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# Release of 5-Fluorouracil from Ethylene-Vinyl Acetate Matrices Containing Hydrophilic Additives

**Seaung-Youl Oh†, Young-Mee Yoo, Sung-Soo Kim, Byung-Chul Shin, Soon-Hong Yuk and Hai-Bang Lee**

*Biomaterial Laboratory, Korea Research Institute of Chemical Technology, P.O. Box 107, Yusung-Gu, Taejeon 305-606, Korea*

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# 수용성 첨가제를 함유하는 에틸렌초산비닐 매트릭스로부터 5-플루오로우라실의 방출

**오승열† · 유영미 · 김승수 · 신병철 · 육순홍 · 이해방**

*한국화학연구소 생체의료고분자실*

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In our previous work, we have studied the effect of lactose and sodium alginate (SA) on the rate of release of 5-fluorouracil (5-FU) from ethylene-vinyl acetate (EVA) matrix. These hydrophilic additives promoted the rate of 5-FU release and the increase in rate was larger when SA was used. Both additives showed better ability to increase the rate than 5-FU itself. In this paper, we extended our study to another hydrophilic additive, Carbopol 940 (CP). Compared to SA or lactose, CP increased the rate of 5-FU release markedly. Release rate increased as the loading amount and the pH of the release medium increased. After release experiment, matrix volume increased up to 15 times of that before release experiment, depending on the amount of CP dispersed in the matrix and the pH of the release medium. On the other hand, the volume of the matrix containing lactose or SA decreased. The weight changes of the dry matrix before and after release experiment imply that CP is not released out of the matrix, to the contrary of lactose and SA. Scanning electron microscope study clearly showed that large cavities and pores are generated on the surface and the inside of the matrix. These results indicate that the mechanism by which CP increases the release rate is quite different from that of monomeric additives such as lactose or SA.

**Keywords**—5-Fluorouracil, Ethylene-vinyl acetate, Carbopol, Matrix, Swelling.

In a hydrophobic matrix type drug delivery device, the drug particles are dispersed homogeneously throughout the polymer matrix. The release mechanism of drug from this matrix is as follows. When the drug loading is low and drug particles are dispersed separately in the matrix, the release of drug is mainly controlled by the diffusion of drug molecules in the polymer matrix, after the water diffuses into the matrix and dissolves the drug.[1)] Diffusion through the cracks formed around the drug particles by the local osmotic stresses may also plays an important role.[2)] If the amount of drug loading is high and the drug particles are almost touching each other, drug release is determined by both matrix diffusion and the diffusion through the interconnected network of aqueous channels, which are formed by water-filled cracks or cavities left behind after the drug is released.[1,3)] In this case, the role of matrix diffusion is minimal and drug release is mainly determined by the diffusion through the aqueous channels.

Drug release from these hydrophobic matrices

† To whom correspondence should be addressed.

is usually very slow unless the loading of hydrophilic drug is high that the drug particles can have a close contact to each other. It has been shown that the rate of drug release from this matrix is affected by various factors, such as the solubility of drug in water, the amount of drug loaded, the size of the dispersed drug particles and the physical properties of the polymer, i.e., hydrophobicity and elasticity.[1,4-9] In order to increase the rate of release, osmotically active additives, such as salts and hydrophilic polymers, have been incorporated into the matrices.[3,7,10-16] In our previous paper,[17] we have studied the effect of lactose and SA on the release of 5-FU from ethylene-vinyl acetate (EVA) matrix. These hydrophilic additives promoted the rate of 5-FU release and the increase in rate was larger when SA was used. Both additives showed better ability to increase the rate than 5-FU itself.

EVA is a nondissolving, biocompatible copolymer and its usefulness as a rate controlling hydrophobic matrix material is well demonstrated in various medical fields.[18-22] Both small molecular weight compounds and large macromolecules such as proteins have been incorporated into the EVA matrices and the release profiles and/or mechanisms have been studied.[1,4,13,15,23-26]

In the present study, we extended our work to another hydrophilic additive, Carbopol 940 (CP), and tested for its potential as the enhancer for drug release, with the prospect of developing an oral matrix type delivery system. CP is a slightly-crosslinked polyacrylic acid and it forms a gel in neutral aqueous medium. It is expected that the release mechanism of 5-FU from matrices containing CP is quite different from that from matrices containing monomeric additives (SA and lactose). Drug release and matrix swelling kinetics were studied in two solutions of different pHs (1.2 and 6.8). The swelling of matrices containing lactose and SA were also studied and the data were compared with those obtained from matrices containing CP. Morphological study of the surface and the dissected area were carried out using SEM before and after release experiment.

