Hydrogel–Hydrogel Composites: The Interfacial Structure and Interaction Between Water and Polymer Chains

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ABSTRACT: This work examines the interfacial structure and interaction between water and polymer chains in the hydrogel–hydrogel composites with the goal of establishing foundations for further investigation of drug diffusion from one hydrogel to another in the soft contact lens. This is based on the ability of the hydrogel–hydrogel composites to release ophthalmic drugs in a sustained manner. The hydrogel–hydrogel composites were synthesized by immersing the glycerol-swollen particles of crosslinked *N*-vinyl-2-pyrrolidone (NVP) into the monomer of hydroxyethylmethacrylate (HEMA) containing initiator benzoylperoxide (BPO) that polymerizes to form a matrix in the presence of the first networks. The hydrogel–hydrogel composites were characterized by UV/Vis spectrophotometer, scanning electronic micrography (SEM), and differential scanning calorimetry (DSC). The results showed that the samples of hydrogel–hydrogel composites of the particles of crosslinked NVP and poly-HEMA were transparent and glassy and suitable for soft contact lens. Three types of the interfacial structure, no interpenetrating interface, partly interpenetrating interface, and fully interpenetrating interface, of the hydrogel–hydrogel composites existed, and the type of the interfacial structure was determined by the degree to which the monomer of HEMA penetrated into the first networks before formation of the matrix. Different from poly-HEMA hydrogels, the peaks near 0°C on DSC curves of the hydrogel–hydrogel composites did not split while they were kept acute, and the amount of freezable-bound water was less. This shows that the water incorporated in the hydrogel–hydrogel composites does not strongly interact with polymer matrix, so the hydrogel–hydrogel composites cannot keep their shape during the phase transition of water. © 2008 Wiley Periodicals, Inc. J Appl Polym Sci 108: 3713–3719, 2008

Key words: hydrogels; composites; interfacial structure; water state

INTRODUCTION

Polymer hydrogels are crosslinked three-dimensional hydrophilic polymer network in which a large volume of water is held as it is insoluble in water because of the chemical or physical cross links.[1–3] One of the most important research field of polymer hydrogels is the controlled drug release system.[4–7] With the development of various advanced drugs over the past decade, common hydrogels that contain a single polymer component cannot satisfy the requirements, and many new methods of controlled delivery for these compounds have been created including hydrogel–hydrogel composites that were formed by incorporating drugs into the first networks before encapsulating them into another. Some of the benefits of this are as follows: (1) elimination of burst release of drugs that are adsorbed on the surface of the first networks, which were encapsulated into another[8,9]; (2) for drugs with their activities depending on their ability to reach the targeted sites while they are being easily degraded by proteases or DNA-degrading enzymes *in vivo* once they enter into the body or are extremely active and are able to react on various tissues within the body in addition to the targeted site, an extra barrier is needed to limit the accessibility of denaturing agents to the drug-loaded hydrogels, and this extra barrier can be another hydrogel[10]; and (3) some hydrogel–hydrogel composites have faster response rate to changes in the surroundings than the common ones.[11] Although some hydrogel–hydrogel composites have been successfully synthesized and characterized in recent years, some questions were still not taken into account.[12–17] For example, what are the characters of the interfacial structure, which exists between the two hydrogels, and the interfacial effect and their influence on diffusion of drug molecules,

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which is an important factor to be considered for hydrogel–hydrogel composite-based controlled drug release system? In addition, hydrogels are networks of polymer chains that absorb and retain a significant amount of water, and the behavior of water within the hydrogels is important to understand because it dominates the physical and transport properties of the hydrogels. How water and polymer chains interact with each other in hydrogel–hydrogel composites and their influence on diffusion of molecule of drugs is another important factor to be considered.

