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# Controlled release of atenolol from the ethylene-vinyl acetate matrix

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**Abstract**

The present study was carried out to evaluate the possibility of using the polymer EVA membrane as an EVA matrix system for transdermal delivery of atenolol. The effects of drug concentration, temperature, and plasticizers on drug release were studied from the atenolol-EVA matrix. The release rate of drug from the EVA matrix increased with increased temperature and drug loading doses. The flux of atenolol versus the reciprocal of the loading dose yielded a straight line. The release of atenolol from the EVA matrix follows a diffusion-controlled model, where the quantity released per unit area is proportional to the square root of time. Among the plasticizers used such as alkyl citrates and phthalates, tributyl citrate (TBC) showed the best enhancing effects. Enhancement factor of TBC was 1.51 from the EVA matrix at 37 °C. The controlled release of atenolol system could be developed using the EVA polymer including the plasticizer.


*Keywords:* Atenolol; Ethylene-vinyl acetate; Matrix; Plasticizer

## 1. Introduction

Atenolol is a beta-adrenergic receptor blocking agent without membrane stabilizing or intrinsic sympathomimetic activities and it has been used for the treatment of hypertension, either alone or with other antihypertensives such as thiazide diuretics (Gennaro, 1990). It is reported that in the case of oral application, it can induce the side effects like diarrhea, nausea, ischemic colitis, mesenteric arterial thrombosis and so on. Therefore, the development of transdermal drug delivery of the antihypertensives maintaining proper blood level for a long time without adverse effects of frequent oral administration is very important. The use of a release controlling membrane is one method to regulate the drug release. The usefulness of EVA copolymer as a drug delivery system for hydrocortisone (Johnson, 1980), fluoride ion (Gennaro et al., 1976), 5-fluorouracil (Miyazaki et al., 1982, 1984) and macromolecules such as proteins was described. However, little reports have dealt with the release of atenolol, antihypertensives, from the EVA copolymer matrices.

Several technologies have been successively developed to control the release rate. Basic components of transdermal devices are polymer matrix, penetration enhancers and excipients (Hadgraft, 1987). The use of drugs dispersed in inert polymer to achieve controlled release by diffusion has considerable attention (Levesque, 1961; Kaplan, 1965). In this laboratory, the transdermal controlled drug delivery using

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polymer membrane (Shin and Cho, 1996; Shin and Byun, 1996) has been studied. The present study was carried out 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 atenolol.

## 2. Materials and methods

### 2.1. Materials

Hyundai Pharm. Co., Ltd. (Korea) kindly supplied atenolol. Ethylene-vinyl acetate copolymer of 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 (DEC) and di-*n*-butyl phthalate (DBP) were from Junsei Chemical Co., Ltd. (Japan). Acetonitrile and methyl alcohol were HPLC grade from J.T. Baker Inc. (USA) and all chemicals were used as received.

### 2.2. Preparation of EVA matrix containing drug and plasticizer

The atenolol-EVA matrix was prepared by casting process (Shin and Byun, 1996). Briefly, about 2.0 g of EVA polymer beads and drug were dissolved in 20 ml of methylene chloride and 5 ml of methanol. 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 unharmed pieces of membrane with no orientation of the molecules (Bodmeier and Paeratakul, 1989). Plasticizers were added in ratios of 5% (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 vaccuo. 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.

### 2.3. In vitro release from the EVA matrix

The in vitro release of atenolol from the EVA matrix was examined by using the modified Keshary–Chien cell (Chien, 1987). 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 phosphate buffer (pH 7.4) was used as receptor solution. The receptor was maintained to 37 °C with circulating water jacket and stirred constantly. At predetermined time intervals, whole solution from the receptor cell was taken and replaced with fresh solution. The cumulative amount of atenolol released from the matrix was determined at 224 nm by HPLC.

### 2.4. HPLC determination of atenolol

The concentration of atenolol was determined by HPLC methods. The column was uBondapak $C_{18}$ (10 um, 3.9 mm × 300 mm) and the mobile phase was combination of methanol/acetonitrile/pH 3 buffer (1:1:4). The flow rate was 1.0 ml/min, the UV detector was operated at 224 nm, and the column temperature was maintained at ambient. Under these conditions, the atenolol peak appeared at the retention time of 6.5 min.