## Experimental

### 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.. b-lactose and SA (low viscosity) were obtained from Sigma chemical Co., St. Louis, MO, U.S.A.. CP was purchased from BF Goodrich Co., NJ, U.S.A.. 5-FU, b-lactose, SA and CP 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 t-heptanesulphonate was obtained from MTM Research Chemicals, Morecambe, England. Sodium phosphate, monobasic, sodium chloride and hydrochloric acid were purchased from Junsei Chemical co., Tokyo, Japan. Sodium phosphate, dibasic, was purchased from Shinyo Pure Chemicals Co., Osaka, Japan. All the chemicals were of analytical grade and used without further purification. Water was doubly distilled and nano-filtered before use.

### Matrix Preparation

EVA copolymer (1 g) was dissolved in methylene chloride (5 m*l*) to give a 20 % w/v solution. 5-FU (200 mg) and additives (particle size 63-125 mm) were suspended homogeneously in the polymer solution, using Super Mixer (Lab Line Instruments, Inc., Melrose Park, IL, U.S.A.). This solution was poured onto a well-leveled glass plate. Using Gardner knife (Gardner Laboratory, Silver Spring, MD, U.S.A.), the solution was spread evenly to a predetermined thickness. After drying overnight at 4°C, 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). The thickness of the matrices used in the experiment is 0.32±0.02 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 weight proportion of 5-FU in the matrix. Experimental determination was made by extraction of 5-FU into aqueous layer after dissolving a weighed amount of the matrix in methylene chloride, using the assay method mentioned below.

**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 ml of 0.05M phosphate buffer (pH 6.8) or 0.05M hydrochloric acid solution (pH 1.2) at 37°C. The vessel was covered for the duration of the release test. The speed of the paddle was 100 rpm. Sampling was carried out at a predetermined time interval and the concentration of 5-FU was determined 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).

**Matrix Swelling and Weight Change Study**

In a separate experiment, we also studied the change in matrix weight with time. Experimental setup is the same as described in the in vitro release study. At a predetermined time interval, sample was taken out of the vessel, dried by blotting using Kimwipes and weighed. The volume of the matrix was also determined before and after experiment, by measuring the x-y-z dimension of the matrix using a digital micrometer (model CD-20, Mitutoyo Corporation, Tokyo, Japan). The weight of the dry matrix after release experiment was also measured after freeze-drying (Dura-Dry, FTS Systems Inc., Stone Ridge, N.Y. U.S.A.).

**Scanning Electron Microscope Study**

The surface morphology of the matrix was studied using a JEOL scanning electron microscope (SEM), model JSM-840A (JEOL Ltd., Tokyo, Japan) before and after the release experiment. The surface was sputter coated with gold using an Hitachi ion coater, model E-101 (Hitachi, Co., Tokyo, Japan). Matrices after release experiment were freeze-dried before SEM study.

## Results and Discussion

**Determination of Drug Content in the Matrix**

The loading amounts calculated agreed well with those determined by experiments. There were less than 3% difference in all cases tested indicating that the drug particles are homogeneously dispersed throughout the matrix.

**In Vitro Release and Swelling Study**

Understanding the factors which affect the release rate is very important in the design of a controlled dosage form. It has been reported that such factors as particle size, loading amount and the thickness of the matrix affect the rate of drug release. Because the rate of drug release from hydrophobic matrices is usually very slow, various water soluble additives have been used to increase the rate of release.[5,17-19] 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 matrix.[5] In our previous study,[17] as hydrophilic additives, we used lactose and SA to increase the rate of release of 5-FU from EVA matrix. These hydrophilic additives promoted the rate of release and the in-

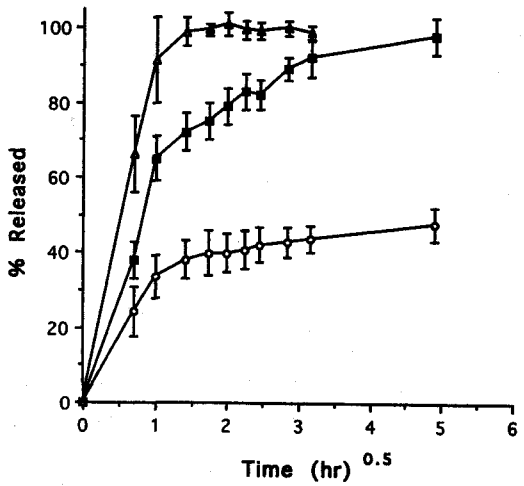


**Figure 1**—Release of 5-FU from EVA matrices containing different amount of CP. The release medium was 0.05 M phosphate buffer solution (pH 6.8). The loading of 5-FU was 20 % in all cases.
key: : 10 %, : 20 %, : 50 %.

