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Controlled Transdermal Delivery of Loxoprofen from an Ethylene-Vinyl Acetate Matrix

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ABSTRACT − Repeated oral administration of loxoprofen can induce many side effects such as gastric disturbances and acidosis. Therefore, we considered alternative routes of administration for loxoprofen to avoid such adverse effects. The aim of this study was to develop an ethylene-vinyl acetate (EVA) matrix system containing a permeation enhancer for enhanced transdermal delivery of loxoprofen. The EVA matrix containing loxoprofen was fabricated and the effects of drug concentration, temperature, enhancer and plasticizer on drug release were studied from the loxoprofen-EVA matrix. The solubility of loxoprofen was highest at 40% (v/v) PEG 400. The release rate of drug from drug-EVA matrix increased with increased loading dose and temperature. The release rate was proportional to the square root of loading dose. The activation energy (Ea), which was measured from the slope of log P versus 1000/T, was 5.67 kcal/mol for a 2.0% loaded drug dose from the EVA matrix. Among the plasticizer used, diethyl phthalate showed the highest release rate of loxoprofen. Among the enhancers used, polyoxyethylene 2-oleyl ether showed the greatest enhancing effect. In conclusion, for the enhanced controlled transdermal delivery of loxoprofen, the application of the EVA matrix containing plasticizer and penetration enhancer could be useful in the development of a controlled drug delivery system.

Key words − Loxoprofen, Ethylene-vinyl acetate, Controlled transdermal delivery, Matrix, Plasticizer, Permeation enhancer

Loxoprofen, non-steroidal anti-inflammatory drug (NSAID) of the 2-arylpropionic acid group, is used for the treatment of rheumatoid arthritis and osteoarthritis. NSAIDs are used for the management of pain and inflammation associated with musculo-skeletal, joint disorders and operative procedures (Yamakawa et al., 2011). However, NSAID administration is associated with gastrointestinal complications such as gastric ulcers and bleeding. Orally administered drugs have disadvantages including gastrointestinal side effects, low absorption, irregular drug concentrations in blood, short duration of action and many side effects. However, a transdermal drug delivery system (TDDS) is a long-acting drug delivery method and has been shown to achieve adequate pain relief with minimal gastrointestinal side effects.

The skin is an attractive route for drug administration because it can avoid first-pass hepatic metabolism of drugs intended for systemic action thereby offering potentially lower drug doses and reduced side effects. The stratum corneum, the outermost layer of the skin, is the primary skin barrier, with a brick wall-like structure: the corneocytes are bricks surrounded by the mortar of the intercellular lipid lamellae. The highly organized crystalline lipid lamellae play an essential role in the barrier properties of the stratum corneum.

One of the most controversial methods to enhance drug transport across the intact skin is to increase the driving force for drug permeation by the use of vesicle formulations as skin delivery systems (Loan and Joke, 2005). Penetration enhancers can also increase the permeability of the stratum corneum (Recta et al., 2005; Zrinka et al., 2008). Some of the intrinsic ingredients in these systems, such as fatty acids, phospholipids and surfactants, enhance penetration through the skin, increasing absorption of the drug (Amit et al., 2007). An ideal enhancer should increase drug transport by reversibly altering the skin barrier function without sensitization or irritation (Kararli et al., 1995).

Ethylene-Vinyl acetate (EVA), which is biocompatible, heat-processible, flexible and inexpensive, has been used for transdermal drug delivery (Suat et al., 2008; Almeida et al., 2011). We used EVA copolymers containing 40% vinyl acetate as a membrane in matrix type TDDS (Cho et al., 2009; Kim et. al., 2010).

The study was carried out to test the potential of transdermal delivery of a loxoprofen matrix by studying its in vitro release characteristics. To validate the controlled release of loxopro-

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fen, release studies with various loading doses in EVA matrix, at various temperatures were studied. To increase the pore size of loxoprofen-EVA, two groups of plasticizers were used. To improve the drug permeation across rat skin from the loxoprofen-EVA matrix, several enhancers were tested. To develop the new formulation with enhanced transdermal delivery of loxoprofen through skin, the loxoprofen-EVA matrix containing an appropriate loaded dose, enhancer and plasticizer was formulated. The aim of this study was to evaluate the possibility of using the polymer EVA membrane as a controlling membrane and further develop an EVA matrix system for transdermal delivery of loxoprofen.

