Fluid Phase Equilibria 361 (2014) 200–207

Contents lists available at ScienceDirect

Fluid Phase Equilibria

journal homepage: www.elsevier.com/locate/fluid

Hydrophilic–hydrophobic copolymer nano-sized particle gels: Swelling behavior and dependence on crosslinker chain length

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ARTICLE INFO

Article history:
Received 3 September 2013
Received in revised form 31 October 2013
Accepted 2 November 2013
Available online 10 November 2013

ABSTRACT

Poly *N*-isopropylacrylamide-*co*-ethylacrylate [P(NIPAM-co-EA)], Poly *N*-isopropylacrylamide-*co*-2-hydroxyethylmethacrylate [P(NIPAM-co-HEMA)], and Poly *N*-isopropylacrylamide-*co*-2-hydroxyethylacrylate [P(NIPAM-co-HEA)] nano-sized particle copolymer hydrogels were synthesized to investigate their volume phase transition behavior. Increasing the hydrophobic or hydrophilic monomer content of hydrogels led to uniform changes in transition temperature and swelling ratio. Different statistical thermodynamic models are presented to describe the swelling behavior of copolymer gels. The classical interaction energy parameter in the thermodynamic model, which is not suitable for accurately representing the equilibrium swelling of a copolymer hydrogel, was modified semi-empirically in order to reflect the individual contribution of each hydrogel constituent. In addition, we investigated the volume phase transition of PNIPAM gels as a function of crosslinker chain length. The crosslinkers used in this study were *N,N′*-methylenebisacrylamide (BIS) and two different molecular weights of Poly(ethyleneglycol) diacrylate (PEGDA, 575 and 700). Interestingly, the use of a long chain crosslinker resulted in a decreased volume change compared to that of a short chain crosslinker without any significant changes in transition temperature. To understand this unexpected result, we used a molecular dynamics simulation for BIS and PEGDA 575 to demonstrate the micro-scale conformation change of crosslinker chain mixed with water or ethanol. The proposed thermodynamic models represent the swelling behavior of the copolymer hydrogels and PNIPAM gels with different length crosslinkers.

1. Introduction

A hydrogel is a hydrophilic chain network that swells and absorbs a significant amount of water or other solvents. Certain hydrogels can exhibit a change in volume in response to changes in surrounding conditions such as temperature [1,2], pH [3,4], chemicals [5], photo-irradiation [6], or electric field [7]. The use of hydrogel technology has grown in many fields including pharmaceuticals, bioadhesives, and biomedical research [8]. Crosslinking of Poly *N*-isopropylacrylamide (PNIPAM) forms what is known as an intelligent hydrogel, which shrinks or swells in water in response to changes in temperature of about 33 °C [9–11], and thus has become the subject of extensive pharmaceutical research.

If a drug carrier undergoes a volumetric response due to changes in pH, temperature, or ionic strength, it should contain ionizable monomers or specific functional groups such as hydroxyl or amide functionalities that induces a significant phase transition under given conditions. Moreover, volumetric responses of such carriers may be controlled by factors such as crosslinker concentration and presence of a comonomer. Over the last two decades, several attractive properties of hydrogels meeting these criteria have been reported. Tanaka et al. showed how two good solvents can become poor solvents when mixed, in a process called cononsolvency [12]. Likewise, the volume phase transition temperature of PNIPAM gels decreases immediately in aqueous solution while the cononsolvency of the methanol fraction increases [13]. Similar phenomena have been observed in other hydrogels including crosslinked Polyvinyl alcohol (PVA) [14]. Maurer et al. studied the volume phase transition of ionic hydrogels consisting of NIPAM and ionizable comonomers such as sodium methacrylate, acrylamino-2-methyl-1-propanesulfonic acid, and N-[3-(dimethylamino)propyl] methacrylamide [15–17]. Specifically, they showed that hydrogels containing both cationic and anionic comonomers exhibit a dual volume phase transition in aqueous sodium chloride solutions. Furthermore, the strong influence of charged functional groups of a polymer chain on pH sensitive hydrogel was recently investigated by Schoener and Peppas [18], who used poly(methacrylic-grafted-ethylene glycol) (P(MAA-g-EG)) in the presence of hydrophobic PMMA nanoparticles.

The decrease in lower critical solution temperature (LCST) of PNIPAM in water can be easily manipulated by copolymerization

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http://dx.doi.org/10.1016/j.fluid.2013.11.004

with other hydrophilic or hydrophobic monomers such as HEMA or N-isopropylmethacrylamide [19,20]. Furthermore, poly(L-lactic) acid, ε-caprolactone, or similar substances can be used to facilitate biodegradability [21,22]. In particular, Poly(2-hydroxyethyl) methacrylate (PHEMA) has received wide attention primarily due to its biological compatibility [23–28] with strong water absorbing and transparent materials, making it useful for contact lenses and implantable materials. However, PHEMA is insoluble in water, which was shown by Shen et al. to be due to the hydrophobicity of the methacrylic chain at room temperature [29]. In addition, an attractive distinction between thermoresponsive (e.g. PNIPAM, PVA gel) and non-thermoresponsive (e.g. PHEMA, PMMA) aqueous polymer solutions is whether their volume phase exhibits certain transition behaviors.

