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RESEARCH ARTICLE

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Generalization of *in-situ* polymerization method for preparing core-shell polymeric nanospheres and hollow spheres

Abstract According to the new method of preparing core-shell nanospheres developed by our group, by using two monomers, 2-hydroxypropyl methacrylate(HPMA) and vinyl acetate(VAc), two kinds of core-shell nanospheres with poly(ε-caprolactone) (PCL) as the core and crosslinked poly(2-hydroxypropyl methacrylate) (PHPMA) or poly(vinyl acetate) (PVAc) as the shell were successfully prepared under similar conditions. After degrading the PCL cores of the two kinds of nanospheres by lipase, the corresponding crosslinked poly(methyl acrylic acid) hollow spheres and crosslinked poly(vinyl alcohol) hollow spheres were obtained. Results indicate that the new method we proposed for preparing core-shell polymeric nanospheres via *in-situ* polymerization can be generalized to a certain extent, and it is suitable for many systems provided the monomer used is soluble in water, while its corresponding polymer is insoluble in water.

Keywords core-shell structure, polymeric nanospheres, hollow spheres, preparation, generalization

1 Introduction

Due to their characteristics of small size, large total surface area, big inner cavity, and stable structure, polymeric hollow nanospheres have potential applications in various fields and thus have become a subject of intensive studies. Core-shell micelles or vesicles of block copolymers are frequently used as the precursor of polymeric hollow spheres [1–7]. The "layer-by-layer (LBL)" technique via alternative deposition of oppositely charged polyelectrolytes on latex particles [8–9], "*in-situ*" polymerization on the templates of organic nanoparticles or vesicles [10–13], and micro- or mini-emulsion polymerization [14–18] all can be used to fabricate hollow spheres. Recently, some new approaches to the hollow spheres have been reported: assembly of amphiphilic graft copolymers at the water-oil interface [19], assembly of silica and gold nanoparticles cooperatively with block copolypeptides [20], "*in-situ*" polymerization of acrylic acid in the presence of chitosan [21], formation of core-shell nanoparticles based on polycondensation of organosilanes and subsequent removal of the non-bonded chains from the core [22].

A novel route to thermosensitive polymeric core-shell aggregates and hollow spheres was reported by our group [23]. Specifically, co-polymerization of N-isopropylacrylamide (NIPAM) and crosslinker methylene bisacrylamide (MBA) was localized around the surface of the poly(ε-caprolactone) (PCL) nanoparticles dispersed in water by using hydrophobic azodiisobutyronitrile (AIBN) as the initiator. As the reaction occured at a temperature above the lower critical solution temperature (LCST) of PNIPAM copolymers, once the polymer chains were formed, they simultaneously collapsed and covered the PCL nanoparticles, and thus leading to nanoparticles with a PCL core and a crosslinked PNIPAM shell. The crosslinked PNIPAM hollow spheres were then obtained after degrading the PCL core by lipase. In this method the assembly of the two polymers and the formation of the shell polymer take place simultaneously, thus it is called an "*in-situ* polymerization method". In principle, the method can be adopted in systems where the monomer is soluble in water while the corresponding polymer is insoluble in water at the reaction conditions.

In order to study the generality of the method, in this paper, two monomers, 2-hydroxypropyl methacrylate(HPMA) and vinyl acetate(VAc), were used. Thus two kinds of core-shell nanospheres with PCL as the core and crosslinked PHPMA or PVAc as the shell were prepared under similar conditions, and the corresponding hollow spheres were further obtained by degradation of PCL with lipase.

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2 Experimental

2.1 Materials

Poly(ε-caprolactone)(PCL) with $M_w = 33\,000$ is a product of Scientific Polymer Product Inc., carrying both hydroxyl and carboxyl groups at the chain ends. Methylene bisacrylamide (MBA) and azodiisobutyronitrile (AIBN) were re-crystallized from methanol twice before use. The 2-hydroxypropyl methacrylate (HPMA, Acros) and vinyl acetate (VAc) were purified by vacuum distillation after overnight drying with calcium chloride. The 2-(diethylamino)ethyl methacrylate (DEA, Acros) was purified by vacuum distillation after overnight drying with calcium hydride. *N,N*-dimethyl formamide (DMF), NaOH and lipase (lipolase, Novozymes Co., Sigma) for PCL degradation were used as received.