Materials and Methods

Materials

Loxoprofen was supplied by Shinpoong Pharm Co., Ltd (Ansan, South Korea). Ethylene-vinyl acetate (EVA, 40% vinyl acetate) was purchased from Sigma-Aldrich Chemical Co., Inc. (St. Louis, MO, U.S.A.) and PEG 400 was from Yakuri Pure Chemical Co., Ltd. (**Osaka,** Japan). Acetyl tributyl citrate (ATBC), tributyl citrate (TBC), acetyl triethyl citrate (ATEC) and triethyl citrate (TEC) were purchased from Morflex, Inc. (U.S.A.). Diethyl phthalate (DEP) and di-n-butyl phthalate (DBP) were from Junsei Chemical Co., Ltd. (**Tokyo,** Japan). Lauric acid, oleic acid and caprylic acid were purchased from Tokyo Kasei Kogyo Co., Ltd. (**Tokyo,** Japan). Myristic acid, linoleic acid, stearic acid and palmitic acid 2-Pyrrolidone, 1-methyl-2-pyrrolidone, polyoxyethylene 2-stearyl ether, polyoxyethylene 2-oleyl ether and polyoxyethylene 23-lauryl ether were purchased from Sigma-Aldrich Co., Ltd. (St. Louis, MO, U.S.A.). Macrogol 6-glycerides, caprylocaproyl macrogol 8-glycerides, propylene glycol laurate and propylene glycol monolaurate were gifts from Gattefose (St. Priest, France). Acetonitrile and methanol of HPLC grade were purchased from Merck Co. Ltd. (Darmstadt, Germany). All reagents were of analytical grade and used without further purification.

Determination of Drug Solubility

Excess amounts of loxoprofen were equilibrated with saline containing various concentrations of PEG 400. Each solution was shaken at 37°C for 24 hr in a shaking incubator. The solution was then filtered through a 0.45 μm filter membrane. The concentration of loxoprofen was determined at 220 nm by UV-Vis spectrophotometry after proper dilution.

HPLC Determination of Loxoprofen

Loxoprofen was assayed by HPLC and the system was consisted of a degasser (DG-1210, Japan), pump (Knauer, DE/K-120, U.S.A.), HPLC injector (Alcott, US/708-autosampler, U.S.A.), RESTEK C_{18} column (250 × 4.6 mm, 5 μm), UV detector (Waters 484, U.S.A.) and an integrator (Youngin Scientific Co., Ltd., D520A, South Korea). The mobile phase was a combination of methanol: distilled water (50:50) and column temperature was maintained at ambient temperature. A flow rate of 1 mL/min yielded an operation pressure of ~1000 psi. The UV detector was operated at the wavelength of 220 nm. Under these conditions, the loxoprofen peak appeared at the retention time of 3.142 min.

Preparation of Loxoprofen-EVA Matrix

The weighted amount of EVA copolymer beads was dissolved in 20 mL of chloroform in a beaker and drug was added. This mixture 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. Then, a sheet of matrix was taken and drug content was calculated from the weight ratio of drug and copolymer used.

In Vitro Release of Loxoprofen from the Drug-EVA Matrix

The *in vitro* release of loxoprofen from the EVA matrix was examined by using the Franz diffusion cell. A unit of the EVA matrix was clamped on the cell cap, the upper side of the cell. The diameter of the cell cap was 2 cm, providing 3.14 cm^2 of effective, constant area between the matrix and the bulk solution of 20 mL. 40% PEG 400 solution was used as a receptor solution. The receptor was maintained to 37°C with a circulating water jacket and stirred constantly at 380 rpm. Before the experiment, the system was tested to remove the remaining air bubbles in the receptor site. At predetermined times, the entire solution from the receptor cell was taken and replaced with fresh solution. The cumulative amount of loxoprofen released from the drug-EVA matrix was determined at 220 nm by UV-Vis spectrophotometer. The effects of drug concentration on its release from the EVA matrix were studied according to drug concentrations of 1.0, 2.0 and 3.0% (w/w) and the effects of temperature on drug release were studied at 27, 32, 37°C and 42°C. Each data point represents the average of three determinations.

