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Release characteristics of quinupramine from the ethylene–vinyl acetate matrix

Jin Kim [a], Woong-Jang Kim [b], Seong-Jin Kim [b], Cheong-Weon Cho [c], Sang-Chul Shin [a,*]

[a] *College of Pharmacy, Chonnam National University, Gwangju 500-757, South Korea*
[b] *Chonnam National University Medical School, Gwangju 501-757, South Korea*
[c] *College of Pharmacy, Chungnam National University, Daejeon 305-764, South Korea*

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Abstract

An ethylene–vinyl acetate (EVA) matrix containing quinupramine was prepared in an attempt to develop a controlled delivery system for quinupramine. Permeation studies of quinupramine through the EVA copolymer membrane were carried out using a two-chamber diffusion cell. The rate of drug permeation through the EVA membrane was proportional to the PEG 400 volume fraction. The release of quinupramine from the EVA matrix was examined using a modified Franz diffusion cell. A plasticizer was added to prepare the pore structure of the EVA matrix in order to increase the rate of drug release. The effects of PEG 400, membrane thickness, drug concentration, temperature, and plasticizer on drug release rate were investigated. The drug release rate from the EVA matrix increased with increasing PEG 400 volume fraction, temperature and drug loading dose. The activation energy for drug release was 5.91, 5.39, 4.68 and 4.52 kcal/mol for a loading dose of 0.5%, 1%, 1.5%, and 2%, respectively. Among the plasticizers used, diethyl phthalate showed the best results. The release of quinupramine 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 quinupramine was achieved using the EVA polymer including a plasticizer.

Keywords: Quinupramine; Ethylene–vinyl acetate; Membrane; Matrix; Controlled release; Plasticizer

1. Introduction

Quinupramine is a new tricyclic antidepressant used in a dose of 5–15 mg daily in the treatment of reactive and endogenous depression (Reynolds, 1996). However, the oral administration of quinupramine may show many adverse side effects such as dry mouth, urinary retention, and daytime drowsiness. Therefore, there is a need to develop a transdermal drug delivery without the adverse effects associated with the frequent oral administration. The basic components of a transdermal device are a polymer matrix, penetration enhancers and excipients (Hadgraft, 1987). The use of a controlled release membrane is one method for regulating the drug release.

Among the many polymers, the ethylene–vinyl acetate (EVA) copolymer is a heat processable, flexible and inexpensive material (Miyazaki et al., 1983). 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., 1982), isosorbide dinitrate (Ocak and Agabeyoglu, 1999), nicardipine (Morimoto et al., 1988) was described. However, few studies have dealt with the release of antidepressants from the EVA copolymer matrices.

Several technologies have been developed to control the release rate. The use of drugs dispersed in an inert polymer to achieve controlled release through diffusion has attracted considerable attention (Kaplan, 1965; Efentakis and Vlachou, 2000; Vlachou et al., 2000). In this laboratory, the transdermal controlled drug delivery using various polymers has been studied (Shin and Byun, 1995; Shin and Cho, 1996; Shin and Lee, 2002).

The present study was carried out to evaluate the possibility of using the EVA membrane as a controlling membrane and to further develop an EVA matrix system for the transdermal delivery of quinupramine.

* Corresponding author. Tel.: +82 62 530 2924; fax: +82 62 530 2949.
E-mail address: shinsc@chonnam.ac.kr (S.-C. Shin).

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2. Materials and methods

2.1. Materials

The quinupramine was kindly supplied by Whanin Pharm. Co. Ltd. (Korea) and the ethylene–vinyl acetate (VA content, 40%) was 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 acquired from Junsei Chemical Co. Ltd. (Japan). Acetonitrile was of HPLC grade and all the other chemicals of reagent grade were used as received.

2.2. Determination of drug solubility

Excess amounts of quinupramine were added to 0.02 M phosphate buffered saline containing various PEG 400 concentrations. Each solution was shaken at 37 °C for 24 h. The solution was filtered through filter paper. The quinupramine concentration was determined by HPLC after the proper dilution.

2.3. Permeation studies through the EVA membrane

2.3.1. Preparation of the EVA copolymer membrane

Ethylene–vinyl acetate membrane was prepared using the casting method. Approximately 2 g of EVA copolymer beads was dissolved in 20 ml of cyclohexane in a glass beaker. This polymer solution was poured onto a glass plate and the solvent was allowed to evaporate off in the hood overnight. The membrane was then removed from the plate.

