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Controlled Release of Prednisolone from Ethylene-Vinyl Acetate Copolymer Matrix[1)]

Shozo Miyazaki,* Kuniaki Ishii, and Tanekazu Nadai

Faculty of Pharmaceutical Sciences, Josai University, Keyakidai 1-1, Sakado, Saitama, 350-02, Japan

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Ethylene-vinyl acetate (EVA) copolymer was evaluated as a carrier for controlled release of prednisolone. The vinyl acetate content of EVA copolymer varied from 8 to 33% w/w. Increase in vinyl acetate comonomer content of EVA copolymer matrix brought about an increase in the release rate. The release rate could be controlled by modifying the ethylene-vinyl acetate ratio in the polymer matrix. Fabrication parameters such as matrix coating and drug content also significantly affected the release kinetics. Matrices composed of EVA copolymer could be useful vehicles for the controlled release of the corticosteroid.

Keywords——ethylene-vinyl acetate copolymer; comonomer ratio; biomaterial; controlled release; drug delivery; prednisolone

Many techniques have been utilized to develop controlled or sustained release drug delivery systems. The release rate of a drug from a polymer matrix may be controlled by variations of the dimensional parameters, the drug concentration, and the polymer system. A wide range

of release rates for a drug can be obtained by simple modification of a polymer system. It has been demonstrated that modifying the monomer ratio in barrier membranes could drastically alter the drug release rate.[2-6]

Ethylene-vinyl acetate (EVA) copolymer is a heat-processable, flexible, nontoxic, and inexpensive material.[7-9] The safety and biocompatibility of EVA copolymer are reflected in its use as a biomaterial[7] for artificial hearts[10] and as an antithrombogenic heparinized polymer.[11] Physico-chemical properties of EVA copolymer can be varied over a wide range by means of changes in the comonomer ratios.[12-14] EVA copolymer shows good biocompatibility and should be useful as a carrier for biomedical implanted, inserted, or surface-applied drug delivery devices.

The usefulness of EVA copolymer as a drug delivery system for pilocarpine,[15] progesterone,[16] fluoride ion,[17] macromolecules such as proteins,[18,19] and hydrocortisone[20] was described. However, few reports have dealt with control of drug release by modifying the ethylene-vinyl acetate ratio in barrier membranes. It seemed worthwhile to further evaluate the possible use of EVA copolymer in controlled drug release. As a part of such an evaluation of EVA copolymer, the effect of comonomer ratio changes on the drug release was examined. EVA copolymers ranging from 8 to 33% w/w of vinyl acetate unit were used in this work.

An anti-inflammatory agent, prednisolone, was chosen for this study because it is useful in the treatment of a large variety of diseases including neoplastic diseases, and because protective films containing steroids have been used for dermatological applications.[21]

Experimental

Materials——Prednisolone was obtained from Merck, Darmstadt, and used without further purification. Ethylene-vinyl acetate copolymers (EVAFLEX) with various comonomer ratios were gifts from Mitsui Polychemical, Tokyo.

Matrix Preparation——A weighed amount of drug powder was dissolved in 100 ml of methylene chloride or toluene in a glass vial. EVA copolymers were dissolved in the drug solution to give a 5% w/v solution at 50°C, except that a copolymer with 8% w/w vinyl acetate content was dissolved in the toluene solution. This mixture 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 d at room temperature *in vacuo*. The residue was melt-pressed at 100°C under 500 kg/cm^2 pressure for 2 min to produce a membrane of uniform thickness (about 0.035 cm), then 1.8×1.8-cm squares were cut from the membrane using a microscope cover glass as a template, and were weighed accurately. The drug content was calculated from the weight ratio of drug and copolymer used.

The effect of coating the matrix with an additional polymer layer was also examined. Each square was coated by dropping it into a vial containing 20 ml of polymer solution, 20% w/v EVA copolymer (33% w/w vinyl acetate) in methylene chloride. After 10 s in the solution, the square was dried at room temperature for 2—3 min and for an additional 2 d *in vacuo*.

***In Vitro* Release Studies**——The squares prepared by the described procedure were placed separately in 20 ml vials containing 6 ml of distilled water. The release was followed with shaking at a rate of 60 strokes/min on the incubator at 37°C. Each square was successively transferred to fresh vials containing 6 ml of water. Analysis of drug release into each 6 ml fraction was carried out spectrophotometrically. Data shown in the figures are averages of at least four experimental runs.

Results and Discussion

In order to study the effect of comonomer ratio changes on drug release kinetics, the release of prednisolone dispersed in matrices composed of different ratios of ethylene and vinyl acetate was investigated.

Higuchi[22] proposed the following equation for diffusion-controlled release of drugs dispersed in a homogenous insoluble matrix:

$$Q = \sqrt{D \cdot (2A - C_s) \cdot C_s \cdot t} \qquad \text{(Eq. 1)}$$

where Q is the amount of drug release per unit area at time t, D is the drug diffusion coefficient in the matrix, A is the total amount of drug per unit volume of the matrix, and C_s is the drug

solubility in the matrix.

This equation describes drug release as being linear with the square root of time.

$$Q = k \cdot t^{1/2} \qquad \text{(Eq. 2)}$$

where k is the release rate constant.