Release of Loxoprofen from the EVA Matrix

A characteristic of a drug release profile of matrix-type drug delivery systems can be represented by the Higuchi's equation

(Higuchi, 1961). The release from a planar system having dispersed drug in a homogeneous matrix should follow the relationship:

$$Q = [D(2A - Cs)\ Cs\ t]^{1/2} \quad (1)$$

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 Cs is the drug solubility in the matrix. Higuchi later derived a similar relationship for planar release from a granular matrix system in which diffusion occurs through channels (Higuchi, 1963):

$$Q = [D/\tau\ (2A - \varepsilon Cs)\ Cs\ t]^{1/2} \quad (2)$$

where D and Cs refer to diffusivity and 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 drug release as being linear with the square root of time (Desai et al., 1965; Simonelli and Higuchi, 1966; Desai et al., 1966; Singh et al., 1967):

$$Q = K_H \cdot t^{1/2} \quad (3)$$

where for the homogeneous matrix system:

$$K_H = [D(2A - Cs)\ Cs]^{1/2} \quad (4)$$

and for the granular matrix system

$$K_H = [D/\tau(2A - \varepsilon Cs)\ Cs]^{1/2} \quad (5)$$

The validity of the relationships has been confirmed experimentally by a number of workers using various systems (Lapidus and Lordi, 1968; Farhadieh et al., 1971).

***In Vitro* Release of Loxoprofen from the Drug-EVA Matrix containing Plasticizer**

Plasticizer reduces brittleness, improves flow, imparts flexibility and increases toughness, strength, tear resistance and impact resistance of the polymer. Increasing the amount of plasticizer can lead to an increase in free film elongation and a decrease in tensile strength and Young's modulus. Plasticizer was dropped into drug-containing EVA solution and mixed for 1 hr. This method was chosen in order to produce large unharmed pieces of the membrane with no orientation of the molecules. This mixture was poured onto a glass plate and the solvent was allowed to evaporate off at room temperature overnight. Plasticizer was added in ratios of 5% (w/w) of the EVA matrix.

The plasticizers used were the alkyl citrates including acetyl tributyl citrate (ATBC), tributyl citrate (TBC), acetyl triethyl citrate (ATEC) and triethyl citrate (TEC). The phthalates including diethyl phthalate (DEP) and di-n-butyl phthalate (DBP) were also used as plasticizers.

Enhancement factor (EF) was calculated using the following equation:

$$EF = Rp/Rc \quad (6)$$

where Rp is the flux of EVA matrix containing plasticizer and Rc is the flux of EVA matrix not containing plasticizer.

Skin Preparation

Male Sprague Dawley rats were with ether. The hair of the abdominal area was carefully removed with an electric clipper. A square section of the abdominal skin was excised after incision, the adhering fat and other visceral debris in the skin were carefully removed from the under surface with tweezers (Durrhein et al., 1980). The excised abdominal rat skin was then immediately used.

Preparation of Loxoprofen-EVA Matrix containing an Enhancer

Enhancer at 5% was added to the loxoprofen-EVA matrix. Six different types of enhancer were used to compare the effects. The enhancers used were propylene glycols (propylene glycol monolaurate, propylene glycol laurate, propylene glycol monocaprylate) non-ionic surfactants (polyoxyethylene 2-oleyl ether, polyoxyethylene 2-stearyl ether, polyoxyethylene 23-lauryl ether), fatty acids (caprylic acid, stearic acid, lauric acid, oleic acid and linoleic acid) pyrrolidones (2-pyrrolidone, N-methyl-2-pyrrolidone, polyvinyl-pyrrolidone (PVP)) and glycerides (oleyl macrogol 6-glycerides, caprylocaproyl macrogol-8-glycerides).

