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Enhanced bioavailability of triprolidine from the transdermal TPX matrix system in rabbits

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Abstract

The pharmacokinetics and bioavailability of triprolidine, antihistamines, were studied to determine the feasibility of enhanced transdemal delivery of triprolidine from the poly(4-methyl-1-pentene) (TPX) matrix system containing polyoxyethylene-2-oleyl ether in rabbits. The triprolidine–TPX matrix (50 mg/kg) was applied to abdominal skin of rabbits. Blood samples were collected via femoral artery for 36 h and the plasma concentrations of triprolidine were determined by HPLC. Pharmacokinetic parameters was calculated using the LAGRAN computer program. The area under the curve (AUC) was significantly higher in the enhancer group (4058 ± 1420 ng/ml h) than that (1902 ± 857 ng/ml h) in control group ($P < 0.05$), showing about 235% increased bioavailability. The average C_{max} was increased significantly in the enhancer group (216 ± 44.3 ng/ml) compared with control group (130 ± 25.8 ng/ml) ($P < 0.05$). The mean T_{max} was increased in the enhancer group (8.0 ± 2.55 h) compared with the control (6.0 ± 2.28 h) but was not significant. The relative bioavailability was 23.1% in the control group and 49.3% in the enhancer group compared to the oral route. As the triprolidine–TPX matrix containing polyoxyethylene-2-oleyl ether as an enhancer and tiethyl citrate as a plasticizer was administered to rabbits via the transdermal routes, the relative bioavailability increased by about 2.13-fold compared to the control group, showing a relatively constant, sustained blood concentration with minimal fluctuation. The results of this study shows that triprolidine–TPX matrix could be developed as a transdermal delivery system providing consistent plasma concentration.

Keywords: Bioavailability; Pharmacokinetics; TPX matrix; Triprolidine; Enhancer; Transdermal administration; Histological change

1. Introduction

Triprolidine, antihistamines, has been orally administered, three times or four times a day for treatment of allergic rhinitis, urticaria, allergic drug reactions (Juhlin et al., 1987; Connell et al., 1982; Diamond et al., 1981) and many adverse effects such as sedation, varying from slight drowsiness to deep sleep, dizziness, dry mouth occurred (Gennaro, 1995). Therefore, the development of transdermal controlled drug delivery system of the antihistamines without adverse effects,

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which could occur when administered orally is very important.

In my previous paper (Shin and Yoon, 2002; Shin et al., 2001), the triprolidine–TPX matrix system containing polyoxyethylene-2-oleyl ether as an enhancer and triethyl citrate as a plasticizer was formulated. The objective of this study was to determine the feasibility of transdermal delivery of triprolidine by studying its in vivo absorption characteristics in rabbits and to develop the triprolidine–TPX matrix system containing a penetration enhancer.

2. Materials and methods

2.1. Materials

Triprolidine and polyoxyethylene-2-oleyl ether were purchased from Sigma Chemical Co., Inc. (USA) and TPX of high molecular weight was from Aldrich Chemical Co., Inc. (USA) and triethyl citrate were from Morflex, Inc. (USA). Heparin sodium and normal saline were from Green Cross (Seoul, Korea). Acetnitrile and methanol was HPLC grade and all other reagents were of analytical grade and used 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 a separating funnel. Some drops of the 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. Drug-containing TPX matrix preparation

The drug–TPX matrix containing 10% enhancer and 5% plasticizer were prepared using polyoxyethylene-2-oleyl ether chosen as the best effective enhancer and tetraethyl citrate chosen as the best effective plasticizer for the TPX matrix in previous experiments (Shin et al., 2001). The TPX matrix containing 4% triprolidine was prepared by solvent casting process. About 1.5 g of TPX polymer beads were dissolved in 25 ml of cyclohexane in a beaker, polyoxyethylene-2-oleyl ether, triethyl citrate, and drug were dissolved in this polymer solution. The above combined 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. A piece of the matrix was then cut from the membrane and weighed accurately.

