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Controlled Release of Pranoprofen from the Ethylene-Vinyl Acetate Matrix Using Plasticizer

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ABSTRACT An ethylene-vinyl acetate (EVA) matrix containing pranoprofen was prepared using the casting method and the release patterns of pranoprofen were observed. The solubility of pranoprofen was determined to be a function of the volume fraction of polyethylene glycol 400. The release of the drug from the matrix was examined as a function of temperature and drug concentration. Plasticizers such as the citrates and the phthalates were added to prepare the membrane in order to increase the flexibility of the EVA matrix. The solubility of pranoprofen was the highest when the PEG 400 concentration was 20% (v/v). The rate of drug release from the EVA matrix increased with increasing temperature and drug loading dose. There was a linear relationship between the flux of pranoprofen and the square root of the loading dose. The activation energy of release (Ea), which was measured from the slope of the log P versus $1000/T$ plots, was estimated to be 17.44, 16.14, 14.88, and 14.78 kcal/mol for loading doses of 0.5, 1, 1.5, and 2%, respectively. Among the plasticizers used such as the citrate and the phthalate groups, diethyl phthalate had the best enhancing effects on drug release. In conclusion, the application of an EVA matrix containing a plasticizer might be useful in the development of a controlled drug delivery system.

KEYWORDS Pranoprofen, Ethylene-vinyl acetate, Controlled release, Plasticizer, Matrix

INTRODUCTION

Pranoprofen is a potent NSAID (nonsteroidal anti-inflammatory drug) that is widely used for the acute and long-term management of rheumatoid arthritis and osteoarthritis (Luders et al., 1977; Gennaro, 1995). To avoid the systemic side effects and gastric disorders due to transient high blood concentration that could be occurred after oral administration, alternative routes of administration have been considered.

The percutaneous delivery of NSAIDs has the advantages of avoiding the hepatic first pass effect and delivering the drug at a sustained level over extended period of time. Percutaneously administered NSAID act mainly at

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the joint and related regions, and the drug can be concentrated at the inflammation site. Several technologies have been successively developed to control the release rate. The use of a release controlling membrane is one method of regulating the drug release. The use of drugs dispersed in an inert polymer to achieve controlled release by diffusion has attracted considerable attention (Efentakis & Vlachou, 2000; Vlachou et al., 2000).

The characteristic structure of the 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 the membrane (Bhardwaj, 2000; Donbrow & Friedman, 1975; Shin & Cho, 1996; Thein & Stevens, 2004). The plasticizers reduce the brittleness, improve flow, impart flexibility, and increase the toughness, strength, tear resistance, and impact resistance of the polymer. Generally plasticizers increase the amount of drug released with increasing chain mobility of the polymer by altering the membrane structure.

Among the many polymers used, ethylene-vinyl acetate (EVA) copolymer is a heat processable, flexible and inexpensive material (Miyazaki, 1982). The usefulness of EVA copolymer as a drug delivery system for hydrocortisone (Johnson, 1980), 5-fluorouracil (Miyazaki et al., 1984), isosorbide dinitrate (Ocak & Agabeyoglu, 1999), nicardipine (Morimoto, 1988), and triprolidine (Shin & Lee, 2002) has been described. However, few studies have examined the release of pranoprofen from an EVA copolymer matrix.

Since the first step in transdermal drug delivery system involves the controlled release of the drug in dosage forms, this study examined the amounts of pranoprofen released from the EVA matrix through in vitro experiments. The overall aim of this study was to evaluate the possibility of developing a pranoprofen-EVA matrix system for the controlled delivery of pranoprofen.

MATERIALS AND METHODS

Materials

The pharmaceutical grade pranoprofen was kindly provided by Kolon Pharm. Co., Ltd. (Korea). The EVA (40% vinyl acetate content) was purchased from Aldrich Chemical Co., Inc. The acetyl tributyl citrate (ATBC), tributyl citrate (TBC), acetyl triethyl citrate (ATEC), and triethyl citrate (TEC) were acquired from Morflex, Inc. The diethyl phthalate (DEP) and di-n-butyl phthalate (DBP) were of reagent grade and purchased from Junsei Chemical Co., Ltd. (Japan). All reagents were of analytical grade and used without further purification. The anhydrous ethyl alcohol was of HPLC grade and purchased from J. T. Baker Inc.

Determination of Drug Solubility

Excess amounts of pranoprofen were shaken with solutions containing various concentrations of PEG solution in test tubes at 37°C for 24 hr. The solution was then filtered through a Millipore filter paper (0.45 μm) and the pranoprofen concentration was determined by HPLC.