About 2 g of EVA copolymer beads were dissolved in 20 mL of chloroform in a glass beaker. Drug and an enhancer were added and stirred vigorously. This mixture was poured onto a glass plate as a casting process and the solvent was allowed to evaporate off at room temperature for 24 h. The membrane was taken from the plate and dried at room temperature.

Penetration of Loxoprofen from the EVA Matrix containing an Enhancer through the Rat Skin

The *in vitro* penetration of loxoprofen from the EVA matrix

through the excised rat skin was examined using the Franz diffusion cell. The freshly excised full-thickness skin was mounted on the receptor site of the diffusion cell with the stratum corneum side facing upwards into the donor compartment and the dermal side facing downwards into the receptor compartment. An appropriate size of the matrix was placed on the stratum corneum side, covered with a round glass plate and clamped. Receptor medium was 40% PEG 400 solution to achieve a sink condition and maintained at 37°C by a circulating water bath. Total samples were withdrawn at predetermined time intervals and immediately replaced with an equal volume of fresh medium. The amount of drug penetrated was determined by HPLC at 220 nm. Each data point represents the average of three determinations.

The enhancer was chosen to affect fluidity of the stratum corneum structure and drugs achieve better permeation through the rat skin.

The enhancement factor (EF) was calculated using the following equation:

$$EF = Re/Rc \quad (7)$$

where *Re* is the flux of EVA matrix containing enhancer and Rc is the flux of that EVA matrix not containing enhancer.

Results and Discussion

Solubility of Loxoprofen

The aqueous solubility for loxoprofen was extremely low and could be improved by addition of a water-miscible hydrophilic polymer like PEG 400 into the aqueous solution as a solubilizer for loxoprofen. PEG 400 was reported to be an excellent solubilizer for many steroids (Chien and Lambert, 1975). In the present investigation shown in Figure 1, the solubility of loxoprofen increased as the volume fraction of PEG 400 increased. The solubility of loxoprofen was highest with 40% PEG 400 solution.

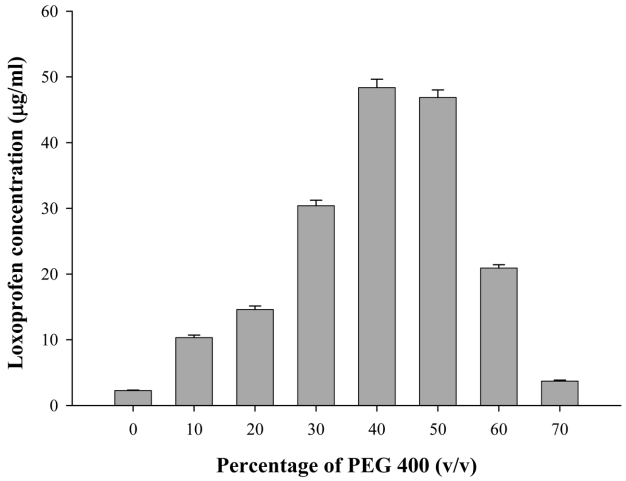

Figure 1. Solubility of loxoprofen in PEG 400 solution depending on the volume percentage of PEG 400. Each value represents the mean ± S.D.

Effects of Drug Loading Dose

The release profiles of loxoprofen from the EVA matrix with different drug loading over 3 hr are shown in Figure 2. The cumulative amount of loxoprofen released (Q) versus the square root of time ($t^{1/2}$) plot shows good linearity for all three different concentrations. As expected from Equation 3, a plot of $Q/t^{1/2}$ versus the square root of loading dose (A) yields a straight line (Figure 2). $Q/t^{1/2}$ increased directly proportional to an increase of the loading dose of loxoprofen.

