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Research paper

Preparation and properties of controllable amphiphilic P(NIPAM-co-LMA) gel for drug delivery

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ABSTRACT

A series of amphiphilic hybrid gels were prepared by the copolymerization of *N*-isopropyl acrylamide (NIPAM) and lauryl methacrylate (LMA). The structures, thermal properties, mechanical strengths, morphologies and the loading ability of both hydrophilic and hydrophobic drugs of the obtained P(NIPAM-co-LMA) hybrid gels were studied in detail using infrared spectrometer (IR), differential scanning calorimetry (DSC), thermomechanical analysis (TMA), scanning electron microscope (SEM) and confocal laser scanning microscope (CLSM). The increase of LMA percentage resulted to the decrease of the phase change temperature, enthalpy and softening point of the hybrid gel. Further, the surface morphologies of the hybrid gel also changed with different LMA percentage. The water and oil served as the model of hydrophilic and hydrophobic drugs were adopted in the absorption experiments; meanwhile, the temperature responsive behavior was also investigated. The results showed that these hybrid gels were amphiphilic, i.e. both hydrophilic and oleophilic. The water and oil absorption capabilities of the hybrid gel could be adjusted by controlling both the components of the gel and the environment temperature. This new kind of hybrid gel can serve as drug carriers for both hydrophilic and hydrophobic species and may be effectively used in artificial intelligence drug release.

1. Introduction

Hydrogel material is a cross-linked polymer material that can rapidly absorb, reserve and release water but not dissolve in water [1,2]. Its application has penetrated into many areas such as biological engineering, tissue engineering, drug delivery, temperature regulation, desert control, energy saving and environmental protection [3–6]. Smart hydrogels play an important role in hydrogel materials; some of their physical or chemical properties can be modulated by the external stimuli such as light, heat, pH, etc. Among them, poly (*N*-isopropyl acrylamide) (PNIPAM) has attracted wide attention as a special temperature-sensitive hydrogel in recent years [1,2]. The lower critical solution temperature (LCST) of PNIPAM hydrogel is 32 °C. When the temperature is above LCST, the PNIPAM hydrogel turns into a hydrophobic gel that can absorb oil. Since the side molecular chain of PNIPAM is too short, very limited amount of oil can be maintained in the gel [7–10]. Besides this, the inadequate mechanical strength of PNIPAM hydrogel also limits its application in many aspects.

Currently, researchers have tried different methods to modify PNIPAM hydrogel. One solution to improve the mechanical strength of PNIPAM was to introduce organic or inorganic components into the network [11–14]. In Hermann's report, the styrene-butadiene rubber was included to modify PNIPAM hydrogels. When the temperature was lower than LCST, the gel exhibited certain hydrophilicity; if the temperature was higher than LCST, the gel turned into a lipophilic gel [15]. Kim et al. synthesized different PNIPAM hybrid gels P (NIPAM-co-HEMA) and P (NIPAM-co-PEDMA) and proved that the water absorption were gradually declining with the increasing content of lipophilic monomers [16]. Zhang et al. introduced the polyhedral oligomeric silsesquioxane into PNIPAM gel to improve its mechanical strength. And the results proved that the thermal and kinetic properties of the gel were increased significantly [17].

Generally, amphiphilic hybrid gel is an important research area in polymer science and has many applications in the fields of drug

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delivery, biology and materials science [18]. The amphiphilic hybrid gel is a composite gel that consists of both hydrophilic and oleophilic segments; it is usually synthesized by the copolymerization of two or more monomers with different solvent affinities.

Lauryl methacrylate (LMA) is frequently used as a common monomer of oil-absorbing resin [19–21]. The C_{12} in pendant group makes LMA submissive and soft, which can be used to improve the flexibility of a hybrid gel. Liu et al. [22] synthesized P (LMA-co-DAEMA) which was proved to have remarkable elasticity. Li et al. used LMA to improve the oleophilic/hydrophobic properties of polyurethane foams for oil spill cleanup.

In this report, NIPAM and LMA were used to prepare P (NIPAM-co-LMA) amphiphilic hybrid gel for drug delivery. LMA was designed to work as the oleophilic segment, meanwhile, the hydrophilicity of NIPAM segment could be adjusted by temperature. The structures and drug loading properties of the hybrid gel were explored in detail. This kind of hybrid gel may expand the application of PNIPAM gel by improving its mechanical strength and oleophilic property.

2. Material and methods

2.1. Materials

N-Isopropyl acrylamide (NIPAM) was bought from Guoyao Co., Nanjing, China and was purified by recrystallization in hexane and dried in vacuum at room temperature before use. Lauryl methacrylate (LMA) was purchased from Aoke Co., Shanghai, China. Divinylbenzene (DVB) was obtained from TCI Co., Japan. *N,N′*-azodiisobutyronitrile (AIBN) was got from Wanqing Co., Nanjing, China. Fluorescein isothiocyanate (FITC) and Nile red were bought from Sigma–Aldrich. All the solvents toluene, carbon tetrachloride, water and ethanol were purchased from Damao Chemical Reagent Co., Tianjin, China.