### 2.5. Data analysis

A characteristic 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:

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

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 $C_s$ 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 (Farhadieh et al., 1971; Lapidus and Lordi, 1996).

## 3. Results and discussion

### 3.1. 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 according to drug concentration of 0.5, 1.0, and 1.5% (w/w). The release rates of atenolol from the EVA matrices of different drug loading dose were studied at 37 °C for 24 h. The drug flux was calculated from the slope of the linear region of the $Q$ versus $t^{1/2}$ release profile. The cumulative amount of atenolol released $Q$ versus the square root of time ($t^{1/2}$) plot showed a good linearity as expected from Eq. (1) for all three different concentrations. The rate of drug release increased about 1.24-fold when the drug-loading dose was increased from 0.5 to 1.5%. A plot of $Q/t^{1/2}$ versus the square root of drug concentration yielded a straight line (Fig. 1).

### 3.2. Effect of temperature on drug release from the EVA matrix

The effects of temperature on drug release from EVA-matrix containing various loading dose was studied at 32, 37, and 42 °C. The dependency of the drug release on temperature is shown in Fig. 2. 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 with respect to $t^{1/2}$. In the EVA matrix containing 1.5% atenolol, the drug flux at 32, 37, and 42 °C were 4.07, 5.33, and 6.99 $\mu g/cm^2/h^{1/2}$, respectively. The higher the temperature, the greater the drug release. It should be noted that the rate of drug release increased about

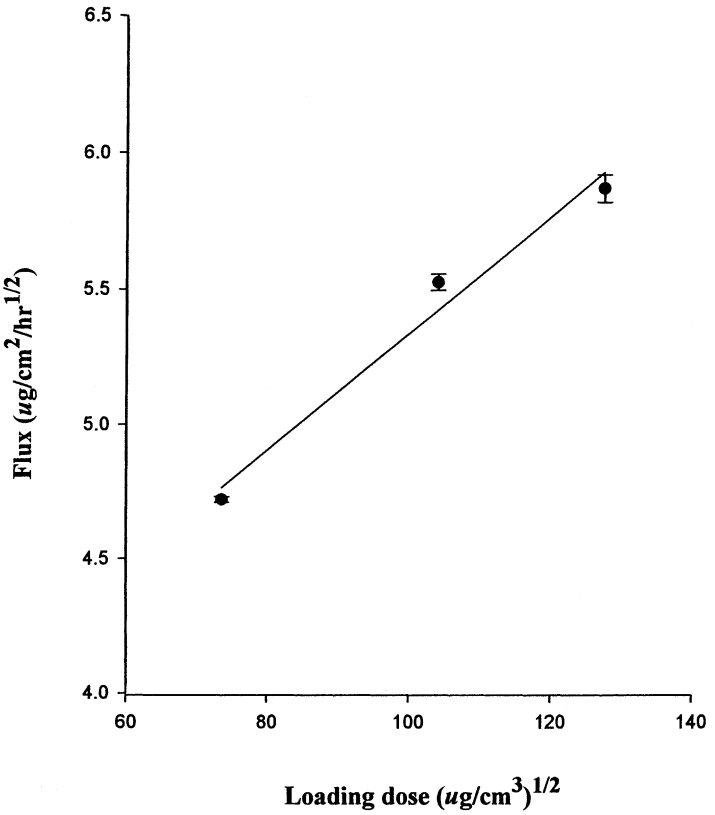


Fig. 1. Relationship between the release rate of atenolol at 37 °C and the drug loading dose in EVA matrix.