In the present work, we aimed to synthesize optically transparent hydrogel–hydrogel composites for soft contact lens with the ability to release ophthalmic drugs in a sustained manner. In this hydrogel–hydrogel composite-based controlled ophthalmic drug release system, the drugs are mainly loaded on the particles of the first networks, which were encapsulated into the second one suitable for soft contact lens and penetrate from the former to the latter, then to the postlens lachrymal fluid. In this article, our attention is especially focused on the interfacial structure between the two hydrogels and the interaction between water and polymer chains in the hydrogel–hydrogel composites, and further investigation of drug diffusion from one hydrogel to another based on this is needed.

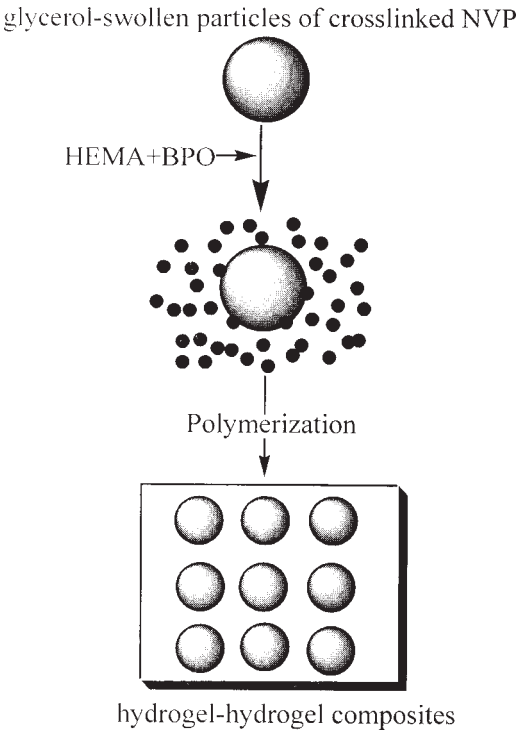

Figure 1 Schematic illustration of the preparation procedure of the hydrogel–hydrogel composites.

EXPERIMENTAL

Materials

N-vinyl-2-pyrrolidone (NVP) was obtained from BASF Co. (Germany) and purified by vacuum distillation at 122°C and 0.097 MPa before use; hydroxyethylmethacrylate (HEMA), ethylene glycol dimethacrylate (EGDMA), and *N*,*N*-methylene bisacrylamide (NMBA) were obtained from Aldrich Co. (United States) and used directly; benzoylperoxide (BPO) as an initiator was obtained from ZhenErCheng Co. (Guangzhao, China), and azobisisobutyronitrile (AIBN) as another initiator was obtained from Guangzhou Chemical Reagent Factory Co. (China); sodium hydrogen phosphate, sodium sulfate, and glycerol were reagent grade and were used without further purification.

Preparation of the particles of crosslinked NVP

A 300-mL four-necked flask equipped with a reflux condenser, a stirring rod, and a thermometer was charged with 80 mL of distilled water, 4 g of sodium hydrogen phosphate, and 4 g of sodium sulfate. The mixture was stirred until sodium hydrogen phosphate and sodium sulfate dissolved. Eight hundred milligram each of initiator AIBN and crosslinking agent NMBA, and 80 g of NVP were introduced into the reactor. The mixture was stirred until AIBN and NMBA dissolved. Air was flushed from the reactor by the addition of nitrogen until the entire process was completed. The stirrer speed was maintained at 100 rpm for the first 15 min, and then stopped. The polymerization was set at 70°C for 60 min. After polymerization, the hydrogels were cooled and washed with plenty of distilled water to get rid of sodium hydrogen phosphate and sodium sulfate in the solution, then dried at 105°C in the vacuum oven. The crosslinked NVP xerogels were smashed into particles and sieved; the samples were used with a particle size of 150 mesh.

Preparation of the hydrogel–hydrogel composites

The preparation procedure of the hydrogel–hydrogel composites is schematically illustrated in Figure 1. Initiator BPO and crosslinking agent EGDMA (the dosage was 0.1 wt % for initiator and 1 wt % for crosslinking agent calculated based on HEMA) were introduced into HEMA and stirred until they dissolved completely. Particles of the dried crosslinked NVP were fully swollen by immersion into plenty of glycerol for 24 h, then introduced into HEMA containing BPO and EGDMA and stirred for some time for even dispersion. The polymerization was carried out at 80°C for 24 h, the product was immersed into

plenty of distilled water for 14 days, and the distilled water changed every 24 h to get rid of glycerol in the particles of crosslinked NVP. Then, the product was dried at 105°C in the vacuum oven for 24 h, and dried composites were obtained.

