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Controlled release of furosemide from the ethylene-vinyl acetate matrix

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Abstract

The ethylene-vinyl acetate (EVA) matrix containing furosemide was prepared by the casting method and the release patterns were observed. The solubility of furosemide was determined as a function of volume fraction of polyethylene glycol 400. The release of drug from the matrix was studied as a function of temperature and drug concentration. Plasticizers such as the citrates and the phthalates were added for preparing the membrane to increase the flexibility of the EVA matrix. The solubility of furosemide was the highest when the concentration of PEG 400 was 40% (v/v). The release rate of drug from the EVA matrix increased with increasing temperature and drug loading doses. A linear relationship was found between the release rate and the square root of the loading dose. The activation energy (E_a), which was measured from the slope of the log P versus $1000/T$ plots, was 12.33 kcal/mol for the 0.5% loading dose, and 11.58 kcal/mol for the 1.0% loading dose, and 11.00 kcal/mol for the 1.5% loading dose. Among the plasticizers used such as the citrates and the phthalates groups, diethyl phthalate showed the best enhancing effects in 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: Furosemide; Ethylene-vinyl acetate; Controlled release; Plasticizer; Matrix

1. Introduction

Furosemide is a potent drug that induces a powerful diuresis, which is followed by the loss of sodium, potassium and chloride into the urine, by acting on the thick ascending limb of the loop of Henle (Giebisch, 1985). In case of oral administration of furosemide, due to transient high blood concentration, it can induce the side effects such as polyurea, dizziness, dry mouth, nausea, and gastric disturbances. Therefore, we considered transdermal route for administration of furosemide. Basic components of transdermal devices are polymer membrane, penetration enhancers and excipients (Hadgraft, 1987).

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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 release by diffusion has attracted considerable attention (Kaplan, 1965; Brucks et al., 1989; Efentakis and Vlachou, 2000; Vlachou et al., 2000).

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 the membrane (Michaels and Bixler, 1961; Donbrow and Friedman, 1975). The plasticizers reduce the brittleness, improve flow, impart flexibility, and increase toughness, strength, tear resistance, and impact resistance of the polymer. Generally plasticizers increase the amount of drug release with the increasing chain mobility of the polymer by changing the membrane structure.

Among the many polymers, ethylene-vinyl acetate (EVA) copolymer is a heat processable, flexible and inexpensive material (Miyazaki et al., 1982). The usefulness of EVA copolymer as a drug delivery system for hydrocortisone (Johnson, 1980), fluoride ion (Halpern et al., 1976), 5-fluorouracil (Miyazaki et al., 1984), isosorbide dinitrate (Ocak and Agabeyoglu, 1999), nicardipine (Morimoto et al., 1988) was described. However, few reports have dealt with the release of furosemide from the EVA copolymer matrix.

This laboratory has been studying the transdermal controlled drug delivery using polymer membrane (Shin and Cho, 1996; Shin and Lee, 2002). This study was carried out to evaluate the possibility of developing the furosemide–EVA matrix system for the controlled delivery of furosemide.

2. Materials and methods

2.1. Materials

The furosemide of the pharmaceutical grade was kindly supplied by Il-yang Pharm. Co. Ltd. (Korea). The EVA (40% vinyl acetate content) was purchased from the Aldrich Chemical Co. Inc. (USA). The acetyl tributyl citrate (ATBC), tributyl citrate (TBC), acetyl triethyl citrate (ATEC), and triethyl citrate (TEC) of the pharmaceutical grade were acquired from Morflex, Inc. (USA). The diethyl phthalate (DEP), di-*n*-butyl phthalate (DBP) of the reagent grade were purchased from Junsei Chemical Co. Ltd. (Japan), and methanol of the HPLC grade purchased from J.T. Baker Inc. (USA).

2.2. Determination of drug solubility

Excess amounts of furosemide were shaken with various PEG 400 concentrations in test tubes at 37 °C for 24 h. The solution was then filtered through a Millipore filter paper (0.45 μm). The furosemide concentration was determined by the HPLC after filtration.

