Double-Network Hydrogel with High Mechanical Strength Prepared from Two Biocompatible Polymers

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ABSTRACT: Novel double-network (DN) hydrogels with high mechanical strength have been fabricated with two biocompatible polymers, poly(vinyl alcohol) (PVA) and poly(ethylene glycol) (PEG), through a simple freezing and thawing method. Some properties of the obtained hydrogels, such as the mechanical strength, rheological and thermodynamic behavior, drug release, and morphology, have been characterized. The results reveal that in sharp contrast to most common hydrogels made with simple natural or synthetic polymers, PVA/PEG hydrogels can sustain a compressive pressure as high as several megapascals, highlighting their potential application as biomedical materials. In addition, a model for describing the structural formation of PVA/PEG DN hydrogels is proposed: the condensed PVA-rich phase forms microcrystals first, which bridge with one another to form a rigid and inhomogeneous net backbone to support the shape of the hydrogel, and then the dilute PEG-rich phase partially crystallizes among the cavities or voids of the backbone; meanwhile, there are entanglements of molecular chains between the two polymers. Moreover, a mechanism is also proposed to explain the high mechanical strength of PVA/PEG DN hydrogels. It is suggested that the free motion of PEG clusters in the cavities of PVA networks can prevent the crack from growing to a macroscopic level because the linear PEG chains in the cavities effectively absorb the crack energy and relax the local stress either by viscous dissipation or by large deformation of the PEG chains.
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Key words: biocompatibility; high performance polymers; hydrogels; mechanical properties; networks

INTRODUCTION

In general, a hydrogel is a hydrophilic and crosslinked polymer network with a great capacity for water or biological fluids, and it can remain insoluble in solution because of the presence of chemical crosslinks (junctions and tie points) or physical crosslinks (crystallites and entanglements).[1,2] A hydrogel appears as a solid with a definite shape and nonfluidity on the macroscopic scale and behaves like a solution on the molecular scale because water-soluble molecules can diffuse in the hydrogel with different diffusion constants dependent on the diffusant size and shape.[3] Over the past 2 decades, polymer hydrogels have attracted more and more attention from researchers because of their special physicochemical properties, such as biocompatibility, responsiveness to stimuli, and water permeability, and they have many more applications, such as the controlled delivery of medicinal drugs, artificial muscles, sensor systems, and bioseparation.[4] However, there still exist some limitations in the mechanical properties, biocompatibility, and reactivity of these materials.[1,5,6] The enhancement of the mechanical strength of hydrogels is a very interesting topic and also a great challenge. It is well known that both poly(vinyl alcohol) (PVA) and poly(ethylene glycol) (PEG) are permitted by the U.S. Food and Drug Administration to be used as biosafety materials in tissue engineering for biomedical and pharmaceutical applications. Therefore, we have chosen PVA and PEG to develop a novel and simple approach to fabricate biocompatible hydrogel materials with high mechanical strength.

Compared with most hydrogels derived from either natural or synthetic sources that suffer from a lack of mechanical strength, PVA is endowed with high mechanical strength, good processability, and long-term temperature and pH stability and is a suitable candidate for artificial articular cartilage.[7] Besides, it is biocompatible, nontoxic, and minimally adsorptive for cells and proteins.[1,8] PVA hydrogels can be

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chemically crosslinked through crosslinking agents or radiation, such as electron beams or γ-radiation.[7,9] However, radiation crosslinking is unfavorable for biocompatible materials because of bubble formation in its processing procedure[10] and the existence of toxic residual chemical components such as initiators, chain-transfer agents, and stabilizers, for the removal of which undesirable time-consuming extraction needs to be performed. Peppas and Merrill[11] examined the partial crystallization of PVA through a process of dehydration and annealing and found that aqueous PVA solutions had unusually characteristic crystallite formation in freezing and thawing cycles. The crystalline regions essentially served as physical crosslinks to redistribute external stresses. This method facilitates biomedical applications because it can avoid the toxicity issue by dispensing with the presence of a crosslinking agent. Such physically crosslinked materials also demonstrate higher mechanical strength than PVA gels crosslinked by traditional chemical or radiative techniques because the mechanical loading can be distributed effectively along the three-dimensional structured crystallites.

