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Release behavior from hydrogen-bonded polymer gel prepared by pressurization

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ABSTRACT

Our previous research showed that a simple ultra-high pressure process made poly(vinyl alcohol) (PVA) solution into a macro-gel and nano-particles. In order to investigate the release properties of PVA hydrogels prepared by ultra-high pressure treatment, the hydrogels containing model drugs were prepared by pressurizing PVA solution with Alfa-G Hesperidin or Oil Blue N as a water-soluble or an oil-soluble model drug, respectively. In the case of oil-soluble drug, oil-in-water (O/W) emulsion, Oil Blue N-containing dodecane in PVA solution, was used by homogenization before pressurization. The average diameter and the diameter distribution of oil droplets before and after the ultra-high pressure treatment were almost the same. However, the PVA hydrogel prepared at 10,000 atm for 10 min exhibited the slowest release rate of model drugs. Thus, it was found that the release rates of model drugs from PVA hydrogel were controlled by the degree of cross-linking in the resultant gel, which was determined from the operation parameters of the ultra-high pressure treatment such as pressure, time and the concentration of PVA solution. Therefore, an ultra-high pressure process is promising for drug carrier development because of a non-harmful simple preparation process.

INTRODUCTION

A considerable number of studies have been devoted to the study of the molecular assembly technology in material processing field such as a molecular machine[1], carbon nanotube for a biological system[2] and a circuit wire[3, 4] and a drug carrier[5, 6] Molecular assembly is organized by non-covalent bonding such as electrostatic interaction, van der Waals force and hydrogen bonding. It is important for the formation of molecular assembles to control these interactions by changing intensive variables[7-9]. Therefore, we showed that pressure also be available for controlling

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the intermolecular forces to generate molecular assembles. We found that a poly(vinyl alcohol)(PVA) solution turned into a macro-gel or nanoparticles through a simple ultra-high pressure process (10,000 atm, 10 min).[10] Our results demonstrated that ultra-high pressure induces a hydrogen bonding in water, which is strong enough to maintain micro-assemblies such as gels and particles. Besides the formation of gels and nanoparticles, we found that the swelling ratio of the gels and the size of nanoparticles were easily controlled by the operative parameters in an ultra-high pressure process. Furthermore, the macro-gel prepared by this process indicated discriminating elasticity, which was never seen in the conventional PVA hydrogels.

Hydrogels are utilized in a wide variety of applications as a soft material including soft contact lens[11], shock absorption material[12], and drug carrier[13,14]. So far, several articles have been made on the drug release behavior from the PVA hydrogel prepared by physical crosslinking[15,16] or chemical crosslinking[17,18]. In these reports, they concluded that PVA hydrogels were suitable for drug delivery because of its excellent drug release characteristics and the biocompatibility. As the ultra-high pressure process does not require any harmful compound for crosslinking, we remarked the hydrogel prepared by ultra-high pressure process as a drug carrier. That is why it is important to clarify the capability of controlled release from the PVA hydrogels produced by an ultra-high pressure process.

In this article, we prepared the PVA hydrogels with the water-soluble drug or the oil-soluble drug through the ultra-high pressure process, and the drug-release behavior from the gels was investigated.

MATERIALS AND METHODS

Materials

PVA, 99.85 mol% hydrolyzed, was used without further purification. This was kindly supplied by Kuraray Co., Ltd.. We used Alfa-G Hesperidin and Oil Blue N as a water-soluble and an oil-soluble model drug, respectively. Alfa-G Hesperidin was kindly supplied by Hayashibara Biochemical Research Labolatory Co., Ltd.. Oil Blue N was purchased from Sigma-Aldrich Japan Co.. The chemical structures of Alfa-G Hesperidin and Oil blue N were indicated in Figure 1.