2.3. HPLC determination of furosemide

Furosemide was assayed by a HPLC method. The mobile phase was a combination of 0.01 M KH_2PO_4 solution:methanol (63:37), the column was a RESTEK C_{18} column (250 mm × 4.6 mm, 5 μm) and the column temperature was maintained at ambient. A flow rate of 1.5 ml/min yielded an operation pressure of around 1000 psi. The UV detector was operated at a wavelength of 274 nm, where the plasticizers such as phthalates or citrates did not absorb. Under these conditions, the furosemide peak appeared at the retention time of 7.4 min.

2.4. Permeation studies through the EVA membrane

2.4.1. Preparation of the EVA copolymer membrane

Approximately 2 g of EVA copolymer beads were dissolved in 20 ml of chloroform in a glass beaker. This polymer solution was poured onto a Teflon coated plate and the solvent was allowed to evaporate off overnight at room temperature (20 °C). The membrane was removed from the plate, dried for 2 days at room temperature, and the bubbles were not found by the microscopic observation. The thickness of the membrane that was measured at several points using a micrometer was approximately 121.2 ± 5.3 μm.

2.4.2. Drug permeation through the EVA membrane

The steady state permeation of furosemide 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 the two halves of the cell and the drug suspension in various concentrations of PEG 400 solution was filled into the donor compartment. In order to prevent the effect of solvent permeation from the donor to the receptor side, the same concentration of PEG 400 as in the donor compartment was added into 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 the drug permeated was determined by the HPLC at a wavelength of 274 nm.

2.5. In vitro release studies from the EVA matrix

2.5.1. Drug-containing EVA matrix preparation

Weighed amounts of the EVA copolymer beads and 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 at room temperature (20 °C) overnight. The matrix was removed from the plate and dried for 2 days. Then, 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.

2.5.2. In vitro release studies from the EVA matrix of various drug concentration and release media temperature

The in vitro release of furosemide 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 3.14 cm^2 effective constant area between the matrix and the bulk solution of 20 ml. A 40% PEG 400 solution was used as the receptor solution. The receptor was maintained at 37 °C with circulating water jacket and was stirred constantly at 300 rpm. At predetermined time, the whole solution from the receptor cell was withdrawn and replaced with fresh solution. The amount of furosemide released from the matrix was determined by the HPLC at a wavelength of 274 nm. The effects of the drug concentration on its release from the EVA matrix was examined at drug concentration of 0.5, 1, and 1.5% (w/w), and the effects of temperature on the drug release was studied at 27, 32, 37, and 42 °C. Each data point represents the average of three determinations.

2.5.3. 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 h. This method was chosen in order 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 ratio of 5% (w/w) of the EVA matrix. The plasticizers used were the alkyl citrates such as ATBC, TBC, ATEC, TEC, and the phthalates such as DEP and DBP.

3. Results and discussion

3.1. Solubility of furosemide

The aqueous solubility of furosemide was extremely low and could be improved by the addition of a water-miscible hydrophilic polymer such as PEG 400 into the aqueous solution as a solubilizer for furosemide. PEG 400 was reported to be an excellent solubilizer for many drugs (Chien and Lambert, 1975). In this study, it was observed that the solubility of furosemide increased as the volume fraction of the PEG 400 increased and was the highest at 40% PEG 400 (Table 1).

3.2. Permeation of furosemide through the EVA membranes

The cumulative amount of the drug (Q) permeating through a unit surface area under stirring condition

Table 1
Effect of PEG 400 on the permeation of furosemide through the EVA copolymer membranes

PEG 400% (v/v)	Equilibrium solubility (μg/ml)	Rate of permeation (μg/cm^2/h)	Permeability coefficient ($\times 10^3$ cm/h)
0	75.042	3.60 ± 0.37	48.07
10	257.97	4.62 ± 0.58	17.91
20	328.67	5.66 ± 0.61	17.22
30	335.40	6.01 ± 0.08	17.91
40	758.50	12.90 ± 0.89	17.00
50	498.56	8.91 ± 2.28	17.88

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) 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 the sink condition (i.e., $C_R \ll C_e$), Eq. (1) can be simplified to:

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

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

$$\frac{Q}{T} = PC_e \quad (3)$$

As expected from Eq. (2), a constant permeation profile would be achieved when the furosemide concentration in the donor solution was at a level greater than its equilibrium solubility (figures, not shown). The rate of permeation (Q/t), which was measured from the slope of Q versus t plots (Eq. (2)), was found to increase with the addition of the PEG 400 solution until the 40% (v/v) PEG 400 solution, and was slightly decreased in the 50% (v/v) PEG 400 solution. As expected from Eq. (3), an increase in the permeation rate (Q/t) was observed to be dependent upon the equilibrium solubility (C_e) of furosemide in the PEG 400 solutions (Table 1).

