[Chem. Pharm. Bull. 32(4)1633—1636(1984)]

Factors Affecting the Release Patterns of 5-Fluorouracil from Ethylene–Vinyl Acetate Copolymer Matrices[1)]

SHOZO MIYAZAKI,*[,a] SHIGEMI TAKEUCHI,[a] MASAHIKO TAKADA,[a] and KUNIAKI ISHII[b,2)]

Faculty of Pharmaceutical Sciences, Higashi-Nippon-Gakuen University,[a] Ishikari-Tohbetsu, Hokkaido 061–01, Japan and Faculty of Pharmaceutical Sciences, Josai University,[b] Sakado, Saitama 350–02, Japan

(Received July 15, 1983)

The effect of fabrication parameters (coating matrix, surface area) on the release patterns of 5-fluorouracil (5-FU) from ethylene–vinyl acetate (EVA) copolymer matrices was studied. Coating the matrix with an additional layer resulted in slower drug release and different release patterns. Decreasing the surface area available for release to one-half produced a proportionate decrease in the release rate.

Studies were also carried out to determine the effect of the release environment (temperature, pH). The release rate increased with increase in temperature. On the other hand, the release characteristics of the copolymer matrix were unaffected by pH in the physiological range of pH values.

Keywords——ethylene–vinyl acetate copolymer; 5-fluorouracil; controlled release; coating effect; surface area effect; temperature effect; pH effect

In the previous papers, an ethylene–vinyl acetate (EVA) copolymer was evaluated as a carrier for controlled release of prednisolone[3)] and 5-fluorouracil (5-FU).[4,5)] It was demonstrated that the release rate of drugs could be easily controlled by modifying the ethylene/vinyl acetate ratio in the copolymer matrices. *In vivo* studies also indicated that implantation of EVA copolymer matrices containing 5-FU may be effective in cancer chemotherapy.[5)]

In order to obtain maximum efficiency of this polymeric system, it seemed desirable to elucidate the effect of some experimental variables on the release process. In the present study, we attempted to investigate the effect of fabrication parameter (coating, surface area) and the release environment (temperature, pH) on the release of 5-FU.

Experimental

Materials——5-Fluorouracil (5-FU) was obtained from Sigma Chemical Co., St. Louis, and was used without further purification. An ethylene–vinyl acetate copolymer (EVAFLEX) containing 33% w/w vinyl acetate was a gift from Mitsui Polychemical Co., Tokyo.

Matrix Preparation——A weighed amount of drug powder was dispersed in 20 ml of methylene chloride in a glass vial. EVA copolymers (1 g) were dissolved in the drug suspension at 50 °C. 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 placed in a steel mold and melt-pressed at 100 °C under 500 kg/cm^2 pressure for 2 min. Then, matrices were cut from the membrane and 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*. The mean thickness of the drug-free EVA copolymer layer was 0.02 cm.

For studying the effect of surface area on drug release, one surface of the planar matrices was covered with aluminum tape. Only the exposed surface (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 each placed in a 20 ml vial containing 5 ml of distilled water, unless otherwise stated. The drug release was followed with shaking at a rate of 60 strokes/min on an incubator at 37 °C. Each matrix was successively transferred to fresh vials containing 5 ml of distilled water. The amount of 5-FU released from the EVA copolymer matrix was measured spectrophotometrically at 266 nm. Data shown in the figures are averages of at least three experimental runs and the results were satisfactorily reproducible.

Results and Discussion

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 acetate was investigated.[5] The vinyl acetate content of EVA copolymer was varied from 8 to 40% w/w. An increase in vinyl acetate comonomer content increased the drug release rate from the polymer matrix. The effect of altering the drug content on the release rate was also tested by using four concentrations of 5-FU (1.9, 3.7, 5.1, and 9.3 mg per matrix). Increase in drug content increased the drug release rate, as expected from Higuchi's equation.[6]

Factors determining the rate of drug release are particularly important in the design and formulation of controlled release preparation. Thus, it is necessary to determine what factors control the release kinetics. We have also begun to examine other fabrication parameters (coating, surface area) that affect the drug release.