PEG is a common hydrophilic and crystallizable polymer. Studies on PEG in solution have shown that PEG typically binds two to three water molecules per ethylene oxide unit.[12] Because of both the high flexibility of the backbone chain and the binding of water molecules, the PEG molecule volume acts as if it were 5–10 times as large as a soluble protein of comparable molecular weight, and this is believed to be the reason for its ability to precipitate proteins, exclude proteins and cells from surfaces, reduce immunogenicity and antigenicity, and prevent degradation by mammalian cells and enzymes.[13] Recently, nontoxic high-molecular-weight PEG has been widely applied in food, cosmetics, and pharmaceuticals.[12] However, to form three-dimensional networks, the formation of a PEG hydrogel must be exposed to some chemical processes, which sometimes are toxic.[14,15]

Gong and coworkers[16–18] induced a double network (DN) in a hydrogel structure and obtained a hydrogel with an especially high mechanical strength. As for the DN structure, the molar ratio of the first network to the second network and their crosslinking density are the crucial parameters. A gel with very high strength can be obtained when the first network is highly crosslinked and the second is slightly crosslinked or even not crosslinked.[2] When the second network has a crosslinking density of 0 mol % (i.e., without crosslinking), the highest fracture strength and strain can be obtained for poly(2-acrylamido-2-methyl-1-propanesulfonic acid)/polyacrylamide DN gels.[19]

Inspired by these results, we attempted to fabricate a biocompatible hydrogel with high mechanical strength through a combination of PVA and PEG with simple cycles of freezing and thawing. The designed PVA/PEG hydrogel structure is formed by a PVA-rich first network and a PEG-rich second component, in which noncrosslinking or just hydrogen bonding exists. It is noted that the adsorption of proteins and deposition of cells in blends of PVA and PEG can be regulated for biomedical and pharmaceutical applications. As a result, interest has been focused on the characterization of polymer–polymer interactions, phase separation, low-weight molecular diffusion, the immobilization of PEG onto a PVA matrix, and the tailoring of its degradation.[7,20–23] On the other hand, it is well accepted that the freezing and thawing method is an environmentally friendly, effective, efficient, and benign manufacturing process for building complex composites.[24,25] To our knowledge, few studies concerning hydrogels composed of PVA and PEG and fabricated through a novel and simple freezing and thawing approach and, in particular, the mechanism of hydrogel formation have been reported to date. In this study, we attempted to prepare a PVA/PEG DN hydrogel with high mechanical strength through a novel and simple approach and to characterize its structure and properties.

EXPERIMENTAL

Materials and sample preparation

PVA (>97.0% hydrolyzed, average degree of polymerization = 1750 ± 50) was purchased from Pekin Yili Chemical, Ltd. (Beijing, China), and PEG (weight-average molecular weight = 7500) was purchased from Wako Pure Chemical Industries, Ltd. (Japan). Both were used as received and without further purification. Pure water was treated with Millipore Biocel. The drug cefazolin sodium was purchased from North China Pharmaceutical Group Corp.

Preparation of the PVA/PEG hydrogels

A PVA aqueous solution with a desired concentration was obtained by the dissolution of a certain amount of PVA in ultrapure water under 90°C with stirring for about 6 h; then, the solution was divided into four shares, and a different amount of PEG was added to each solution. The mixture that formed was stirred for 2 h more. The solutions were cast into polytetrafluoroethylene molds of the desired sizes for different measurements later. All samples were exposed to repeated cycles of freezing at −20°C for 8 h and thawing at room temperature for 4 h.

Tests and measurements

Mechanical measurements

The measurements of the tensile and compressive stress and strain for water-swollen gels were

performed on a tensile compressive tester (WDT-10, Shenzhen Kaiqiangli Instruments, Ltd., Shenzhen, China). For tensile stress–strain measurements, dumbbell-shaped gel samples ($65 \times 5 \times 2$ mm^3) were fixed with two tensile clamps at each end and elongated at a speed of 5 mm/min. For compressive stress–strain measurements, cylindrical gel samples with a diameter of 25 mm and a thickness of 25 mm were set on the lower plate and compressed by the upper plate at a strain rate of 5 mm/min.

Rheological measurements

Dynamic viscoelastic measurements of the hydrogel samples were conducted on a Rheometrics ARES stress-controlled rheometer (Rheometric Scientific, Inc., United States) in a parallel-plate mode to measure the dynamic storage modulus, the dynamic loss modulus, and the loss tangent. The diameter of the plates was 25 mm, and the gap between the two parallel plates was adjusted to 1.0 mm. All measurements were carried out at 25°C from an initial frequency of 0.05 rad/s to a final frequency of 100 rad/s. The linear viscoelasticity for the hydrogel samples was checked before the measurements of the elastic and viscous moduli were started.

