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Research paper

Controlled release of triprolidine using ethylene-vinyl acetate membrane and matrix systems

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Abstract

The studies on the permeability of triprolidine through ethylene-vinyl acetate (EVA) copolymer membrane using two-chamber diffusion cell was carried out to develop the controlled delivery system. To evaluate the effect of drug concentration in reservoir, polyethylene glycol (PEG) 400 was added to saline solution as a solubilizer and a sink condition was maintained in the receptor solution. The permeation rate of drug through EVA membrane was proportional to PEG 400 volume fraction. A linear relationship existed between the permeation rate and the reciprocal of the membrane thickness. Triprolidine-containing matrix was fabricated with EVA copolymer to control the release of the drug. The plasticizers was added for preparing the pore structure of EVA membranes to increase the drug release. The effects of PEG 400, vinyl acetate (VA) contents of EVA, membrane thickness, drug concentration, temperature, and plasticizers, on drug release were studied. The release rate of drug from the EVA matrix increased with PEG 400 volume fraction, increased temperature and drug loading doses. An increased vinyl acetate comonomer content in EVA membrane increased the drug release rate and permeability coefficient. Among the plasticizers used such as alkyl citrates and phthalates, tetra ethyl citrate showed the best enhancing effects showing the enhancement factor of 1.88. The release of triprolidine from the EVA matrix follows a diffusion controlled model, where the quantity released per unit area is proportional to the square root of time. The controlled release of triprolidine could be achieved using the EVA polymer including the plasticizer.

Keywords: Triprolidine; Ethylene-vinyl acetate; Membrane; Matrix; Controlled delivery; Plasticizer; Permeability coefficient

1. Introduction

In the last decades, transdermal dosage forms have been introduced for providing the controlled delivery via skin into the systemic circulation. The usefulness of transdermal delivery systems has been demonstrated for the drugs, such as nitroglycerin, scopolamine and clonidine [1].

Triprolidine, an anti-histamine, 7.5 mg is orally administered, three or four times a day [2] and many adverse effects such as sedation, varying from slight drowsiness to deep sleep, dizziness, dry mouth can occur. Therefore, the development of a transdermal drug delivery system for the antihistamine without adverse effects of frequent oral administration is very important.

Basic components of transdermal devices are polymer matrix, penetration enhancers and excipients [3]. The use of a release controlling membrane is one method to regulate the drug release. The use of drugs dispersed in inert polymer matrices to achieve controlled release by diffusion has drawn considerable attention. Ethylene-vinyl acetate (EVA) copolymer is a heat processable, flexible and inexpensive material [4]. The safety and biocompatibility of EVA copolymer are reflected in its use as a biomaterial for artificial hearts and as an antithrombogenic material. The usefulness of EVA copolymer as a drug delivery system for pilocarpine, progesterone, hydrocortisone [5], fluoride ion [6], 5-fluorouracil [7], isosorbide dinitrate [8], nicardipine [9] and macromolecules such as proteins has been described. However few reports have dealt with the release of antihistamine from EVA copolymer matrices.

Since the first step in transdermal drug delivery involves controlled drug release from the dosage form, the present investigation was undertaken to determine the amounts of a potent antihistamine, triprolidine, released from EVA copolymer matrices. Several technologies have been successively developed to control the release rate. The use of drugs dispersed in an inert polymer to achieve controlled release by diffusion has drawn considerable attention [10].

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In this laboratory, transdermal controlled drug delivery using polymer membrane [11–17] has been studied.

The present study was carried out to evaluate the possibility of using the various EVA membranes as a controlling membrane and to further develop an EVA matrix system for the 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 18, 33 and 40% (w/w) VA content were purchased from Aldrich Chemical Co., Inc. (USA). Acetyl tributyl citrate (ATBC), tributyl citrate (TBC), acetyl triethyl citrate (ATEC) and triethyl citrate (TEC) were purchased from Morflex, Inc. (USA). Diethyl phthalate (DEP) and di-n-butyl phthalate (DBP) were obtained from Junsei Chemical Co., Ltd. (Japan). Acetonitrile and ethyl alcohol were high-performance liquid chromatography grade from J.T. Baker Inc. (USA) and all chemicals were used as received.

