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Factors Affecting the Rate of Release of 5-Fluorouracil from Ethylene-Vinyl Acetate Matrices

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We have studied the effect of loading amount and particle size on the rate of release of 5-fluorouracil (5-FU) from ethylene-vinyl acetate (EVA_c) matrix. Release rate increased as the loading amount and particle size increase. We also studied the effect of additives (lactose and algin) on the rate of release of 5-FU. Both algin and lactose promoted the rate of release. The ability to increase the rate is in the order of algin>lactose>5-FU. Scanning electron microscope study clearly shows that large cavities and cracks are created. The results imply that, by the proper combinations of the amount of the additive, EVA_c and drug, the rate of drug release can be modulated over a wide range of values.

Keywords—5-Fluorouracil, Ethylene-vinylacetate, Lactose, Algin, Matrix

Introduction

In a matrix type drug delivery device, drug is dispersed homogeneously throughout the polymer matrix as either molecules or particles. There are, in general, three types of polymers used as matrix material; nondissolving, dissolving and eroding polymers.[1] The release mechanisms of drug from these matrices are diffusion, dissolution and erosion, respectively.[1] Also it can be any combination of these mechanisms.

In nondissolving, hydrophobic matrix type devices, the release of drug is dependent upon the amount of drug loaded in the matrix.[2, 3] When the amount is low and drug particles are dispersed separately in the matrix, release of drug is mainly controlled by the diffusion of drug molecules in the polymer matrix.[2] If the amount of drug particles is high enough to have close contact with each other, drug release is determined by both matrix diffusion and the diffusion through the aqueous channels formed after the drug particles are dissolved and diffused out of the matrix.[4] Aqueous cracks might also be created by the osmotic effect of the drug particles, that is, after the imbibition lof water, drug particles can produce high local swelling stresses which lead to the formation of cracks.[5] Actually the role of matrix diffusion is minimal and drug release is mainly determined by the diffusion through the aqueous channels and cracks.[1, 2]

Ethylene-vinyl acetate is a nondissolving, biocompatible copolymer which has been employed in various drug delivery systems.[3] Its usefulness as a rate controlling hydrophobic matrix material are well demonstrated in various medical fields.[6-10] Both small molecular weight compounds and large macromolecules such as proteins have been incorporated into the EVA_c matrices and the release profiles and/or mechanisms have been studied.[2-4, 11-14]

In this paper, we have investigated the factors

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which affect the release of a model drug from EVAc matrix. We used 5-FU as a model drug. We have studied such factors as loading amount and particle size. We also studied the effect of additives, such as algin and lactose, on the rate of release, and compared the results with the self-promoting effect of 5-FU itself.

Materials and Methods

Materials

Ethylene/vinyl acetate (vinyl acetate content 40%) copolymer (waxed beads, lot no. 01405TY) and 5-FU were purchased from Aldrich Chemical Co. (Milwaukee, WI, U.S.A.). β-Lactose and algin (low viscosity) were obtained from Sigma Chemical Co. (St. Louis, MO, U.S.A.). 5-FU, β-lactose and algin particles were sieved to certain size ranges, using standard sieve (Chung gye sang gong, Seoul, Korea). Methylene chloride and acetic acid were obtained from J.T. Baker Inc. (Phillipsburg, NJ, U.S.A.). Sodium 1-heptanesulphonate was obtained from MTM Research Chemicals (Morecambe, England). Sodium phosphate, monobasic and sodium phosphate, dibasic were purchased from Junsei Chemical Co. (Tokyo, Japan) and Shinyo Pure Chemicals Co. (Osaka, Japan), respectively. All the chemicals were of analytical grade and used without further purification. Water was doubly distilled and nano-filtered before use.

Matrix Preparation

EVAc copolymer (1 g) was dissolved in methylene chloride (5 m*l*) to give a 20% (w/v) solution. A weighed amount of 5-FU powder was suspended homogeneously in the polymer solution, using Super Mixer (Lab Line Instruments, Inc., Melrose Park, IL, U.S.A.). The 5-FU solution was poured onto a well-leveled glass plaste. Using Gardner knife (Gardner Laboratory, Silver Spring, Md, U. S.A.), the solution was spread evenly to a predetermined thickness. After drying overnight at room temperature, the polymer matrix was removed from the glass plate. The thickness of the matrix was determined using a digital micrometer, model CD-20 (Mitutoyo Corporation, Tokyo, Japan).