The effect of PEG 400 on the permeability coefficient (P) of furosemide across the EVA membrane can be determined by using Eq. (4):

$$P = \frac{Q/T}{C_e} \quad (4)$$

Table 1 shows that the permeability coefficient (P) decreased with the addition of the PEG 400 solution in the saline solution.

3.3. Release of furosemide from the EVA matrix

A characteristic drug release profile of the matrix-type drug delivery systems can be represented by the Higuchi's equation (Higuchi, 1961). The release from a system containing dispersed drug in a homogeneous matrix should follow the following relationship:

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

where Q is the amount of drug released after time t per unit exposed area, D the diffusivity of the drug in the matrix, A 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 from a granular matrix system in which diffusion occurs through channels (Higuchi, 1963):

$$Q = \left[\frac{D\varepsilon}{\tau}(2A - \varepsilon C_s)C_s t\right]^{1/2} \quad (6)$$

where D and C_s are the diffusivity and the solubility in the permeability field, respectively; τ 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 (Lapidus and Lordi, 1966; Singh et al., 1967):

$$Q = K_H t^{1/2} \quad (7)$$

where for the homogeneous matrix system:

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

and for the granular matrix system

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

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

3.4. Effects of drug loading dose

The release of furosemide from the EVA matrices with different drug loading dose was examined over a 24 h period. As expected from Eq. (6), a plot of $Q/t^{1/2}$ versus the square root of the loading dose (A) yielded a straight line (data not shown). The cumulative amount of furosemide released (Q) versus the square root of time ($t^{1/2}$) plot showed a good linearity for all three concentrations (Fig. 1). As Fig. 1 indicates, the $Q/t^{1/2}$ increased directly proportionally to the increase in furosemide loading.

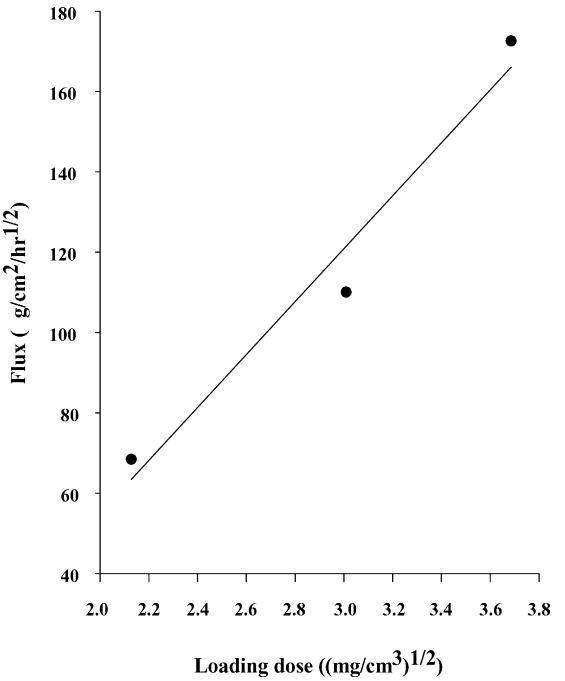

Fig. 1. Relationship between furosemide flux and drug loading dose in the EVA matrix at 37 °C. PEG 400 volume fraction was maintained at 40% (v/v).