2.4. Route of administration and withdrawal of blood samples

Male rabbits weighing 2.0–2.4 kg were housed individually over 2 weeks in a temperature-controlled environment (20–25 °C). The relative humidity varied between 50 and 60%. They had free access to a diet and water 1 week before experiments unless otherwise noted. They were fasted 24 h before experiments. The rabbits were fixed on a plate and anesthetized by subcutaneous injection of 25% urethane-physiological saline (4 ml/kg) and the abdominal skin of rabbits was shaved 1 h prior to application. The teeth of the rabbits were fixed on the plate, while the tongue was kept tightly on the lower teeth. An infusion set equipped with a 22-gauge (0.8 mm) hypodermic needle and winged adapter was inserted into a right femoral artery to facilitate sampling of blood for drug analysis. Blood samples were collected via femoral artery for 36 h and the plasma concentrations of triprolidine were determined by HPLC.

Triprolidine (50 mg/kg) from the triprolidine–TPX matrix was applied to abdomen skin of rabbits and 2.5 ml of blood specimens were taken at specific time intervals from the cannulae inserted into the femoral artery in a haparinized-glass tubes and centrifuged at 5000 rpm for 5 min to obtain 1 ml of the plasma and frozen until analyzed. A single dose of 2 mg/kg of triprolidine was administered by a rapid injection via the ear vein for the intravenous administration. Blood samples were taken before and at 2, 4, 6, 8, 10, 12, 24 and 36 h after transdermal administration and

7.5, 15, 30 min and 1, 2, 4, 8, 12 and 24 h after oral or intravenous administration. After taking the blood specimen, heparinized physiological saline (75 IU/ml) was inserted into the set to prevent blood coagulation. The homeostasis of the rabbits was maintained by injection of same volume of physiological saline via the ear vein.

2.5. Determination of triprolidine in rabbit plasma

The determination of triprolidine in the plasma was carried out by the Simons method (Simons et al., 1986). A 0.5-ml aliquot of plasma was pipetted into a 15-ml centrifuge tube, 0.2 ml of 10% KOH solution and 3 ml of ether were added and shaken for 10 min by mechanical shaking. After centrifugation for 10 min at 3000 rpm, 2.6 ml of the organic solvent phase was transferred to another tube and evaporated to dryness on a centrifugal evaporator under nitrogen gas at 40 °C. The residue was dissolved in 0.25 ml of 0.05% phosphoric acid by vortex mixing for 3 min, then 50 μl of this solution was injected into the HPLC after centrifuging at 5000 rpm for 5 min.

2.6. HPLC conditions

The HPLC system consisted of a solvent delivery pump (model 910, Waters, USA), a variable UV absorbance detector, and computing integrator. The column was u-Bondapak C_{18} column. The mobile phases was a 30:70 combination of acetnitrile: 0.075 M phosphate buffer (pH 2.5) including 0.5 ml/l of diethylamine and used after degasing. The HPLC was operated at the wavelength of 229 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 7.34 min at room temperature (Fig. 1).