The effect of coating the matrices with an additional polymer layer was examined. A matrix with a copolymer of 33% w/w vinyl acetate content was prepared as described previously[5] and the release patterns of uncoated matrix and matrix coated with 20% w/v polymer solution were compared. As shown in Fig. 1, coating the matrix with an additional polymer layer resulted in slower drug release and different release patterns. A twofold difference in release rate, determined from the slope in mg/d, was observed between uncoated samples and samples coated with 20% w/v polymer solution. There appeared to be a release

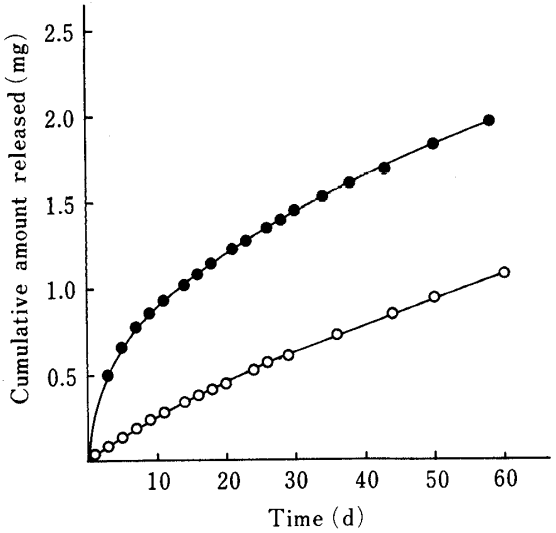

Fig. 1. Effect of Coating on the 5-FU Release from EVA Copolymer Matrix with 33% w/w Vinyl Acetate Content at 37 °C (13.1 mg of 5-FU per Matrix)

●, uncoated matrix; ○, matrix coated with 20% w/v copolymer solution.
The size of the matrix used was 1.1 × 1.4 × 0.2 cm. The volume of the release medium was 10 ml.

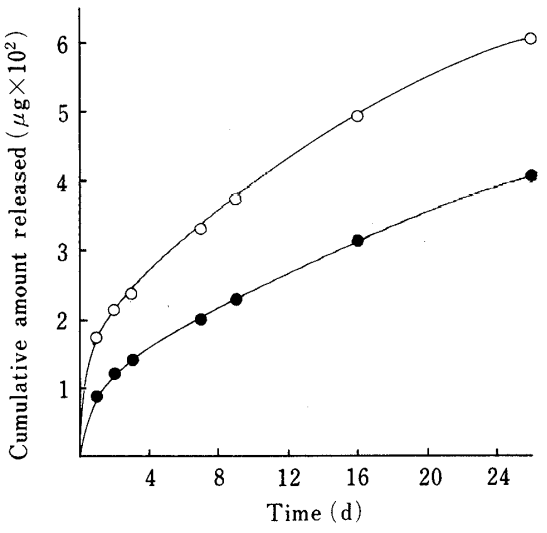

Fig. 2. Effect of Surface Area on the 5-FU Release from EVA Copolymer Matrix with 33% w/w Vinyl Acetate Content at 37 °C (1.3 mg of 5-FU per Matrix)

○, 2.1; ●, 1.1 cm^2.
The size of the matrix used was 1.0 × 1.0 × 0.03 cm.

period in the coated matrix that was roughly linear with respect to time (zero-order rate). These effects may be due to the reduced amount of drug on the matrix surface. Thus, a coating can also be used to control drug release kinetics.

The surface area of the drug delivery matrices also affected the drug release rate (Fig. 2). 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 decrease in 5-FU release. Fick's law of diffusion can be applied to explain this relation.[7]

The release rate of 5-FU from the EVA copolymer matrix can be varied significantly by manipulating four fabrication parameters, *i.e.*, coating the matrix and altering the surface area as well as varying the monomer content and drug content in the matrix.[8] Matrices able to provide a controlled release of 5-FU could be made simply by altering the fabrication parameters of the matrix.

Since EVA copolymer is available for clinical use as a carrier for implanted, inserted, or surface-applied drug delivery devices, we have also examined the effect of the release environment (temperature, pH) on drug release.

The dependency of the drug release profile on temperature is illustrated in Fig. 3. The cumulative amount of drug released (Q) is plotted *versus* the square root of time ($t^{1/2}$).[6] After an initial period of drug release, the 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 5 to 26 d. The higher the temperature, the greater the drug release $Q/t^{1/2}$ values. The $Q/t^{1/2}$ values at 20, 30, and 37 °C were 11.80, 37.89, and 55.56 $\mu g/cm^2/d^{1/2}$, respectively. It should be noted that the rate of drug release increased 4.7-fold 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 EVA copolymer matrix is an energy-linked process.[9]

The activation energy of release, as determined from the slope of a plot of $\log Q/t^{1/2}$ *versus* the reciprocal of the absolute temperature, was 16.7 kcal/mol. The linear increase in release with increasing temperature suggests that the release characteristics of the copolymer would change over the body temperature range. This finding indicates that special precautions