2.2. The preparation of P (NIPAM-co-LMA) hybrid gel

The reaction was carried out in a 100 ml three-necked flask equipped with thermometer, nitrogen gas inlet and reflux condenser. 1.0 g NIPAM was dissolved in 30 ml toluene in the flask, and then 0.02 g AIBN was added into the flask and the mixture was stirred at room temperature for 30 min. Subsequently, a mixture containing certain amounts of LMA (0, 0.1, 0.4, 0.8 g) and 0.05 g DVB were added into the flask at once. The mixture was allowed to stir for 10 min. Then, the mixture was heated to 70 °C for 6 h under the protection of nitrogen atmosphere. The obtained P (NIPAM-co-LMA) hybrid gel was washed with ethanol and deionized water for several times, then dried at 60 °C under vacuum for 48 h.

2.3. Water and oil absorption capacity test

The water and oil sorption capacity of the hybrid gel was measured according to ASTMF726-99: Standard test method for sorbent performance of adsorbents. For water absorption measurement, firstly, 40 ml deionized water was poured into a 250 ml beaker. The dry P(NIPAM-co-LMA) gel was weighed and the weight was recorded as M_1. Then the gel was immersed into the deionized water for about 12 h. After that, the gel was taken out and cleaned by adsorption paper to remove the water attached on the surface. The gel was weighed immediately and the weight was recorded as M_2. The water sorption of P (NIPAM-co-LMA) could be calculated using the following equation:

$$\text{Water Absorption (g/g)} = (M_2/-M_1)/M_1 \tag{1}$$

The M_1 was the initial weight of dry hybrid gel and the M_2 was the weight of water saturated hybrid gel.

While for the oil absorption test, the gel that was saturated with water was immersed into 100 ml toluene in beaker. The beaker was shaken for 12 h and stood for 2 h. The gel was taken out and weighted immediately after cleaned by adsorption paper. The weight was recorded as M_3. The following equation was used to calculate the oil sorption of P (NIPAM-co-LMA) gel:

$$\text{Oil absorption (g/g)} = (M_3 - M_2)/M_2 \tag{2}$$

The M_2 was the weight of water saturated hybrid gel, and the M_3 was the weight of the hybrid gel saturated with both water and oil.

2.4. Characterization

The morphology of the P (NIPAM-co-LMA) gel was observed by field emission scanning electron microscopy (FE-SEM, FEI F50, Hong Kong, China). The hybrid gel was freeze-dried and then a small slice was cut off. The small piece of the hybrid gel was fixed on a silicon chip by conductive tape and sprayed with gold before conducting SEM tests. The FTIR spectrum of P (NIPAM-co-LMA) hybrid gel was recorded by a Fourier transform infrared (FTIR Prestige-21, Bruker, Germany). All of the samples were scanned from 4000 cm^{-1} to 400 cm^{-1}. The phase transition temperature of the hybrid gel was measured by differential thermal scanners (DSC, SDT-Q600, TA, USA) at 1 K/min rate up to 40 °C under N_2 atmosphere. The mechanical properties of the hybrid gel were investigated by static thermal mechanical analyzer (TMA 402 F3, Netzsch, Germany) at the temperature range from 20 °C to 60 °C and rate of 5 °C/min.

2.5. The distribution of the internal water/oil

In order to research the distribution of the internal water/oil phase in the hybrid gel, FITC-BSA and Nile red were used to dye oil phase and water phase. Firstly the hybrid gel was immersed into the FITC-BSA solution (0.01 g FITC-BSA was dissolved in 50 ml deionized water). Next, the hybrid gel was transferred to the Nile red solution (0.01 g Nile red was dissolved in 50 ml toluene). Then the gel was taken out and cleaned for next step measurements. Confocal laser scanning microscopy (CLSM: TCSP, Bruker, Germany) was used to scan the distribution of water and oil phase. The excitation wavelength was 488 nm and the green and red fluorescence spectrums were collected simultaneously by the detector respectively and integrally.

3. Results and discussion

3.1. The chemical structure of the P (NIPAM-co-LMA) hybrid gel

In this paper, P (NIPAM-co-LMA) hybrid gel was prepared by the copolymerization of LMA and NIPAM. Fig. 1 shows the schematic map of the preparation of P (NIPAM-co-LMA) hybrid gel. Totally, five different hybrid gels were synthesized and their formulas are shown in Table 1. Among them, the usages of NIPAM, DVB, AIBN and toluene were fixed and the mass of LMA was increased from 10 wt% to 80 wt% of NIPAM gradually.

FTIR was used to study the copolymerization of LMA and NIPAM and the results are shown in Fig. 2. All the samples had the absorption peaks at the range of 2880–2900 cm^{-1}, 1650–1750 cm^{-1} and 1050–1150 cm^{-1}, which were attributed to the stretching vibration of —C—H—, —C═O— and —C—O— respectively. The samples labeled with A, B, C, and D that contained NIPAM monomer had absorption peaks of N—H stretching at 3000-3500 cm^{-1}. In P