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Flow and aggregation characteristics of thermo-responsive poly(*N*-isopropylacrylamide) spheres during the phase transition

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Abstract

To date, a great many researches were focused on improving stimuli-responsive and controlled-release properties of thermo-responsive hydrogel carriers, whereas for the research on flow characteristics during the phase transition, prior reports have not been found. In this paper, poly(*N*-isopropylacrylamide) (PNIPAM) spheres with thermo-responsive phase transition characteristics were prepared by cross-linked polymerization. In a transparent Pyrex glass pipe with hydrophilic inner wall, flow and aggregation characteristics of PNIPAM spheres during the phase transition from low temperature which was lower than the lower critical solution temperature (LCST) to high temperature ($T >$ LCST) was studied for the first time. Many interesting phenomena about the flow and aggregation behaviors of PNIPAM spheres were found. The velocity of PNIPAM spheres in horizontal pipe decreased from 1.07 cm/s before the phase transition to 0.65 cm/s or even became zero after the phase transition, which is what targeting drug delivery systems desired. When the initial distance was about 5.5 mm at the entrance of testing pipe section, the PNIPAM spheres could aggregate together after the phase transition and subsequently roll forward; but when the initial distance was as large as 8.5 mm, the distance became close at first during the phase transition and then far after the phase transition. Similar results were also found as mentioned above in vertical pipe. When 10 spheres aggregated together, they stopped at a certain position just after the phase transition in horizontal pipe. If the flowrate was more than 40 ml/min, the aggregation configurations such as triangle, tetrahedron, hexahedron and octahedron which formed after the phase transition at flowrate of 20 ml/min disappeared. The results provided valuable information for future applications of thermo-responsive PNIPAM spheres.

Keywords: Fluid mechanics; Gels; Polymers; Laminar flow; Thermo-responsive poly(*N*-isopropylacrylamide); Phase transition

1. Introduction

Environmental stimuli-responsive systems are getting more and more attention all over the world. These systems can respond to changes in environmental temperature (Okano et al., 1990; Yoshida et al., 1994, 1995; Cammas et al., 1997; Chung et al., 2000; Ichikawa and Fukumori, 2000; Chu et al., 2001, 2002b, 2003, 2005; Xiao et al., 2003, 2004), pH (Yoshida et al., 1999; Caykara and Aycicek, 2005; Jin and Hsieh, 2005; Nho et al., 2005; Tripodo et al., 2005; Wang et al., 2005), light (Rasmussen et al., 2002) and other information (Chu et al., 2002a; Chu et al., 2004). There are many cases where environmental temperature fluctuations occur naturally, and in which the environmental temperature stimuli can be easily designed and artificially controlled. Recently, much attention has been focused on thermo-responsive controlled-release systems. In these systems, temperature variation triggers alteration of polymer configurations, leading to the change of release rate of compounds incorporated in the systems. Thermo-responsive hydrogels are the most commonly studied class of environmental stimuli-responsive polymer systems. The inverse temperature-dependent hydrogels are made of polymer chains that either possess moderately hydrophobic groups or contain a mixture of hydrophilic and hydrophobic segments (Qiu and Park, 2001). Poly(*N*-isopropylacrylamide) (PNIPAM) has both isopropyl (hydrophobic) and amidogen (hydrophilic) groups, hydrogels made of PNIPAM can deswell as the temperature increases above the lower critical solution temperature (LCST) and swell as the temperature decreases below

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the LCST. Because of the dramatic thermo-responsive characteristics, PNIPAM has been extensively used in environmental stimuli-responsive systems.

Many applications for environmental stimuli-responsive controlled-release systems were focused on the field of pharmaceutical and drug delivery systems. Various environmental stimuli-responsive drug carriers with good controlled-release property have been prepared, e.g., thermo-responsive hydrogel spheres. Some applications for environmental stimuli-responsive hydrogel spheres were focused on cell separation (e.g., Arai et al., 2005), enzyme immobilization (e.g., Kondo and Fukuda, 1997) and so on. Most of the previous researches were focused on improving stimuli-responsiveness (e.g., Lizawa et al., 2005; Wei et al., 2005; Zhang and Chu, 2005) and controlled-release properties (e.g., Hsiue et al., 2002; Eeckman et al., 2003; Huang et al., 2004); however, for the flow characteristics of the hydrogel spheres during the phase transition, prior reports have not been found to the best of our knowledge. For drug delivery and other applications, kinetic characteristic of the hydrogel spheres is one of the important factors which have direct effect on applications.