2.3.2. Drug permeation through the EVA membrane

The steady state permeation of quinupramine through the EVA membrane was determined using a two chamber-diffusion cell. Each half-cell has a volume of approximately 7 ml and an effective diffusion 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 in PEG 400–PBS solution was filled into the donor compartment. In addition, the same concentration of a PEG 400–PBS solution (without the drug) was added to the receptor compartment, in order to prevent solvent permeation from the donor to the receptor side through the membrane. The cell was shaken horizontally at the rate of 150 rpm in order to minimize the boundary effect. The total volume of the receptor solution was removed at the predetermined intervals and replaced with 7 ml of a fresh solution. The amount of drug permeated was determined by HPLC.

2.3.3. HPLC determination of quinupramine

Quinupramine was assayed by the HPLC, which consisted of a pump (Waters 501, USA), ultraviolet detector (Waters 484, USA), a 3.9 mm × 300 mm stainless-steel column packed with μ-Bondapak C_{18} (Waters, USA), degasser, and an integrator (D520A, Youngin Scientific Co. Ltd., Korea). The mobile phase was a combination of acetonitrile:0.025 M potassium dihydrogen phosphate (10:7), and the column was maintained at ambient temperature. A flow rate of 1.0 ml/min yielded an operating pressure of ≈1000 psi. The UV detector was operated at a wavelength of 250 nm. Under these conditions, the quinupramine peak appeared at a retention time of 5.8 min.

2.4. In vitro release studies from the EVA matrix

2.4.1. Preparation of the EVA matrix containing quinupramine

The casting process was used to prepare the EVA matrix containing quinupramine. A weighted amount of EVA copolymer beads was dissolved in 20 ml of cyclohexane in a beaker, which was followed by adding the drug.

The mixture was poured onto a glass plate and the solvent was allowed to evaporate at room temperature.

The matrix was removed from the plate and a piece of matrix was then cut properly and the thickness was measured before the experiment. The drug content was calculated from the weight ratio of the drug and copolymer used.

2.4.2. In vitro release studies

The in vitro release of quinupramine from the EVA matrix was examined using a modified Franz diffusion cell. A unit of the EVA matrix was clamped between the cell cap and receptor cell. The diameter of the cell was 2 cm, which provided an effective surface area of 3.14 cm^2 and a receptor medium of 21 ml. A 40% PEG 400–PBS solution was used as the receptor solution. The receptor was maintained to 37 °C with a circulating water jacket and stirred constantly at 350 rpm. Before the experiment, the system was tested to remove any air bubbles remaining in receptor site. At predetermined time, the whole solution from the receptor cell was taken and replaced with a fresh solution. The total amount of quinupramine released from the matrix was determined by the HPLC.

The effects of the drug concentration on its release from the EVA matrix was examined at 0.5%, 1%, 1.5%, 2% (w/w), and the effects of temperature on the drug release rate was studied at 28, 32, 37, and 42 °C. In addition, the effect of the EVA matrix thickness on the release rate was investigated. Each data point represents an average of three determinations.

2.4.3. In vitro release studies from the EVA matrix containing the plasticizer

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

as acetyl tributyl citrate (ATBC), tributyl citrate (TBC), acetyl triethyl citrate (ATEC) and triethyl citrate (TEC), and phthalates such as diethyl phthalate (DEP), di-*n*-butyl phthalate (DBP). The other conditions were the same as those in the release experiments method.

The effectiveness of plasticizer was defined by comparing the drug flux in the presence and absence of each plasticizer, and the ratio was defined as the enhancement factor (EF), which was calculated using the following equation:

$$\mathrm{EF} = \frac{\text{flux of the EVA matrix containing plasticizer}}{\text{flux of the control sample}}$$

2.5. Calculations

The permeation rate was calculated from the slope of the linear region of the permeation profile. The flux was calculated from the slope of the linear region of Q versus the $t^{1/2}$ release profile.

3. Results and discussion

3.1. Solubility of quinupramine

The aqueous solubility of quinupramine is extremely low but can be improved by the addition of a water-miscible hydrophilic polymer such as PEG 400 into the aqueous solution as a solvent for quinupramine. PEG 400 was reported to be an excellent solvent for many drugs (Chien and Lambert, 1975). Table 1 shows that the solubility of quinupramine increased with increasing PEG 400 volume fraction in PBS solution. A 40% PEG 400–PBS medium that showed the highest solubility was used as a receptor medium to maintain sink condition in diffusion study.