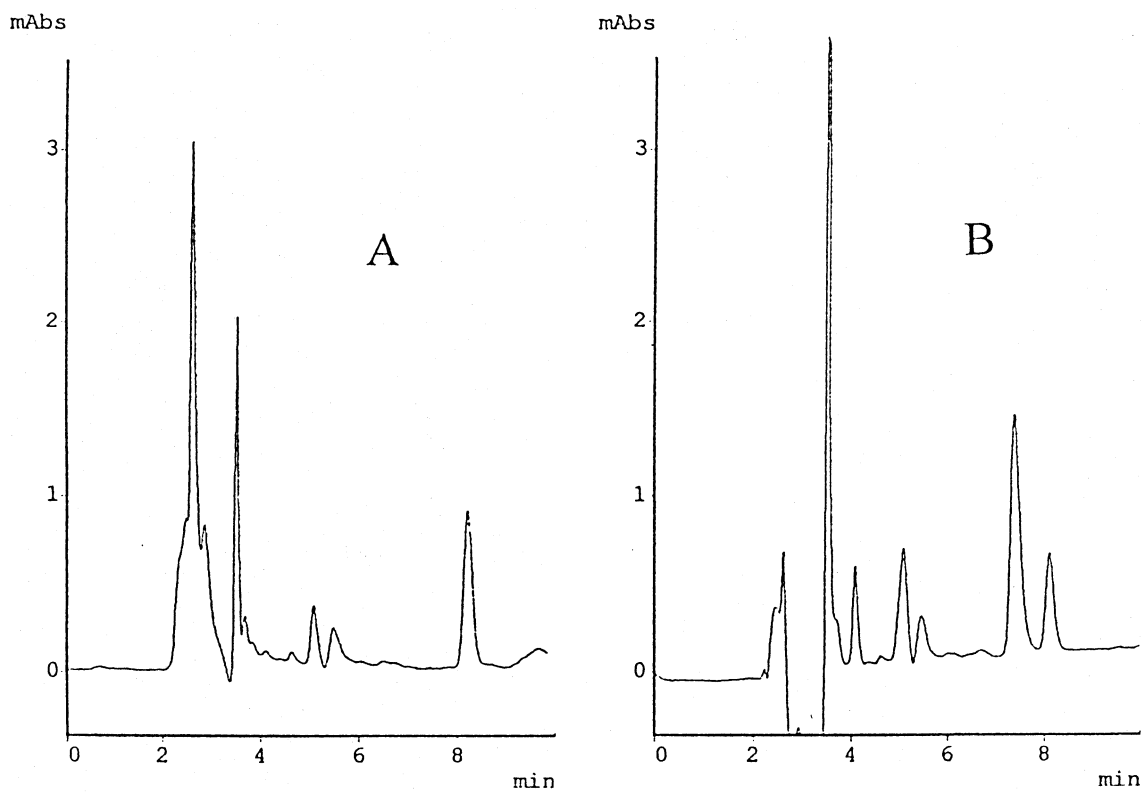

Fig. 1. Chromatograms of blank plasma (A) and plasma taken from the triprolidine–TPX transdermal systems (B) (7.34 min).

2.7. Pharmacokinetic data analysis

The noncompartmental pharmacokinetic analysis was performed with the LAGRAN computer program (Rocci and Jusko, 1983) which employs the Lagran method to calculate the AUC of plasma concentration (C_p) as a function of time (t). The area under the curves were computed by the LAGRAN method to reduce the errors by the trapezoidal rule. Mean residence time (MRT) was calculated as area under the first moment curve (AUMC) divided by area under the curve (AUC). AUMC was determined using a plot of plasma concentration multiplied by time ($C \cdot t$) versus time and calculation of its area under the curve by the LAGRAN. The maximum plasma concentration (C_{max}) and time to reach maximum plasma concentration (t_{max}) were determined by visual inspection of the experimental data. The elimination rate constant (K_{el}) was calculated by the regression analysis from the slope of the line and the half-life ($t_{1/2}$) of the drug was obtained by $0.693/K_{el}$. The absolute bioavailability of triprolidine after transdermal administration per the IV administration was calculated as follows:

$$\text{Absolute bioavaailability (AB)} = \frac{\text{Sample AUC}}{\text{IV AUC}} \times \frac{\text{IV dose}}{\text{Sample dose}} \times 100$$

The statistical significance of the differences between formulations was tested by the Student's paired t-test. It was defined to be statistically significant when $P < 0.05$. All values were reported as mean $\pm$ standard deviation.

2.8. Histological examination of the skin

Histological changes on the skin after experiment were examined. After animal experiment, the excised skin was fixed in 10% neutralized-formalin for 12 h by the conventional procedure, microtomed as 3 μm thickness, and stained with hematoxylin–eosin and examined under a microscope (Aioi et al., 1993). The skin untreated was served as a control.