In Vitro Release Study

Release of 5-FU from the matrix was carried out by paddle stirring method, using a dissolution tester, model DST-600A (Fine Scientific Instruments, Seoul, Korea). A square shaped matrix (1 cm×1 cm) in a cylindrical cage was placed in a vessel containing 250 m*l* of 0.05 M phosphate buffer (pH 6.8) at 37℃. The vessel was covered for the duration of the release test. The speed of the paddle was 100 rpm. Sampling was casrried out at a predetermined at 254 nm using a HPLC system (Japan Spectroscopic Co., Hachioji city, Japan) with a μ-bondapak C_{18} column (Waters-Millipore, Milford, MA, U.S.A.). The mobile phase was aqueous solution of sodium 1-heptanesulphonate (5 mM) and acetic acid (5 mM).

Determination of Drug Content in the Matrix

Drug content in the matrix was determined by both calculation and experiment. Determination by calculation was done simply from the ratio of 5-FU to EVAc used in the matrix preparation. Experimental determination was made by extraction 5-FU into aqueous layer after dissolving a weighed amount of the matrix in methylene chloride, using the assay method mentioned above.

Scanning Electron Microscope Study

The surface morphology of the matrix was studied using a Hitachi scanning electron microscope (SEM), model S-2250N (Hitachi Co., Tokyo, Japan) before and after the release test. The surface was sputter coated with gold using an Hitachi ion coater, model E-101 (Hitachi, Co., Tokyo, Japan).

Results and Discussion

Determination of Drug Content in the Matrix

The loaded amounts calculated agreed well

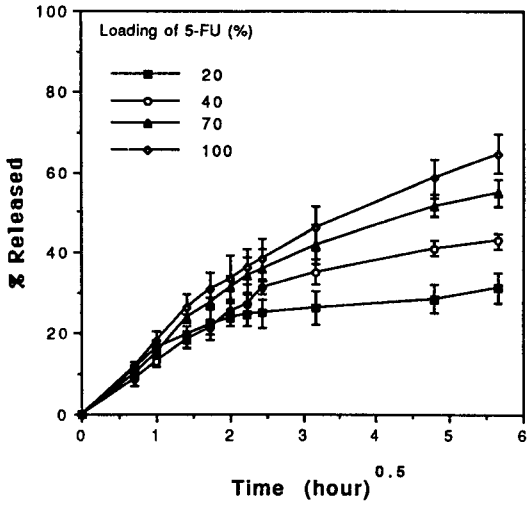

Figure 1—Effect of loading amount on the release of 5-FU from EVA_c matrix with a thickness of 0.30 ± 0.01 mm. The size of 5-FU particle used was in the rang eof 63~125 μm.

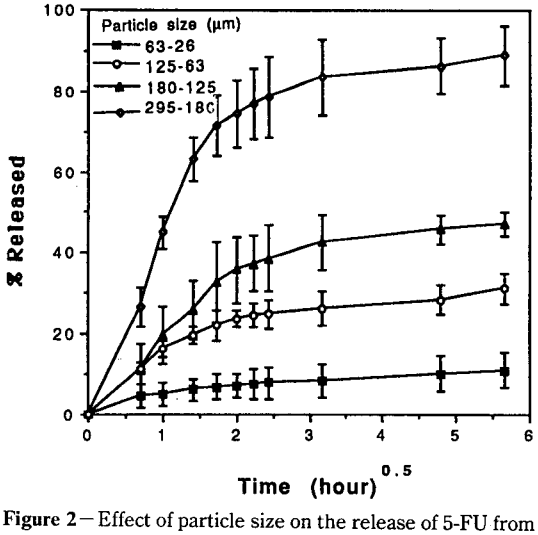

Figure 2—Effect of particle size on the release of 5-FU from EVA_c matrix with a thickness of 0.30 ± 0.01 mm. Loading of 5-FU was 20%.

with those determined by experiments. There were less than 5% difference in all cases tested. This indicates that the drug particles are homogeneously dispersed throughout the matix.

