Thermosensitive capsules via a facile water-based core-removal process

Yan Chen [a], Shahriar Sajjadi [b],*

[a] Department of Mechanical Engineering, Kings' College London, London, UK
[b] Department of Physics, Kings' College London, London, UK

ABSTRACT

The use of water-soluble polyNIPAM nanoparticles as core templates for making capsules offers significant advantages over conventional core materials which need extra efforts for removal. In this work, a seeded semicontinuous heterophase polymerisation was applied to fabricate fully water-disintegrable polyNIPAM core materials. This novel core template could be easily and completely removed via disintegration and dissolution in water at room temperature, in contrast to the cores made via conventional method which had limited water solubility and at best could produce semi-hollow capsules. The advantage of the suggested one-pot method is more pronounced if capsules with thicker shells are sought.

© 2013 Elsevier Ltd. All rights reserved.

1. Introduction

Functional nanomaterials with cavity-containing or hollow structures have found great interest in recent years due to their potential applications as drug carrier and delivery systems, microreactors, protective shields for bioactive materials and biosensors [1–3]. The most conventional strategy used to prepare polymeric nanocapsules is based on templates [4–8], which provides a good control of cavity size as well as the monodispersity of final products. Poly(n-isopropylacrylamide) (polyNIPAM) has been investigated as a potential core template due to its thermosensitive phase transition at the lower critical solution temperature (LCST), which is around 32 °C in the water phase [9]. Application of poly-NIPAM as core templates for making nanocapsules [10] [11–13], first reported by Weda et al. [13], offers significant advantages over conventional core materials which need multistep procedures for removal such as hydration, degradation with enzyme or wet etching with toxic or corrosive chemicals [4, 14–17]. Du et al. used polyNIPAM polymer produced via solution polymerisation at a temperature below LCST as a reusable template which could form core aggregates at temperature above LCST [10]. However, this method has several drawbacks, such as low solids content (<0.5 wt %), limited stability and high polydispersity of resulting particles [10]. The polydispersity of particles can be improved in the

presence of surfactant [13]. Uniform particles can be best obtained via emulsifier-free heterophase polymerisation [18]. Qian and Wu [11] produced crosslinker-free polyNIPAM particles via batch heterophase polymerisation above LCST and used them as the core material for making nanocapsules in water above LCST. Heterophase polymerisation of NIPAM appears to be an ideal choice for marking water-soluble polyNIPAM nanoparticles. However, conventional heterophase polymerisation usually produces polyNIPAM particles that are not fully soluble in water (below LCST) even in the absence of crosslinker [19–21]. This has been mainly attributed to physical entanglements of the chains [19] or network formation due to chain transfer to polymer [20]. We have found that only particles formed using a very low monomer concentration ([NIPAM] < 0.25 wt%), which have a low molecular weight ($\overline{M}_w$ < 170 kDa) and small size (D_z < 160 nm), are fully water soluble when temperature is below LCST [21]. A limited solubility in water can be considered as an obstacle for the use of polyNIPAM particles as core materials. The use of redox initiation system can improve the water solubility of polymer but introduces significant instability to the particles so that the use of surfactants such as sodium dodecyl sulphate becomes inevitable. For many applications, the presence of surfactant is usually not desirable because it can adversely affect the characteristics of the final products [19].

Very recently, we have discovered that polyNIPAM particles produced via semicontinuous heterophase polymerisation in the absence of crosslinker can dissolve in water quickly and completely below the LCST temperature [21]. We attribute this feature to the low molecular weight and layered orientation of polymer chains at

* Corresponding author. Tel.: +44 (0) 20 78482322.
E-mail address: shahriar.sajjadi-emami@kcl.ac.uk (S. Sajjadi).

the surface of particles, which allow the chains to disentangle and dissolve simultaneously. This finding suggests that the semicontinuous route may be an ideal way for making the core materials for polyNIPAM nanocapsules. The advantage of using crosslinked polyNIPAM as the shell membrane is that the hydrophilicity, permeability as well as the capacity of capsules can be controlled by temperature. In this case, the load and release behaviour of the capsule can be easily switched via changing the temperature, which is a desired feature for biomedical applications.

In this work, in order to verify such hypothesis, crosslinker-free polyNIPAM particles were synthesized via semicontinuous heterophase polymerisation and used as templates to produce polyNIPAM nanocapsules. Semicontinuous approach is usually used for producing the shell in core–shell particles [22]. In this research, however, we also use it for making the cores. The conventional batch heterophase polymerisation was also carried out to produce the cores for the sake of comparison. The crosslinked polyNIPAM shells with different thickness were always produced using the semicontinuous route for both types of cores. Furthermore, the release behaviour of preformed shell membrane was also studied.

2. Experimental

Chemicals: Analytical grade potassium persulfate (KPS) (Aldrich) and sodium hydrogen carbonate (Aldrich) were used as initiator and buffer, respectively. *N*-isopropylacrylamide monomer was supplied at 99% purity by ACROS. *N,N'*-Methylene bisacrylamide (MBA) was received from Aldrich.