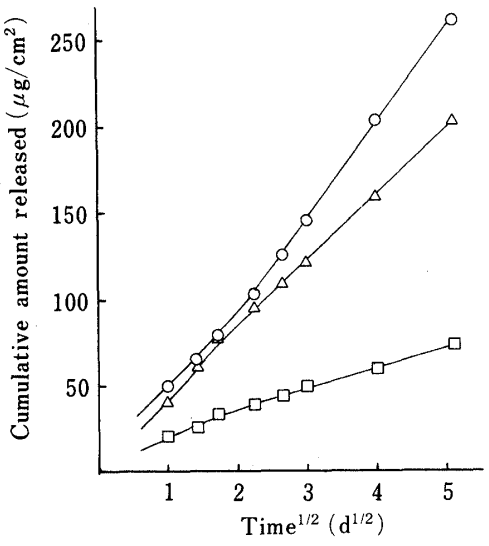

Fig. 3. Effect of Release Media Temperature on the 5-FU Release from EVA Copolymer Matrix with 33% w/w Vinyl Acetate Content (1.3 mg of 5-FU per Matrix)

□, 20; △, 30; ○, 37 °C.
The size of the matrix used was 1.0 × 1.0 × 0.03 cm.

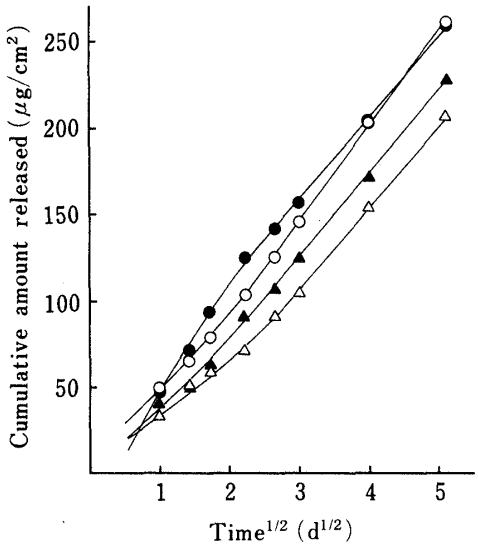

Fig. 4. Effect of Release Media pH on the 5-FU Release from EVA Copolymer Matrix with 33% w/w Vinyl Acetate Content at 37 °C (1.3 mg of 5-FU per Matrix)

○, water; △, pH 6.0; ●, pH 7.3; ▲, pH 8.0.
The size of the matrix used was 1.0 × 1.0 × 0.03 cm.

should be taken with regard to monitoring body temperature in practical applications.

The effect of pH on the release patterns was examined in water and 1/15 M phosphate buffer media with different pH values. The results are shown in Fig. 4. No difference was observed in the buffer media; the $Q/t^{1/2}$ values of steady-state release at pH 6.0, 7.3, and 8.0 were 47.30, 47.01, and 48.34 $\mu g/cm^2/d^{1/2}$, respectively. The release rate in water ($Q/t^{1/2} = 55.56\,\mu g/cm^2/d^{1/2}$) was slightly larger than that in the buffer media. Thus, the release characteristics of the copolymer matrix should not change significantly in the physiological range of pH values.

Acknowledgement The authors are grateful to Mitsui Polychemical Co. for the supply of ethylene–vinyl acetate copolymer (EVAFLEX).

References and Notes

1) Pharmaceutical Application of Biomedical Polymers, Part X. Part IX: S. Miyazaki, S. Takeuchi, M. Sakamoto, and M. Takada, *Chem. Pharm. Bull.*, **31**, 3707 (1983).
2) Present address: *Taisho Pharmaceutical Co., 1–403 Yoshino-cho, Omiya, Saitama 330, Japan.*
3) S. Miyazaki, K. Ishii, and T. Nadai, *Chem. Pharm. Bull.*, **29**, 2714 (1981).
4) S. Miyazaki, K. Ishii, and M. Takada, *Yakuzaigaku*, **42**, 259 (1982).
5) S. Miyazaki, K. Ishii, K. Sugibayashi, Y. Morimoto, and M. Takada, *Chem. Pharm. Bull.*, **30**, 3770 (1982).
6) T. Higuchi, *J. Pharm. Sci.*, **50**, 874 (1961).
7) R. E. Lacey and D. R. Cowsar, "Controlled Release of Biologically Active Agents," ed. by A. C. Tanquary and R. E. Lacey, Plenum Press, New York, 1974, pp. 118—123.
8) N. Ueno, M. F. Refojo, and L. H. S. Liu, *J. Biomed. Mater. Res.*, **16**, 669 (1982).
9) Y. W. Chien and E. P. K. Lau, *J. Pharm. Sci.*, **65**, 488 (1976).