***In Vitro* Release Study**

Understanding the factors which affect the release rate is very important in the design of a controlled dosage form. We have studied such factors as loading amount and particle size. Fig. 1 shows the effect of loading amount on the release of 5-FU. The particle size of 5-FU dispersed in the matrix was 63~125 μm and the thickness of the matrix was 0.3 ± 0.01 mm. As the loading of 5-FU increases, release rate increased. In this paper, the loading % means $w/w_{polymer}$. When the loading was 20% ($W_{5\text{-}FU}/W_{EVA}$), only about 30% was released after 24 hours. Fig. 2 shows the effect of particle size. The thickkness of the matrix was 0.30 ± 0.01 mm and the loading of 5-FU was 20%. As the particle size of 5-FU increases, release rate increased. This is due to the higher chance of larger particles to touch the surface. This also explains why the % released from the matrix containing particles with size 297~180 μm is so high when compared to other cases; the thickness of the membrane is only slightly larger than particle size.

For a diffusion-controlled release of drug dispersed homogeneously in an insoluble slab-shaped matrix, Higuchi[15] proposed the equation, $Q = 2[(2A\text{-}C_s)C_sDt]^{0.5}$ where Q is the cumulative amount of drug released per unit area at time t, D is the drug diffusion coefficient in the matrix, A is drug concentration in the matrix, C_s is the drug solubility in the matrix. This eqation applies when the concentration of drug in the matrix is higher than the solubility of drug in the matrix and the drug particles are dispersed separately in the matrix. If the concentration of drug is even higher, such that drug particles can have close contact with each other, the equation should be $Q = 2[2A - \varepsilon C_{sl})C_{sl}Dt/\tau]^{0.05}$ where C_{sl} is the solubility of drug in the liquid filling the channel created by the dissipation of drug, ε and τ is the porosity and tortuosity of the matrix, respectively.[16] In any case the equations can be reduced to $Q = kt^{0.5}$ where k is a constant. Hence a plot of the amount of drug released versus the square root of time should give a linear slope. For the early period of release (first 3~4 hours), the slo-

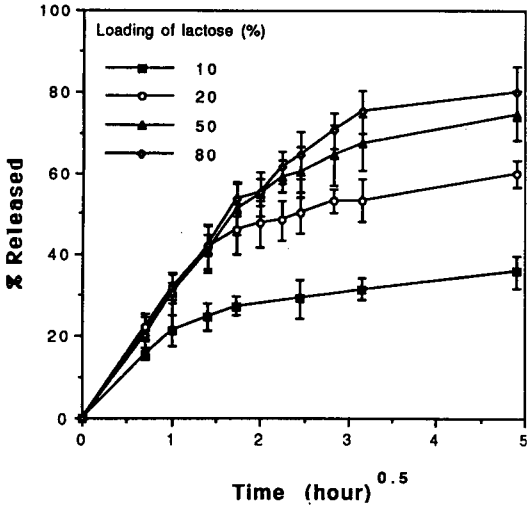

Figure 3—Effect of lactose on the release of 5-FU from EVA_c matrix. The loading of 5-FU was 20% in all cases. The size of 5-FU particle and lactose used was in the range of 63~125 μm. The thickness of the matrix was 0.30 ± 0.01 mm.

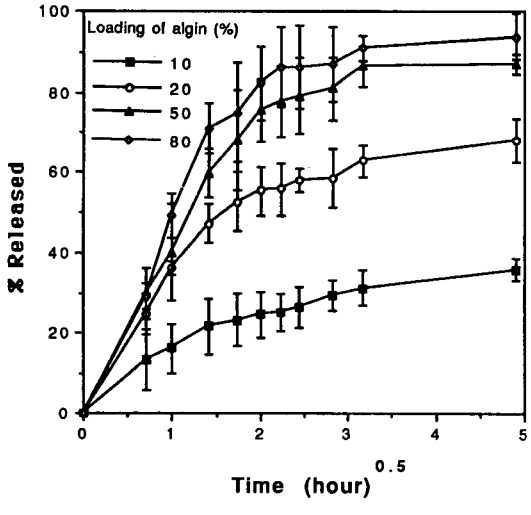

Figure 4—Effect of algin on the release of 5-FU from EVA_c matrix. The loading of 5-FU was 20% in all cases. The size of 5-FU particle and algin used was in the range of 63~125 μm. The thickness of the matrix was 0.30 ± 0.01 mm.

pes of the plots in Fig. 1 are approximately linear with respect to $t^{0.5}$ and after that release taperfed off. Similar behavior was observed in Fig. 2, except for the result of 26~63 μm.