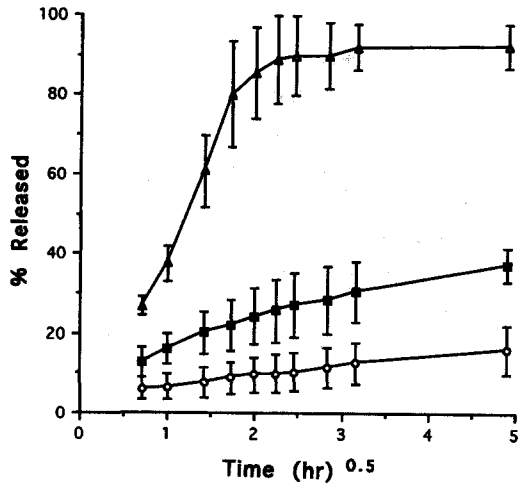


**Figure 2**—Release of 5-FU from EVA matrices containing different amount of CP. The release medium was 0.05 M hydrochloric acid solution (pH 1.2). The loading of 5-FU was 20 % in all cases.
key: : 10 %, : 20 %, : 50 %.

crease in rate was larger when SA was used. Both additives showed better ability to increase the rate than 5-FU itself. However the increase in release rate using these additives was not enough to release the drug completely in a short time period (for example; several hrs). To achieve this goal, we incorporated CP as a rate controlling additive, which forms a hydrogel in aqueous medium at neutral pH.

Figure 1 shows the effect of CP on the release of 5-FU in pH 6.8 phosphate buffer solution. As the loading (%) of CP increases, release rate increased. In this paper, the loading (%) means the weight ratio between additive (or 5-FU) and EVA (Wadditive/WEVA). When the loading was 10%, only about 40% was released in 4 hrs and then the release was very slow. At 20% loading of CP, more than 60% was released in an hr and complete release was achieved in 24 hrs. Marked increase in release rate was observed when 50% was loaded in the matrix. In 2 hrs, 100% release of 5-FU was observed. Release of 5-FU in pH 1.2 solution is shown in Figure 2. Compared to the release in pH 6.8 solution, the rate was much slower. When the

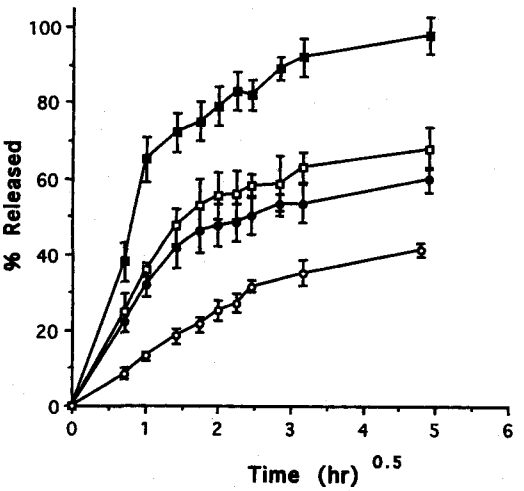


**Figure 3**—Comparison on the capability of increasing the release rate of 5-FU from EVA matrices. The release medium was 0.05 M phosphate buffer solution (pH 6.8). The loading of 5-FU was 20 % in all matrices containing additives. Data on 5-FU, lactose and SA are borrowed from our previous paper.[17]
key: : 5-FU 40 %, : lactose 20 %, : SA 20 %, : CP 20 %.

loading of CP was 20%, less than 40% was released after 24 hrs in pH 1.2 solution, whereas more than 90% was released in pH 6.8 solution. In Figure 3 and 4, the release of 5-FU from matrices containing 20% and 50% additives are

