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Application of TPX polymer membranes for the controlled release of triprolidine

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Abstract

Oral administration of triprolidine, antihistamines, may cause many adverse effects such as dry mouth, sedation, dizziness and transdermal drug delivery was considered. Poly(4-methyl-1-pentene) (TPX) membrane, which has good mechanical strength was fabricated by the casting method. TPX membranes was a little brittle and the plasticizers was added for preparing the membranes. The present study was carried out to evaluate the possibility of using the polymer TPX membrane as a controlling membrane and further develop a TPX matrix system for transdermal delivery of triprolidine. The effects of molecular weights of TPX, plasticizers, polyethylene glycol (PEG) 400, drug concentration, and temperature on drug release were studied. The solubility of triprolidine increased exponentially as the increased volume fraction of PEG 400 in saline, and the rate of permeation through TPX membrane was proportional to PEG 400 volume fraction. The release rate of drug from the TPX matrix increased with increased temperature and drug concentration. Among the plasticizers used such as alkyl citrates, phthalates and sebacate, tetra ethyl citrate (TEC) showed the best enhancing effects. Enhancement factor of TEC was 3.76 from TPX matrix at 37 °C. The transdermal controlled release of triprolidine system could be developed using the TPX polymer including the plasticizer.

Keywords: Triprolidine; TPX; Matrix; Permeation; Plasticizer; Polymer

1. Introduction

In the last decades, transdermal dosage forms have been introduced for providing controlled delivery via skin into the systemic circulation.

Triprolidine, anti-histamines, 7.5 mg is orally administered, three times or four times a day (Gennaro, 1995) and many adverse effects such as sedation, varying from slight drowsiness to deep sleep, dizziness, dry mouth might occur. The development of transdermal drug delivery of the antihistamine without adverse effects of frequent oral administration is very important.

Several technologies have been successively developed to control the release rate. The use of a release controlling membrane is one method to regulate the drug release. The use of drugs dispersed in inert polymer to achieve controlled re-

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lease by diffusion has considerable attention (Levesque, 1961; Kaplan, 1965). In this laboratory, the transdermal controlled drug delivery using polymer membrane (Shin and Byun, 1995, 1996; Shin and Cho, 1996) and gel systems (Shin and Kim, 2000; Shin et al., 1999, 2000) have been studied. Among many polymers used, ethylene vinyl acetate (EVA) copolymer memebrane was a heat processable, flexible and inexpensive material (Miyazaki et al., 1982). But, the strength of EVA membrane was too weak and too flexible.

Poly(4-methyl-1-pentene) (TPX), asymmetric membrane, consisting of a porous sublayer was used for osmotic drug delivery and biodegradable release devices (Witte et al., 1993). The characteristic structure of asymmetric membranes is suitable for transdermal drug delivery because the porous sublayer can function as a drug reservoir and the dense skin can control the drug release rate. TPX polymer membrane known for its good mechanical strength (He and Porter, 1987), was used to prepare rate-controlling membranes or matrix system. But the TPX membranes was so much brittle that the plasticizer has to be used. The plasticizer reduces the brittleness, improve flow, impart flexibility, and increase toughness, strength, tear resistance, and impact resistance of the polymer.

The present study was carried out to evaluate the possibility of using the polymer TPX membrane as a controlling membrane and further develop a 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). Poly (4-methyl-1-pentene) (TPX) were purchased from Aldrich Chemical Co. (USA). Dibutyl sebacate (DBS), acetyl tributyl citrate (ATBC), tributyl citrate (TBC), acetyl triethyl citrate (ATEC) and triethyl citrate (TEC) were purchased from Morflex (USA). Diethyl phthalate (DEC) and di-*n*-butyl phthalate (DBP) were from Junsei Chemical Co., Ltd (Japan). Acetonitrile, ethyl alcohol were HPLC grade from J.T. Baker Inc. (USA).

2.2. Methods

2.2.1. Extraction 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.

2.2.2. Determination of drug solubility

An excess amount of triprolidine was equilibrated with 10 ml of various concentration of polyethylene glycol (PEG) 400-saline at 37 °C for 24 h with constant shaking. The concentration was determined after proper dilution at 230 nm by spectrophotometer.

