Radiation Physics and Chemistry 86 (2013) 145–154

Contents lists available at SciVerse ScienceDirect

Radiation Physics and Chemistry

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

Synthesis of fast response crosslinked PVA-g-NIPAAm nanohydrogels by very low radiation dose in dilute aqueous solution

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HIGHLIGHTS

- A new radiation polymerization method is offered in dilute aqueous solution.
- This method provides PVA-g-NIPAAm nanohydrogels by radiation dose of 1–20 Gy.
- Using THPC and H_2O_2 leads to the polymerization with much less radiation dose.
- The obtained nanohydrogels exhibit fast swelling/deswelling rate.
- Nanohydrogels indicate good rheological properties and biocompatibility.

ARTICLE INFO

Article history:
Received 7 September 2012
Accepted 3 February 2013
Available online 16 February 2013

Keywords:
Thermosensitive
Nanohydrogels
Dilute solution
Radiation
Oxygen scavenger
Crosslinking density

ABSTRACT

Nanohydrogels of poly(vinyl alcohol)-g-N-isopropylacrylamide (PVA-g-NIPAAm) are synthesized by PVA and NIPAAm dilute aqueous solution using much less radiation dose of 1–20 Gy via intramolecular crosslinking at ambient temperature. The radiation synthesis of nanohydrogels is performed in the presence of tetrakis (hydroxymethyl) phosphonium chloride (THPC) due to its rapid oxygen scavenging abilities and hydrogen peroxide (H_2O_2) as a source of hydroxyl radicals. The effect of radiation dose, feed composition ratio of PVA and H_2O_2 is investigated on swelling properties such as temperature and pH dependence of equilibrium swelling ratio as well as deswelling kinetics. Experimental data exhibit high equilibrium swelling ratio and fast response time for the synthesized nanohydrogels. The average molecular weight between crosslinks (M_c) and crosslinking density (ρ_x) of the obtained nanohydrogels are calculated from swelling data as a function of radiation dose, H_2O_2 and PVA amount. Fourier transform infrared spectroscopy (FT-IR), elemental analysis of nitrogen content and thermogravimetric analysis (TGA) are used to confirm the grafting reaction. Lower critical solution temperature (LCST) is measured around 33 °C by differential scanning calorimetry (DSC) for PVA-g-NIPAAm nanohydrogels. Dynamic light scattering (DLS) data demonstrate that the increase of radiation dose leads to the decreasing in dimension of nanohydrogels. Also, rheological studies are confirmed an improvement in the mechanical properties of the nanohydrogels with increasing the radiation dose. A cytotoxicity study exhibits a good biocompatibility for the obtained nanohydrogels. The prepared nanohydrogels show fast swelling/deswelling behavior, high swelling ratio, dual sensitivity and good cytocompatibility, which may find potential applications as biomaterial.

1. Introduction

Nanometer-sized hydrogels (nanohydrogels), which exhibit properties of both nanoparticles and hydrogels, have attracted much attention as objects of study in basic science and as components of materials for cosmetics, biotechnology, encapsulation of bioactive molecules and drug delivery systems (Morimoto et al., 2008; Cherian et al., 2007). In particular, stimuli-responsive hydrogel particles are of great interest since their properties, including their swelling/deswelling behaviors and permeability of substances, can be easily and rapidly controlled by external stimuli, such as temperature, light, pH, and chemical species (Maeda et al., 2009). Among this large group of polymeric materials, temperature-sensitive nanohydrogels based on poly (*N*-isopropylacrylamide) (PNIPAAm) have gathered great interest. One of the most important properties of smart nanohydrogels for potential applications is their swelling/deswelling behavior. The so-called response time of the swelling/deswelling

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http://dx.doi.org/10.1016/j.radphyschem.2013.02.005

