[Chem. Pharm. Bull. 31(10)3707—3713(1983)]

Controlled Release of 5-Fluorouracil from Hydrophilic Ethylene–Vinyl Alcohol Copolymer Matrices[1,2]

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(Received April 23, 1983)

Ethylene–vinyl alcohol (EVAl) copolymer was evaluated as a carrier for controlled release of 5-fluorouracil (5-FU). In order to study the effect of comonomer ratio modifications on the drug release kinetics, the release of 5-FU dispersed in polymer matrices composed of different ratios of ethylene and vinyl alcohol was investigated. The ethylene content of EVAl copolymer was varied from 32 to 60 mol%. An increase in ethylene comonomer content decreased the drug release from the polymer matrix. The release rate could be controlled by modifying the ethylene/vinyl alcohol ratios in the polymer matrices.

Fabrication parameters such as drug content and surface area of matrices also affected the release kinetics. The release rates were shown to be proportional to release media temperature, but independent of the pH.

Matrices composed of EVAl copolymer appeared to be stable on long-term storage with respect to release rate and could be useful vehicles for the controlled release of hydrophilic drugs.

Keywords——ethylene–vinyl alcohol copolymer; drug carrier; biomedical polymer; comonomer ratio; controlled release; drug delivery; 5-fluorouracil

Many attempts have been made to develop controlled release drug delivery systems. Synthetic polymer membranes have been used as rate-determining barriers for drug release. Much of the previous work on controlled release drug delivery has utilized polydimethylsiloxane (silicone rubber). In general, silicone membranes exhibit lipophilic characteristics; the polymer shows a relatively high permeability for lipophilic drugs.[3] In the previous studies, hydrophobic ethylene–vinyl acetate (EVAc) copolymer was evaluated as a carrier for controlled release of prednisolone[4] and 5-fluorouracil (5-FU).[5] It was demonstrated that the release rate for both drugs could be easily controlled by modifying the ethylene/vinyl acetate ratios in the copolymer matrices.

In addition to studying the hydrophobic EVAc copolymer, we have had an ongoing interest in the development of a biocompatible, hydrophilic polymer as a drug delivery carrier. Ethylene–vinyl alcohol (EVAl) copolymer prepared from EVAc is nontoxic, flexible, and heat-processable. The unique characteristic of this copolymer, different from EVAc copolymer, is its hydrophilicity.[6] The safety and biocompatibility of the copolymer are reflected in its use as hemodialysis membrane.[7] Physicochemical properties of EVAl copolymer can be varied over a wide range by means of changes in the comonomer ratios.[8] EVAl can be applied for the controlled release of hydrophilic drugs because of its hydrophilic character. However, no attention appears to have been directed to EVAl copolymer as a drug carrier except for our preliminary studies.[9,10]

In the present study, EVAl copolymer was evaluated as a new hydrophilic carrier for controlled release of drugs. The drug studied was a potent anticancer agent, 5-FU. *In vitro* release of 5-FU dispersed in polymer matrices composed of different ratios of ethylene and vinyl alcohol was investigated. We have also examined the effect of fabrication parameters

(drug content, surface area) and the release environment (temperature, pH) on the drug release kinetics.

Experimental

Materials——Ethylene–vinyl alcohol (EVAl) copolymers ranging from 32 to 60 mol% of ethylene unit were gifts from Kuraray Co., Tokyo. They were prepared from EVAc copolymer solution by saponification. The melting points of the copolymer with 32, 43, 54, and 60 mol% of ethylene contents were 180, 162, 145, and 135 °C, respectively.

Preparation of EVAl Matrices——Copolymer matrices containing the drug in the form of a monolithic system were prepared by dissolving the EVAl copolymer (1 g) and the required amount of drug in 20 ml of solvent (*n*-propyl alcohol : water = 3 : 1) at 80—85 °C. This mixture was poured onto a polyester film and the solvent was allowed to evaporate off at room temperature overnight. The membrane was removed from the film and dried for 2 d at room temperature *in vacuo*. The residue was melt-pressed at the melting point under 500 kg/cm^2 pressure for 3 min to produce a membrane of uniform thickness. The thickness of the membranes when measured with a micrometer (Mitsutoyo, Type 102-230) was 0.02—0.03 cm. Then, 1 × 1 cm squares (2.1 cm^2 in area available for release) were cut from the membrane and weighed accurately. The drug content was calculated from the weight ratio of drug and copolymer used.

For studying the effect of surface area on drug release, one surface of the planar matrices was covered with "alumi-tape." Only the exposed surface area (1.1 cm^2) was available for release. The matrix was examined visually at the end of each experiment. No visible peeling of the tape from the matrix was observed.