3.2. Drug permeation through the EVA membranes

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

$$Q = P(C_\mathrm{D} - C_\mathrm{R})t \tag{1}$$

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

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

$$Q = PC_\mathrm{e}t \tag{2}$$

and a constant permeation profile should be yielded. The rate of permeation can then defined as:

$$\frac{Q}{T} = PC_\mathrm{e} \tag{3}$$

The rate of permeation (Q_t/t), which was measured from the slope of Q versus t (Eq. (3)), increased with increasing PEG 400 in the PBS solution until 40% (v/v), and not so much increased in the 50% (v/v) PEG 400 solution. As expected from Eq. (3), the increase in the permeation rate (Q/t) was found to be dependent upon the equilibrium solubility (C_e) of quinupramine in the PEG 400–PBS solutions.

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

$$P = \frac{Q/T}{C_\mathrm{s}} \tag{4}$$

Table 1 shows that the permeability coefficient (P) decreased with increasing PEG 400 volume fraction in the PBS solution.

3.3. Release of quinupramine from the EVA matrix

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

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

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

$$Q = \left[\frac{D\varepsilon}{T}(2A - \varepsilon C_\mathrm{s})C_\mathrm{s}t\right]^{1/2} \tag{6}$$

Table 1
Effect of PEG 400 on the permeation of quinupramine 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	151.9	1.2 ± 0.11	7.9
10	431.8	2.2 ± 0.18	5.2
20	797.9	4.0 ± 0.41	5.0
30	1006.3	5.0 ± 0.48	5.0
40	2029.1	9.9 ± 0.91	4.9
50	1650.2	10.3 ± 1.0	6.3

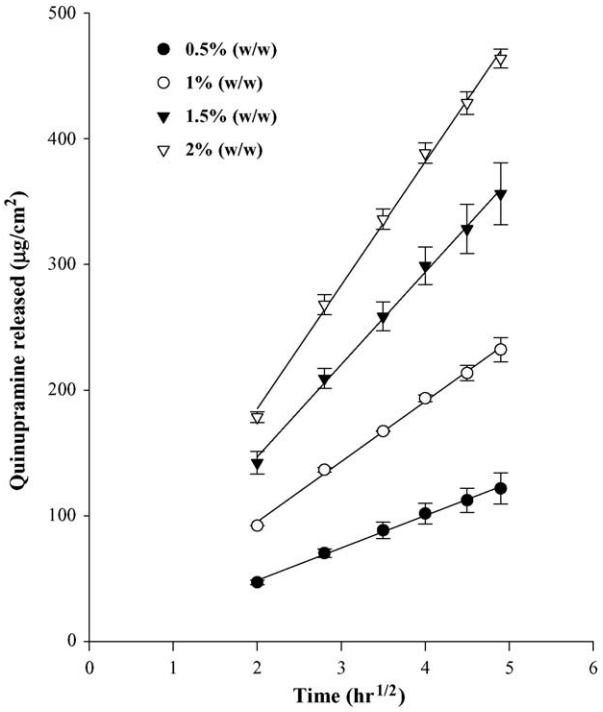

Fig. 1. Effect of the drug-loading dose on the release of quinupramine from the EVA matrix at 37 °C. The PEG 400 volume fraction was maintained at 40% (v/v).

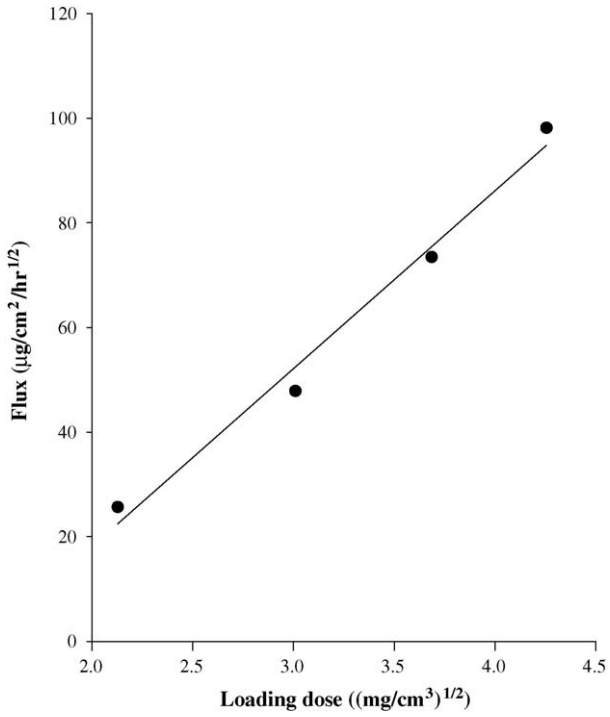

Fig. 2. Relationship between the quinupramine flux and the drug-loading dose in the EVA matrix at 37 °C.