Observation of the morphologies

The morphologies were observed with scanning electron microscopy (SEM; S-4300 field emission scanning electron microscope, Hitachi, Japan) at 15 kV. The hydrogel samples were frozen under −20°C and freeze-dried (FD-1-55, Pekin Boyikang Laboratory Apparatus, Ltd., Beijing, China) to preserve the morphologies of the PVA/PEG hydrogels, and then they were broken off in liquid nitrogen to obtain fractured sections. The samples that were obtained were affixed to aluminum stubs with electroconductive adhesive tape, and the sample surfaces were sputter-coated with Pt.

Thermal analysis

The crystalline nature of the PVA/PEG hydrogels prepared by the freezing and thawing process was examined with differential scanning calorimetry (DSC; model 822^e, Mettler–Toledo, Switzerland) to determine the degrees of crystallinity of samples with different concentrations of PEG. The difference in the heat flow between a sample and an inert reference was measured as a function of time and temperature. The hydrogels were frozen under −20°C and vacuum-freeze-dried before being measured. The measurements were conducted at a scanning rate of 5°C/min from 20 to 250°C under nitrogen gas.

Drug release tests

For drug release experiments, the drug-loaded hydrogels were formed by the dissolution of 0.05 wt % cefazolin sodium in aqueous solutions of PVA and PEG to ensure a homogeneous dispersion throughout the hydrogel matrix, and then the solutions were treated with three cycles of the freezing and thawing process. The cefazolin sodium concentration was measured *in situ* with a UV spectrophotometer (UV-1600, Institute of Chemistry, Chinese Academy of Sciences, China) at the maximum absorbance wavelength of cefazolin sodium (265.0 nm), and the data-collection interval was 300 s. The release mechanism of cefazolin sodium could be described by the Peppas equation as follows:[26]

$$M_t/M_\infty = Kt^n \quad (1)$$

where M_t/M_∞ is the fraction of drug released, K is a kinetic constant dependent on the system, t is the release period, and n is the diffusion exponent indicative of the release mechanism for matrices of various shapes and swelling of nonswelling systems. For a cylinder, $n = 0.45$ represents Fickian release, and a value between 0.45 and 0.89 is indicative of anomalous transport, in which there must be some influence of swelling and/or erosion. $n = 0.89$ indicates a case II relaxation mechanism involving stresses and state transitions that occur in the swelling.

RESULTS AND DISCUSSION

Hereafter, the hydrogels are labeled P_1-x_1-y_1/P_2-x_2-y_2, where P_i, x_i, and y_i ($i = 1$ or 2) are the abbreviated polymer name, weight concentration, and number of freezing and thawing cycles, respectively. In stark contrast to most common hydrogels made by simple natural or synthetic polymers, which are easily broken either by pressing with a finger or pulling with the hands, the obtained PVA/PEG hydrogels can sustain a compressive pressure as high as several megapascals. Figure 1 presents photographs demonstrating how a PVA/PEG DN gel sustains high compression. The PVA-6-1/PEG-4-1 hydrogel is so tough that it can resist strong compression and reverse to its original shape after being treated with a single cycle of freezing and thawing, even if it contains a 90 wt % concentration of water. Moreover, this hydrogel exhibits both high values and good reproducibility with respect to the mechanical strength.

Table I lists the tensile and compressive properties of PVA/PEG hydrogels at room temperature. It is obvious that the addition of PEG to PVA can remarkably enhance the mechanical strength of the obtained hydrogels. The elastic modulus increases from 0.03 MPa for the pure PVA-6-3 hydrogel to