***In Vitro* Release Studies**——The matrices prepared by the above procedure were placed separately in 10 ml vials containing 5 ml of distilled water. The drug release was followed with shaking at a rate of 60 strokes/min on the incubator at 37 °C. At each time point, each matrix was successively transferred with forceps to fresh vials containing 5 ml of water. The released 5-FU concentration was determined spectrophotometrically by measuring the absorption at 266 nm. Data shown in the figures are averages of three experimental runs; the results were satisfactorily reproducible.

Determination of Water Content in Hydrated EVAl Copolymer——Hydration studies were performed by immersing control matrices (2 × 2 cm squares) containing no drug in water at 37 °C for 2 weeks with shaking (60 strokes/min). The wet matrices were quickly blotted to remove excess surface water, weighed, and dried at 50 °C for 2 d. They were then weighed again to determine the dry weight. The weight loss was considered to correspond to the water content of the hydrated matrices.

Results and Discussion

Controlled Release of 5-FU from the EVAl Copolymer Matrices

For studying the effect of comonomer ratio changes on the drug release kinetics, the release of 5-FU dispersed in matrices composed of different ratios of ethylene and vinyl alcohol was investigated. In this study, both the initial drug content in the matrix (1 ± 0.1 mg) and the temperature (37 °C) were held constant, while the ethylene content of the EVAl copolymer was varied (32, 43, 54, and 60 mol%).

Higuchi[11] proposed the following equation for diffusion-controlled release of drugs dispersed in a homogeneous insoluble matrix:

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

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.

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

where k is the release rate constant.

Figure 1 shows plots of the data, expressed as the cumulative amount of drug (Q) released from a unit area of matrix, *versus* the square root of time ($t^{1/2}$). Except for the matrix with 32 mol% ethylene content, there appeared to be three release phases:[4] (a) an initial

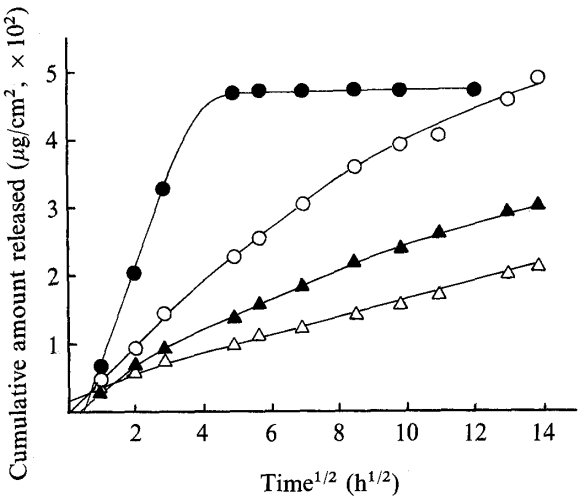

Fig. 1. Cumulative Amount of 5-FU Release from EVAl Copolymer Matrices at 37 °C (1 mg of 5-FU per matrix)

●, 32; ○, 43; ▲, 54; △, 60 mol% ethylene.

TABLE I. Effect of Ethylene Content of EVA1 Copolymer Matrices on Rate Constant of Drug Release and Water Content

Ethylene content (mol%)	Release rate constant (k, μg/cm²/h$^{1/2}$)		Water content[c,d] (%)
	Initial state[a]	Steady state[b]	
32	142.49	—	8.80
43	53.09	37.08	5.50
54	36.67	21.65	4.29
60	18.19	12.41	3.74

a) Initial state rate of drug release is calculated from the slope of first 8 h release profile.
b) Steady state rate of drug release is calculated from the slope of the Q–$t^{1/2}$ profile up to 72 h.
c) % water content = (wet weight − dry weight)/wet weight.
d) Average of two determinations.

period of rapid release of the drug (*i.e.*, burst effect); (b) a period when release was approximately linear with respect to $t^{1/2}$; and (c) a final period when release tapered off.

The initial-state (a) and steady-state (b) rates of drug release (k) were estimated from the slope of the first 8 h of drug release and the slope of the linear $Q-t^{1/2}$ profile up to 72 h, respectively. The results are shown in Table I as a function of the ethylene content. The effect of increasing ethylene content in the copolymer matrix was to cause a marked decrease in both the initial- and steady-state rates of drug release. A linear relationship between the ethylene content and the log of the drug release rate was observed with this hydrophilic matrix, as previously decomonstrated by Borodkin and Tucker.[12] This means that by selecting a particular EVAl composition, one can obtain different systems each having a different release rate. It should also be pointed out that sustained release can be obtained by using EVAl copolymer containing more ethylene.