HPLC Determination of Pranoprofen

The pranoprofen concentration was examined by HPLC methods. The HPLC system was consisted of a pump (Waters 501,), ultraviolet detector (Waters 484), a 3.9 × 300 mm stainless-steel column packed with μ-Bondapak C_{18} (Waters), degasser, and an integrator (D520A, Youngin scientific Co., Ltd., South Korea). The column was μ-Bondapak C_{18} (Waters), the mobile phase was a combination of 0.03 M ammonium acetate in methyl alcohol: water (30:70), and the column temperature was maintained at ambient. A flow rate of 1.0 mL/min yielded an operation pressure of ~1200 psi. The UV detector was operated at a wavelength of 247 nm. Under these conditions, the pranoprofen peak appeared at a retention time of 7.7 min.

Preparation of the EVA Copolymer Membrane

Two grams of EVA copolymer beads were dissolved in 20 mL of chloroform in a glass beaker. The polymer solution was then poured onto a Teflon coated plate and the solvent was allowed to evaporate overnight at room temperature (20°C). The membrane was removed from the plate, dried for 2 days at room temperature. No bubbles were observed by the microscopic observation.

Drug Permeation through the EVA Membrane

The steady state permeation of pranoprofen through the EVA membrane was determined using a two-chamber diffusion cell. Each half-cell had a volume of approximately 7 mL and an effective diffusion area of 0.79 cm^2. A piece of the EVA membrane was clamped between two halves of the cell and the donor compartment was filled with the drug suspension containing various concentrations of the PEG 400 solution. In order to prevent the effect of solvent permeation from the donor to the receptor side, the same PEG 400 concentration as in the donor compartment was added to the receptor compartment. The assembled cell was stirred at 150 rpm to minimize the boundary effect. The total volume of the receptor solution was removed at the predetermined intervals and replaced with 7 mL of fresh solution. The amount of permeated drug was determined by HPLC at a wavelength of 247 nm.

Drug-Containing EVA Matrix Preparation

Weighed amounts of the EVA copolymer beads and the drug were dissolved in 20 mL of chloroform in a beaker. This mixture was poured onto a glass plate and the solvent was allowed to evaporate off overnight at room temperature (20°C). The matrix was removed from the plate and dried for 2 days. A piece of the matrix was cut from the matrix and weighed accurately. The drug content was calculated from the weight ratio of the drug and the copolymer used.

In Vitro Release Studies from the EVA Matrix of Various Drug Concentration and Release Media Temperature

The in vitro release of pranoprofen from the EVA matrix was examined using a modified Keshary-Chien cell. One unit of the EVA matrix was clamped between the cell cap and the receptor cell. The diameter of the cell was 2 cm, providing an effective constant area of 3.14 cm^2 between the matrix and the bulk solution (20 mL). A 40% PEG 400 solution was used as the receptor solution. The receptor was maintained at 37°C with a circulating water jacket and stirred constantly at 300 rpm. At a predetermined time, the whole solution from the receptor cell was withdrawn and replaced with a fresh solution. The amount of pranoprofen released from the matrix was determined by HPLC at a wavelength of 247 nm. The effects of the drug concentration on its release from the EVA matrix was examined at a drug concentration of 0.5, 1, 1.5, and 2% (w/w), and the effects of temperature on the amount of drug released was studied at 27, 32, 37, and 42°C. Each data point represents the average of three determinations.

In Vitro Release Studies from EVA Matrix containing the various Plasticizers

The plasticizer reduces the brittleness, improves the flow, and imparts flexibility to the polymer. It also increases the toughness, tear and impact resistance, and the strength of the polymer. Increasing the amount of plasticizer can lead to an increase in the free film elongation and a decrease in the tensile strength and Young's modulus.

A plasticizer was added to the drug-containing EVA solution and mixed for 1 hr. This method was chosen to produce a membrane with no molecular orientation. This mixture was poured onto a glass plate and the solvent was allowed to evaporate overnight at room temperature. A plasticizer was added at a ratio of 5% (w/w) of the EVA matrix. Alkyl citrates such as ATBC, TBC, ATEC, TEC, and the phthalates such as DEP and DBP were used as plasticizers.