Swelling study

The equilibrium water content (EWC) of the crosslinked NVP hydrogels and the hydrogel–hydrogel composites were determined by a gravimetric method and vacuum oven drying. The sample was immersed into distilled water at 37°C for 48 h, then taken out, the surface dried carefully using a filter paper, the total wet mass (W_{wet}) measured by a balance, and finally the sample was dried in a vacuum oven at 105°C for 24 h. The mass of dried samples (W_{dry}) was measured after cooling in a desiccator.

The EWC equation is as follows:

$$\mathrm{EWC}\% = \frac{W_{wet} - W_{dry}}{W_{wet}} \times 100. \quad (1)$$

Characterization of the hydrogel–hydrogel composites

The transparency of the samples was examined by using UV/Vis spectrophotometer. The measurements were performed from 230 to 700 nm wavelength with 1.0 mm thickness of the fully swollen sample at room temperature. Differential scanning calorimetry (DSC) equipment (DSC 6100, Seiko Instruments) was used to measure the thermal properties of the samples. Fully swollen sample was sealed in the aluminum (Al) pan and cooled to −70°C at a rate of 5°C/min and maintained for 10 min, and the temperature was then increased to 250°C at a rate of 5°C/min. TG-DTA curve was obtained using NETZSCH TG209 instrument from 20 to 500°C at a rate of 10°C/min under N_2 with a flowing rate of 40 mL/min. SEM imaging was obtained by SEM LEO 1430VP with the samples dried in a vacuum oven at 105°C for 24 h and gold sputtered before imaging.

RESULTS AND DISCUSSION

Transparency

It was found that hydrogel–hydrogel composites of poly-HEMA and particles of crosslinked NVP are colorless and transparent glassy hydrogels. They exhibited a high transparency of more than 94% in the wavelength range of 400–700 nm when fully swollen in physiological saline water, while the transparency suddenly decreased below 340 nm because the carbonyl group on NVP can absorb the UV, as shown in Figure 2. Composition of the composites has no significant effect on transparency. But if the particles of crosslinked NVP did not swell in glycerol before formation of poly-HEMA matrix, certain parts of the hydrogel–hydrogel composites remained opaque. These results indicate that the hydrogel–hydrogel composites are useful biomaterials for soft contact lens (SCL) in terms of light transmittance in the range of visible light wavelengths.

Interfacial structure of the hydrogel–hydrogel composites

The microscopy images of the hydrogel–hydrogel composites and poly-HEMA hydrogels are shown in Figure 3. Although the particles of crosslinked NVP were synthesized initially, and the hydrogel matrix (poly-HEMA) formed in the presence of the first networks, the microstructures of the samples that were synthesized under different reaction conditions are different. The microstructure of poly-HEMA hydrogels is uniform (Sample d in Fig. 3), and the particles of crosslinked NVP were encapsulated into the matrix of poly-HEMA hydrogels for the hydrogel–hydrogel composites (Samples a, b, and c in Fig. 3). However, there is no obvious interpenetrating interface between the two hydrogels for Sample a, whereas the particles of crosslinked NVP are almost fully interpenetrated with the matrix of poly-HEMA hydrogels for Sample c, and there is a thin layer of interpenetrating interface that shrinks because of the different EWC between the two hydrogels for Sample b. A schematic diagram of the three kinds of different interfacial structures is shown in Figure 4.