In order to understand the mechanism of drug release from EVAl copolymer matrices, several factors concerning the release must be considered.

It is known that increase in crystallinity reduces the diffusivity of the drug within the polymer.[13] However, the crystallinity of this system increases with increased vinyl alcohol comonomers (that is, decreased ethylene content) in the range of composition studied.[14] It seems to be difficult to explain the greater barrier characteristics obtained with increased

ethylene contents in the matrices on the basis of the crystallinity of copolymers.

In order to estimate the hydrophilic property of the copolymer, water content was determined as a measure of hydrophilicity. As shown in Table I, the water content depended upon the ethylene content (the surface hydroxyl group content)[15] of the copolymer. Copolymer samples of increasing mole percent ethylene composition showed less water content, indicating lesser degrees of hydrophilic nature. Based on this finding, it may be inferred that the water content affects the release rate of the drug. The general trend observed was that the release rate decreased as the water content in the matrix decreased, that is, as the hydrophilicity decreased.[16] Although systematic studies on the mechanism of the drug release have not been done, it is anticipated that the mechanism of drug release from EVAl copolymer matrices depends on the hydration volume. The free polymer volume[17,18] available for 5-FU diffusion in the copolymer would be directly related to the hydration volume of the matrix. The free volume would consist of thermally transient random holes or voids in the polymer matrix, which would serve as passages for diffusing molecules. Increased free volume may provide more holes or voids for diffusion, which would facilitate the movement of water into, and drugs out of, the matrix.

Factors Affecting the Release Kinetics

To obtain maximum efficiency of a polymeric system, it is important to understand the factors determining the rates of drug release in the design of controlled release drug delivery systems. Thus, fabrication parameters (initial drug content, surface area) that affect the drug release were studied. In addition, it seemed desirable to elucidate the effect of the release environment (temperature, pH) on the release process. A matrix with a copolymer of 43 mol% ethylene content was prepared in the usual manner and permitted to release the drug into aqueous solutions.

To effect of drug concentration on the release rate was tested at three concentrations of 5-

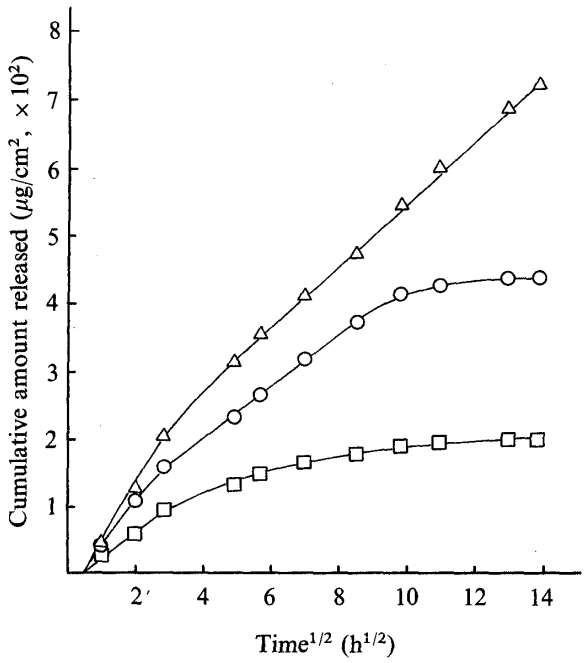

Fig. 2. Effect of Drug Content on 5-FU Release from the Copolymer Matrix with 43 mol% Ethylene Content at 37 °C

△, 2.0; ○, 1.0; □, 0.4 mg per matrix.

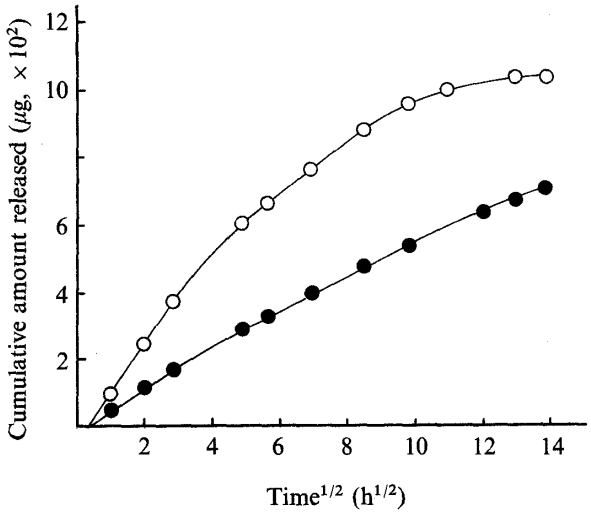

Fig. 3. Effect of Surface Area on 5-FU Release from the EVAl Copolymer Matrix with 43 mol% Ethylene Content at 37 °C (1 mg of 5-FU per matrix)

○, 2.1; ●, 1.1 cm².