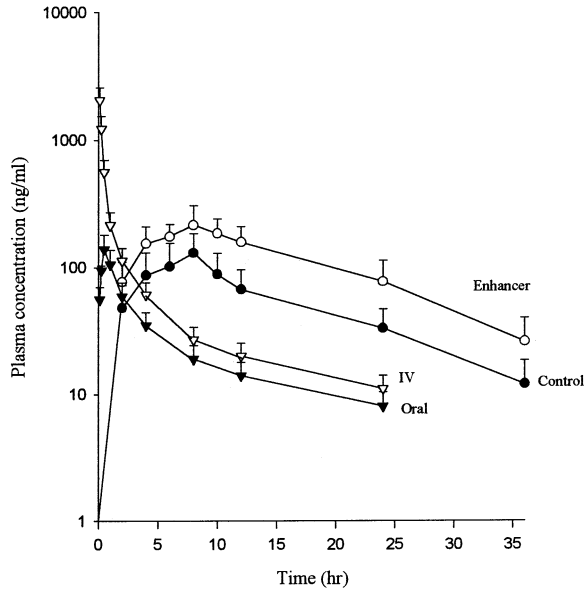

Fig. 2. Plasma concentration–time profile of triprolidine following oral (4 mg/kg), IV administration (2mg/kg) and transdermal administration (50 mg/kg) from the triprolidine–TPX matrix system containing enhancer, to rabbits ($n = 8$). The error bar represents the standard deviation of the mean: ●, without enhancer (control); ○, with enhancer (polyoxyethylene-2oleyl ether); △, oral administration; ▲, IV administration.

3. Results and discussion

3.1. Pharmacokinetics

3.1.1. Area under the concentration–time curve

For the purpose of studying the biopharmaceutical aspects of transdermal absorption of triprolidine, one of the prerequisites is that the pharmacokinetic parameter after the i.v. administration should correlate with that after the transdermal absorption of triprolidine. The plasma–time concentration curve for triprolidine after the transdermal administration of 50 mg/kg of triprolidine is shown in Fig. 2 with oral and i.v. administration to rabbits.

The average areas under the serum concentration–time curves, the value of AUC was 659 ± 184 h ng/ml for oral administration, 1537 ± 988 h ng/ml for intravenous administration. Following transdermal administration of a single 50 mg/kg of triprolidine to rabbits, the value of AUC of

transdermal administration with enhancer was 4058 ± 1420 h ng/ml and that without enhancer was 1902 ± 857 ng/ml (Table 1). Within each study, significant differences were observed among the formulations.

The absolute bioavailability of AUC value of transdermal administration without an enhancer showed about 4.5% compared to intravenous administration. However, the absolute bioavailability of the AUC value of transdermal administration of triprolidine from the TPX matrix containing polyoxyethylene-2-oleyl ether as an enhancer showed about 10.6% compared to intravenous administration. The transdermal administration of triprolidine from the matrix system containing polyoxyethylene-2-oleyl ether was higher than that from the matrix system without an enhancer. As the triprolidine–TPX matrix containing polyoxyethylene-2-oleyl ether was administered via the transdermal routes to rabbits, the relative bioavailability showed about 2.13-fold compared to the control group ($P < 0.05$).

Transdermal administration of triprolidine matrix containing polyoxyethylene-2-oleyl ether to rabbits showed a relatively constant, sustained blood concentration with minimal fluctuation without showing 'flip–flop' effect and better bioavailability with comparing control group (Fig. 2).

3.1.2. Peak concentration (C_{max}) and peak time (t_{max})

Statistical analysis of the $C_{\max}$ and $t_{\max}$ values observed following the transdermal administration of the triprolidine formulations shows that the enhancer group exhibited higher average $C_{\max}$ values of 216 ± 44.3 ng/ml than those of 130 ± 25.8 ng/ml which was achieved by the control group, whose differences were statistically significant ($P < 0.05$). 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 (Table 1). The relative bioavailability of the enhancer group was about 213% when comparing with the control group, which means enhanced absorption. The transdermal administration of triprolidine–TPX matrix containing an enhancer showed a sustained and enhanced absorption.

