 mL of 1N KOH at 37 °C for 24 h. The Evans blue was extracted by incubation with 9 mL of 0.6 N phosphoric acid: acetone (5:13) at room temperature. The absorbance of the samples after filtration was measured with a spectrophotometer at 620 nm wavelength. The statistical significance of the differences between formulations was measured by the student's paired *t*-test. The difference was considered statistically significant when $p<0.05$. The values reported are the mean values and their standard deviations.

RESULTS AND DISCUSSION

The amounts of Evans blue after transdermal application of the triprolidine-TPX matrix system

An increase in vascular permeability by vasoactive mediators released from mast cells is a hallmark of anaphylaxis reaction (Holgate *et al.*, 1991; Stevens and Austen, 1989). Various histamine H_1 receptor antagonists have been shown to partially inhibit the vascular permeability increase of immediate hypersensitivity that is induced by specific antigens. In this study, the antihistamine effects of the triprolidine-TPX matrix system were compared by determining the dye amounts that showed a vascular permeability increase induced by histamine in rats. For the purpose of studying the efficacy of the transdermal absorption of triprolidine, one of the prerequisites is that the pharmacokinetic parameter, after the transdermal absorption of triprolidine, correlates with the antihistamine effects.

A statistical analysis of the C_{max} and T_{max} values, following the transdermal administration of the triprolidine formulations, showed that the enhancer group exhibited higher average C_{max} values (216 ± 44.3 ng/mL) than the control group (130 ± 25.8 ng/mL). The T_{max} of the enhancer group was 8.00 ± 2.55 h while it was 8.00 ± 2.28 h for the control group (Shin and Choi, 2002).

Table I shows the amounts of Evans blue from the excised circle section of the dorsal skin measured at 620 nm. The amounts of Evans blue was about 67.2% for the TPX matrix containing triprolidine, TEC and POE, while about 78.7% of the TPX matrix containing only triprolidine, when compared with the control (TPX membrane containing no additives). The decreased amounts of Evans blue shown (Table I) from the triprolidine-TPX matrix

Table I. Effects of the various triprolidine-TPX transdermal systems on the amounts of Evans blue in dorsal skin after injection of histamine into rat tail vein

System	Amounts of Evans blue (%)
TPX membrane only (blank)	100
TPX matrix containing triprolidine (control)	78.7* ± 7.9
TPX matrix containing triprolidine and TEC	77.7 ± 7.0
TPX matrix containing triprolidine and POE	76.0 ± 6.3
TPX matrix containing triprolidine, TEC and POE	67.2* ± 5.5

Each value represents the mean ± S.D. of five determinations
* $p<0.05$ compared to control

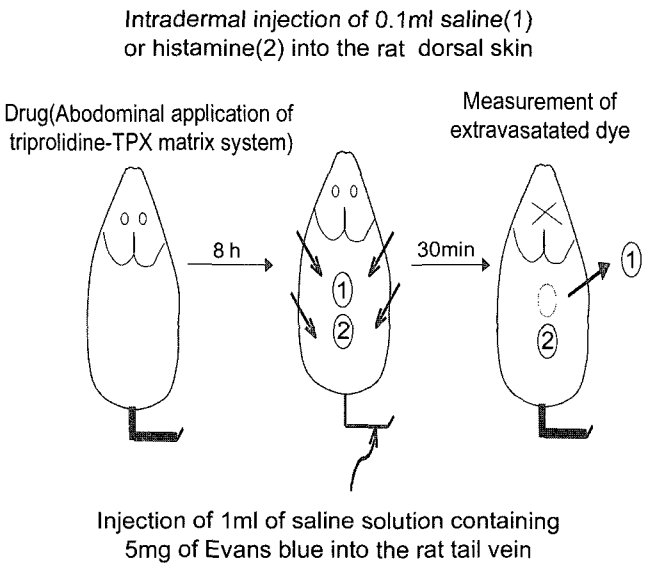

Fig. 1. The experimental method of determining the vascular permeability increase induced by saline (1) and histamine (2) in rats.

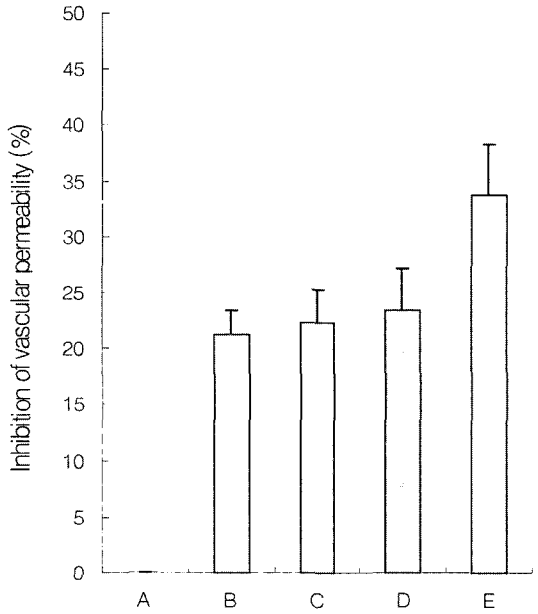

Fig. 2. Effects of the various triprolidine-TPX transdermal systems on the inhibition of vascular permeability increase induced by histamine in rats A: TPX matrix only (blank), B: TPX matrix containing triprolidine (control), C: TPX matrix containing triprolidine and TEC, D: TPX matrix containing triprolidine and POE, E: TPX matrix containing triprolidine, TEC and POE.

containing TEC, POE indicated significant inhibition of vascular permeability increase induced by histamine.

The inhibition of vascular permeability increase induced by histamine in rats

The triprolidine-TPX matrix containing TEC and POE showed about 33.8% inhibition of vascular permeability increase induced by histamine, while the TPX membrane containing only triprolidine showed about 21.3% inhibition of vascular permeability increase comparing with the blank (Fig. 2). Histamine-induced vascular permeability increase was inhibited by the histamine H_1 receptor antagonist, triprolidine, and the vascular permeability increase was significantly reduced by the application of the triprolidine-TPX system containing TEC and POE. Both the plasticizer and penetration enhancer played an important role in skin permeation of triprolidine and increased the antihistamine effects. The antihistamine effects after the transdermal administration of triprolidine-TPX matrix correlated with the pharmacokinetic parameter described in a previous paper (Shin and Choi, 2002). These results show that the triprolidine-TPX matrix system containing plasticizer and enhancer could be a transdermal delivery system providing increased antihistamine effects.

CONCLUSION

The triprolidine-TPX matrix containing plasticizer and penetration enhancer could be a transdermal delivery system providing the increased antihistamine effects.

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