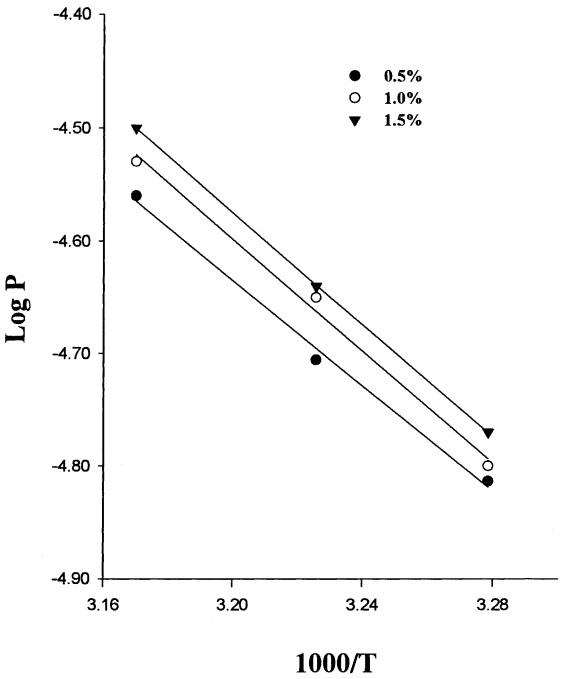


Fig. 2. Effects of temperature on atenolol release from the EVA matrix containing various loading dose.

1.72-fold when the temperature of the drug release system was raised from 32 to 42 °C.

The relationship between partition coefficient and temperature is given by Eq. (2):

$$P = P_0 \, e^{-E_a/RT} \quad (2)$$

where $P$ is partition coefficient, $P_0$ is a constant, $E_a$ is activation energy of permeation, and $R$ is gas constant. When the logarithm of the permeation coefficients was plotted as a function of the reciprocal of temperature, a linear relationship was observed with the correlation coefficient 0.943 (Fig. 2). The apparent permeation coefficients was calculated using the equation for the drug release and was increased with increasing temperature.

The activation energy ($E_a$), which was measured from the slope of $\log P$ versus $1000/T$ plots was 2.85 kcal/mol for 0.5% loading dose, 2.43 kcal/mol for 1.0% loading dose, and 2.25 kcal/mol for 1.5% loading dose from the EVA matrix. This observation clearly indicates that the release of atenolol from the EVA matrix is an energy-linked process (Miyazaki et al., 1983). 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 the practical use, 37 °C was chosen to reflect the temperature of the stratum corneum (Chien and Lau, 1976). This finding indicates that special precautions should be taken with regard to monitoring body temperature in practical applications.

### 3.3. Effects of plasticizers on drug release from the EVA matrix

For most rate-controlling polymeric membranes, the release rates are adjusted by varying the chemical or physical properties of membranes. Besides varying the chemical or physical properties of membranes, the release rate can be adjusted by changing the membrane structure (Donbrow and Friedman, 1975; Michaels and Bixler, 1961). 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 was studied at 37 °C according to kinds of plasticizers. The effectiveness of plasticizer was determined by 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.

The release rates of atenolol from the EVA matrix containing plasticizers such as citrate group and phthalate group at 37 °C are shown in Table 1. Plasticizers in EVA matrix increased the rate of drug release. Increasing the amount of plasticizer could lead to an increase in free film elongation and a decrease

Table 1
Effect of plasticizers on the flux of atenolol from the EVA matrix

| Plasticizer | | Flux ($\mu g/cm^2/h^{1/2}$) | Enhancement factor |
|---|---|---|---|
| Citrate group | ATEC | 5.608 | 1.05 |
| | ATBC | 7.034 | 1.32 |
| | TEC | 7.540 | 1.42 |
| | TBC | 8.056 | 1.51 |
| Phthalate group | DEP | 5.589 | 1.05 |
| | DBP | 5.763 | 1.08 |
| Control | – | 5.327 | 1.00 |

in tensile strength. A strong interaction between a drug and a polymer has been reported to influence drug release significantly through a polymeric film (Bodmeier and Paeratakul, 1989). 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 atenolol released from the EVA matrix containing TBC as a citrate group plasticizer increased about 1.51-fold, showing the best enhancing effects (Table 1). Comparing the alkyl radicals of the plasticizers such as citrate groups, phthalates groups, the butyl group plasticizers increased the drug release better than the ethyl group plasticizers.

## 4. Conclusions

The flux of atenolol versus the reciprocal of the loading dose yielded a straight line. The release of atenolol from the EVA matrix follows a diffusion-controlled model, where the quantity released per unit area is proportional to the square root of time. Among the plasticizers used such as alkyl citrates and phthalates, tributyl citrate (TBC) showed the best enhancing effects. The controlled release of atenolol system could be developed using the EVA polymer including the plasticizer.

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