Additives dispersed in the matrix can also alter

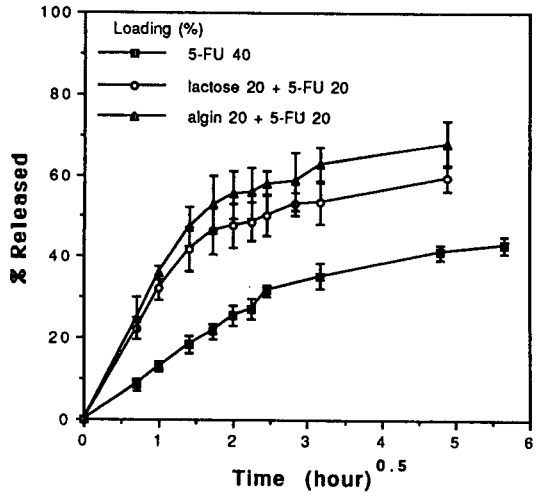

Figure 5—Comparison on the capability of increasing the release rate of 5-FU from EVA_c matrix. (data from Fig. 1, 3 and 4).

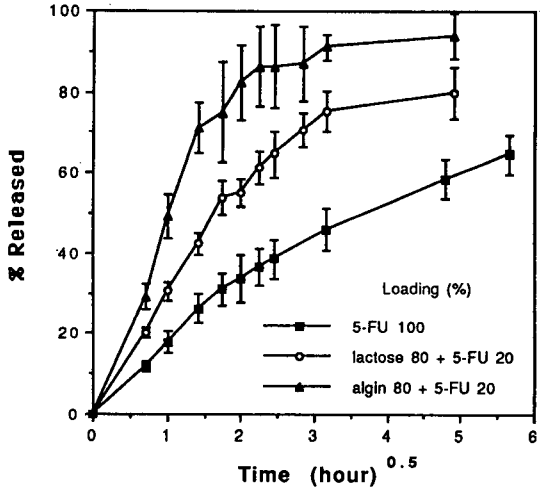

Figure 6—Comparison on the capability of increasing the release rate of 5-FU from EVA_c matrix. (data from Fig. 1, 3 and 4).

the release rate markedly. Various water soluble additives have been studied.[5, 17-19] They studied mainly silicone matrix. These additives enhanced the rate of drug release to various degree and this promoting effect can be explained by the stronger osmotic effect of these additives, as compared to that of drug itself. These additives seem to be developing aqueous cracks and cavities in the

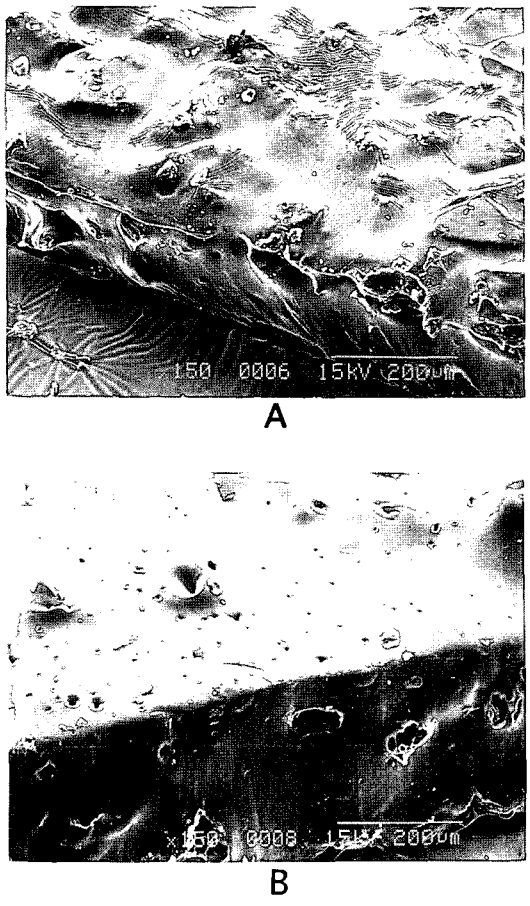

Figure 7—Surface morphology of EVA_c matrices containing 20% algin and 20% of 5-FU : (a) before release, (b) after release experiment for 24 hours.