2.2. 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 a 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. Preparation of EVA copolymer membranes

About 0.5 ~ 2.5 g of EVA copolymer beads were dissolved in 10 ~ 20 ml of methylene chloride or cyclohexane in a glass beaker. The vinyl acetate content of EVA copolymer varied from 18 to 40% (w/w). This polymer solution was poured onto a Teflon coated 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 using a micrometer and the mean values were obtained.

2.4. Preparation of EVA matrix containing drug and plasticizer

The triprolidine-EVA matrix was prepared by a casting process. About 1.5 g of EVA polymer beads and drug were dissolved in 25 ml of cyclohexane. Plasticizer was dropped into drug-containing EVA solution with mixing at 60°C for 30 min. This method was chosen in order to produce large undamaged pieces of membrane with no orientation of the molecules [18]. Thereafter, the stirring was continued for 30 min, which is the time that has been reported necessary for 95% of the plasticizer to mix properly. Plasticizers were added in ratios of 10% (w/w) of EVA matrix. The plasticizers used were alkyl citrates such as ATBC, TBC, ATEC, TEC, 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.

2.5. Drug permeation through EVA membranes

For the determination of steady state permeation of triprolidine through EVA membranes, two-chamber diffusion cell was used. Each half-cell whose volume of about 7 ml had the effective diffusional area of 0.79 cm^2. A piece of EVA membrane was clamped between the two halves of the cell and the assembled cell was placed in a shaking incubator at 37°C. A drug suspension of above its solubility limit in various concentrations of PEG 400-saline solution was placed in the donor compartment. The 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 predetermined intervals and replaced by 7 ml of fresh solution. The amount of drug permeated was determined by measuring the absorbance at 230 nm with a UV spectrophotometer.

2.6. In vitro release from the EVA matrix

The in vitro release of triprolidine from the EVA matrix was examined for 24 h by using the modified Keshary-Chien cell [19]. A unit of EVA 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 at 37°C with circulating water jacket and stirred constantly at 350 rpm. At predetermined time intervals, the 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 230 nm where the plasticizers used did not absorb. The effects of plasticizers, drug concentration, and temperature were also studied.

2.7. Calculations

2.7.1. Kinetics of drug permeation through membrane

The cumulative amount of drug permeating through a unit surface area (Q) can be expressed mathematically by following relationship:

$$Q = P(C_D - C_R)t \quad (1)$$

where P is the permeability coefficient; and C_D and C_R are the drug concentration in the donor (D) and the receptor (R) solutions, respectively.

When the drug concentration in the donor solution (C_D) is maintained at a level greater than the equilibrium solubility (i.e. $C_D > C_e$) and the drug concentration in the receptor solution (C_R) is maintained under the sink condition (i.e. $C_D \ll C_e$), Eq. (1) can be simplified to:

$$Q = PC_e t \quad (2)$$

and a constant permeation profile should be obtained. The rate of permeation is then defined by:

$$Q/t = PC_e \quad (3)$$

The permeation rate was calculated from the slope of the linear region of the permeation profile. Lag time was calculated from the intercept on the time axis by extrapolation from the steady-state permeation profile [20,21].

2.7.2. Kinetics of drug release from the matrix

A characteristic drug release profile of matrix-type drug delivery systems can be represented by the Higuchi's equation [22]. The release from a planar system having dispersed drug in a homogeneous matrix should follow the relationship:

$$Q = (D(2A - C_s)C_s t)^{1/2} \quad (4)$$

where Q is the amount of drug released after time t per unit exposed area, D is the diffusivity of the drug in the matrix, A is the initial drug concentration, and C_s is the drug solubility in the matrix. The flux was calculated from the slope of the linear region of the Q versus $t^{1/2}$ release profile. The validity of the relationships has been confirmed experimentally by a number of workers using various systems [23,24].

3. Results and discussion

3.1. Permeation of triprolidine through EVA polymer membrane

3.1.1. Effects of receptor medium on drug permeation

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 [25]. In previous studies [17], we have observed that the aqueous solubility of triprolidine was increased exponentially by increasing the volume fraction of PEG 400 in the saline solution. When the drug concentration in the donor solution is maintained at a level greater than the solubility limit, the drug concentration in the receptor solution is maintained under sink conditions 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 (Table 1).

As expected from Eq. (3), the increase in the permeation rate (Q/t) was dependent upon the equilibrium solubility (C_e) of triprolidine in the PEG 400-saline solutions. From the permeation rate data and the saturated concentration (= equilibrium solubility), a low permeation rate of triprolidine was observed in the saline solutions containing less than 30% (v/v) PEG 400. This might be attributed to the lower equilibrium solubility of triprolidine in receptor solutions.