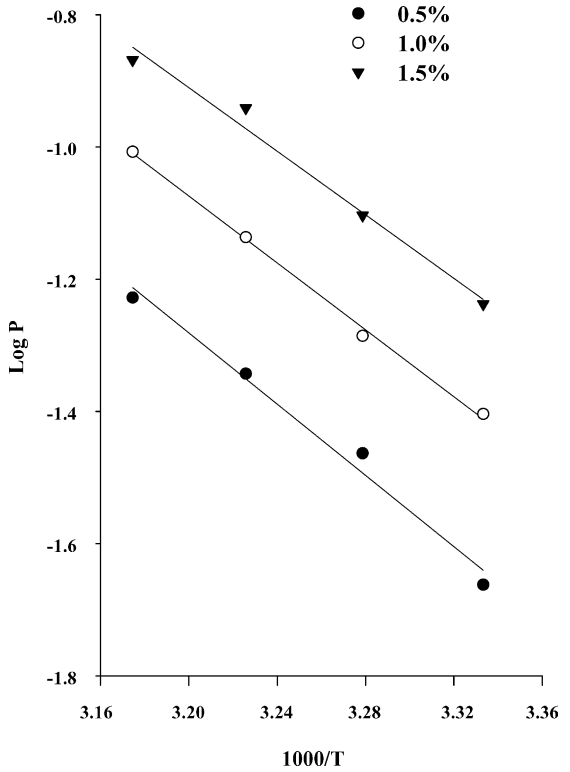

Fig. 2. Effects of temperature on the release of furosemide from the EVA matrix containing various loading dose.

3.5. 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. Fig. 2 shows the dependency of drug release on temperature. 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 h.The permeability coefficient can then be defined by:

$$P = \frac{\text{flux}}{\text{solubility}} \quad (11)$$

$$P = P_0\, e^{-E_a/RT} \quad (12)$$

$$\log P = \log P_0 - \frac{E_a}{R \times 2.303 \times 1000}\frac{1000}{T} \quad (13)$$

As expected from Eq. (13), a plot of log P versus 1000/T yields a straight line (Fig. 2). The E_a (activation energy) was measured from the slope of the log P versus 1000/T plots (Eq. (15))

$$\text{slope} = -\frac{E_a}{R \times 2.303}\frac{1}{1000} \quad (14)$$

$$E_a = -\text{slope} \times R \times 2.303 \times 1000\,\text{cal} = -\text{slope} \times 1.987 \times 2.303\,\text{kcal} \quad (15)$$

The drug flux from the EVA matrix containing 1.5% furosemide at 27, 32, 37, and 42 °C were 59.5, 78.0, 110.0, and 148.2 μg/cm^2/h$^{1/2}$, 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. The activation energy (E_a) that was measured from the slope versus 1000/T plots (Fig. 2) was 12.33 kcal/mol for the 0.5% loading dose, 11.58 kcal/mol for the 1% loading dose, and 11.00 kcal/mol for the 1.5% loading dose. The higher the drug content in the EVA matrix, the energy for drug permeation might be smaller.

This observation clearly indicates that the release of furosemide from the EVA matrix is an energy-linked process (Miyazaki et al., 1982). The temperature effects could be on either the increased solubility of the drug and/or effects on diffusion.

3.6. 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 (Bodmeier and Paeratakul, 1989; 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 2
Effects of the citrates and the phthalates on the release of furosemide from the EVA matrix with 1.5% loading dose at 37 °C

Plasticizer	Flux ± S.D. (μg/cm^2/h$^{1/2}$)	Enhancement factor (EF)
Control	21.97 ± 1.39	1
Citrate group		
TEC	25.10 ± 0.79	1.14
TBC	22.54 ± 1.97	1.03
ATEC	24.91 ± 2.41	1.13
ATBC	22.23 ± 1.15	1.01
Phthalate group		
DEP	31.02 ± 4.25	1.41
DBP	26.48 ± 1.26	1.21

Table 2 shows the release of furosemide from the EVA matrix containing the citrate group and the phthalate group as a plasticizer. The amount of furosemide released from the EVA matrix containing DEP as a phthalate group plasticizer increased about 1.41-fold, that containing TEC as a citrate group plasticizer increased about 1.14-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 with plasticizers can be an effect of the plasticizer or solubility of the drug in the membrane material and/or effects on diffusivity. 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.

4. Conclusions

A linear relationship between the release rate and the square root of loading dose was found. The activation energy of release was estimated to be 12.33 kcal/mol for the 0.5% loading dose, 11.58 kcal/mol for the 1% loading dose, and 11.00 kcal/mol for the 1.5% loading dose. Among the plasticizers used such as the citrates and the phthalates 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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