Effects of Release Media Temperature

The dependency of the drug release profile on temperature is illustrated in Figure 3. The cumulative amount of drug released (Q) is plotted versus the square root of time ($t^{1/2}$). After an initial period of drug release, the release was approximately linear

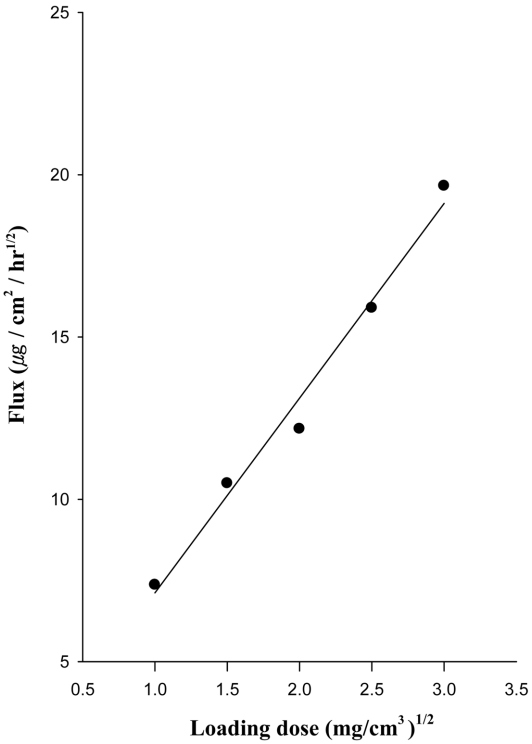

Figure 2. Relationship between loxoprofen flux and drug loading dose in the EVA matrix at 37°C. PEG 400 volume fraction was maintained at 40% (v/v).

with respect to $t^{1/2}$. The steady-state rate of drug release ($Q/t^{1/2}$) was estimated from the slope of the linear Q-$t^{1/2}$ profile from 0 to 8 hr. The higher the temperature, the greater the drug releases. It should be noted that the rate of drug release increased about 1.65-fold when the temperature of the drug release system was raised from 27°C to 42°C. But for practicality, 37°C was chosen to reflect the temperature of the stratum corneum (Chien and Lau, 1976).

This observation clearly shows that the release of loxoprofen from the EVA matrix is an energy-linked process (Miyazake et al., 1982). The increase in release with increasing temperature suggests that release characteristics of the copolymer 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. The permeability coefficient is then defined by:

$$P = Flux/Solubility \tag{8}$$

$$P = P_0 \times e^{-Ea/RT} \tag{9}$$

$$Log\ P = \text{Log}\ P_0 - E_a/\text{R}/2.303/1000 \times 1000/T \tag{10}$$

$$Slope = -E_a/R/2.303 \times 1/1000 \tag{11}$$

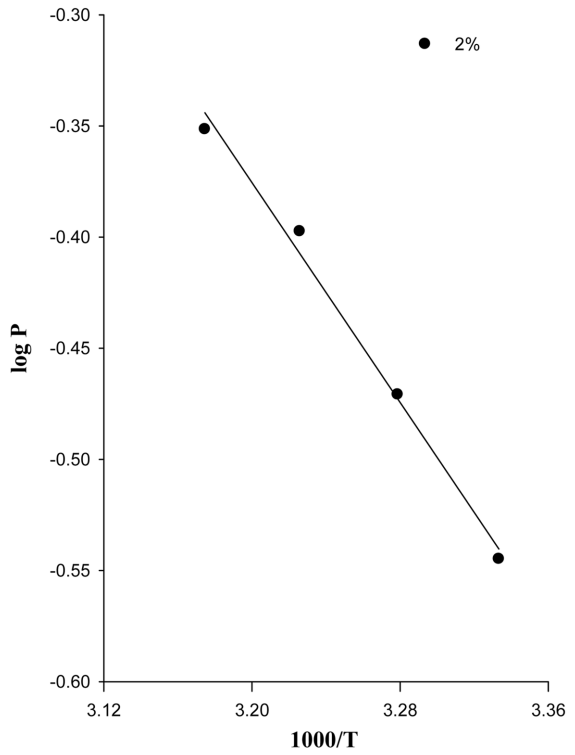

Figure 3. Effects of temperature on the loxoprofen release from the EVA matrix containing 2.0% loading dose.