RESULTS AND DISCUSSION

Solubility of Pranoprofen

The aqueous solubility of pranoprofen is extremely low but could be improved by adding a water-miscible hydrophilic polymer (such as PEG 400) to the aqueous solution as a solubilizer for pranoprofen. PEG 400 was reported to be an excellent solubilizer for many drugs (Chien & Lambert, 1975). In this study, it was found that the solubility of pranoprofen was highest at 20% PEG 400 (Fig. 1).

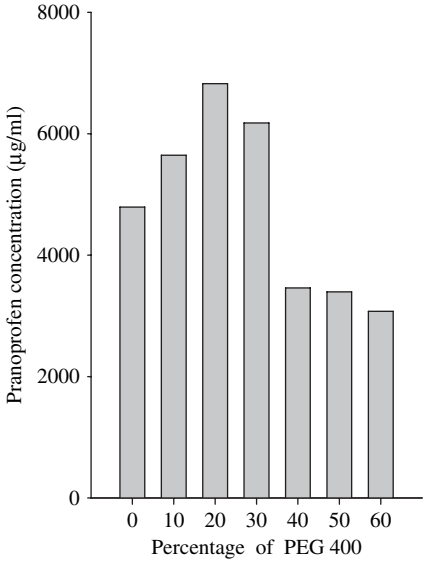

FIGURE 1 **Solubility of pranoprofen in various percentage of PEG 400 solution.**

Permeation of Pranoprofen through the EVA Membranes

The cumulative amount of the drug (Q) permeating through a unit surface area under constant stirring can be expressed mathematically using following equation:

$$Q = P(C_D - C_R)t \tag{1}$$

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

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

$$Q = P \cdot C_e \cdot t \tag{2}$$

and a constant permeation profile should be observed. The rate of permeation is then defined as follows:

$$\frac{Q}{T} = P \cdot C_e \tag{3}$$

As expected from Eq. (2), a constant permeation profile would be achieved when the pranoprofen concentration in the donor solution was at a level greater than its equilibrium solubility (data not shown). The effect of PEG 400 on the permeability coefficient (P) of pranoprofen across the EVA membrane can be determined using Eq. (4):

$$P = \frac{Q/T}{C_s} \tag{4}$$

Release of Pranoprofen from the EVA Matrix

The characteristic drug release profile of matrix-type drug delivery systems can be represented using the Higuchi's equation (Higuchi, 1961; Singh et al., 1967). The release from a system containing a dispersed drug in a homogeneous matrix can be expressed using the following equation:

$$Q = [D(2A - C_s)\ C_s\ t]^{1/2} \tag{5}$$

where Q is the amount of drug released at time t per unit exposed area, D is the diffusivity of the drug in the matrix, A is the initial drug loading dose dispersed in the polymer matrix, and C_s is the drug solubility in the matrix. A similar relationship was later derived for the release of a drug from a granular matrix system in which diffusion occurs through channels (Farhadieh et al., 1971):

$$Q = [\frac{D_\varepsilon}{\tau}(2A - \varepsilon C_s)C_s t]^{1/2} \tag{6}$$

where D and C_s are the diffusivity and the solubility in the permeability field, respectively; τ is the tortuosity of the matrix and ε is the porosity of the matrix. Although the two equations are for different mechanisms, they both describe the release of the drug as being linear with the square root of time (Higuchi, 1963):

$$Q = K_H \cdot t^{1/2} \tag{7}$$

where for a homogeneous matrix system:

$$K_H = [D(2A - C_s)\ C_s]^{1/2} \tag{8}$$

and for a granular matrix system

$$K_H = [\frac{D_\varepsilon}{\tau}(2A - \varepsilon C_s)C_s]^{1/2} \quad (9)$$

The validity of the relationships has been confirmed experimentally by a number of studies using various systems (Jenquin et al., 1990).

Effects of Drug Loading Dose

The effect of drug concentration on its release from the pranoprofen-EVA matrix was examined at different drug loading dose of 0.5, 1.0, 1.5, and 2.0 (w/w). The release rates of pranoprofen from the EVA matrices of different loading dose were studied at 37°C for 24 hr. 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 pranoprofen released (Q) versus the square root of time ($t^{1/2}$) plot showed a good linearity (Fig. 2).

The $Q/t^{1/2}$ increased directly proportionally to the increase in loading dose of pranoprofen. As expected from equation 6, a plot of $Q/t^{1/2}$ versus the square root of the loading dose (A) yielded a straight line for all four concentrations (Fig. 3).