where D and C_s refer to the 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 correspond to different mechanisms, they both describe drug release as being linear with the square root of time (Higuchi, 1963; Desai et al., 1965; Lapidus and Lordi, 1966; Desai et al., 1966; Singh et al., 1967):

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

where

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

for the homogeneous matrix system, and

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

for the granular matrix system. The validity of these relationships has been confirmed experimentally in a number of studies using various systems (Lapidus and Lordi, 1968; Farhadieh et al., 1971).

3.3.1. Effect of drug loading dose

Fig. 1 shows the quinupramine release profiles from the EVA matrices with a different drug loading over a 24 h period. A plot of the cumulative amount of quinupramine released (Q) versus the square root of time ($t^{1/2}$) shows a good linearity for all four concentrations (Fig. 1). As expected from Eq. (8), a plot of $Q/t^{1/2}$ versus the square root of the loading dose (A) yields a straight line (Fig. 2). As Fig. 2 indicates, $Q/t^{1/2}$ increased in direct proportion to the increase of drug-loading dose in the EVA matrix. The release of quinupramine from the EVA matrix followed a diffusion-controlled model, where the quantity released per unit area is proportional to the square root of time.

3.3.2. Effect of release media temperature

Fig. 3 shows the dependency of the drug release profile on the temperature. The total amount of the drug released (Q) was plotted versus the square root of time ($t^{1/2}$). After an initial period of drug release, the rate of release was approximately linear 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 4 to 24 h. The rate of drug released increased with increased temperature. In the EVA matrix containing 2% quinupramine, the $Q/t^{1/2}$ values at 28, 32, 37, and 42 °C were 81.8, 85.2, 98.1, and 112.8 μg/cm²/h$^{1/2}$, respectively. It should be noted that the rate of drug release increased approximately 1.4-fold when the temperature of the drug release system was increased from 28 to 42 °C. However, for the practical uses 37 °C was chosen to reflect the temperature of the stratum corneum.

This observation clearly indicates that the release of quinupramine from the EVA matrix is an energy-linked process (Miyazaki et al., 1984). The temperature effects could be on either the increased solubility of drug and/or the effects on diffusion.

The permeability coefficient can then be defined as follows:

$$P = \frac{\text{flux}}{\text{solubility}} \tag{10}$$

$$P = P_0\, e^{-E_a/RT} \tag{11}$$

$$\log P = \log P_0 - \frac{E_a}{R \times 2.303 \times 1000}\frac{1000}{T} \tag{12}$$

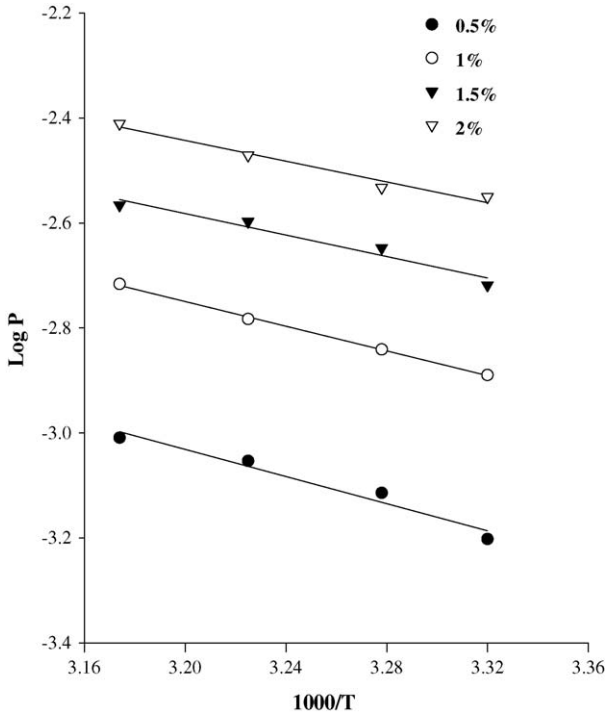

Fig. 3. Effects of temperature on quinupramine release from the EVA matrix containing various loading dose.