3.1.3. Mean residence time (MRT), K_{el} and $T_{1/2}$

The average MRT after transdermal administration was 17.00 h in the control group and 17.00 h in the enhancer group. The average K_{el} was 0.074 ± 0.020 h^{-1} in the enhancer group and 0.074 ± 0.013 h^{-1} in the control group and a little decreased from the transdermal administration, while 0.077 ± 0.031 h^{-1} in intravenous administration group, but statistically insignificant. The average $T_{1/2}$ was 9.38 ± 1.97 h in the enhancer group and 9.42 ± 1.35 h in control group and a

Table 1
Pharmacokinetics of triprolidine from the transdermal TPX matrix system containing enhancer, oral and IV administration in rabbits

Groups parameters	Control	Enhancer	Oral	IV
AUC (ng/ml h)	1902 ± 857	4058 ± 1420*	659 ± 184	1537 ± 988
$C_{\max}$ (ng/ml)	130 ± 25.8	216 ± 44.3*	139 ± 38.8	–
$T_{\max}$ (h)	8.00 ± 2.28	8.00 ± 2.55	0.5 ± 0.13	–
K_{el} (h^{-1})	0.074 ± 0.013	0.074 ± 0.020	0.068 ± 0.018	0.077 ± 0.031
$T_{1/2}$ (h)	9.42 ± 2.25	9.38 ± 1.97	10.17 ± 2.64	8.98 ± 1.48
MRT	17.0 ± 4.76	17.0 ± 4.29	13.0 ± 3.51	7.2 ± 2.02
A.B. (%)	4.5	10.6	21.4	100
R.B. (%)	23.1	49.3	100	

Each value represents the mean $\pm$ S.D. of eight determinations. AUC, area under the plasma concentration–time curve from time zero to time infinity; $C_{\max}$, maximum plasma concentration; $T_{\max}$, time of $C_{\max}$; K_{el}, elimination rate constant; $T_{1/2}$, terminal half-life; MRT, mean residence time; A.B., absolute bioavailability to IV group; R.B., comparative bioavailability to oral group. Transdermal dose of control and enhancer group = 50 mg/kg, oral dose = 4 mg/kg, IV dose = 2 mg/kg.

* $P < 0.05$ compared to control.