The effect of PEG 400 on the permeability coefficient (P) of triprolidine across EVA membrane can be determined by the use of Eq. (3′):

$$P = \frac{Q/t}{C_e} \quad (3')$$

The results (Table 1) showed that even though the equilibrium solubility increased in higher volume fraction of PEG 400, the permeability coefficient (P) decreased upon increasing the volume fraction of PEG 400 in the saline solution. In the experiments, 40% PEG 400 was chosen to ensure sink conditions, since permeability coefficients between 40% PEG and 50% PEG were similar.

3.1.2. Effects of membrane thickness on drug permeation

Factors determining the rate of drug release are particularly important in the design and formulation of controlled release preparations. Thus, it is necessary to determine which factors control the release kinetics. In order to find out the effects of membrane thickness, the effects of variation in membrane thickness on the triprolidine permeation rate were studied (Fig. 1). The permeation rate (dQ/dt) was proportional to the reciprocal of the membrane thickness (h). The result demonstrates that a linear relationship exists between the rate of permeation and the reciprocal of the

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

PEG 400 % (v/v)	Solubility (μg/ml)	Rate of permeation (μg/cm^2 per h)	Permeability coefficient (cm/h)
0	111.87	457.08	4.09
10	178.77	667.22	3.73
20	312.05	1036.00	3.32
30	774.08	1350.84	1.75
40	1789.08	2850.33	1.59
50	2161.95	3392.10	1.57

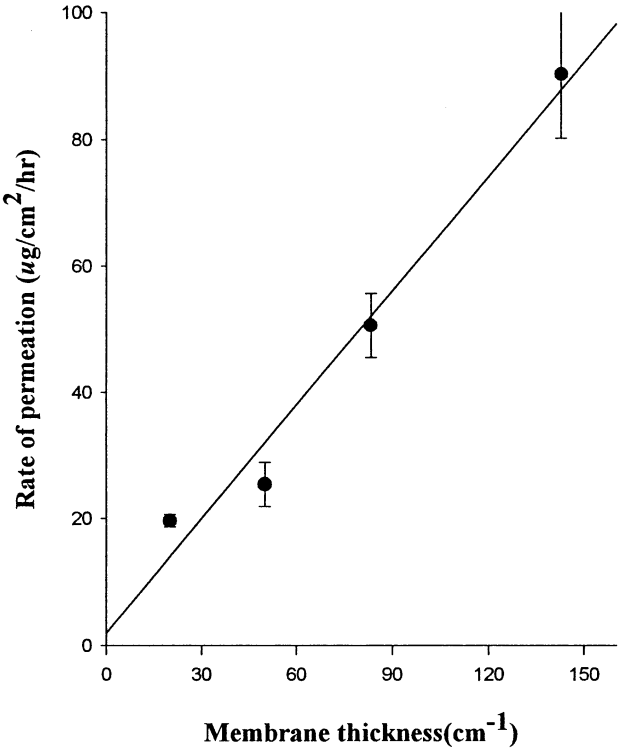

Fig. 1. Plot of steady-state flux (Q) against the reciprocal of EVA membrane thickness ($1/h$). EVA composed of 33% vinyl acetate content was used.

membrane thickness. This suggests that the permeation of triprolidine is highly controlled by the membrane thickness.

3.2. Release of triprolidine from the EVA matrix

3.2.1. Effects of comonomer ratio on drug release from the EVA matrix

To study the effect of comonomer ratio modifications of EVA on drug permeation, the release of triprolidine from the EVA matrix composed of different VA content was investigated [7]. Fig. 2 shows the representative plot of the release of triprolidine from the EVA matrix of various VA contents at 37°C where the cumulative amount of drug released into the receptor solution is plotted against time. An increase in VA comonomer content increased the drug release rate.

The EVA copolymer membrane is classified as an ester-type partition membrane. The release from the EVA matrix is governed primarily by partition of the drugs into the membrane material. Since permeability coefficient is proportional to the product of partition coefficient and diffusion coefficient, it may be correlated with partition coefficient if diffusion coefficient may be considered to be of the same order of magnitude among EVA copolymer membranes used. On the other hand, it is known that increase in crystallinity reduces the diffusivity of polymer [26–28], and that the introduction of VA comonomers to a highly crystalline polyethylene decreases the crystallinity of the system [29,30]. Kamath and Wakefied [29] predicted that EVA copolymer becomes totally amorphous if VA concentration is 43% (w/w) above. Therefore, the result suggested that the diffusivity of the drug within the membrane might be one of the possible factors in controlling permeation rate through EVA membranes.