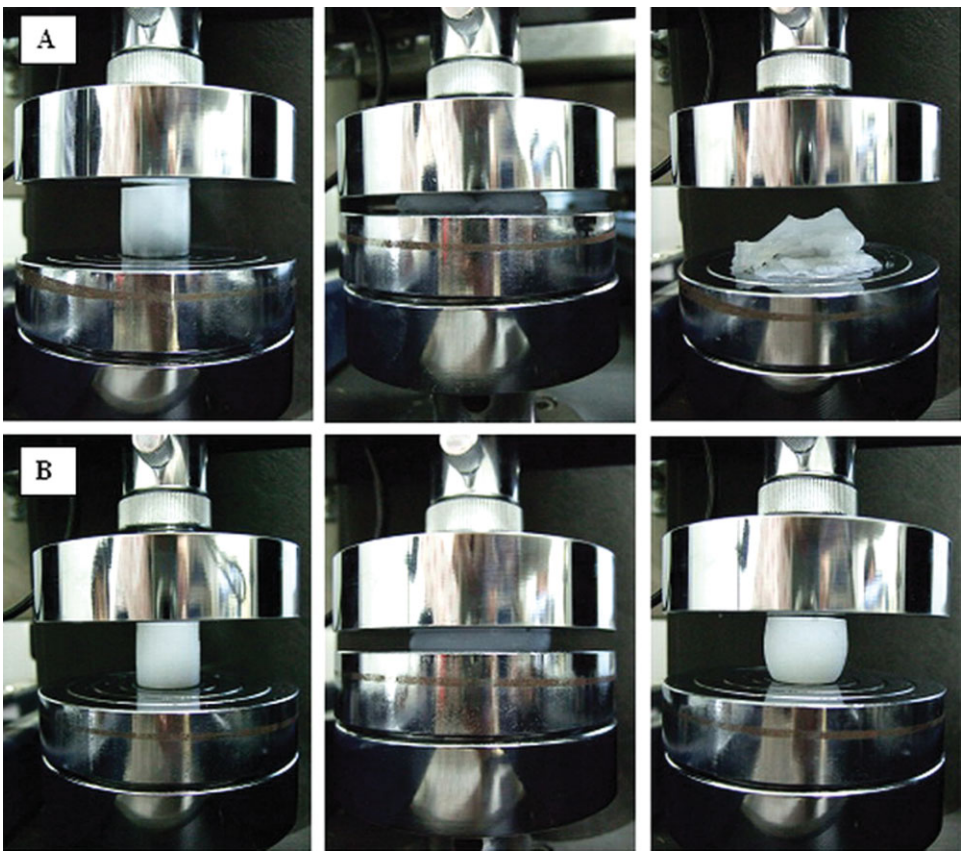

Figure 1 Photographs demonstrating how a PVA/PEG DN gel sustains high compression: (A) the pure PVA-6-1 hydrogel and (B) the PVA-6-1/PEG-6-1 DN hydrogel (compressed stress for the pure PVA-6-1 hydrogel = 1.21 MPa, compressed stress for the PVA-6-1/PEG-6-1 DN hydrogel = 10.06 MPa). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

0.11 MPa for the PVA-6-3/PEG-2-3 hydrogel under tensile testing and from 1.49 MPa for the former to 15.6 MPa for the latter under compressive testing. On the other hand, with an increase in the amount of PEG, the elastic modulus increases remarkably. However, the enhancement will level off as phase separation occurs. It should be noted that biocompatible and mechanically strong DN gels can be obtained by a suitable physical combination of PVA and PEG through cycles of simple freezing and thawing. Hence, it is believed that these biocompatible hydrogels have great potential applications as biomedical materials.

Figure 2 depicts the evolution of the dynamic storage modulus and loss modulus with the frequency for the pure PVA hydrogel and PVA/PEG DN hydrogels containing different concentrations of PEG. The dynamic storage modulus increases as the amount of PEG in the hydrogels increases, and this indicates the promotion of the elastic property of the hydrogels.

Previous research has revealed that the microcrystals in PVA hydrogels play an important role in physical crosslinking and form a three-dimensional network, which results in their relatively high mechanical strength.[2] On the molecular level, the

TABLE I
Effects of the PEG Concentration in the Feed on the Fracture Stress (σ_{max}), Fracture Strain (λ_{max}), and Elastic Modulus (E) of the Pure PVA Hydrogel and PVA/PEG DN Hydrogels in Compression and Elongation Measurements

Sample	Elongation			Compression		
	σ_{max} (MPa)	λ_{max} (mm/mm)	E (MPa)	σ_{max} (MPa)	λ_{max} (mm/mm)	E (MPa)
PVA-6-3	1.51	434.17	0.03	3.03	89.67	1.49
PVA-6-3/PEG-2-3	4.12	324.56	0.11	12.76	96.04	15.60
PVA-6-3/PEG-4-3	5.15	320.99	0.12	23.82	97.26	29.95
PVA-6-3/PEG-6-3	6.10	307.15	0.16	25.15	95.11	29.71