Effects of Temperature of Release Medium

The effects of the temperature of the release medium on the drug release from the EVA matrix were examined at 27, 32, 37, and 42°C. The cumulative amount of the drug released (Q) was plotted versus the square root of time ($t^{1/2}$) (Figures, not shown). After an initial period of drug release, the release was approximately linear with respect to $t^{1/2}$. The steady-state rate of the drug release ($Q/t^{1/2}$) was estimated from the slope of the linear Q-$t^{1/2}$ profile from 4 to 24 hr. The drug flux from the EVA matrix containing 2% pranoprofen at 27, 32, 37, and 42° were 38.3, 54.7, 69.0, and 153.1 μg/cm^2/hr$^{1/2}$, respectively. It should be noted that the drug release was increased with increasing temperature. The rate of drug release increased approximately 2.49-fold when the temperature of the drug release system was increased from 27 to 42°C.

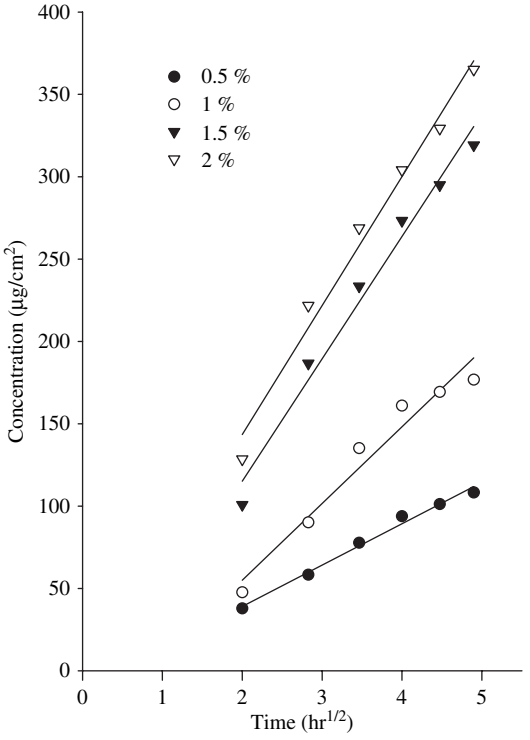

FIGURE 2 Effects of drug concentration on the release of pranoprofen from the pranoprofen-EVA matrix containing various loading dose at 37°C. PEG 400 volume fraction was maintained at 20% (v/v).

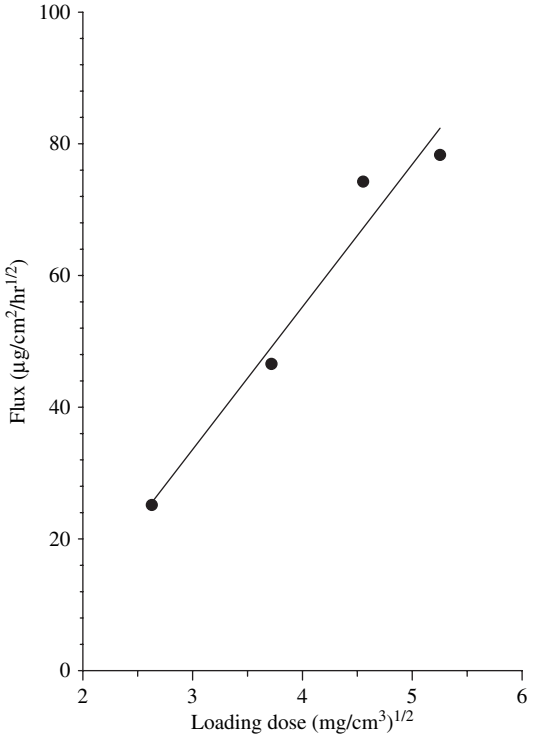

FIGURE 3 Relationship between pranoprofen flux and drug loading dose in the EVA matrix at 37°C.

The permeability coefficient can then be defined by:

$$P = \frac{\text{Flux}}{\text{Solubility}} \tag{10}$$

$$P = P_0 \cdot e - \frac{E_a}{RT} \tag{11}$$

$$\text{Log } P = \text{Log } P_0^{-} \quad \frac{E_a}{R \cdot 2.303 \cdot 1000} \cdot \frac{1000}{T} \tag{12}$$

As expected from Eq. (12), a plot of log P versus $1000/T$ yields a straight line (Fig. 4). The E_a (activation energy) was measured from the slope of the log P versus $1000/T$ plots (Eq. (14)).