Preparation of cylindrical PVA hydrogels

10 or 20 w/v% PVA aqueous solutions were prepared by using autoclave. PVA aqueous solution mixed with 10 w/v% Alfa-G Hesperidin aqueous solution was treated under ultra-high pressure. The ultra-high pressure apparatus was Dr. CHEF which was made by Kobe Steel, Ltd.. The treatment conditions were as follows: the ultra-high pressure treatment condition was 6,000 – 10,000 atm, the treatment time was 1 – 60 min, and the treatment temperature was kept at 313 K at which no ice crystals were formed.[19] After the treatment, the prepared gels were cut out to the desired shape. The representative photograph of the prepared gel was shown in figure 2a. The shape of gel was cylindrical. The length was 10 mm and the diameter was 5 mm.

Dodecane solution dissolving 0.1 w/v% Oil Blue N was mixed with 10 w/v% PVA aqueous solution. The solution was homogenized for 10 min at 6,000 rpm to prepare o/w emulsions with a homogenizer. After that, the emulsion

solution was treated under ultra-high pressure. The ultra-high pressure treatments were carried out by 6,000 – 10,000 atm for 1 – 60 min at 313 K. The typical prepared gel was shown in figure 2b. The diameter of dodecane droplets was measured under a microscope before and after ultra-high pressure treatment.

Evaluation of the model drug release behavior from the gels

The release behavior of water-soluble model drug from the PVA hydrogel was evaluated in ultra-pure water. The hydrogel in the vial with ultra-pure water was placed in the thermostatic water bath at 303 K. The solution was shaken at 100 spm to keep concentration constant. Samples were withdrawn at the predetermined intervals for measuring the amount of the released Alfa-G Hesperidin. The concentration of Alfa-G Hesperidin in a sample was determined by measuring the absorption at the wavelength of 282.5 nm with UV-Vis spectrophotometer (U-2000A, Hitachi Ltd.).

The release behavior of oil-soluble model drug from the PVA hydrogel was evaluated in ethanol solution.[20] The hydrogel in the vial with ethanol solution was placed in the thermostatic water bath at 303 K. The solution was shaken at 100 spm to keep concentration constant. The released Oil Blue N was determined by measuring the concentration of Oil Blue N in the collected samples at the predetermined intervals at 642.5 nm with UV-Vis spectrophotometer.

The release data were shown with a Higuchi plot, cumulative amount of released drug vs. the square root of the duration time ($hr^{0.5}$).[21] It was available with the estimation of an initial drug release rate because the release data in the early stages were proportional to the root of the duration time.

RESULTS AND DISCUSSION

Release behavior of Alfa-G Hesperidin from the gels

The PVA hydrogels, as shown in figure 2a, were obtained in the case that the PVA aqueous solution dissolving Alfa-G Hesperidin was treated under the ultra-high pressure. The prepared PVA hydrogels were uniformly yellowish, which is based on Alfa-G Hesperidin, so that Alfa-G Hesperidin was homogeneously distributed in hydrogels. The PVA hydrogels with Alfa-G Hesperidin prepared in this study were of elastic and flexible as well as the gel without any solutes.

Figure 3 shows the release behavior of Alfa-G Hesperidin from the PVA hydrogels. We found that Alfa-G Hesperidin, the water-soluble model drug, was completely released from 5 w/v% PVA gel within about 3 hours. However, the complete release of Alfa-G Hesperidin from 10 w/v% PVA gel took for about 12 hours. This delay in the release behavior of water-soluble compound is caused by the dense polymer network in 10 w/v% PVA gel.

The release rate was estimated from the initial slopes in figure 3 and was shown in figure 4. The release rates from the hydrogels treated at higher pressure (9,000 – 10,000 atm) were lower than that from the hydrogel treated under 8,000 atm because the treatment at a higher pressure enhanced crosslinking in the polymer network and induced more elastic and stronger hydrogel. Whereas, the treatment time in ultra-high pressure process at 8,000 atm hardly affected the release rates of Alfa-G Hesperidin. Generally, the release behaviors are affected by the crosslinking density in the gels, and which is derived from the swelling ratio of the gels. In our previous report, we found that the swelling ratio of PVA hydrogels prepared by ultra-high pressurization was decreased with increasing the pressure

and was constant when applying a fixed pressure (> 6,000 atm) for more than 10 minutes[10]. Since these drug-release behaviors indeed correspond to the crosslinking state in the gels, the treatment pressure plays most important role in the operation parameters of ultra-high pressure treatment to control the release rate from the gel. The effect of PVA concentration on the release property was found to be significant; the release rates from 10 w/v% PVA gels were approximately half of those from 5 w/v% PVA gels. From the result shown in figure 3 and 4, the effect of the treatment pressure and treatment time on the release rate of Alfa-G Hesperidin was smaller than that of PVA concentration.