2.2.3. Preparation of TPX polymer membranes

About 1.5 g of TPX polymer beads was dissolved in 25 ml of cyclohexane in a glass beaker. This polymer solution was poured onto a glass plate and the solvent was allowed to evaporate off at room temperature overnight. The membrane was removed from the plate and dried for 2 days at room temperature in vacuo. The thickness of the membranes was measured at several points by micrometer and the mean values were obtained.

2.2.4. Preparation of TPX matrix containing drug and plasticizer

The matrix devices of TPX containing triprolidine and plasticizer were prepared by casting process. About 1.5 g of TPX polymer beads and drug were dissolved in 25 ml of cyclohexane. Plasticizer was dropped into drug-containing TPX solution during mixing at 60 °C, for 30 min. This method was chosen in order to produce large unharmed pieces of membrane with no orientation of the molecules (Bodmeier and Paeratakul, 1989). Thereafter, the stirring was continued for 30 min, which is the time that has been reported necessary for 95% of the DBS to mix properly.

Plasticizers were added in ratios of 10% (w/w) of TPX matrix. The plasticizers used were alkyl citrates such as ATBC, TBC, ATEC, TEC, and sebacate such as DBS, and phthalates such as DEP, DBP. This polymer solution was poured onto a glass plate and the solvent was allowed to evaporate off at room temperature overnight. The membrane was removed from the plate and dried for 2 days at room temperature in vacuo. 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 polymer used.

2.2.5. Drug permeation through TPX membranes

Permeation of triprolidine through TPX membranes was studied using two-chamber diffusion cell. Each half-cell has a volume of about 7 ml and an effective diffusional area of 0.79 cm^2. A piece of TPX membrane was clamped between the two halves of the cell. A drug suspension of above solubility in various concentrations of PEG 400-saline solution was filled into the donor compartment. And a same concentration of PEG 400-saline solution (without drug) was added into the receiver compartment, in order to prevent the effect of solvent permeation from the donor to the receiver side on the triprolidine permeation through the membrane. The 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 UV spectrophotometer at 230 nm.

2.2.6. In vitro release from the TPX matrix

The in vitro release of triprolidine from the TPX matrix was examined by using the modified Keshary–Chien cell. A unit of TPX matrix was clamped between the cell cap and receptor compartment. The diameter of the cell was 1.5 cm, providing 1.77 cm^2 effective constant area and PEG 400-saline solution was used as receptor solution. The receptor was maintained to 37 °C with circulating water jacket and stirred constantly at 350 rpm. At predetermined time intervals, whole solution from the receptor cell was taken and replaced with fresh solution. The cumulative amount of triprolidine released from the matrix was determined at 230nm. The effects of volume fraction of PEG 400, molecular weights of TPX, plasticizers, concentration, and temperature were also studied.

2.2.7. Scanning electron microscopy

The membrane structure were examined by a JEOL (model JSM 5400) scanning electron microscope (SEM). Membrane samples were fractured in liquid nitrogen and gold coated to about 500×10^{-8} cm thickness using an JFC-1100 coater under a high vacuum, 0.1 Torr, high voltage, 1.2 kV and 50 mA. Coated samples were examined using SEM.

3. Results and discussion

3.1. Permeation of triprolidine through TPX polymer membrane

The aqueous solubility of triprolidine is extremely low and could be improved by addition of a water-miscible hydrophilic polymer like PEG 400, which was reported to be an excellent solubilizer for many steroids (Chien and Lambert, 1975). In the present solubility studies, it was observed that the aqueous solubility of triprolidine was increased exponentially as increasing the volume fraction of PEG 400 in the saline solution (Fig. 1).

When the drug concentration in the donor solution is maintained at a level greater than the equilibrium solubility and the drug concentration in the receptor solution is maintained under sink condition and a constant permeation profile should be achieved. The rate of permeation, which was measured from the slope of Q versus t plots was found to increase with the addition of PEG 400 in the saline solution (Fig. 2).

The effects of PEG 400 on the permeability coefficient (P) of triprolidine across TPX membrane showed that the permeability coefficient (P) decreased as increasing the volume fraction of PEG 400 in the saline solution (Table 1). In this experiments, 40% PEG 400 was chosen to make sink condition, since permeability coefficients between 40% PEG and 50% PEG were similar.