Figure 1 shows plots of the data, expressed as the cumulative amount of the steroid released, *versus* the square root of time ($t^{1/2}$). There appeared to be three release phases: (a) an initial period of rapid release of the drug, termed the burst effect, due to the release of drug molecules at the matrix surface; (b) a period when release was approximately linear with respect to $t^{1/2}$; and (c) a final period when release tapered off, due to the increased difficulty of diffusion of drug occluded inside the matrix with decrease of the initial drug concentration in the matrix.

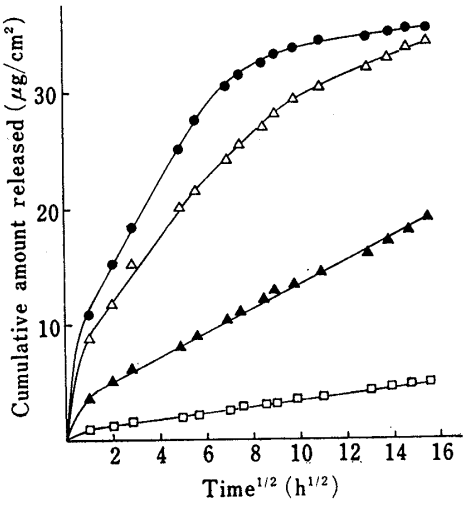

Fig. 1. Cumulative Release of Prednisolone from EVA Copolymer Matrices at 37°C (0.22 mg of Prednisolone per Matrix)

□: 8, ▲: 19, △: 25, ●: 33% w/w vinyl acetate.

The steady-state rate of drug release (k) was estimated from the slope of the linear Q–$t^{1/2}$ profile up to 32 h. The k values for the matrices with 8, 19, 25, and 33% w/w vinyl acetate contents were 0.25, 1.08, 2.73, and 3.53 μg/cm²/h$^{1/2}$, respectively. The effect of increasing vinyl acetate content in the copolymer matrix was to cause a marked increase in the release rate for prednisolone. With this system, matrices varying in release pattern could be easily obtained by changing the proportions of ethylene and vinyl acetate. It should also be pointed out that sustained release can be obtained by using EVA copolymer containing less vinyl acetate.

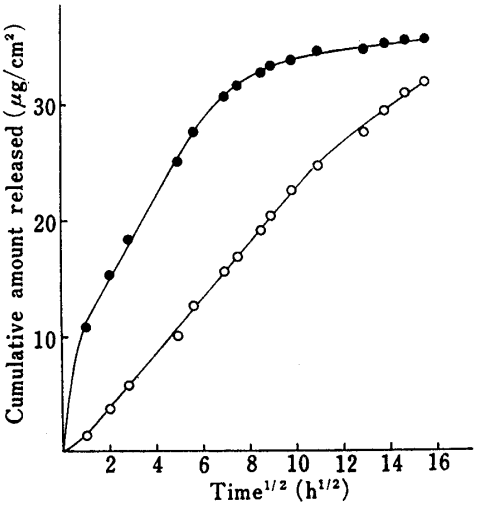

Fig. 2. Effect of Coating on the Cumulative Release of Prednisolone from EVA Copolymer Matrix with 33% w/w Vinyl Acetate Content at 37°C (0.22 mg of Prednisolone per Matrix)

●: uncoated matrix, ○: matrix coated with 20% w/v copolymer solution.

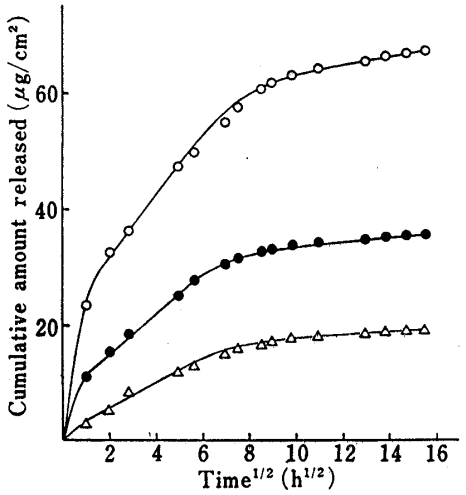

Fig. 3. Effect of Initial Drug Content on the Cumulative Release of Prednisolone from EVA Copolymer Matrix with 33% w/w Vinyl Acetate Content at 37°C

△: 0.11 mg, ●: 0.22 mg, ○: 0.45 mg per matrix.

Other factors that affect the drug release were studied. Coating the matrix also significantly affected drug release rates (Fig. 2). The release patterns of uncoated matrix and matrix coated with 20% w/v polymer solution were compared. Coating the matrix with an additional polymer layer results in slower drug release and different release patterns. The effects may be due to the reduced amount of drug on the matrix surface. There appeared to be a release period in the coated matrix that was roughly linear with respect to $t^{1/2}$. Thus, a coating can also be used to control drug release kinetics.

To further control drug release, the effect of drug concentration on the release rate was tested using three concentrations of prednisolone (0.11, 0.22, and 0.45 mg per matrix). As shown in Fig. 3, variation in the initial drug content of the matrix affects the drug release; increasing the drug content increases the drug release rate. The results showed a linear relationship between k and the square root of drug concentration.

A wide spectrum of release rates can be achieved by coating the matrix and altering the drug content; thus, EVA copolymers can be useful vehicles as polymer matrices for the controlled release of corticosteroids.

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