In the present study, thermo-responsive PNIPAM spheres were prepared by the well-known cross-linked polymerization. Thermo-responsiveness of the PNIPAM spheres were investigated via measuring the temperature-dependent volume variation, and flow and aggregation characteristics of the PNIPAM spheres during the phase transition in a transparent glass pipe with hydrophilic inner wall were studied systematically. The temperature range in the testing pipe section was designed from 23 to 43 °C in order to cross over the LCST of PNIPAM. The PNIPAM spheres were put into the pipe at a certain fluid flowrate, and a digital pickup camera was used to record the flow and aggregation behaviors of the spheres during the phase transition. The average velocities of the PNIPAM spheres were calculated through the distance and time interval.

2. Experimental

2.1. Materials

N-isopropylacrylamide (NIPAM) was kindly provided by Kohjin Co., Japan, and was used after purifying three times by recrystallization in hexane and acetone. *N*,*N*-Methylene-bis-acrylamide (MBA) and ammonium persulpnate (APS) were purchased from Chengdu Kelong Chemicals. Tetramethylethylenediamine (TEMED) and paraffin oil were purchased from Chengdu Sitong Chemicals.

2.2. Preparation of PNIPAM hydrogel spheres

PNIPAM spheres were prepared by the well-known cross-linked polymerization. First, NIPAM (1.13 g) and MBA (0.0154 g) were dissolved in 10 ml of de-ionized water (solution A) and 0.2 ml TEMED was dissolved in 4 ml of de-ionized water (solution B). Then, 0.3 ml of 10% APS solution and 0.3 ml of solution B were added in succession to solution A. The solution was quickly stirred and then dropped dropwise into paraffin oil by glass syringe. The solution forms spherical droplets on the bottom surface of the dish. The droplets become gels within 5 min. Then, the hydrogel spheres were put into de-ionized water with room temperature (about 20°C), in which they swelled with the water. In the preparation, the temperature of the paraffin oil was kept at a constant 50 °C using a thermostatic unit. The diameter of the sphere was controlled by the size of needle and the extruding speed. The PNIPAM spheres with the same diameter were picked out for the measurement of flow and aggregation characteristics.

2.3. Measurement of thermo-responsive volume change characteristics of PNIPAM spheres

The prepared PNIPAM spheres were taken out of the paraffin oil and put into de-ionized water for a week, exchanging with fresh de-ionized water every 12–24 h to remove surplus oil and impurities until they reached the swelling/deswelling equilibrium state with de-ionized water. Then, PNIPAM spheres were put into thermostated water bath, in which the water temperature was changed from 10 to 49 °C. The diameter of the sphere was measured every 3 °C, and the volume of the sphere was calculated as a function of temperature. The volume change ratio was defined as the ratio of the volume of the sphere at every fixed temperature to that at 49 °C.

2.4. Measurement of flow characteristics of PNIPAM spheres during the phase transition

The apparatus for measuring flow characteristics was designed as shown in Fig. 1. The inner wall of the transparent Pyrex glass pipe was pre-treated to be hydrophilic. In the section between points A and B, the temperature range was designed to include the LCST of PNIPAM. The interior diameter of the pipe was 6.4 mm, and the length of section AB was 400 mm. Digital pickup camera was used to record flow behaviors of PNIPAM spheres inside the pipe during the phase transition. Because the operating temperature of the rotameter flowmeter should be room temperature (about 20 °C), much lower than outlet temperature (about 43 °C), a cooling bottle was used. Before the experiment of measuring the flow characteristics of the spheres, the following considerations should be confirmed.

First, it was necessary to confirm that the range of Reynolds number fell in laminar flow, since the character of blood flow is viscous laminar flow in micro-blood circulation system. The pressure drops were measured at different flowrates, the results showed that in this experiment, the Reynolds number for laminar flow should be lower than 547. Therefore, the flowrates in the subsequent experiments were selected from 20 to 60 ml/min. At each flowrate, PNIPAM hydrogel spheres with the same diameter were put into the pipe and the motions were recorded.

Second, the temperature distribution along the testing tube should be confirmed. Considering the classical principle of convection heat transfer in the counterflow heat exchanger, the boundary conditions of constant thermal flow density was used