$$\text{Slope} = -\frac{E_a}{R \cdot 2.303} \quad \frac{1}{1000} \tag{13}$$

$$\begin{aligned} Ea &= -\text{Slope} \times R \times 2.303 \times 1000 \text{cal} \\ &= -\text{slope} \times 1.987 \times 2.303 \text{kcal} \end{aligned} \tag{14}$$

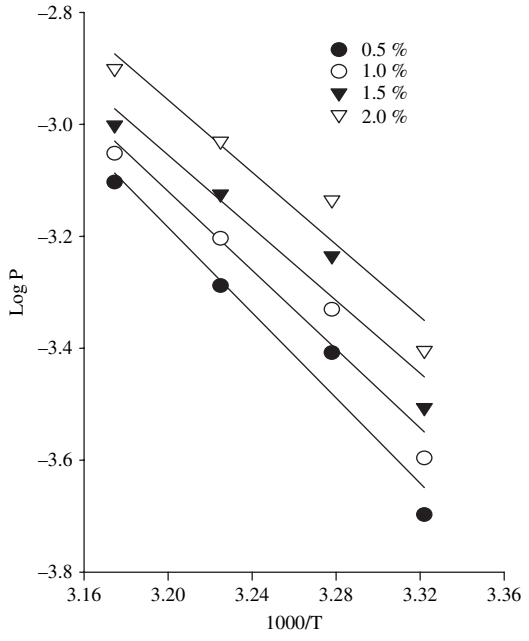

FIGURE 4 **Effects of temperature on the release of pranoprofen from the EVA matrix containing various loading dose.**

Figure 4 shows the dependency of drug release on temperature. The activation energy (E_a) that was measured from the slope versus $1000/T$ plots (Fig. 4) was 17.44 kcal/mol for the 0.5% loading dose, 16.14 kcal/mol for the 1% loading dose, 14.88 kcal/mol for the 1.5% loading dose, and 14.78 kcal/mol for the 2% loading dose. The higher the drug content in the EVA matrix, the energy for drug release might be smaller. This observation clearly indicates that the release of pranoprofen from the EVA matrix is an energy-linked process (Johnson, 1980). The temperature effects could be on either the increased solubility of the drug and/or effects on diffusion.

Effect of Plasticizers on Drug Release from the EVA Matrix

Generally plasticizers increase the amount of drug release with the increasing chain mobility of the polymer. Increasing the amount of plasticizer can lead to an increase in the free film elongation and a decrease in the tensile strength. A strong interaction between a drug and a polymer has been reported to significantly influence the drug release through a polymeric film (Jenquin et al., 1990). The effects of plasticizers on drug release from the EVA-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 EVA matrix containing plasticizers divided by that without plasticizer.

Table 1 shows the release of pranoprofen from the EVA matrix containing the citrate group and the

TABLE 1 **Effects of the citrates and the phthalates on the release of pranoprofen from the EVA matrix with 2% loading dose at 37°C**

	Plasticizer	Flux± SD ($\mu g/cm^2/hr^{1/2}$)	Enhancement factor(EF)
Control	Control	72.56 ± 3.39	1.0
	TBC	74.56 ± 3.79	1.03
	TEC	80.84 ± 4.97	1.11
Citrate	ATBC	73.55 ± 4.41	1.02
group	ATEC	84.65 ± 4.15	1.17
Phthalate	DBP	74.03 ± 4.26	1.02
group	DEP	120.79 ± 5.22	1.66

phthalate group as a plasticizer. The amount of pranoprofen released from the EVA matrix containing DEP as a phthalate group plasticizer increased about 1.66-fold, that containing ATEC as a citrate group plasticizer increased about 1.17-fold. Among the plasticizers used such as the citrates and the phthalates groups, diethyl phthalate showed the best enhancing effects.

The increase in release rate from membranes containing plasticizers can be an effect of the plasticizer or solubility of the drug in the membrane material and/or effects on diffusivity. Also, the addition of plasticizers could change the physicochemical properties of the matrix that might increase the porosity (Repka et al., 1999; Shin & Yoon, 2002). Comparing the alkyl radicals of the plasticizers such as the citrate groups, the phthalate groups, the ethyl group plasticizers increased the drug release better than the butyl group plasticizers.

CONCLUSION

The flux of pranoprofen versus the square root the loading dose yielded a straight line. Among the plasticizers used such as the citrate and the phthalate groups, diethyl phthalate showed the best enhancing effects in drug release. In conclusion, the application of an EVA matrix containing plasticizer might be useful for the development of a controlled drug delivery system.

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