Release behavior of Oil Blue N from the gels

The PVA hydrogel with dodecane droplets was obtained by ultra-high pressure treatment (Figure 2b). Figure 5 shows the o/w emulsion droplets dissolving Oil Blue N in solution and that in the PVA hydrogel prepared by ultra-high pressure treatment. Figure 6 shows the diameters and the coefficients of variation(CV) of dodecane droplets before/after the ultra-high pressure treatment. Dodecane droplets were stably dispersed in the media. According to figure 6, it was found that the average diameter and the diameter distribution before and after the ultra-high pressure treatment were almost the same. Under an ultra-high pressure, the volumes of oil and water phase seem to be decreased, and the density and the concentration of the solution were enhanced. Such a condition may involve the droplet instability through the interfacial tension change. In fact, however, we observed no droplet coalescence in the gels. This result suggests that homogeneously hydrophobic drug-dispersed hydrogel was prepared by an ultra-high pressure process if the stable O/W emulsion was obtained in PVA solution.

The release behavior of Oil Blue N was shown in figure 7. It was clear that the release behavior was almost the same over a wide range of the treatment pressure and treatment time. The release rates from this PVA hydrogels was about 75 ($hr^{-0.5}$), which was slightly higher than those from the hydrogels. This difference on the release rate between water-soluble and oil-soluble model drug may suggest the diffusion resistance of a drug in PVA matrix. That is, Alfa-G Hesperidin was incorporated in PVA hydrogel matrix by the hydrogen bonding which was formed between hydroxyl groups of Alfa-G Hesperidin and those of PVA. Therefore, the release rate of an oil-soluble model drug from PVA hydrogels was slightly higher than that of a water-soluble model drug from PVA hydrogels.

In addition, the effects of ethanol concentration on the release rate of a model drug were shown in figure 8. As seen in this figure, the release rate of Oil Blue N from PVA hydrogel increased with increasing ethanol concentration in the solution. In the case of water (0 wt% ethanol) used as the medium, no release of Oil Blue N was observed. According to the results shown in figure 7 and 8, it was supposed that the diffusion of ethanol into hydrogel was a predominant step for the release of an oil-soluble drug.

CONCLUSIONS

As the PVA solution dissolving a water-soluble model drug or dispersing an oil-soluble model drug was treated under the ultra-high pressure, the hydrogel was obtained. It was found that the release rate of each model drug from PVA hydrogel was controlled by the operation parameters of ultra-high pressure treatment such as pressure, time and the concentration of PVA solution. The average diameter and diameter distribution of dodecane droplets before and after the ultra-high pressure treatment were almost the same. Thus we expect this technique as the preparation

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technique of innocuous sustained release materials.

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FIGURE LEGENDS

Figure 1. Chemical structures of model drugs: a) Alfa-G Hesperidin, b) Oil blue N

Figure 2. Photograph of the PVA gel prepared by ultra-high pressure treatment (10,000 atm, 10 min, 313 K). a) PVA gel with 5 w/v% Alfa-G Hesperidin, water-soluble model drug. PVA concentration was 10 w/v%. b) PVA gel with 0.1 w/v% Oil Blue N, oil-soluble model drug. PVA concentration was 10 w/v%.

Figure 3. Release behavior of Alfa-G Hesperidin from PVA hydrogels. 5 w/v% PVA solution with 5 w/v% Alfa-G Hesperidin solution was treated under conditions such as (●)10,000 atm, 10 min, (■)9,000 atm, 10 min, (▲)8,000 atm, 10 min, (▼)8,000 atm, 20 min. 10 w/v% PVA solution with 5 w/v% Alfa-G Hesperidin solution was treated under conditions such as (○)10,000 atm, 10 min, (□)9,000 atm, 10 min, (Δ)8,000 atm, 10 min, (▽)8,000 atm, 20 min.