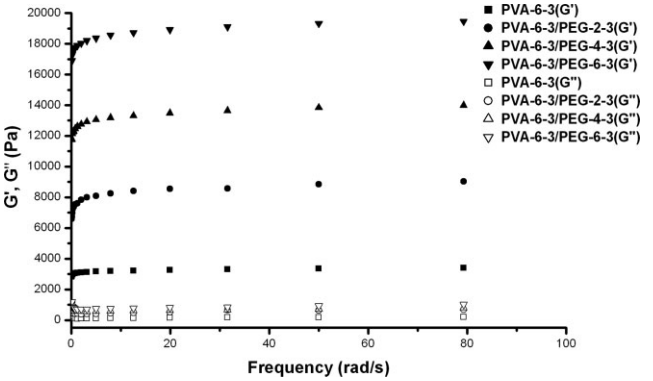

Figure 2 Storage modulus (G') and loss modulus (G'') as a function of frequency for the pure PVA hydrogel and PVA/PEG DN hydrogels with different concentrations of PEG.

crystallites of PVA can be described as a double-layered structure held together by hydroxyl bonds while weak van der Waals forces operate between them, and less crystallinity appears to be due to intramolecular hydrogen bonding. According to Inamura and coworkers,[27,28] a PVA and PEG aqueous solution can separate into two phases over a certain concentration, that is, a condensed phase with a high PVA concentration and a dilute phase with a high PEG concentration. We propose a novel model dealing with structural formation for a PVA/PEG DN hydrogel having high mechanical strength; that is, in the phase-separated system, high crystallization appears in the condensed PVA-rich phase first, and then the microcrystals bridge with one another to form a net backbone to support the shape of the hydrogel. Moreover, the dilute PEG-rich phase partially crystallizes among the cavities or voids of the backbone. Also, there exist entanglements of molecular chains between the two polymers. The addition of PEG to a PVA aqueous solution leads to more distinct phase separation as the interaction of water with PEG is stronger than it is with PVA, as PEG can typically bind two to three water molecules per ethylene oxide unit.[12,27] The PVA condensation induced by PEG results in an increase in the apparent degree of crystallization for PVA, which has been validated by our DSC results. The degree of crystallinity based on the dry gel is calculated by the division of the corrected ΔH (change of the enthalpy) value by the heat required for melting a 100% crystalline PVA sample (138.6 J/mol).[29] Figure 3 shows that the apparent degree of crystallization of PVA in the hydrogel is 45% for the pure PVA-6-3 hydrogel and approaches 57% for the hydrogel with the addition of an equal percentage of PEG. The sharp peak at approximately 230°C represents the melting of PVA, and the peak at 50–60°C is the melting point of PEG. When the content of PEG is less than 2 wt %, the peak is single, and the maximal point appears around 50°C. However, as the content of PEG increases, a second peak at 60°C appears and enlarges with an increase in the amount of PEG; this is the same as the melting point of pure PEG. On the basis of the DSC results, we assume that the PVA chains can inhibit the PEG crystallization process and that the interface between PVA and PEG acts as a crystal nucleus for PEG crystallinity; this is called heterogeneous nucleation-induced crystallization. When the amount of PVA is insufficient for the nucleation as the concentration of PEG increases, homogeneous nucleation-induced crystallization occurs in the rest of the PEG and is similar to that in the pure PEG matrix. We believe that this multicrystallizability possibly facilitates the interaction of the two crystal polymers, resulting in increased mechanical strength of the obtained hydrogel.

Figure 4 presents SEM images of PVA/PEG hydrogels with different contents of PEG. On the microscale, the morphological structure of the PVA/PEG hydrogels with different contents of PEG is distinctly diverse. For the pure PVA hydrogel fabricated by the freezing/thawing method, the microstructure of PVA is a three-dimensional network supported by cracklike and thin crystal PVA walls. However, for PVA/PEG hydrogels with different ratios of PEG, only a limited porous structure composed of close-gained thick walls of polymer blends can be found. On the other hand, the greater the amount of PEG is, the more compact the wall matrix is, and this can be attributed to the formation of a thicker supporting wall due to the accumulation of PEG around the PVA backbone and the cavities of the network. Hence, it is reasonable for us to believe that the porous structure that is formed may be a key to the high mechanical strength of the PVA/PEG hydrogels.