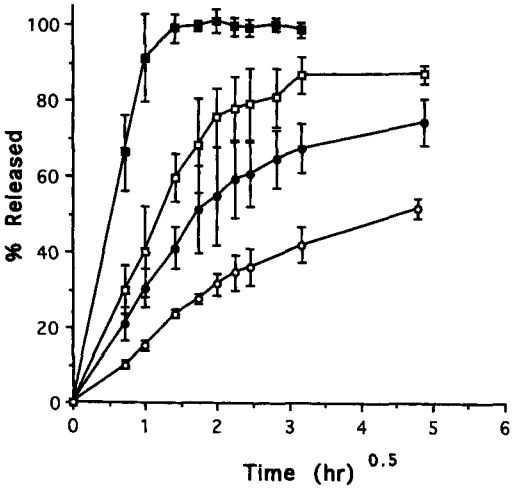


**Figure 4**—Comparison on the capability of increasing the release rate of 5-FU from EVA matrices. The release medium was 0.05 M phosphate buffer solution (pH 6.8). The loading of 5-FU was 20 % in all matrices containing additives. Data on 5-FU, lactose and SA are borrowed from our previous paper.[17]
key: ; 5-FU 70 %, ; lactose 50 %, ; SA 50 %, ; CP 50 %.

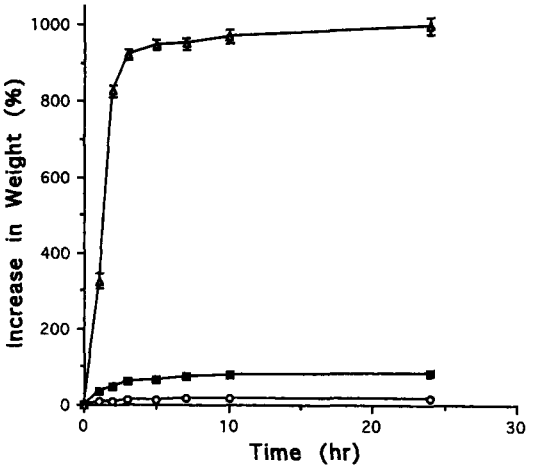


**Figure 5**—The increase in matrix weight with time in 0.05 M phosphate buffer solution (pH 6.8). Matrices containing 10, 20 and 50 % CP were studied. The loading of 5-FU was 20 % in all cases.
key: ; 10 %, ; 20 %, ; 50 %.

**Table I**—*Volume and Weight Change after Release Experiment for 24 Hours in 0.05 M Phosphate Buffer Solution (pH 6.8) at 37°C. Data is Expressed as the Percentage of the Weight and Volume of Matrix before Release Experiment. Matrices with 10, 20 and 50% of CP Loading are Studied. The Loading of 5-FU is 20% in All Samples.*

| Changes in volume and weight after release experiment (%) | CP 10% | CP 20% | CP 50% |
|---|---|---|---|
| Volume (before freeze drying) | +69 | +225 | +1150 |
| Weight (before freeze drying) | +18 | +86 | +995 |
| Weight (after freeze drying) | -7 | -12 | +1 |
| *Weight fraction of 5-FU in matrix before release experiment | +15 | +14 | +12 |

compared. The loading of 5-FU is 20% in all cases. The release from matrix containing 40% or 70% of 5-FU is also plotted. Compared to SA, lactose or 5-FU itself, the ability of CP to increase the release rate was much larger.

The swelling of matrices in pH 6.8 solution is shown in Figure 5. The changes in volume and weight are summarized in Table I. The degree of swelling is expressed as the increase in matrix weight (in percentage of the weight of dry matrix before release experiment). When the loading of CP was 10%, 18 and 69% increase in weight and volume, respectively, were observed after 24 hrs in the release medium. This 18% increase in weight was reached in about 10 hrs. When the loading of CP was 20%, 86 and 225% increase in weight and volume were observed after 24 hrs. Marked increase in weight and volume was observed when the loading of CP was 50%. In about 3 hrs, nearly 10 to 11 fold increase in volume and weight was observed. The change in weight after freeze-drying of the swollen matrix is also shown in Table I. When the loading of CP was 10%, 7% loss in weight was observed. The weight fraction of 5-FU in the matrix before release experiment was 15%. Because 45% of 5-FU is released after 24 hrs, weight decrease should be about 7%. This result suggests that CP is not released to the medium. When the loading was 20%, 12% decrease in weight was observed. Because 100% of 5-FU was released in 24 hrs, the weight de-

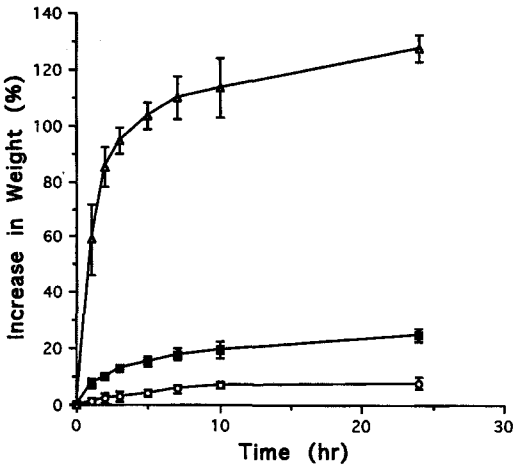


**Figure 6**—The increase in matrix weight with time in 0.05 M hydrochloric acid solution (pH 1.2). Matrices containing 10, 20 and 50 % CP were studied. The loading of 5-FU was 20 % in all cases. key: : 10 %, : 20 %, : 50 %.