2.2 Preparation of core-shell polymeric nanospheres

Initiator AIBN was dissolved in a solution of PCL in DMF. The solution was then added dropwise into water purged with nitrogen at a ratio of 1:10(*V*/*V*), and constant stirring was applied for 0.5 h followed by adding monomer HPMA or VAc and the cross-linker MBA (all dissolved in water). After 15 min of stirring, the temperature was raised to 76°C, and the reaction was allowed to proceed for about 4 h. The solution was then transferred to a dialysis bag and dialyzed against de-ionized water for 3 d to remove DMF, un-reacted monomer and cross-linker. Finally, a little of indissoluble impurities in the solution were removed by filtration.

2.3 Preparation of polymeric hollow spheres

Lipolase solution (Novozymes Co.) was added at a ratio of 1:20(*V*/*V*) to the dispersions of the resultant nanospheres followed by mild stirring for 5 d at room temperature. The solution was then dialyzed against water for 3 d and allowed to stand for several days. The dispersions of hollow spheres were obtained after discarding insoluble products settled on the bottom.

2.4 Characterization of core-shell polymeric nanospheres and hollow spheres

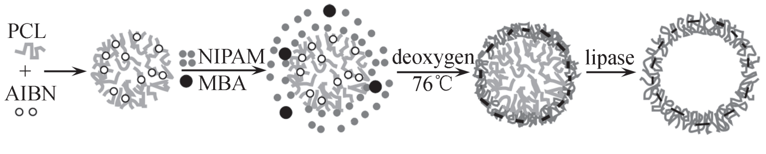
Light scattering measurements were carried on a Malvern Autosizer 4 700 at 90° and (25 ± 0.1)°C. Fourier transform infrared (FTIR) spectra were obtained on a Nicolet Magna-550 spectrometer. Transmission electron microscopy (TEM) observations were performed on a Philips CM120 electron microscope at an accelerating voltage of 80 kV.

3 Results and discussion

The process for preparing PCL/PNIPAM core-shell nanospheres and crosslinked PNIPAM hollow spheres via "*in-situ* polymerization method" is illustrated in Scheme 1 [23]. First, the soapless PCL nanoparticles loaded with AIBN were prepared; hydrophilic monomer NIPAM and crosslinker MBA were then added. After that, the temperature was raised to initiate polymerization. At the initial stage of the reaction, the reaction centres, i.e. radicals, mainly resided on the surface of the hydrophobic PCL nanoparticles. As a result, most of the hydrophilic monomers and crosslinkers in the water would polymerize on the surface of PCL nanoparticles. Of course, due to the presence of a very small amount of AIBN, minor polymerization also occurred in the water phase.

After the reaction was initiated, the monomers and crosslinkers absorbed onto the surface of PCL nanoparticles polymerized first. At the reaction temperature, once the crosslinked PNIPAM chains formed, they collapsed immediately. The water would then be excluded from the interface of crosslinked PNIPAM and PCL nanoparticles due to the hydrophobic interactions. Hence, with the assistance of the interpolymer hydrogen bonding, the crosslinked PNIPAM would cover the PCL nanoparticles, and make it difficult for radicals produced in inner core of PCL nanoparticles to diffuse into the water phase, which allows localized polymerization around the surface of PCL nanoparticles. On the other hand, the first PNIPAM layer formed could further trap the monomer and crosslinker from the water phase, so that the polymerization would continue and the shell grow, and thus core-shell micellar structure forms.

From the mechanism of the formation of PCL/PNIPAM nanospheres described above, one can understand that the initiation on the surface of hydrophobic nanoparticles, the hydrophilicity of monomer and crosslinker, and the hydrophobicity of the polymer at the reaction condition are the key points in preparing the nanospheres. The monomers and crosslinkers, which may meet the requirements, all could possibly lead to the formation of core-shell nanospheres. In order to verify the generality of the method, we studied the preparation of core-shell nanospheres for other two systems, i.e. HPMA and VAc where the monomers are water-soluble



Scheme 1 Schematic illustration of the preparation route to PCL/PNIPAM core-shell nanospheres and hollow spheres of cross-linked PNIPAM

and the corresponding polymers are water-insoluble. The preparations were carried out at the following conditions: the concentration of the PCL/DMF solution, the feed weight ratio of the total monomer to PCL, the target crosslinking degree of the shell, and the content of AIBN (molar percent of the total monomer) were 7.5 mg/mL, 2:1, 5 mol.% and 1.5 mol.%, respectively. The obtained dispersions of PCL/PHPMA and PCL/PVAc core-shell nanospheres were denoted as NH7.5-2-5 and NV7.5-2-5, respectively.