Figure 4. The release rate constants of Alfa-G Hesperidin from PVA hydrogels derived from the initial slopes of released curve of Alfa-G Hesperidin from PVA hydrogels. Compositions of gels are as follow: 5 w/v% PVA and 5 w/v% Alfa-G Hesperidin (*white bar*), 10 w/v% PVA and 5 w/v% Alfa-G Hesperidin (*black bar*).

Figure 5. Photographs of o/w emulsion droplets. a) in solution (before pressurization). b) in PVA hydrogel (after pressurization).

Figure 6. Diameter distributions of dodecane droplets before/after ultra-high pressure treatment.

Figure 7. Release behavior of Oil Blue N from 10 w/v% PVA hydrogels in ethanol. Pressurized conditions are (○)10,000 atm, 10 min, (□)9,000 atm, 10 min, (Δ)8,000 atm, 10 min, (▽)8,000 atm, 20 min, (◊)8,000 atm, 60 min.

Figure 8. Effect of ethanol concentration on the release rates. All hydrogels were prepared by pressurization (Treatment condition: 10,000 atm, 10 min). Ethanol concentrations are as follows. (○)100 wt%, (□)75 wt%, (Δ)50 wt%, (▽)25 wt%, (◊)0 wt%.

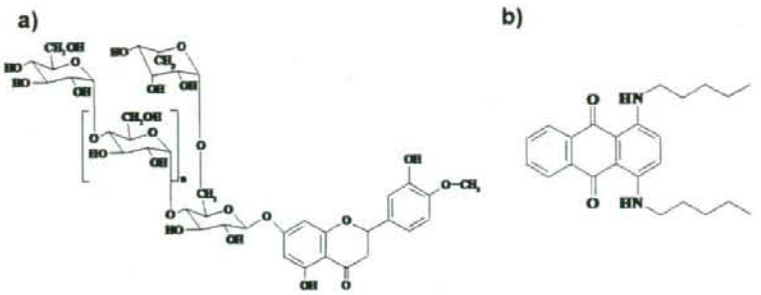

Figure 1. Chemical structures of model drugs: a) Alfa-G Hesperidin, b) Oil blue N
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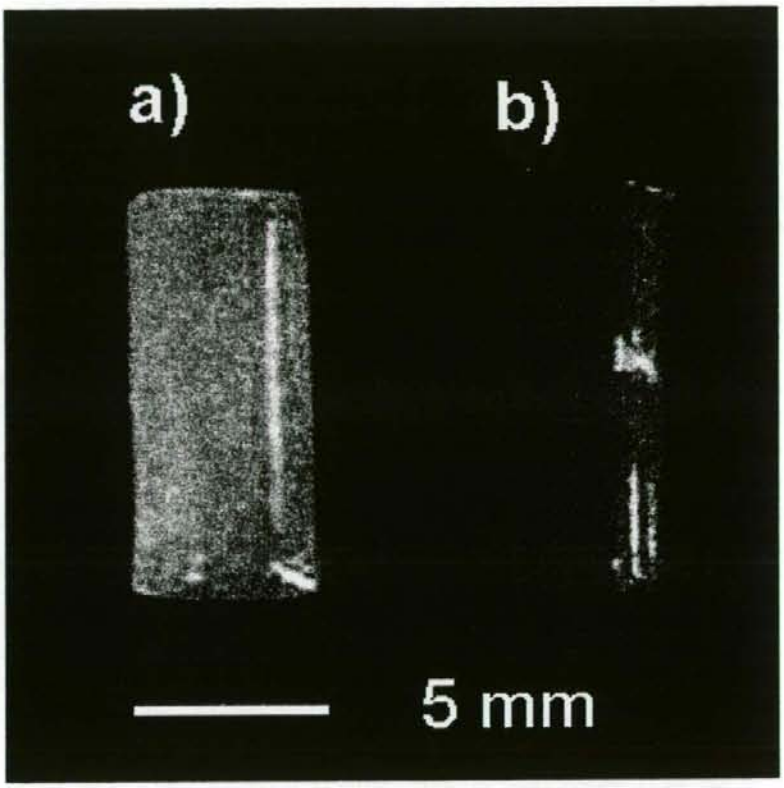