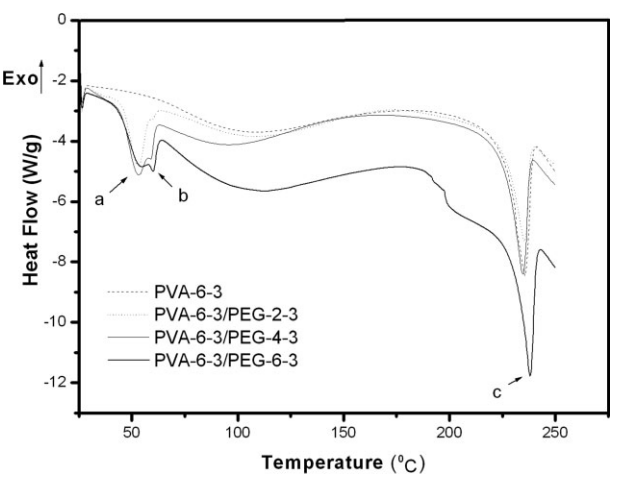

Figure 3 Thermograms for pure PVA and PVA/PEG samples exposed to repeated cycles of freezing and thawing.

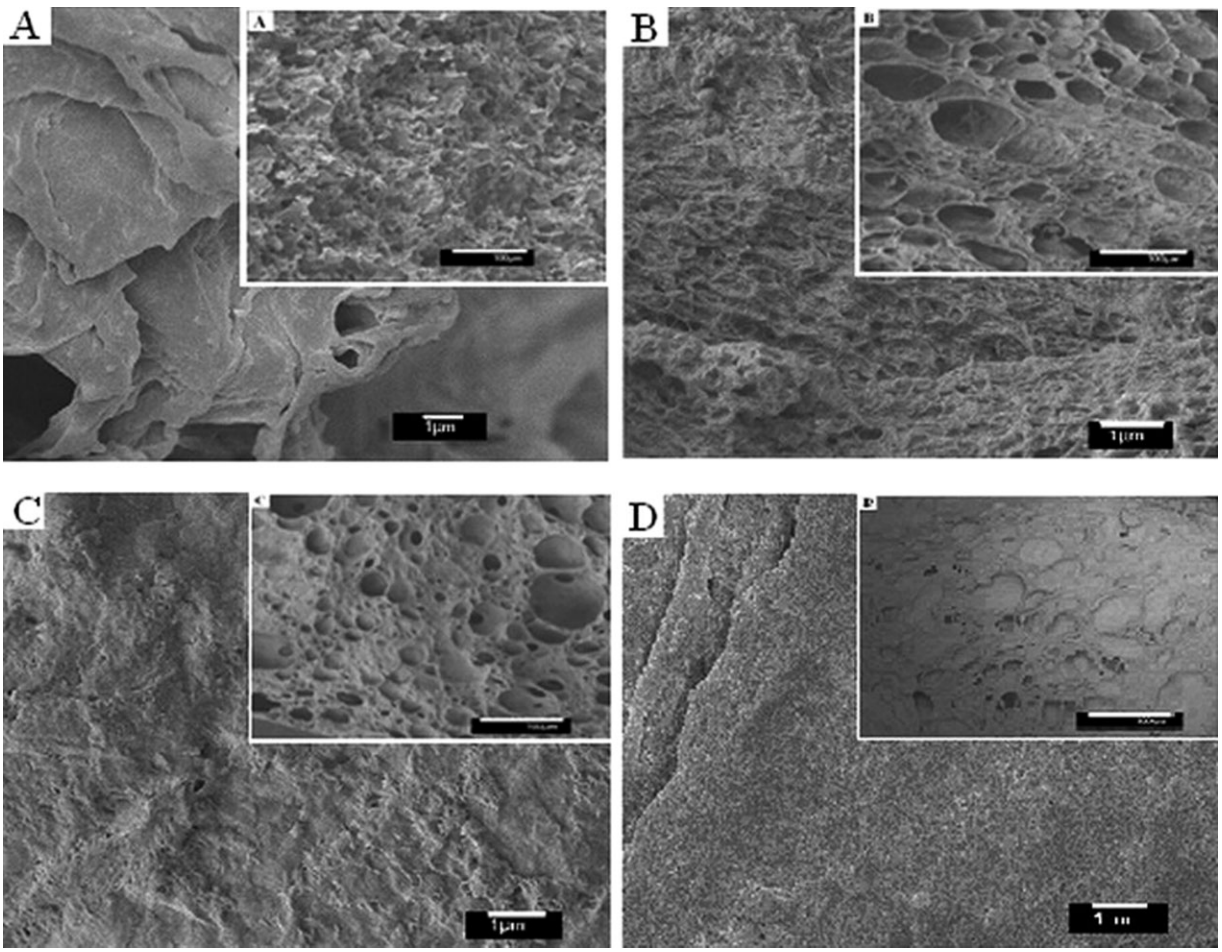

Figure 4 SEM images of PVA/PEG hydrogels with different contents of PEG: (A) 0, (B) 2, (C) 4, and (D) 6% (larger scale views are inset, and the bar represents 100 μm).

In general, there is an increase in the degree of physical crosslinking with an increasing number of freezing/thawing cycles for the pure PVA hydrogel.[29] Table II presents the effect of the number of freezing and thawing cycles on the mechanical strength for the pure PVA hydrogel and PVA/PEG DN hydrogels in compression testing. The influence of the number of freezing and thawing cycles on the PVA/PEG DN hydrogel is more pronounced in comparison with the pure PVA hydrogel. Moreover, as the number of freezing and thawing cycles increases, the increase in the elastic modulus for the PVA/PEG DN hydrogel is more remarkable than that for the pure PVA hydrogel. This suggests that the spatial obstacle of the PEG molecular chain may affect the crystallization process of PVA. It has been noted that PEG chains have hydrophilic and hydrophobic segments, which can result in its dissolvability in both water and organic solvents.[6] From this point of view, PEG can behave like a lubricant for the PVA crystallization process and can promote crystallizability. However, sometimes this spatial obstacle may also hinder the

TABLE II
Effects of the Number of Freezing and Thawing Cycles in the Feed on the Maximal Load (*F*), Fracture Stress (σ_{max}), and Elastic Modulus (*E*) of the Pure PVA Hydrogel and PVA/PEG DN Hydrogels in Compression Testing

	Compression				Compression		
Sample	*F* (N)	σ_{max} (MPa)	*E* (MPa)	Sample	*F* (N)	σ_{max} (MPa)	*E* (MPa)
PVA-6-1	7.208	0.015	0.120	PVA-6-1/PEG-4-1	42.943	0.087	0.676
PVA-6-3	87.992	0.179	0.811	PVA-6-3/PEG-4-3	142.371	0.290	2.035