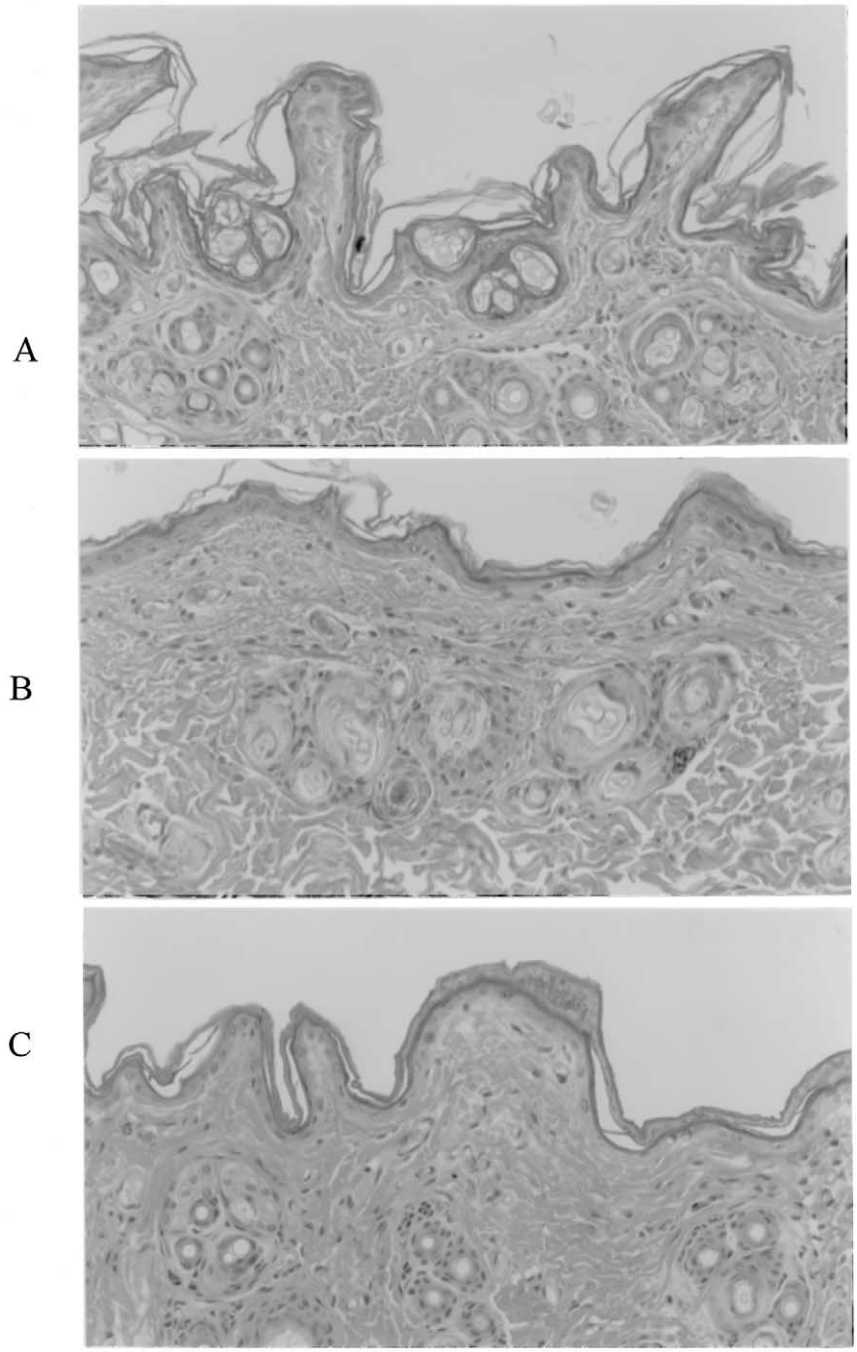

Fig. 3. Morphology of abdominal skin of rabbits after transdermal administration of the triprolidine–TPX matrix system containing an enhancer. (A) Control (before application); (B) after application of the triprolidine–TPX matrix without enhancer; (C) after application of the triprolidine–TPX matrix containing the enhancer.

little sustained from the transdermal administration, while 8.98 ± 1.48 h in intravenous administration group, but statistically insignificant.

3.2. Histological examination of the skin

A histological examination was carried out in order to study the effects of an enhancer in triprolidine penetration through the skin of the rabbits. Intact skin was composed of stratum corneum, epidermis, dermis and subcutaneous fats and has well-weavered structures. The skin treated with an enhancer group showed that stratum corneum was loosely layered and intercellular spaces were wide, but no inflammatory cells were observed. In fact, there was no globular, cellular changes between the normal and enhancer groups (Fig. 3).

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References

Aioi, A., Kuriyama, K., Shimizu, T., Yoshioka, M., Uenoyama, S., 1993. Effects of vitamin E and squalene on skin irritation of a transdermal absorption enhancer, laurylsarcosine. Int. J. Pharm. 93, 1–6.

Connell, J.T., Williams, B.O., Allen, S., Cato, A., Perkins, J.G., 1982. A double-blind controlled evaluation of actipid and its individual constituents in allergic rhinitis. J. Int. Med. Res. 10, 341.

Diamond, L., Gerson, K., Cato, A., Peace, K., Perkins, J.G., 1981. An evaluation of triprolidine and pseudoephedrine in the treatment of allergic rhinitis. Ann. Allergy 47, 87.

Gennaro, A.R., 1995. The Science and Practice of Pharmacy, 19th edn. Mack Publishing Company, Easton, PA, pp. 1207–1218.

Juhlin, L., Gibson, J.R., Harvey, S., Huson, L.W., 1987. Acrivastine versus clemastine in the treatment of chronic idiopathic urticaria. A double-blind, placebo-controlled study. Int. J. Dermatol. 12, 653–654.

Rocci, M.L., Jusko, W.J., 1983. LAGRAN program for area and moments in pharmacokinetic analysis. Comput. Prog. Biomed. 16, 203–216.

Simons, K.J., Singh, M., Gillespie, C.A., Simons, E.R., 1986. An investigation of the H-receptor antagonist triprolidine: pharmacokinetics and antihistaminic effects. J. Allergy Clin. Immunol. 77, 326–330.

Shin, S.C., Yoon, M.K., 2002. Application of TPX polymer membranes for the controlled release of triprolidine. Int. J. Pharm. 232, 131–137.

Shin, S.C., Kim, J., Yoon, M.K., Oh, I.J., Choi, J.S., 2001. Transdermal delivery of triprolidine using TPX polymer membrane. Int. J. Pharm. accepted for publication.