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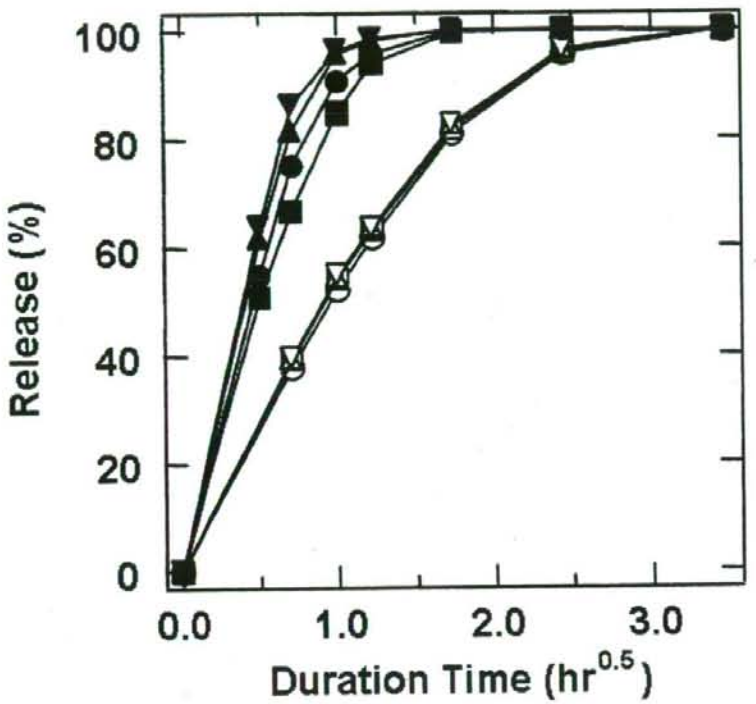
55x55mm (600 x 600 DPI)



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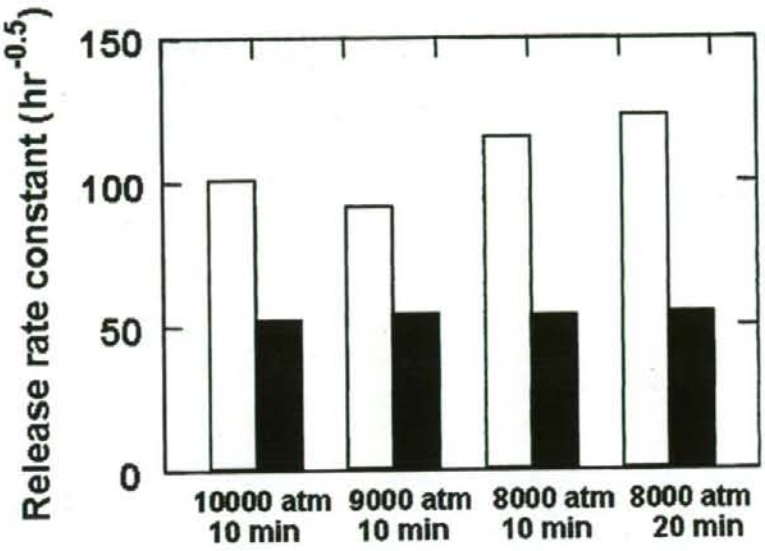

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86x65mm (600 x 600 DPI)