3.2.2. Effects of drug loading dose on drug release from the EVA matrix

The effects of drug concentration on its release from the EVA-matrix was studied at 37°C at drug concentrations of 0.5, 1, 2.5, 5.0, and 10.0% (w/w). The release rates of triprolidine from the EVA matrices of different drug loading were studied at 37°C for 24 h. The drug fluxes 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 as expected from Eq. (4) 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. Effect of temperature on drug release from the EVA matrix

The effects of temperatures on drug release from EVA-matrix containing 10% drug were studied at 28, 32, 37, and 42°C. The dependence of drug release on temperature (°K) is shown in Fig. 4. The cumulative amount of drug released (Q) is plotted versus the square root of time. After an initial period of drug release, the release was approximately linear

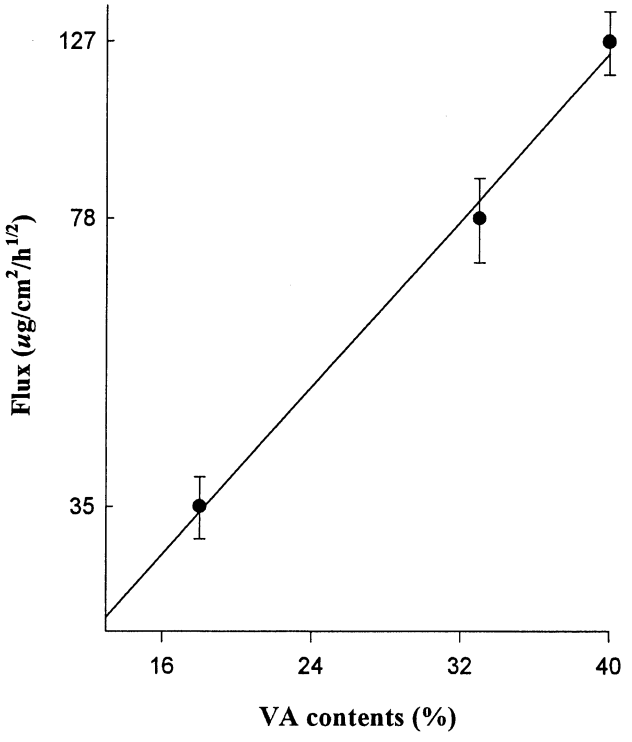

Fig. 2. Effects of vinyl acetate content of EVA on the flux of triprolidine from the EVA matrix.

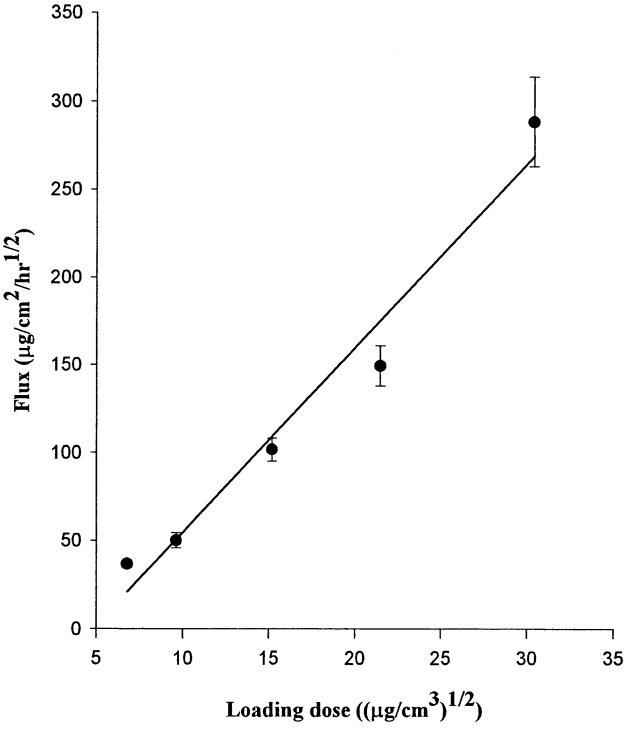

Fig. 3. Relationship between the release rate of triprolidine and the drug loading dose in EVA copolymer matrix at 37°C. EVA composed of 33% vinyl acetate content was used.