Table I. *Effect of plasticizers on the flux of loxoprofen from the EVA matrix. Each value represents the mean±S.D. (n=3)*

Plasticizers	Flux (μg/cm^2/hr$^{1/2}$)	EF
Control	12.86±0.85	1.00
ATBC	13.48±0.89	1.05
TBC	14.96±0.99	1.16
ATEC	16.24±1.21	1.26
TEC	17.09±1.13	1.33
DBP	18.05±1.38	1.40
DEP	19.95±1.44	1.55

$$E_a = -Slope \times R \times 2.303 \times 1000\ \text{cal} = -Slope \times 1.987 \times 2.303\ \text{kcal} \tag{12}$$

As expected from Equation 10, a plot of log P versus 1000/T yields a straight line (Figure 3). The E_a (activation energy), which was measured from the slope of log P versus 1000/T plot, was 5.67 kcal/mol for a 2.0% loading dose from EVA matrix (Equation 12).

Effects of Plasticizers on Drug Release from the EVA Matrix

Generally, plasticizers increase the amount of drug release with increased chain mobility of the polymer. The plasticizers will interpose themselves between the polymer chains and interact with the forces held together by extending and softening the polymer matrix (Entwistle and Rowe, 1979). The plasticizers reduce the brittleness, improve flow, impart flexibility and increase toughness, strength, tear resistance and impact resistance of the polymer. The selection of a suitable plasticizer and its concentration has a profound influence on the mechanical properties as well as on the permeability of drugs (Crawford and Esmerian, 1971). 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 significantly influence drug release through a polymeric film (Bodmeier and Paeratakul, 1989; Jenquin et al., 1990). The release profiles of loxoprofen from the EVA matrix containing citrate and phthalate groups as the plasticizers are shown in Table II. In case of the citrate group, there was a slight increase in release of drug. On the other hand, the phthalate group showed a more increased release rate than that of the citrate group.

Effects of the Enhancers on the Penetration of Loxoprofen through the Rat Skin

Fatty acids are currently receiving much attention as pen-

Table II. *Enhancement factor according to various enhancers. Each value represents the mean±S.D. (n=3)*

Enhancer	Flux (μg/cm^2/hr)	EF
control	0.203±0.04	1.00
polyoxyethylene 23-lauryl ether	0.316±0.05	1.57
polyoxyethylene 2-stearyl ether	0.421±0.08	2.07
polyoxyethylene 2-oleyl ether	0.557±0.10	2.74
oleic acid	0.277±0.03	1.36
linoleic acid	0.240±0.05	1.18
lauric acid	0.459±0.08	2.26
caprylic acid	0.391±0.07	1.93
stearic acid	0.330±0.06	1.63
oleyl macrogol-6 glycerides	0.441±0.08	2.17
caprylocaproyl macrogol-8 glycerides	0.492±0.09	2.42
propylene glycol monocaprylate	0.418±0.08	2.06
propylene glycol laurate	0.435±0.07	2.14
propylene glycol monolaurate	0.378±0.07	1.86
N-methyl-2-pyrrolidone	0.420±0.08	2.07
2-pyrrolidone	0.246±0.06	1.21
Polyvinyl-pyrrolidone	0.333±0.07	1.64

etration enhancers (Tanojo et al., 1997; Oh et al.. 1998). This class of enhancer presents the advantage of being an endogenous component of human skin. Fatty acids can differ in several features: chain length, characteristics of the double bonds (position, number, configuration), branching schema and substituents, and these structural variations can influence skin penetration (Takeuchi et al., 1998; Bhatia et al., 1998; Taguchi et al., 1999). Fatty acids are capable of inserting into the hydrophobic tails of the stratum corneum lipid bilayer, disturbing their packing, increasing their fluidity and decreasing the diffusional resistance to permeants (Golden et al., 1987, Barry and Bennett, 1987; Green and Hadgraft, 1987). The efficacy of fatty acids is intrinsically linked to their structure, with differences evident between saturated and unsaturated forms and those of different hydrocarbon chain length (Kandimalla et al., 1999). Unsaturated fatty acids, particularly those of the cis conformation and C18 chain lengths, have been shown to be more effective enhancers than their saturated counterparts by promoting the permeation of such penetrants as naloxone (Aungst et al., 1986) and flurbiprofen (Chi et al., 1995). When introduced into the predominantly saturated, straight-chained lipid environment of the stratum corneum, these kinked fatty acids are seen to intercalate and disrupt the ordered lipid array (Green et al., 1988) and form separate fluid states that disorder endogenous lipids (Naik et al., 1995). Saturated fatty acids with a linear shape and low solubility have less capability to disrupt the lipid packing of the stratum corneum and to insert themselves into the lipid bilayers than kinked unsaturated fatty acids of high solubility. Among the saturated fatty acid group, lauric acid showed the highest increase penetration rate. Among the unsaturated fatty acid such as oleic acid and linoleic acid, linoleic acid showed significant increases in penetration rate of loxoprofen from the EVA matrix. With respect to the loxoprofen-EVA matrix, the saturated fatty acid group showed slightly increased penetration rate than that of the unsaturated fatty acid group. Within each study, significant differences were observed among the formulations.