**Table II**—*Volume and Weight Change after Release Experiment for 24 Hours in 0.05 M Phosphate Buffer Solution (pH 6.8) at 37°C. Data is Expressed as the Percentage of the Weight and Volume of Matrix before Release Experiment. Matrices Loaded with 180% of Lactose, 120% of SA and 50% of CP are Studied. The Loading of 5-FU is 20% in All Samples.*

| Changes in volume and weight after release experiment (%) | Lactose 180% | SA 120% | CP 50% |
|---|---|---|---|
| Volume (before freeze drying) | -33 | -30 | +1150 |
| Weight (before freeze drying) | -35 | +16 | +995 |
| Weight (after freeze drying) | -65 | -58 | +1 |
| *Weight fraction of (additive+5-FU) before release experiment | 67 | 58 | +41 |

crease is expected to be 14%, which is the weight fraction of 5-FU in the matrix before release experiment. The actual weight loss was 12%. This discrepancy is probably originated from the incomplete freeze-drying, due to the strong hydrophilicity of the ionized carboxyl groups and ions around them. Similar trend was observed when the CP loading was 50%. The discrepancy in weight loss between calculated value and measured value is larger in this case (13%) than the previous case (2%), probably due to the increased amount of CP in the matrix.

The swelling of matrices in pH 1.2 solution is shown in Figure 6. Swelling was much slower in all matrices, when compared to that in pH 6.8 solution. When the loading of CP was 10%, 8 and 46% increase in weight and volume, respectively, were observed after 24 hrs in the release medium. The increase in weight and volume was 25% and 91%, when the loading of CP was 20%. When the loading of CP was 50%, 128 and 144% increase in weight and volume were observed after 24 hrs. This increase is only about 13% of that observed in pH 6.8 solution. The pH dependence of swelling and drug release is due to the carboxyl group in the CP. The ionization of carboxyl group at neutral pH induces the swelling of the matrix, and thus increases the rate of drug release.[27]

In order to test whether additives other than CP can be released from the matrix to the release medium, we further studied the changes in weight and volume after release experiment using matrix containing lactose (180%) or SA (120%). The results are shown in Figure 7 and Table II, together with the result from the matrix containing 50% of CP. When lactose was the additive, the volume and weight of the matrix decreased 33 and 35%, respectively, after release experiment for 24 hrs. After freeze-drying of the matrix, the weight decreased 30% further (total 65% decrease). This value (65%) is very close to the weight fraction of lactose and 5-FU before release experiment (67%). When SA was the additive, the volume decreased 30 %. However the weight increased 16 %, due to the inbibition of water into the matrix. The decrease in weight after freeze-drying was 58% and this value is also very similar to the weight fraction of SA and 5-FU before release experiment. When CP was incorporated into

the matrix, the weight increased slightly (1%), after freeze-drying. If CP is released out of the matrix, there should be a 41% decrease in weight, which is the weight fraction of CP and 5-FU in the matrix. These results strongly indicate that lactose and SA are released from the matrix, whereas CP is not. This conclusion can be further supported by the rehydration experiment of the freeze-dried matrix with 50% CP loading. When the matrix is rehydrated, it returns back to the same weight as that before freeze-drying.

These results and indications suggest that CP is different from other monomeric additives (lactose and SA) in its mechanism of increasing the rate of release. 5-FU molecules are released from the matrix by the diffusion through the aqueous channels and cracks. When lactose and SA particles are released out of the matrix, they leave large pores behind. These pores can form aqueous channels through which the drug can diffuse out. Hence they work as the pore forming agents. As these additives leave the matrix, the volume and weight of the matrix decrease, as shown in Table II and Figure 7. CP, on the other hand, increases the volume of the matrix markedly. It works as a strong osmotic agent. CP particles are not released from the matrix, because they are very large in size (cross-linked polyacrylic acid) and, furthermore, they swell up in the matrix. This volume increase by swelling causes large stresses to the chains around them, and thus induces marked increase in porosity and decrease in tortuosity.[8]