For Sample c, the particles of crosslinked NVP were immersed into HEMA for 12 h before formation of the matrix polymer networks, so there is enough time for HEMA to penetrate into the first

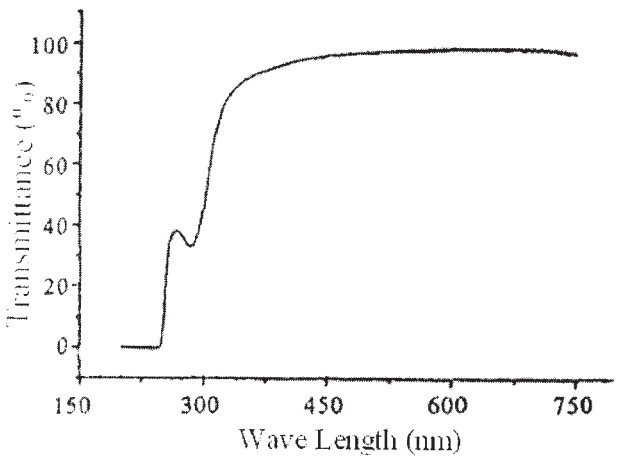

Figure 2 Transmittance of the hydrogel–hydrogel composites.

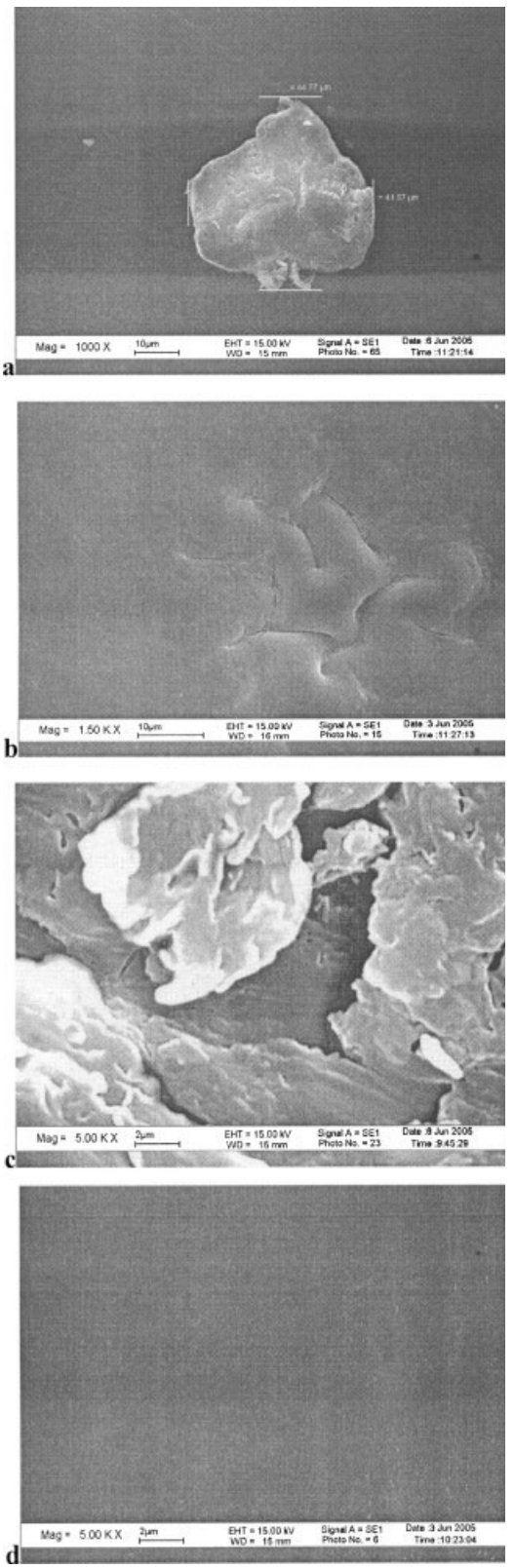

Figure 3 Micrography of the samples.

network and substitute glycerol that it contained, and polymerization took place *in situ* in the first network to form the matrix of poly-HEMA hydrogels. Thus a fully interpenetrated interface between the two kinds of hydrogels formed. On the other hand, for Sample a, polymerization of the monomer of HEMA took place when the particles of crosslinked NVP immersed into HEMA, and the reaction rate was higher because of higher temperature. The monomer of HEMA did not have enough time to penetrate into the network of crosslinked NVP and substitute glycerol that it contained. There is an obvious boundary other than interpenetrating interface between the two hydrogels. As for Sample b, the monomer only penetrated into part of the particles of crosslinked NVP, and a thin layer of interpenetrating interface formed. Thus, the interfacial structure of hydrogel–hydrogel composites can be controlled by the time at which the monomer forms the matrix by penetrating into the first networks.