Procedure: Polymerisations were carried out at 60 ± 1.0 °C in a conventional stirred vessel under nitrogen atmosphere [21]. The reactor was initially charged with 200 ml of de-ionised water, buffer (0.0672 g, 4.0 mmol·l_{aq}^{-1}), KPS (0.2163 g, 4.0 mmol·l_{aq}^{-1}) and NIPAM (0.50 g, 0.25 wt%). The rest of the monomer was placed in a jacketed dosing funnel and melted at 60 °C with the help of a few drops of water. After 20 min into reactions, the melted monomer was added dropwise to the reaction vessel at a constant rate. Crosslinked shells were then manipulated on the surface of preformed seed particles by the gradual addition of the monomer/crosslinker mixture (containing 98 wt% of NIPAM and MBA at ratios given in Table 1 plus 2.0 wt% of water) at 60 °C to the reactor at a constant rate. Polymerisations involved several stages as given in Table 1. When polymerisations were completed, a simple core removal process was carried out. Latexes were cooled to room

Table 1
Recipes for synthesis of polyNIPAM core–shell particles. Reaction temperature: 60 °C, $C_{KPS} = C_{Buffer} = 4$ mmol·l_{aq}^{-1}.

Stage-process[a]	Description	[NIPAM] (wt%)	[MBA] (wt%)	Feed rate (g min^{-1}·l_{aq}^{-1})	D_z[b] (nm)
1-B	Seed formation	0.25	0.0	–	108
2-S	Seed growth	0.75	0.0	0.22	285
3-S	Shell formation	1.0	0.1	0.24	370[c]
		2.0	0.2	0.24	435[d]
4	Core-removal	–	–	–	300[c]
	process	–	–	–	350[d]

[a] B and S stand for batch and semicontinuous processes, respectively. Two experiments were conducted with [NIPAM] = 1.0 and 2.0 wt%, and labelled as S1 and S2, respectively. For the sake of comparison, the conventional route for seed synthesis, in which stages 1 and 2 were combined in one batch heterophase polymerisation, was also carried out, followed by the same procedures as described for stages 3 and 4. Latexes with [NIPAM] = 1.0 and 2.0 wt% were labelled as B1 and B2, respectively. The z-average diameter of core and core–shell particles from this route were the same as those described above for the corresponding seeded semicontinuous runs.
[b] z-average diameter of particles was measured by DLS at 60 °C.
[c,d] The z-average diameter of core-shell particles and corresponding diameter of capsules, respectively, after core removal.

temperature, diluted with de-ionised water by 10 times, and then stored in stirred sealed glass bottles for a week. Selected samples, taken at desired time intervals, were then washed via centrifugation to separate the serum from the gel. The serum (top layer) was used for the release measurements, and the bottom layer for morphology study of particles.

Characterisation: Conversions were estimated gravimetrically. Around 1 g of polymer latexes was removed from the reactor and placed in a weighed aluminium foil plate. The polymerisation was stopped by adding a small amount of methanol and hydroquinone to the sample. The polymer precipitated, and then the mixture was dried in an oven at an elevated temperature (80 °C) to a constant weight (for 48 h). NIPAM monomer was found to sublime under such conditions [21].

Particles morphology was visualized by SEM (Hitachi, S4000) and TEM (Nippon, 200 kv). For SEM study, a drop of latexes was placed on a small piece of glass substrate, dried and then coated with a layer of carbon. For TEM study, a drop of latexes was deposited on a copper grid coated with carbon and dried.

The weight-average molecular weight ($\overline{M}_w$) of particles was measured via Static Light Scattering mode of Zetasizer Nano (Malvern, UK) using toluene and water as standard and solvent, respectively. Samples from stage 2 latexes (as defined later) were diluted with de-ionised water, and then stored in stirred sealed glass bottles at room temperature for a week. The sol, extracted from the gel by centrifugation, was dried in the oven and the polymer content was weighed (similar approach was also used for monitoring the release efficiency in core-removal process). Polymer aqueous solutions with a range of concentrations from 0.25 to 1.0 g·l_{aq}^{-1} were produced. For each sample, the scattering intensity of four concentrations of the polymer solution was measured and used to construct a Debye plot, from which the weight-average MW could be obtained.

The z-average diameter of particles (D_z) was measured at desired temperature using DLS (Zetasizer Nano; Malvern, UK). By examination of selected samples of crosslinked particles with TEM, the conversion factor of $C_f = 0.90$ was obtained, and used for converting D_z data from DLS to the volume-average diameter of particles (D_v) from TEM. The number of particles (N_p) was calculated using the equation $N_p = 6m_p/\pi D_v^3 \rho_p$, where m_p gives the mass of polymer in the system at any given time and ρ_p is the density of polyNIPAM which is 1.269 g·ml^{-1} [23]. A correction has been made in the calculation of N_p, so that $N_{p,corrected} = 1.4 N_p$. This is based on the assumption that 32 wt% of polyNIPAM phase above LCST is water [24].

The temperature dependence of the phase transition of polyNIPAM was determined using ultraviolet-visible spectroscopy (PerkinElmer, USA). The transmittance was measured as a function of temperature (°C) at the wavelength of 600 nm. Samples taken from the reactor at the end of stage 2 (core growth) were not allowed to cool down and directly used, after dilution with water, for measurements.

3. Results and discussion

3.1. Methodology

Fabrications of nanocapsules were carried out according to the following four stages, as depicted in Scheme 1:

Stage 1- Fabrication of seed core particles via batch heterophase polymerisation: Crosslinker-free polyNIPAM particles were synthesised as core template via surfactant-free heterophase polymerisation at 60 °C with 0.25 wt% of NIPAM monomer. This concentration of monomer was found to be the threshold