3.2. Release of triprolidine from the TPX matrix

3.2.1. Effects of plasticizers on drug release from TPX matrix

The characteristic structure of asymmetric membranes is suitable for transdermal drug delivery because the porous sublayer can function as a drug reservoir and the dense skin can control the drug release rate (Coutel-Egros et al., 1992). For most rate-controlling polymeric membranes, the release rates are adjusted by varying the chemical or physical properties of membranes. For asymmetric membranes, besides varying the chemical or physical properties of membranes, the release rate can be adjusted by changing the membrane structure (Donbrow and Friedman, 1975; Michaels and Bixler, 1961).

The plasticizers reduce the brittleness, improve flow, impart flexibility, and increase toughness, strength, tear resistance, and impact resistance of the polymer. The effects of plasticizers on drug release from the TPX-matrix was studied at 37 °C according to kinds of plasticizers. The effectiveness of plasticizer was determined by the comparing the drug release rate in the presence and absence of plasticizer. It was defined as the enhancement factor (EF), which was calculated by the drug release rate from the TPX matrix containing plasticizers divided by that without plasticizer. Plasticizers in TPX matrix increased the rate of drug release (Table 2). Increasing the amount of plasticizer could lead to an increase in free film elongation and a decrease in tensile strength. A strong interaction between a drug and a polymer has been reported to influence significantly drug release through a polymeric film (Bodmeier and

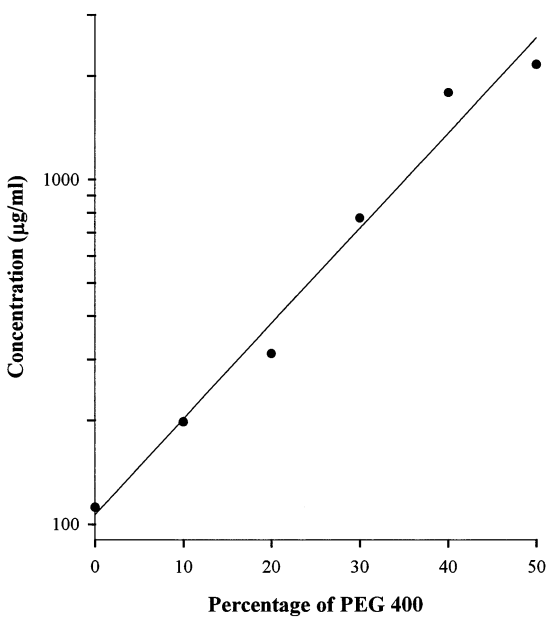

Fig. 1. Semilogarimethic relationship between the equilibrium solubility in PEG-saline of triprolidine and volume fraction of PEG 400.

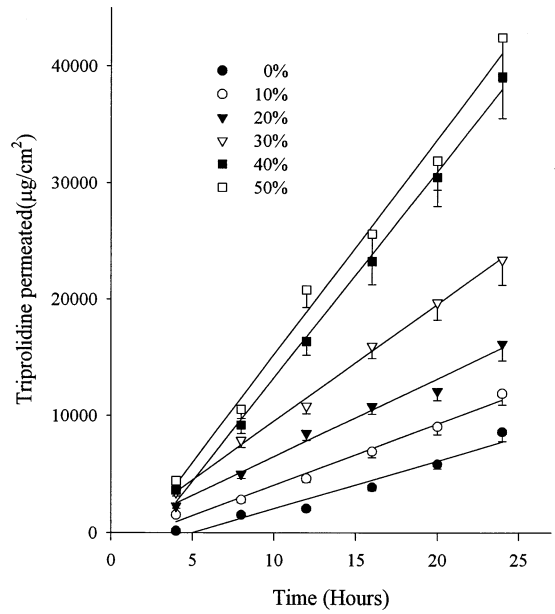

Fig. 2. Effects of PEG 400 volume fraction in saline on the permeation of triprolidine through TPX polymer membrane.