FU (0.4, 1.0, and 2.0 mg per matrix). As shown in Fig. 2, variation in the initial drug content of the matrix affects the drug release; increasing the drug content increases the drug release rate. The k values for the matrices with 0.4, 1.0, and 2.0 mg of the drug were 36.78, 63.22, and 86.88 $\mu g/cm^2/h^{1/2}$ (initial state) and 12.90, 39.39, and 44.80 $\mu g/cm^2/h^{1/2}$ (steady state), respectively. As much as a 3-fold increase in the steady-state release rate was caused by increasing the drug content from 0.4 to 2.0 mg per matrix.

The surface area of the drug delivery matrices also affected the drug release rates (Fig. 3). In this study, release rates from the entire surface (2.1 cm^2) were compared with those from one surface (1.1 cm^2). Decreasing the surface area available for release to one-half produced a proportionate decrease in the release rate, determined from the slope in $\mu g/h^{1/2}$. The same

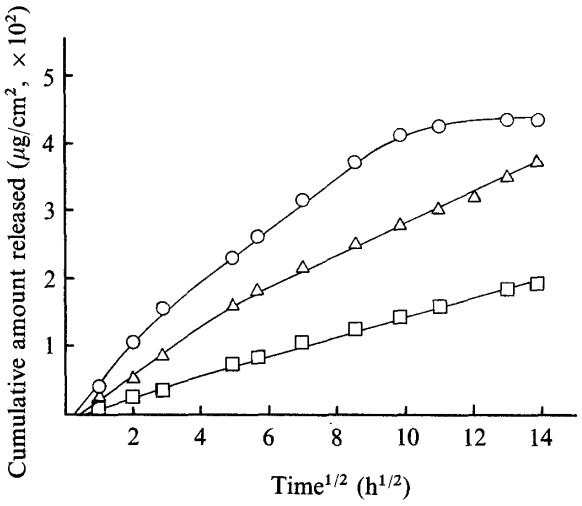

Fig. 4. Effect of Release Media Temperature on 5-FU Release from the EVAl Copolymer Matrix with 43 mol% Ethylene Content (1 mg of 5-FU per matrix)

□, 20; △, 30; ○, 37 °C.

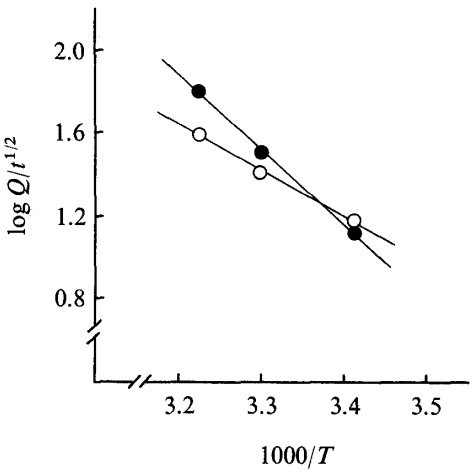

Fig. 5. Temperature Dependency of the Release Profile of 5-FU

●, initial state; ○, steady state.

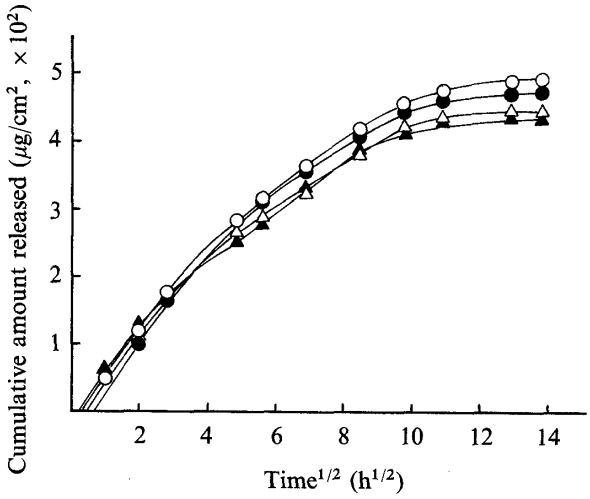

Fig. 6. Effect of Release Media pH on 5-FU Release from the EVAl Copolymer Matrix with 43 mol% Ethylene Content at 37 °C (1 mg of 5-FU per matrix)

○, water; ●, pH 5.9; △, pH 7.2; ▲, pH 8.0.