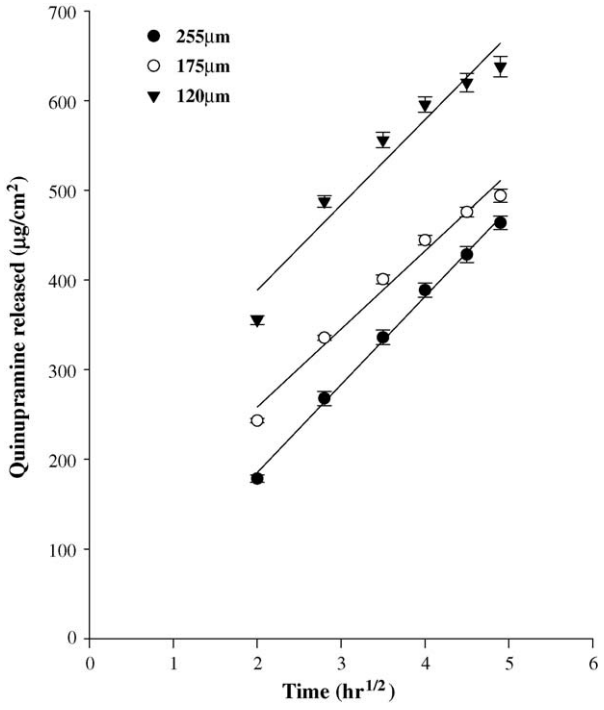

Fig. 4. Effects of the matrix thickness on the release of quinupramine from the EVA matrix with a 2% loading dose at 37 °C.

As expected from Eq. (12), a plot of $\log P$ versus $1000/T$ yielded a straight line (Fig. 3) from which the E_a (activation energy) was calculated from Eq. (14):

$$\text{slope} = -\frac{E_a}{R \times 2.303}\frac{1}{1000} \tag{13}$$

$$E_a = -\text{slope} \times R \times 2.303 \times 1000\,\text{cal} = -\text{slope} \times 1.987 \times 2.303\,\text{kcal} \tag{14}$$

The activation energy for drug release was 5.91, 5.39, 4.68 and 4.52 kcal/mol for a loading dose of 0.5%, 1%, 1.5% and 2%, respectively.

3.3.3. *Effect of matrix thickness on the release of quinupramine*

Fig. 4 shows the quinupramine release profiles from the EVA matrix of various thickness. The cast films whose thickness varied would clearly exhibit release characteristics associated with migration of drug to the surface during their preparation. As shown in Fig. 4, the amount of quinupramine released initially increased with decreasing matrix thickness.

3.3.4. *Effect of plasticizer on the drug release from the matrix*

The plasticizer reduces the brittleness, improves the flow, imparts flexibility, and increases the toughness, strength, tear resistance, and impact resistance of a polymer. Generally, plasticizers increase the amount of drug released with increasing chain mobility of the polymer. Increasing the amount of a plasticizer can lead to an increase in free film elongation and a decrease in tensile strength. A strong interaction between a drug and a polymer was reported to significantly influence the rate of drug released through a polymeric film (Jenquin et al., 1990; Bodmeier and Paeratakul, 1989). Table 2 shows the effects of plasticizers such as the citrate and the phthalate groups on the flux of quinupramine from the EVA matrix. The phthalate group showed a slight increase in release rate. Among the plasticizers used such as the alkyl citrates and the phthalates, diethyl phthalate showed the best results. The release of quinupramine from the EVA matrix followed a diffusion-controlled model, where the quantity released per unit area is proportional to the square root of time.

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

Plasticizer	Flux (μg/cm²/h)	Enhancement factor
Citrate group		
TEC	87.2 ± 5.9	1.04
TBC	86.0 ± 6.2	1.03
ATEC	93.1 ± 6.3	1.11
ATBC	92.9 ± 6.0	1.11
Phthalate group		
DEP	99.0 ± 7.1	1.19
DBP	96.7 ± 7.0	1.16
Control	83.5 ± 6.1	1.00

4. Conclusions

The release rate of drug from the EVA matrix increased with increased PEG 400 volume fraction, temperature and drug loading dose. The activation energy for drug release at a loading

dose of 0.5%, 1%, 1.5%, and 2% was 5.91, 5.39, 4.68, and 4.52 kcal/mol, respectively. Among the plasticizers used, diethyl phthalate showed the best results. The release of quinupramine from the EVA matrix followed a diffusion-controlled model, where the quantity released per unit area is proportional to the square root of time. The controlled release of quinupramine might be achieved using an EVA polymer containing a plasticizer.

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