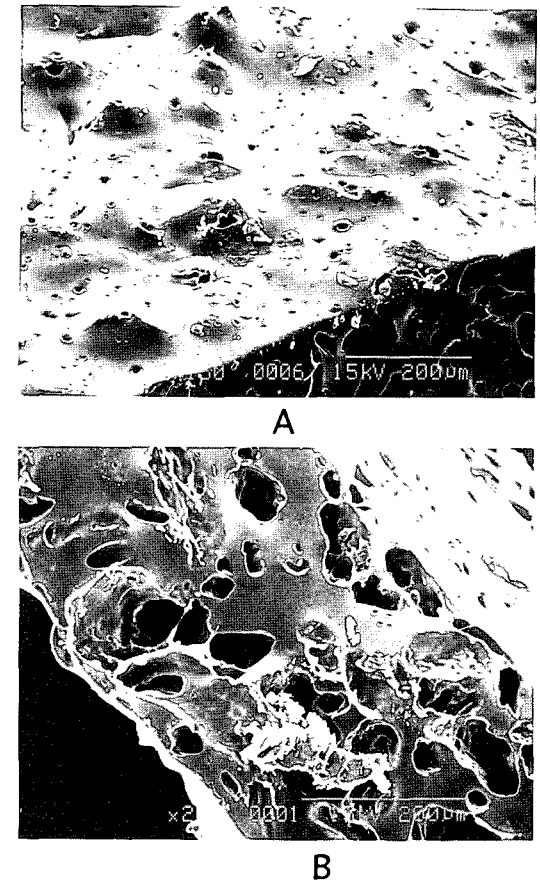

Figure 8—Surface morphology of EVA_c matrices containing 80% algin and 20% of 5-FU : (a) before release, (b) after release experiment for 24 hours.

matrix.[5] Fig. 3 and 4 show the effect of lactose and algin on the rate of release, respectively. The particle size of 5-FU, lactose and algin dispersed in the matrix was 63~125 μm and the thickness of the matrix was 0.30 ± 0.01 mm. The loading 5-FU was 20% in all cases. As the loading of lactose or algin increased, release rate increased. This can be explained by both the Higuchi equation mentioned above and the osmotic effect which may develope cracks and cavities in the matrix. The increase was larger for algin than lactose. This is shown well in Fig. 5 and 6, where the relese from matrices containing 20% and 80% ($W_{additive}/W_{EVA}$) additives are compared. the loading of 5-FU was 20% for both cases. Matrix containing 40% and 100% 5-FU are also plotted. It seems that algin is better osmotic agent than lactose and 5-FU itself. The slopes of the plots in Fig. 3 seem linear with respect to $t^{0.5}$ and until 50~60% of 5-FU was released., except for the case of lowest lactose loading. Similar pattern was observed in Fig. 4.

Scanning Electron Microscope Study

Fig. 7 shows the SEM pictures from the matrix containing 20% 5-FU and 20% algin (the matrix studied in Fig. 4). Fig. 7a is the typical morphology of surface of algin-containing matrix before release. The surface is rather rough. Fig. 7b shows

the top and side view of the matrix after release. Large pores can be observed from the side. Because the side of the matrix is in direct contact with the bathing medium during release experiment, all the drug and algin particles residing at side will be released quickly and completely, leaving pores behind. The top view shows large and small pores. The large pores seem to be created by those particles located right underneath the surface (shown in Fig. 7a as protrusions). The small pores are probably created by the osmotic effect of the dispersed particles, which produces high swelling stresses around the particles. Fig. 8 shows the SEM pictures from a matrix containing 20% 5-FU and 80% algin (the matrix studied in Fig. 4). Fig. 8a shows the top and side view of the matrix after release experiment. Large pores can be seen clearly from the side. Large and small pores can be seen from the top view and the number is much larger than those observed in Fig. 7b. One thing interesting is the debris locating around the pores. We think that these debris are the pieces of EVA_c which were pushed out by the swelling stress from inside the matrix. Fig. 8b shows the shape inside the matrix after release experiment. The picture was obtained by cutting the matrix of Fig. 8a in the middle and taking a picture of the exposed area. Large empty pores are covering most of the surface. They seem to be connected to each other and form channels.

Conclusions

We have studied the factors which affect the rate of release of 5-FU from EVA_c matrix. Such factors as loading amount, particle size and incorporation of additives were studied. The results imply that, by the proper combinations of the amount of additive, EVA_c and drug, the rate of release can be modulated over a wide range of values.

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