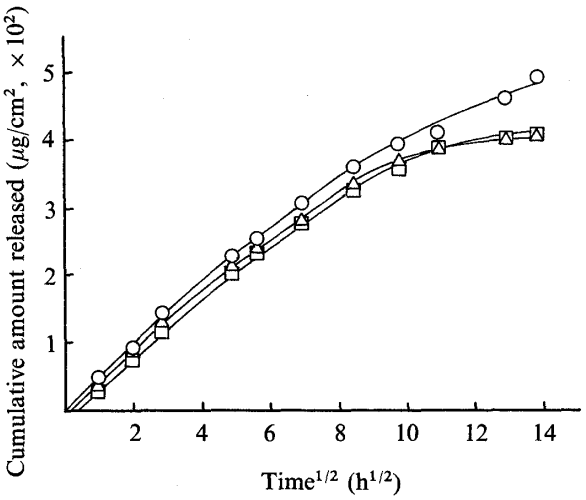

Fig. 7. Cumulative Release of 5-FU from the EVAl Copolymer Matrix with 43 mol% Ethylene Content at 37 °C (1 mg of 5-FU per matrix)

○, 6 d; △, 3.5 months'; □, 5 months' storage.

result was obtained with a matrix with a copolymer of 32 mol% ethylene content (not shown). Fick's law of diffusion can be applied to explain this relation.[19,20]

The release rate of 5-FU from EVAl copolymer matrix can be varied by manipulating three fabrication parameters, *i.e.*, drug content and surface area as well as monomer content in the matrix.[20] Thus, EVAl copolymer can be a useful vehicle for the controlled release of this anticancer agent.

Since EVAl could be clinically used as a carrier for implanted, inserted, or surface-applied drug delivery devices, we have also examined the effects of the release environment (temperature, pH) on drug release. Release studies were conducted for 5-FU at 20, 30, and 37 °C. The dependency of the drug release profile on temperature is illustrated in Fig. 4. The higher the temperarture, the greater the drug release k values. It was noted that the rate of drug release was increased approximately 5-fold (initial state) and 2.5-fold (steady state) when the temperature of the drug release system was raised from 20 to 37 °C. This observation clearly indicates that the release of 5-FU from the EVAl copolymer matrix is an energy-linked process.[21]

The activation energies of release, as determined from the slope of a plot of log k *versus* the reciprocal of the absolute temperature (T), illustrated in Fig. 5, where 16.8 and 10.4 kcal/mol for the initial state and steady state, respectively. The linear increase in release with increasing temperature suggests that the release characteristics of the copolymer would be altered over the body temperature range.

The effect of pH on the release pattern was examined in water and 1/15 M phosphate buffer media with different pH values and the results are shown in Fig. 6. These curves indicate that there was only a slight difference in the buffer media; the k values of steady-state release at pH 5.9, 7.2, and 8.0 were 33.94, 33.45, and 38.61 $\mu g/cm^2/h^{1/2}$, respectively. The release rate in water ($k = 37.07$) was almost identical with that in the buffer media. The release characteristics of the copolymer matrix thus would not change significantly in aqueous media at physiological pH values.

Stability of EVAl Copolymer Matrices

The release rates of matrices stored for 3.5 and 5 months at room temperature were compared with those obtained with matrices placed on test within 6 d of preparation (Fig. 7). As can be seen by comparing these plots, there was no significant change in release rate on storage. The steady-state k values for the matrices stored for 6 d, 3.5 months, and 5 months were 37.08, 32.85 and 32.56 $\mu g/cm^2/h^{1/2}$, respectively. The matrix appears to be stable on long-term storage with respect to release rate.

Conclusions

The results of the present investigation suggest that EVAl copolymer can be used as a controlling membrane for the release of 5-FU. The rate of diffusion can be easily adjusted to obtain the desired release rate by using EVAl copolymer having different ethylene contents. 5-FU release rates from the EVAl matrices are also dependent on the drug content and surface area of matrices. Matrices containing 5-FU to provide a constant release rate could be made by simple alteration in the fabrication parameters of the matrix.

Other studies demonstrated a marked effect of temperature on the release kinetics; that is, the release rate increased with an increase in temperature. The use of either water or phosphate buffers (pH 5.9, 7.2, and 8.0) as release media resulted in only a slight difference in drug release kinetics.

Acknowledgement The authors are grateful to Mr. H. Ohkata and Mr. S. Harita of Kuraray Co. for valuable suggestions and for supplying ethylene–vinyl alcohol copolymers.

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