Table 1
Effect of PEG 400 on the permeation of triprolidine through the TPX polymer membranes

PEG 400 % (v/v)	Rate of permeation (μg/cm² per h)	Permeability coefficient (cm/h)
0	407.43	3.64
10	521.38	2.92
20	665.74	2.13
30	1004.83	1.30
40	1580.98	0.88
50	1851.08	0.86

Table 2
Effect of plasticizers on the flux of triprolidine from the TPX matrix

Plasticizer		Flux (μg/cm^2 per h$^{1/2}$)	Enhancement factor
Citrate group	ATBC	162.38	3.12
	ATEC	178.20	3.42
	TBC	189.46	3.64
	TEC	196.17	3.76
Phthalate group	DBP	60.95	1.17
	DEP	65.23	1.25
Sebacate group	DBS	181.79	3.49
Control	–	52.12	1

Paeratakul, 1989; Jenquin et al., 1990). The release rates of triprolidine from the TPX matrix containing citrate group, phthalate group and sebacate group as a plasticizer at 37 °C are shown in Table 2. The amount of triprolidine released from the TPX matrix containing TEC as a citrate group plasticizer increased about 4-fold, that containing DEP as a phthalate group plasticizer increased about 1.3-fold, that containing DBS as a sebacate group plasticizer increased about 3.6-fold (Table 2). Comparing the alkyl radicals of the plasticizers such as citrate groups, phthalates groups, the ethyl group plasticizers increased the drug release better than the butyl group plasticizers.

3.2.2. Effects of drug concentration

The effects of drug concentration on its release from the TPX-matrix was studied at 37 °C according to drug concentration of 1, 1.5, 2, 3, and 4% (w/w). The release profiles of triprolidine from the TPX matrices of different drug loading at 37 °C for 24 h were studied. The release rates of drug were calculated from the slope of the linear region of the Q versus $t_{1/2}$ release profile. The cumulative amount of triprolidine released Q versus the square root of time ($t_{1/2}$) plot showed a good linearity for all five different concentrations. A plot of $Q/t_{1/2}$ versus the square root of drug concentration yielded a straight line (Fig. 3).

3.2.3. Effects of temperature of release medium

The effects of temperatures on drug release from TPX-matrix containing 4% drug was studied at 28, 32, 37, and 42 °C. The dependency of the drug release profile on temperature is shown in Fig. 4. The higher the temperature, the greater the drug release. The drug release rate from the TPX matrix containing 4% triprolidine at 28, 32, 37 and 42 °C were 9.07, 21.20, 50.26, and 89.30 g/cm^2 per h$^{1/2}$, respectively. It should be noted that the rate of drug release increased about 9.85-fold when the temperature of the drug release system was raised from 28 to 42 °C. But for the practical use temperature, 37 °C was chosen to reflect the temperature of the stratum corneum. The activation energy (E_a), which was measured from the slope of log P versus $1000/T$ plots was 40.41 kcal/mol for 1% loading dose, 37.20 kcal/mol for 1.5% loading dose, and 34.05 kcal/mol for 2% loading dose, 32.26 kcal/mol for 3% loading dose and 30.71 kcal/mol for 4% loading dose from TPX matrix.

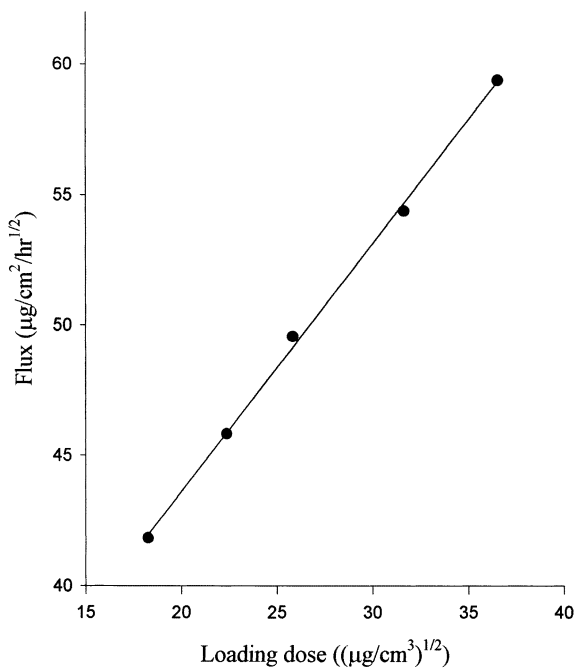

Fig. 3. Relationship between the release rate of triprolidine and the loading doses in TPX polymer matrix.