Surfactants have been reported to enhance the permeability of drugs (Lopez et al., 2000; Shin et al., 2001; Shokre et al., 2001). They have effects on the permeability of several biological membranes including skin (Lopez et al., 2000) and for this reason they can enhance the skin penetration of other compounds in the formulation (Aungst et al., 1986; Shin et al., 2001). The skin pre-treated with non-ionic surfactant showed that the stratum corneum was loosely layered and that intercellular spaces were wide (Shin et al., 2001). Among the non-ionic surfactants, polyoxyethylene-2-oleyl ether showed the highest enhancing effect while polyoxyethylene-2-stearyl ether and polyoxyethylene-23-lauryl ether also showed an increased penetration rate. Within each study, significant differences were observed among the formulations.

The glycerides show high tolerance and low toxicity. Caprylocaproyl macrogol-8-glyceride is included as a pharmaceutical excipient in European Pharmacopoeia as of 2003 (Rama et al., 2003). Oleyl macrogol-6-glyceride is a PEG derivative, used as a co-surfactant in pharmaceutical systems such as microemulsions. This substance is biocompatible and biodegradable (Gao et al., 2005). Among the glycerides, oleyl macrogol-6-glyceride showed significant penetration rates of loxoprofen. Within each study, significant differences were observed among the formulations.

The propylene glycols (PGs) are widely used as a vehicle for penetration enhancement and permeate well through the human stratum corneum. PGs readily permeate the skin and make drug molecules cross the stratum corneum (Squillante et al., 1998). The penetration of PGs through the tissue could alter thermodynamic activity of the drugs in the vehicle which would in turn modify the driving force for diffusion. PGs may partition into the tissue facilitating uptake of the drug into skin and there may be some minor disturbances to the intercellular lipid packing within the stratum corneum bilayers (Adrian and Barry, 2004). Among the propylene glycols, propylene glycol

laurate showed a significant penetration rate of loxoprofen. Within each study, significant differences were observed among the formulations.

The pyrrolidones have been used as penetration enhancers in human skin for hydrophilic and lipophilic permeants (Williams, 2004). In terms of mechanisms of action, the pyrrolidones partition well into human stratum corneum. Within the tissue, they may act by altering the solvent nature of the membrane and pyrrolidones have been used to generate 'reservoirs' within skin membranes. Such a reservoir effect offers potential for sustained release of a permeant from the stratum corneum over extended time periods (Jungbauer et al., 2001). Among the pyrrolidones, N-methyl-2-pyrrolidone showed highest penetration rate of loxoprofen.

Enhancement factor according to various enhancers was described in Table II. Among all enhancers used in this study, polyoxyethylene-2-oleyl ether showed the highest enhancing effect.

Conclusion

Increasing temperature and drug loading increased the release rate from an EVA matrix. The activation energy of loxoprofen at a 2.0% loading dose was 5.67 kcal/mol. Among the plasticizers used, diethyl phthalate was the most suitable in terms of enhancement of loxoprofen release, while among the enhancers used, polyoxyethylene-2-oleyl ether was the most effective in enhancing the penetration of loxoprofen into the skin. In conclusion, for enhanced controlled transdermal delivery of loxoprofen, an EVA matrix modulated with suitable plasticizer and penetration enhancer may be useful for the development of a transdermal drug delivery system.

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