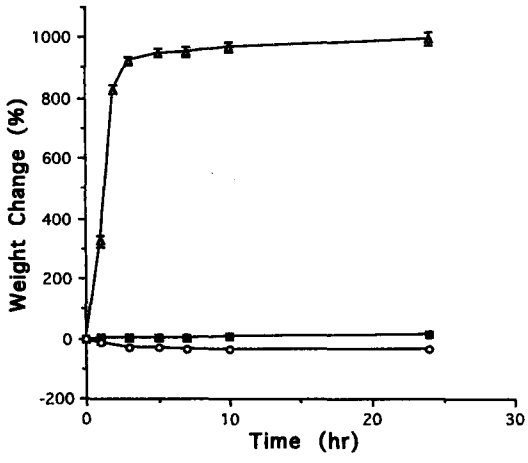


**Figure 7**—The change in matrix weight with time in 0.05 M phosphate buffer solution (pH 6.8). Matrices containing lactose, SA and CP were studied. The loading of 5-FU was 20 % in all cases.
key: : lactose 180 %, : SA 120 %, : CP 50 %.

**Scanning Electron Microscope Study**

Figure 8 shows the SEM pictures from the matrix containing 50% CP. Figure 8a shows the morphology of the surface before release experiment. The surface seems smooth without notable structures. This is the typical surface shape of all matrices prepared in this work. Figure 8b shows the surface shape of the matrix containing 50% CP after release experiment in pH 1.2 solution. Numerous pores with various sizes (several μm to 40 mm) are created on the surface. The large pores (~ 30-40 μm) seem to be created by those particles located right underneath the surface. The small pores are probably created by the osmotic effect of the dispersed particles, which produces high swelling

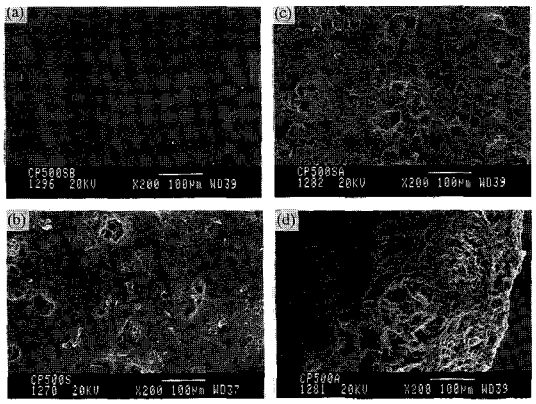


**Figure 8**—Morphology of the surface and dissected area of the matrix containing 50 % CP and 20 % 5-FU: (a) surface morphology before release experiment, (b) surface morphology after release experiment in 0.05 M hydrochloric acid solution (pH 1.2), (c) surface morphology after release experiment in 0.05 M phosphate buffer solution (pH 6.8), (d) morphology of the dissected area after release experiment in 0.05 M phosphate buffer solution (pH 6.8).

stresses. One thing interesting is the debris locating around some pores. It seems that these debris are the pieces of EVA which were pushed out, but remaining around the pores, by the swelling stress from inside the matrix. Figure 8c shows the morphology of the surface after release experiment in pH 6.8 solution. It looks quite different from that of Figure 8b. Numerous pores with larger sizes (~ 10 μm-40 mm) can be seen throughout the surface. Furthermore these pores seem to be interconnected to each other inside the matrix to form channels. The morphology of the dissected area demonstrates this point more clearly (Figure 8d). The right-hand side of Figure 8d (bright side) is the dissected area and the left-hand side (dark side) is the surface. The structure of the matrix looks similar to that of sponge. Large pores and cavities, which are connected to each other, could be seen clearly.

## Conclusions

We have studied the effect of CP on the rate of 5-FU release from EVA matrix. Compared to SA or lactose, CP increased the rate of 5-FU release markedly. After release experiment in pH 6.8, the volume of the matrix increased to 1-15 times of that before release experiment, depending on the amount of CP dispersed in the matrix. The weight change of the matrix before and after release experiment indicates that CP is not released out of the matrix, to the contrary of lactose and SA. The mechanism by which CP increases the release rate is the increase in porosity and the decrease in tortuosity, due to the marked swelling of the matrix. Release rate and the swelling of the matrix in the pH 1.2 solution were much smaller. Scanning electron microscope study clearly showed that large cavities and pores are generated on the surface and the inside of the matrix.

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