Interaction between water and polymer chains in the hydrogel–hydrogel composites

The interaction of water and polymer chains in hydrogels has been researched extensively, and the model of three-state water was often used to explain this interaction. In this model, water in hydrogels can be divided into three types according to the phase-transition temperature[18,19]: Free water is defined as the water with the same phase-transition temperature as that of bulk water. Freezable-bound water is water whose phase transition is lower than

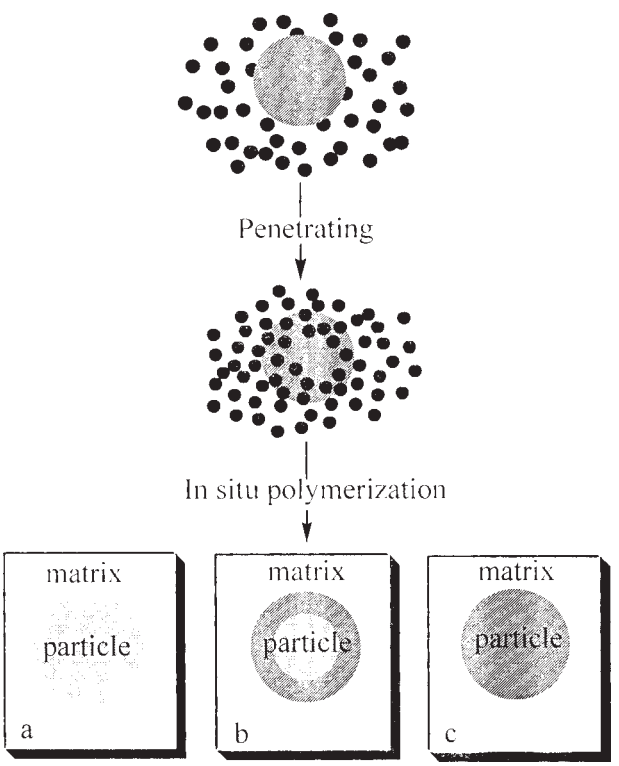

Figure 4 Schematic illustration of the formation procedure of the interpenetrating interface.

0°C. This depression is usually ascribed to the fact that the water interacts weakly with the polymer chains of the hydrogels and/or to capillary condensation in the hydrogels. Nonfreezable water is defined as water with no detectable phase transition from −70 to 50°C. This water is assumed to be influenced by a strong interaction of hydrogen bond with the polar moieties of the polymer chains.

DSC is often used to estimate the amounts of free, freezable-bound, and nonfreezable water in hydrogels. With DSC analysis, one can calculate the amount of free water and freezable-bound water from the enthalpies of melting or crystallization of water associated with the polymer. The amount of nonfreezable water can be calculated by the difference with the total weight of water in the hydrogels from the area of each peak of the DSC curve and the amount of free water from the enthalpy of melting of pure water (332 J/g) by integration of the peak at 0°C; the enthalpy of melting of different states of freezable water can be calculated.[20,21] It was reported that hydrogels containing freezable-bound water and free water display a DSC trace characterized by a double melting peak, as the amount of sorbed water increases, and the two peaks merge to form a single broad peak characterized by the presence of a small shoulder at low temperature.[22,23]