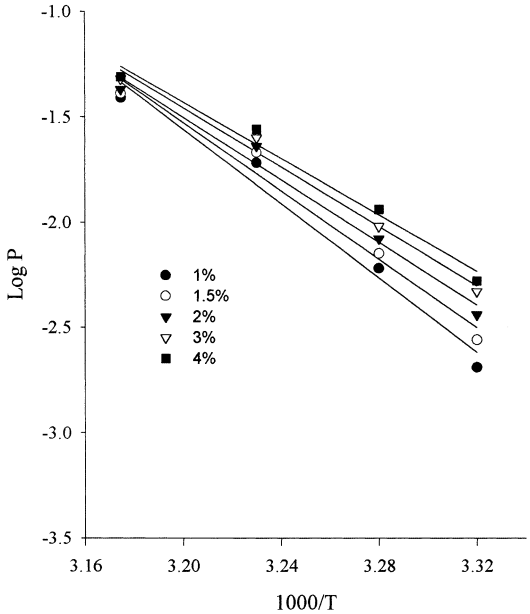

Fig. 4. Effects of temperature on drug release from the TPX matrix containing various loading dose.

This observation indicates clearly that the release of triprolidine from the TPX matrix is an energy-linked process (Miyazaki et al., 1983). The increase in release with increasing temperature suggests that release characteristics of drug from the polymer would change over the body temperature range. This finding indicates that special precautions should be taken with regard to monitoring body temperature in practical applications.

3.2.4. Scanning electron microscopy

The TPX membrane structure were examined by SEM. The TPX membrane structure (Fig. 5A) is homogeneously dense and has no visual pores, indicating that the porosity is very small and the release rate of triprolidine from TPX matrix is low. For TPX, a very inert material, it is not easy to change the chemical properties of membranes. To increase the porosity of asymmetric TPX membranes and to prevent the shrinkage of membranes during the formation process, plasticizer such as TEC was added to the casting solution (Fig. 5B). Membranes with different drug release could be fabricated by adding different kinds of plasticizers and adjusting the adding amount. The experimental results indicate that the addition of plasticizer (TEC) in TPX/cyclohexane solution could lead to the formation of sponge, finger (macrovoid) and 'cellular surface' (Fig. 5B and C). It was found that the addition of plasticizers could have drastic effect on membrane morphology and could be used to control effectively the porosity of TPX membranes and the effects of plasticizers on membrane porosity could be well correlated with the release rate of triprolidine from TPX matrix.

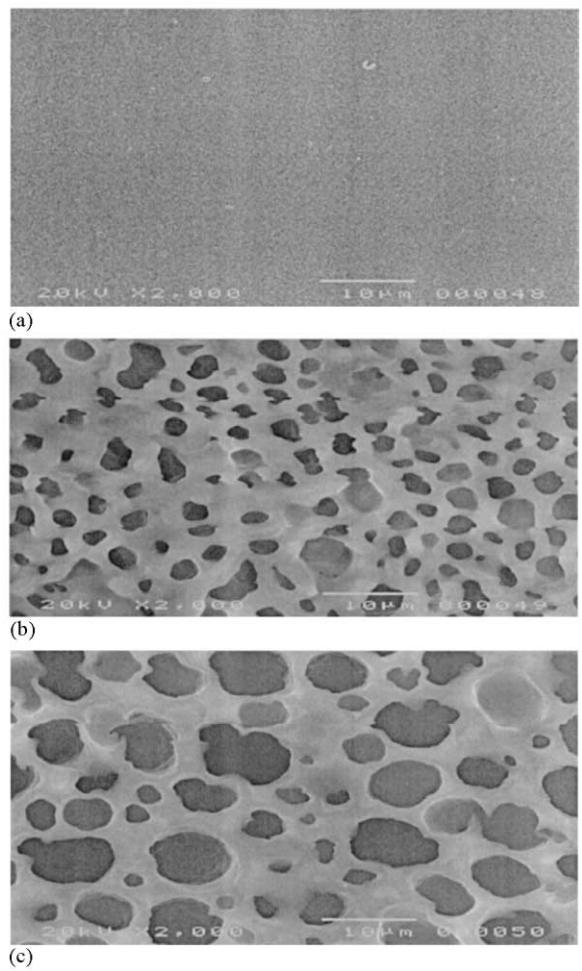

Fig. 5. Scanning electron microscopy of TPX membrane system, (A) TPX memebrane; (B) TPX membrane containing TEC; (C) TPX membrane containing TEC and triprolidine.

These characteristic structure of asymmetric membranes is suitable for transdermal drug delivery because the porous sublayer can function as a drug reservoir and increase the release rate of triprolidine from the TPX matrix, so the drug release rate could be controlled by the addition of plasticizers in casting solution.

Acknowledgements

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