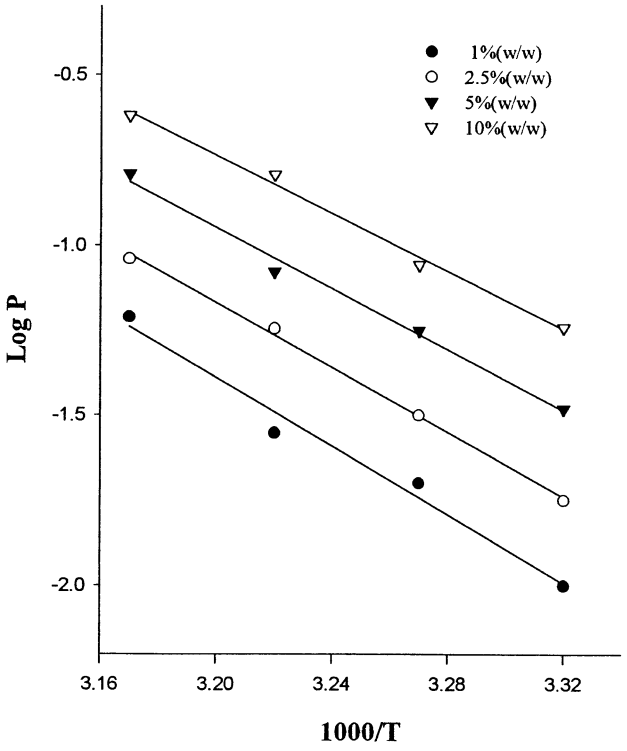

Fig. 4. Effects of temperature on triprolidine release from the EVA matrix containing different loading doses.

with respect to $t^{1/2}$. The steady-state drug flux was estimated from the slope of the linear $Q - t^{1/2}$ profile. In the EVA matrix containing 10% triprolidine, the drug fluxes at 28, 32, 37, and 42°C were 128.92, 156.71, 288.49, and 340.25 μg/cm^2 per h$^{1/2}$, respectively. The higher the temperature, the greater the drug release. It should be noted that the rate of drug release increased about 2.64-fold when the temperature of the drug release system was raised from 28 to 42°C.

The activation energy (E_a), which was measured from the slope of log P versus 1000/T plots was 23.04 kcal/mol for 1% loading dose, 21.82 kcal/mol for 2.5% loading dose, and 20.51 kcal/mol for 5% loading dose, and 19.45 kcal/mol for 10% loading dose from EVA matrix. This observation clearly indicates that the release of triprolidine from the EVA matrix is an energy-linked process [31]. The temperature effects could be on either the solubility of the drug in the membrane and/or effects on diffusion. The increase in release with increasing temperature suggests that release characteristics of drug from the polymer would change over the body temperature range. But, for practical use, a temperature of 37°C, was chosen to reflect the temperature of the stratum corneum [32]. This finding indicates that special precautions should be taken with regard to monitoring body temperature in practical applications.

3.2.4. Effects of plasticizers on drug release from the EVA 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 skin can control the drug release rate [33]. 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 [26–28]. 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 EVA-matrix were 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 which was calculated by the drug release rate from the EVA matrix containing

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

Plasticizer		Flux (μg/cm^2 per h$^{1/2}$)	Enhancement factor
Citrate group	ATBC	155.09	1.15
	ATEC	176.92	1.31
	TBC	217.89	1.61
	TEC	254.72	1.88
Phthalate group	DBP	171.27	1.26
	DEP	216.83	1.60
Control	–	135.46	1.00

plasticizers divided by that without plasticizer. Plasticizers in EVA 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 drug release significantly through a polymeric film [18,34]. The release rates of triprolidine from the EVA matrix containing plasticizers such as citrate and phthalate at 37°C are shown in Table 2. The increase in release rate from membranes with plasticizers can be an effect of the plasticizer or solubility of the drug in the membrane material and/or effects on diffusivity. The amount of triprolidine released from the EVA matrix containing TEC as a citrate group plasticizer increased about 1.88-fold, that containing DEP as a phthalate group plasticizer increased about 1.6-fold (Table 2). Comparing the alkyl radicals of the citrate and phthalates plasticizers, it is clear that the ethyl derivatives increased the drug release better than the butyl group plasticizers.

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