DSC curves of the hydrogel–hydrogel composites and poly-HEMA hydrogels are shown in Figure 5. EWC values of the particles of crosslinked NVP hydrogels, the hydrogel–hydrogel composites, and poly-HEMA hydrogels obtained by a gravimetric method are shown in Table I, along with the amount of water in the samples at different states calculated according to gravimetric and DSC data. As reported in most of the previous articles, the peak of −0.5°C on the DSC curve of poly-HEMA hydrogels splits into two and they correspond to freezable-bound water and free water. In the initial swelling process of poly-HEMA hydrogels, water molecules first disrupt the intermolecular hydrogen bonds and then bind to the hydrophilic sites. These water molecules, which are isolated and uniformly distributed throughout the polymer, have greatly restricted mobility and are referred to as bound or nonfreezable water. Above a certain level of bound water, the additional water is preferentially oriented around the bound water and the polymer network structure as a secondary or tertiary hydration shell, which is in a form generally called ''clusters.'' These cage-like structures result from the tendency of water molecules to form the maximum amount of hydrogen bonds among them in the available space, thus forming the freezable-bound water.[24,25] As more water entered the network, no obvious interaction took place between water molecule and polymer chains—they were termed free water.

But for DSC curve of hydrogel–hydrogel composites (Samples a, b, and c) in Figure 3, the peak of 0.8 or 0.9°C did not split and was maintained acute,

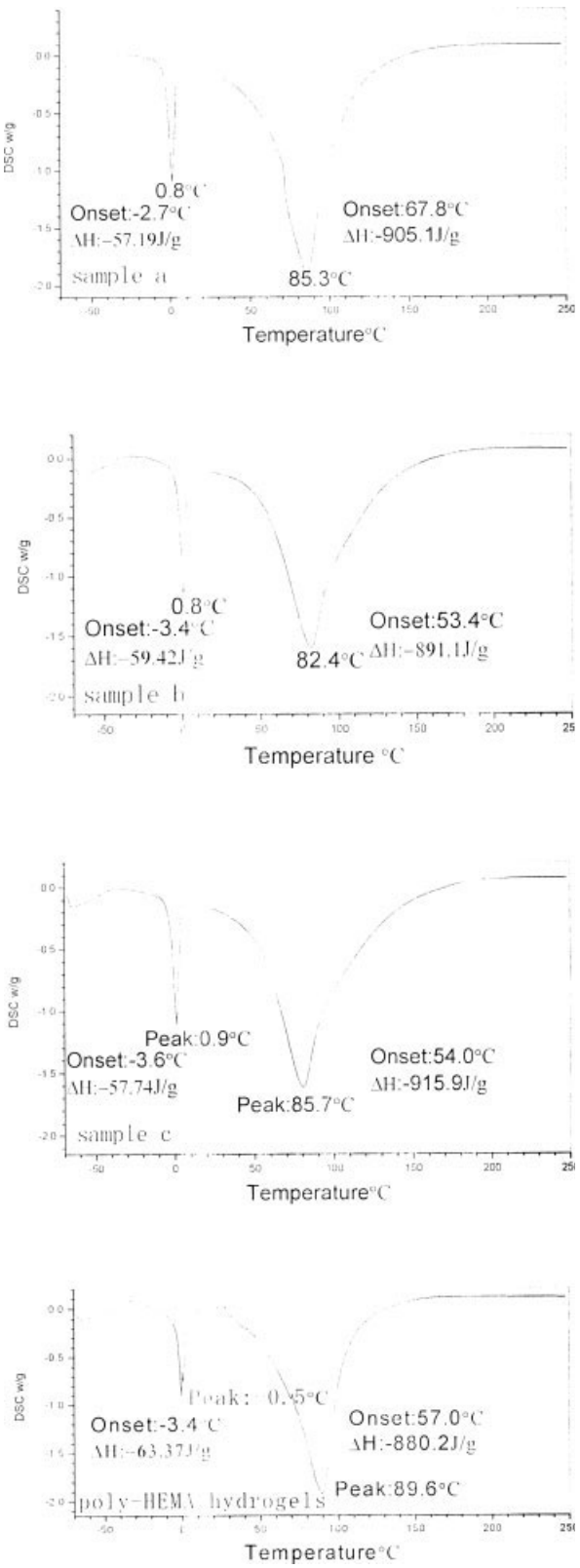

Figure 5 DSC curves of the hydrogel–hydrogel composites and poly-HEMA hydrogels.