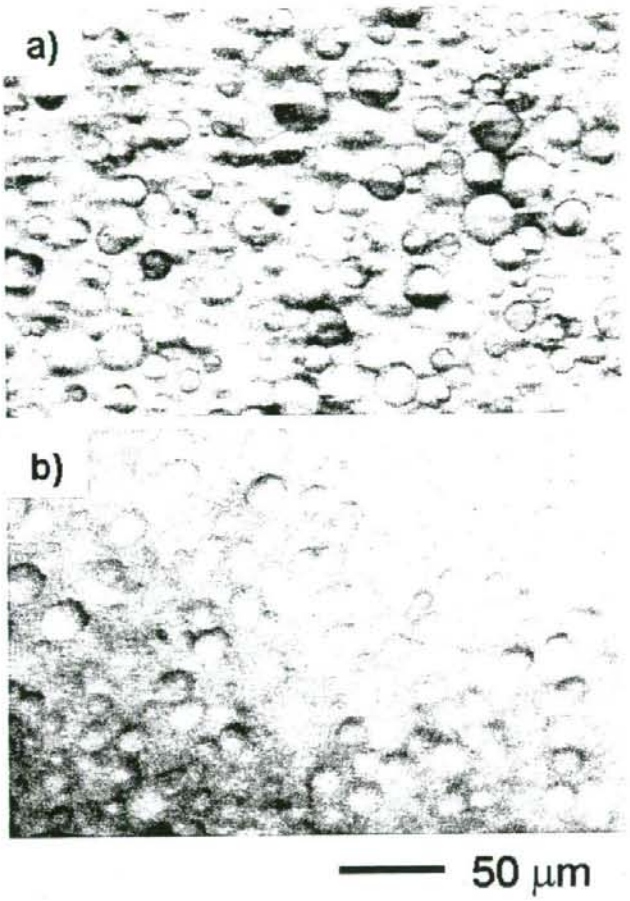


Figure 5. Photographs of o/w emulsion droplets. a) in solution (before pressurization). b) in PVA hydrogel (after pressurization).
71x106mm (600 x 600 DPI)

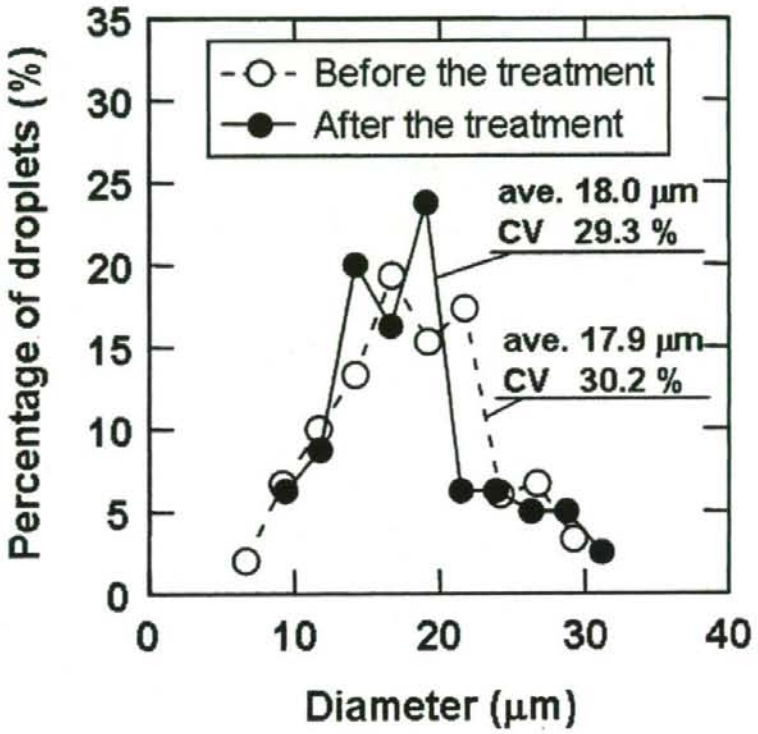


Figure 6. Diameter distributions of dodecane droplets before/after ultra-high pressure treatment.
79x77mm (600 x 600 DPI)