Crosslinkers are an important part of most hydrogels. The crosslinker most widely used with PNIPAM is *N,N′*-methylenebisacrylamide (BIS) [10,12,13,30] because its solubility in water is very similar to that of the PNIPAM monomer. Various crosslinkers to replace BIS have been introduced. Nizam and El-din showed that PNIPAM/ethylene glycol dimethacrylate (EGDMA) gels have a higher thermal stability than pure PNIPAM hydrogels [31]. Likewise, Hu et al. [32] synthesized PNIPAM/EGDMA gels in the presence of supercritical CO_2 to demonstrate higher absorption when immersed into water and ethanol. They also investigated hydrophilic and hydrophobic crosslinkers and copolymers using ethylene dimethacrylate and glycidyl methacrylate to examine the effects of several reaction parameters on hydrogel properties, including crosslinker type and concentration, medium polarity, and monomer concentration [33].

Homogeneous Poly(ethylene glycol) (PEG) exhibits a curious combination of properties. Despite having one of the simplest molecular structures, PEG exhibits complicated miscibility in water in the form of closed-loop miscibility [34,35] whereas short chain PEG is extremely soluble in water as well as a variety of organic solvents. The oriented interaction energy between water and PEG is energetically favored, however, the entropically unfavored configuration characteristics of the nonspecific interaction outweighs the oriented interaction energy. Conversely, if methacrylic or acrylic functional groups are replaced on both ends of the PEG chain (i.e., PEGDA or PEGDMA, respectively) their thermodynamic properties such as solubility parameters or miscibility change immediately. These PEG derivative crosslinkers induce different degrees of swelling in hydrogels compared with short chain crosslinkers [36–40].

A number of studies have analyzed the swelling properties of PNIPAM copolymer gels or crosslinkers; however, fundamental research on these hydrogels including batch comparison is not well established. Therefore, we explored PNIPAM-based hydrogels generated with various crosslinkers and comonomers under identical conditions to study the interrelationship between phase transition temperature and swelling capacity. We included three different types of copolymer gels, namely, P(NIPAM-co-EA), P(NIPAM-co-HEMA) and P(NIPAM-co-HEA). These comonomers share a similar molecular structure whereby the HEA has a hydroxyl functional group at the end of EA and HEMA has a methyl functional group at the backbone chain of HEA. Using these hydrogels, characteristic changes in copolymer hydrogels with respect to hydrophilicity and hydrophobicity were clarified both experimentally and theoretically. Furthermore, to investigate the effect of different crosslinker chain length, PNIPAM based hydrogels were synthesized with BIS, PEGDA575, and PEGDA700. We found that the specific combinations analyzed provided enthalpic contributions to the chemical potential of gel networks in equilibrium toward the volumetric phase transition behavior of hydrogels. We also measured the hydrodynamic radius of gel particles using photo correlation spectroscopy (PCS) at various temperatures. We used three different statistical thermodynamic models to describe our experimental results; however, in order to perform quantitative analysis, a slight model change was implemented because classical thermodynamic models cannot be used to describe the individual contributions of each chemical substance. We classified these contributions into binary interaction energy parameters, which were related to the net energetic contribution of each hydrogel component. Furthermore, we utilized molecular dynamics simulations to determine the hydrodynamic conformation of crosslinkers.

Table 1
Experimental set of crosslinkers and copolymers.

Sample no.		Crosslinker	Molar ratio
1	NIPAM	BIS	1
2	NIPAM	PEGDA575	1
3	NIPAM	PEGDA700	1
4	NIPAM-EA-1	BIS	9:1
5	NIPAM-EA-2	BIS	8:2
6	NIPAM-EA-3	BIS	7:3
7	NIPAM-HEMA-1	BIS	9:1
8	NIPAM-HEMA-2	BIS	8:2
9	NIPAM-HEMA-3	BIS	7:3
10	NIPAM-HEA-1	BIS	9:1
11	NIPAM-HEA-2	BIS	8:2
12	NIPAM-HEA-3	BIS	7:3
13	NIPAM-HEMA-2	PEGDA575	8:2

2. Experiment

2.1. Materials

NIPAM, HEMA, HEA, and EA were obtained from Sigma–Aldrich Co. and used without further purification. BIS, PEGDA575, and PEGDA700 were used as crosslinkers and ammonium persulfate was used as an initiator, all of which were obtained from Sigma–Aldrich Co. In this work, no stabilizers were applied to prohibit volumetric change at phase transition temperature. Distilled deionized water was used as a solvent for synthesizing and measuring gel particles.

2.2. Hydrogel preparation

PNIPAM hydrogels with different crosslinkers were prepared by precipitation polymerization. The typical procedure for the polymerization was as follows: NIPAM 0.72 g (6.36×10^{-3} mol) and crosslinker (2 mol% for NIPAM monomer) were placed in a 3 joint neck round bottom flask with 50 ml deionized distilled water. Next, the mixture temperature was raised to 90 °C and stirred for 30 min. After stabilization, 1.2 ml of aqueous ammonium persulfate solution (1 wt% of aqueous solution) was inserted into a flask. After adding all of the chemicals, the mixture was left at a constant temperature and stirred (2 rad/s) for 4 h. The synthesized nano-sized gel solution was filtered immediately using a hydrophobic PTFE syringe filter (mesh size of 0.45 μm) at a solution temperature above 70 °C. To further quench polymerization, the filtered solution was placed into an excess of deionized distilled water at a ratio of five parts water temperature above 70 °C to one part hydrogel solution. This step was emphasized because hysteresis has a decisive effect on the non-reversible transition of nano-sized hydrogels. In addition, we stored all of the stock solutions at 60 °C [29,41]. NIPAM-EA, NIPAM-HEMA, and NIPAM-HEA hydrogels were synthesized using the same procedure. For different monomer ratios of the copolymer gel, the total monomer quantity was maintained at 6.36×10^{-3} mol. The experimental set is listed in Table 1.