TABLE I
EWC and the Amount of Water with Different State in the Hydrogel–Hydrogel Composites and the Particles of Crosslinked NVP

Entry	The cross-linked NVP	Sample a	Sample b	Sample c	Poly-HEMA
EWC (%)	91.94	44.80	44.10	43.20	40.70
Freezable water (%)	–	25.27	24.53	23.12	20.04
Freezable-bound water (%)	–	16.17	16.30	16.80	17.9
Nonfreezable water (%)	–	3.36	3.27	3.28	2.76

as in Sample d, instead of broad, and the amount of sorbed water was almost the same as for poly-HEMA, as if there was very little freezable-bound water in them, whereas the freezable-bound water in the hydrogel–hydrogel composite does exist but less than that in poly-HEMA hydrogels according to the data shown in Table I. It was thought that the formation of three-state water in the hydrogel–hydrogel composites is a dynamic process. In the initial swelling process, not all the hydrophilic sites on the polymer chains in the hydrogel–hydrogel composite was held by water molecules that entered the network, and not all the water molecules that entered the network bound to the hydrophilic sites because water is made up of ''molecular cluster'' instead of single molecule for the sake of hydrogen bond, nonfreezable water and freezable-bound water are existing despite of the amount of freezable-bound water being much less than that of nonfreezable water. As more water entered the network, all the hydrophilic sites are held by water molecules, more freezable-bound water forms, and free water appears. During this process, the network expands and the pores form to produce more freezable-bound water; but for the sake of the EWC of the crosslinked NVP being much larger than that of the matrix in the composite, leading to the crosslinked NVP cannot fully swell because of its expansion being restricted by the matrix, and its polymer chains cannot extend adequately; so the pores in the hydrogel–hydrogel composites are smaller than those in poly-HEMA hydrogels, and the amount of freezable-bound water is less. In the melting process, the freezable-bound water incorporated in the pores came out and was converted to the free water, so the onset of the peak on the DCS curve of the hydrogel–hydrogel composites is below 0°C whereas the peak is above 0°C and does not split but continues to be acute. This result indicates that water incorporated in the hydrogel–hydrogel composites does not strongly interact with the matrix so the composites cannot keep their shape during the phase transition of water. Because diffusion of solute in hydrogels is mainly influenced by free water, this interaction between water and polymer chains would have an extensive influence on the diffusion of solute in the hydrogel–hydrogel composites.

CONCLUSION

The hydrogel–hydrogel composites of the particles of crosslinked NVP and poly-HEMA were successfully synthesized, the interfacial structure was studied by SEM, and the interaction between water and polymer chains was studied by DSC. It was concluded that transparent and glassy hydrogel–hydrogel composites of the particles of crosslinked NVP and poly-HEMA can be successfully synthesized by immersing the glycerol-swollen particles of crosslinked NVP into the monomer of HEMA containing initiator BPO and the latter polymerizing to form a matrix in the presence of the first network. Three types of the interfacial structure of no interpenetrating interface, partly interpenetrating interface, and fully interpenetrating interface of the hydrogel–hydrogel composites existed, and the formation of the three types of interfacial structure resulted from a degree different from that of the monomer of HEMA penetrating into the first network. The interfacial structure between the two kinds of hydrogels in the hydrogel–hydrogel composites can be controlled by changing the reaction conditions when forming the polymer matrix. The expansion of particles of the crosslinked NVP was restricted by the matrix of poly-HEMA during the swelling process of the hydrogel–hydrogel composites because EWC of the former is much larger than that of the latter, as the pores formed during the swelling process were smaller and freezable-bound water was less, and the water incorporated in the hydrogel–hydrogel composites does not strongly interact with polymer matrix such that the hydrogel–hydrogel composites cannot keep their shape during the phase transition of water.

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