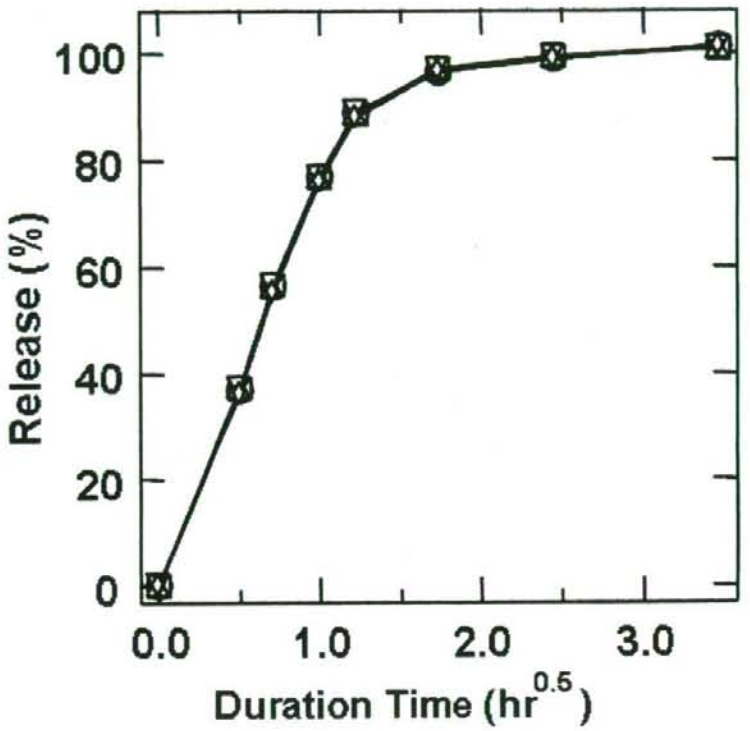
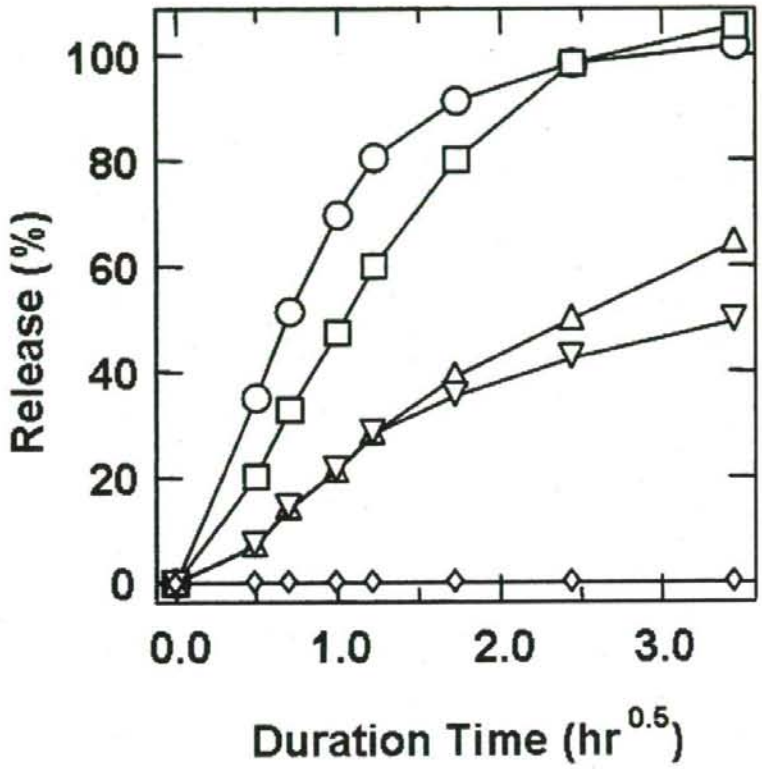


Figure 7. Release behavior of Oil Blue N from 10 w/v% PVA hydrogels in ethanol. Pressurized conditions are (◯)10,000 atm, 10 min, (□)9,000 atm, 10 min, (△)8,000 atm, 10 min, (▽)8,000 atm, 20 min, (◇)8,000 atm, 60 min.
77x74mm (600 x 600 DPI)



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74x74mm (600 x 600 DPI)