process depends on nanohydrogel size and the decrease of hydrogel size has been considered to be the best way to obtain products with sufficient response times (Mendrek et al., 2009; Schmidt et al., 2005; Wang et al., 2011; Kumari et al., 2012; Tasdelen et al., 2004a). Conventional PNIPAAm hydrogels show a relatively slow response rate, poor biodegradability and mechanical properties; while, pure PVA hydrogels are not sensitive to environmental stimuli, but have good mechanical properties, biocompatibility and nontoxicity. Therefore, combining the advantages of PVA and PNIPAAm is needed to prepare a new kind of material (Tan et al., 2010; Zhang et al., 2009a). Many investigations have been performed to synthesize PVA/PNIPAAm interpenetrating (IPN) and semi-interpenetrating (semi-IPN) polymeric network as macroscopic gels to enhance response time and mechanical strength via radical polymerization in the presence of crosslinking agents (Kim et al., 2003a, 2003b, 2003c; Zhang et al., 2003; Szilagyi and Zrinyi, 2005; Molina et al., 2011). However, the use of a chemical crosslinker can lead to structural inhomogeneities. These agents not only affect the integrity of the substances to be entrapped but these agents are often toxic compounds which have to be removed/ extracted from the gels before they can be applied (Gao and Frisken, 2003; Hennink and Nostrum, 2002; Loh et al., 2010; Robinson and Peppas, 2002). In addition, radiation techniques are very suitable tools for the synthesis of biomaterials, especially hydrogels due to the additive-free initiation and easy process control (Rosiak et al., 2003; Ulanski et al. 2002a). It is reported that the irradiation of diluted aqueous solutions (each macromolecule is separated) of poly(vinyl alcohol) PVA with pulsed electron beams (generation of a large number of radicals on each separate polymer chain in a short time) leads to the intramolecular combination of the produced radicals resulting the formation of nanohydrogels. But, radiation polymerization techniques require high radiation dose between tens or hundreds kGy (Ulanski et al., 1998; Tasdelen et al., 2004b; Kadlubowski et al., 2003; Zhuang et al., 2003; Bhardwaj et al., 2003; Panda et al., 2000). Therefore in this work, a convenient radiation preparation method is proposed for the synthesis of PVA-g-NIPAAm nanohydrogels according to advantages of fast response time of nanohydrogels and PVA suitable properties. To perform the polymerization with much less radiation dose (1–20 Gy) that provides a facile and simple equipment method for the synthesis of nanohydrogels in comparison with methods applying high radiation dose or crosslinking agents, the tetrakis(hydroxymethyl)phosphonium chloride (THPC) as rapid oxygen scavenger and H_2O_2 as a source of hydroxyl radicals are used. Synthesis of PVA-g-NIPAAm nanohydrgels are performed with different feed composition ratio of PVA, H_2O_2 and radiation dose to investigate the structure, the swelling behavior, size distribution, LCST, thermal and rheological properties of synthesized nanohydrogels. To evaluate the structure and properties of the obtained nanohydrogels, the theory of Flory (Flory, 1959; Peppas and Merrill, 1977) is used for the case of a swollen network to calculate volume fraction of polymer network after preparation ($v_{2,r}$), volume fraction in the swollen state ($v_{2,s}$), polymer–solvent interaction (χ), the number average molecular weight between crosslinks (M_c) and crosslinking density (ρ_x).

2. Experimental

2.1. Materials

NIPAAm is used as purchased by Acros Organic. PVA with average molecular weight 1.95×10^5 and a degree of saponification of 98 mol% and dialysis membrane (Dialysis benzoylated tubing, MWCO=2000) are used without further purification as supplied by Aldrich. THPC (Merck) and H_2O_2 30% (Scharlau) are used as received.

2.2. Preparation of PVA-g-NIPAAm nanohydrogels

PVA is dissolved in deionized water and heated at 80 °C for 1 h to make a desired aqueous solution. The dissolved PVA solution is mixed with NIPAAm at room temperature. After NIPAAm monomers completely dissolved in the mixture, H_2O_2 30% and THPC are added in the mixture. Then, the mixture is transferred into the glass cells of diameter 15 mm and irradiated with 9 MW radiation beam of X-ray produced by Neptun linear accelerator with fixed dose rate of about 4.5 Gy/min at room temperature. The samples are irradiated inside a water bath and to prevent a gradient and insure the homogeneous dose distribution in the samples, they turned 180° half way through the irradiation. The calibration of the used X-ray Neptun linear accelerator instrument is down according to IAEA protocol and the uncertainty of the given dose is estimated within ±0.5%. Table 1 lists the nanohydrogels' codes, feed ratio and applied dose. After polymerization, the irradiated solution is purified by dialysis against distilled water with dialysis membrane (molecular weight cut off 2000) in order to remove the THPC and unreacted NIPAAm monomers. The deionized water is replaced every 8 h. Then, the nanohydrogel dispersions are freeze-dried and for more purification dried nanohydrogels are immersed in distilled water with water changed repeatedly and then soaked in hot water to remove any sol fractions that are not incorporated into the crosslinked network. Finally, the PVA-g-NIPAAm nanohydrogels are freeze-dried again. The crosslinked PVA and PNIPAAm nanohydrogels are synthesized by the same polymerization method to compare some of their properties with obtained PVA-g-NIPAAm nanohydrogels.

2.3. Characterization of the nanohydrogels by FT-IR

FT-IR spectra of prepared PVA and PVA-g-NIPAAm nanohydrogels are recorded using a Broker Tensor 27 spectrometer with KBr at room temperature. In fact, FT-IR spectra are utilized to confirm occurring NIPAAm polymerization reaction on PVA chains during the grafting process.

2.4. Determination of the nanohydrogels composition

Elemental analysis is performed with an Elementar vario MAX instrument. The NIPAAm content of nanohydrogels is estimated by elemental analysis of nitrogen content.

Table 1
Code, feed ratio and preparation conditions of PVA-g-NIPAAm nanohydrogels.

Codes	PVA (wt%)	NIPAAm (wt%)	THPC (mL)	H_2O_2 (μL)	Radiation dose (Gy)
NHG1	1	1	2	60	1
NHG2	1	1	2	60	5
NHG3	1	1	2	60	10
NHG4	1	1	2	60	15
NHG5	1	1	2	60	20
NHG6	0.5	1	2	20	10
NHG7	2	1	2	20	10
NHG8	1	1	2	20	10
NHG9	1	1	2	40	10
NHG10	1	1	2	80	10
NHG11	1	1	2	120	10
NHG12	1	–	2	60	20
NHG13	–	1	2	60	20
NHG14	1	1	–	60	20