PVA-6-5	104.690	0.213	1.194	PVA-6-5/PEG-4-5	352.648	0.718	7.156

crystallization, and the formation of hydrogen bonding presents as temporary crosslinks. Therefore, it is a complex result for the effect of PEG chains on PVA crystallization.[5,30]

The drug release ability of cefazolin sodium in the PVA/PEG hydrogel is similar to that of the pure PVA hydrogel (Fig. 5). In other words, the addition of PEG has no significant effect on the drug release behavior of the PVA hydrogel. Diffusion exponent n is 0.5 (lower than that of 0.89) for both the pure PVA and PVA/PEG hydrogels, implying a case I relaxation mechanism in which anomalous transport of cefazolin sodium exists in the pure PVA and PVA/PEG hydrogels instead of a case II relaxation mechanism involving the stresses and state transitions that occur in the swelling.

Accordingly, we propose a structural model for describing PVA/PEG DN gels with high mechanical strength. Figure 6 presents a schematic representation of the structural model and the mechanism for preventing crack development in PVA/PEG DN hydrogels. The network of the PVA component is rigid and heterogeneous, and some large cavities exist because of the specific freezing and thawing treatment. Except for the PEG chains interpenetrating the PVA network, the rest enter the cavities of the PVA network and act as energy dissipaters. As a result, partial entanglement of PEG with the PVA network can absorb crack energy and relax the energy through molecular chain movements. If we consider the highly crosslinked network of PVA, which has a high Young's modulus but is brittle, it is easy to understand that the dramatically enhanced mechanical strength results from an effective relaxation of stress by the loosely crosslinked second component. Furthermore, because of the free motions of PEG clusters in cavities of the PVA network, PEG in the cavities effectively absorbs the

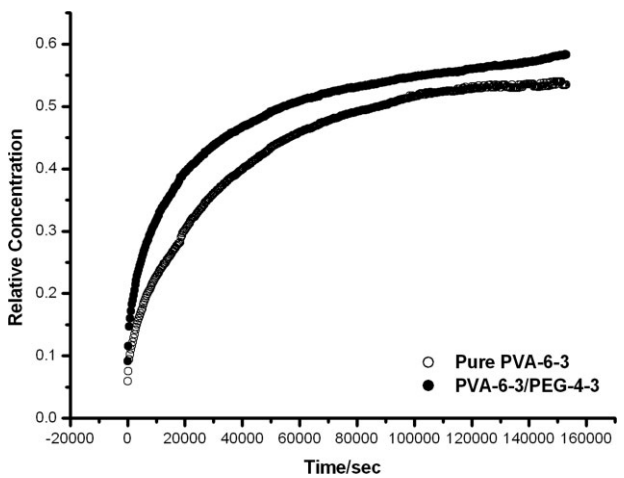

Figure 5 Cefazolin concentration measured *in situ* with a UV spectrophotometer at the maximum absorbance wavelength of cefazolin (265.0 nm).

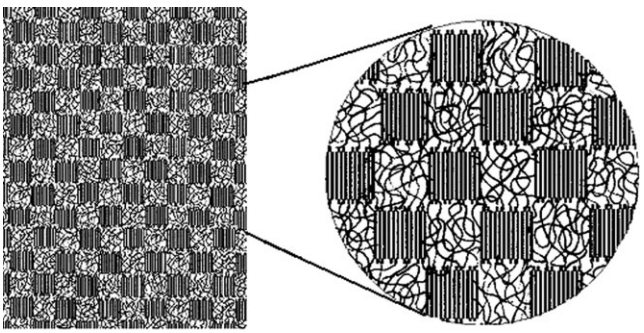

Figure 6 Schematic representation of the structural model and mechanism to prevent crack development in PVA/PEG DN hydrogels.

crack energy either by viscous dissipation or by large deformation of its chains, preventing the cracks from growing to a macroscopic level. Therefore, the incorporation of a second polymer component with a higher crosslinking density will result in substantial lowering of the mechanical strength of the DN gel. In other words, the increased mechanical strength of the DN gel results from the effective relaxation of locally applied stress and the dissipation of the crack energy through diffusive vibrations of the PEG (cluster). It is suggested that the part of PEG entangled with the PVA network could act as an anchor, and PEG with a high molecular weight may stretch significantly and rupture during the fracture process, leading to consumption of the crack energy. It is worth emphasizing that the structural model proposed here is different from the conventional interpenetrating polymer network and semi-interpenetrating polymer network structural models, which usually are equimolar in composition and can hardly exhibit substantial improvements in the mechanical strength.[31]

CONCLUSIONS

A novel and simple method for preparing hydrogels, that is, the treatment of polymer aqueous solutions with cycles of freezing and thawing, has been proposed, and a biocompatible DN PVA/PEG hydrogel with excellent high mechanical strength has been prepared. Besides mechanical measurements, rheological and thermodynamic properties, morphological structures, and drug release properties have also been determined to illuminate the special properties of the PVA/PEG DN hydrogel. The PVA/PEG hydrogel can sustain a compressive pressure as high as several megapascals; this is in stark contrast to most common hydrogels made by simple natural or synthetic polymers. The hydrogel formation process can be divided into two stages: first is the formation of a three-dimensional rigid and inhomogeneous network backbone composed mainly of the microcrystals of the condensed PVA-rich phase, which

bridge with one another to support the shape of the hydrogel, and second is the partial crystallization of the dilute PEG-rich phase among the cavities or voids of the backbone. It is believed that the entanglement of molecular chains between these two polymers acts as an anchor for the PEG chains to the PVA backbone. A mechanism has also been proposed to explain the high mechanical strength of the PVA/PEG DN hydrogel. The reason for the effective relaxation of locally applied stress and the dissipation of the crack energy through viscous dissipation or large deformation of the PEG chains is proposed to be the combination of the rigid and inhomogeneous first component network with the tough and freely movable second component in the cavities of the network. It is suggested that this biocompatible hydrogel with excellent high mechanical strength may have great potential in biomedical applications.

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