Figure 1 displays FTIR spectra of soapless PCL nanoparticles, nanospheres NH7.5-2-5 and NV7.5-2-5. Poly(ε-caprolactone) (PCL), poly(2-hydroxypropyl methacrylate) (PHPMA), and poly(vinyl acetate) (PVAc) are all esters and similar in their structures. One can differentiate PHPMA from PCL by the hydroxyl groups. From spectrum (B) of Fig. 1 one can see a clear absorption peak characteristic of hydroxyls around 3 400 cm^{-1}, which indicates a layer of crosslinked PHPMA covering the surface of PCL nanoparticles. Although there are no characteristic groups for differentiating between PCL and PVAc, spectra (A) and (C) in Fig. 1 do show some differences in figure-print regions (1 500−500 cm^{-1}). For example, spectrum (C) displays a band around 1 170 cm^{-1}, characteristic of the vibration absorption of C—C skeleton of the side alkane; in addition, the absorption band around 720 cm^{-1} in spectrum (A) has larger intensity and lower peak location than those in spectrum (C), revealing the structure of several contiguous methylene of PCL. Therefore, a shell layer of crosslinked PVAc was also produced on the surface of nanospheres NV7.5-2-5.

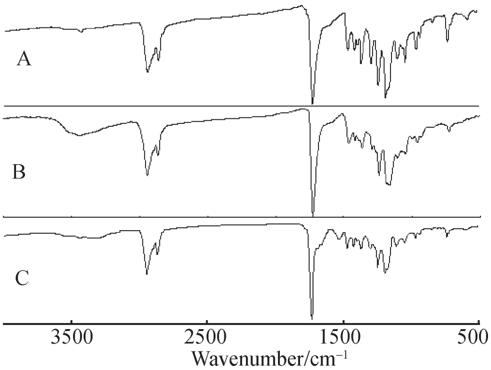


Fig. 1 FTIR spectra of (A) PCL nanoparticles; (B) nanospheres NH7.5-2-5; (C) NV7.5-2-5

Figure 2 exhibits hydrodynamic diameter distribution curves of as-prepared, stored, and sonicated NH7.5-2-5 dispersions. It can be seen from Fig. 2 that the as-prepared NH7.5-2-5 dispersion has a very narrow size distribution, its <D_h> and polydispersity index (PDI) are 131.9 nm and 0.07, respectively. The diameter of nanosphere NH7.5-2-5 is larger than that of the template PCL nanoparticles (116.9 nm, determined by dynamic light scattering, DLS), demonstrating that a shell layer of crosslinked PHPMA is formed on the surface of PCL nanoparticles via "*in-situ* polymerization". Although both the PCL and PHPMA are hydrophobic, PCL/PHPMA nanospheres NH7.5-2-5 can exist stable in water. The possible reason is that the hydrophobic layer of PHPMA is formed *in-situ* on the surface of the PCL nanoparticles. During polymerization the hydrophilic hydroxyl groups of PHPMA may selectively distribute on the outer surface of the nanospheres. Consequently, PCL/PHPMA nanospheres can exist in water with a fairly good stability. DLS results show that the <D_h> (234.9 nm) and PDI (0.24) of the dispersion of PCL/PNIPAM nanospheres increased substantially after it was stored for a period of time, indicating some aggregations between the nanospheres. However, after sonification of the dispersion, the aggregated PCL/PHPMA nanospheres could be re-dispersed perfectly, its <D_h> (136.1 nm) and PDI (0.07) are very close to those of the as-prepared dispersion. This suggests that the aggregation between the nanospheres during the storage is loose and can be recovered to single nanospheres.

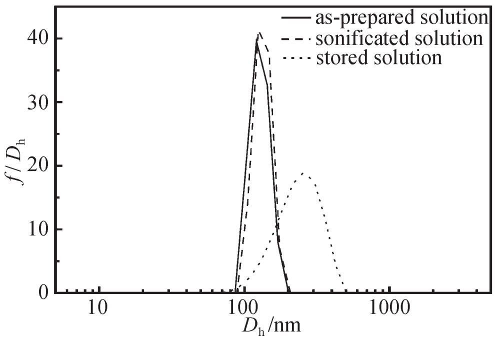


Fig. 2 Hydrodynamic diameter distribution curves of as-prepared NH7.5-2-5 dispersion, stored NH7.5-2-5 dispersion and sonicated NH7.5-2-5 dispersion

When lipase was added to the dispersion of PCL/PHPMA nanospheres prepared without crosslinker MBA, the blue tint of the dispersion disappeared after stirring mildly for several days, and no nanospheres were detected by DLS measurements. This is because the ester of PHPMA is also degraded by the lipase. As a result, after degradation by lipase, the original hydrophobic PHPMA is converted to water-soluble poly(methyl acrylic acid) (PMAA), and thus the shell is also disintegrated. By degradation with lipase crosslinked PMAA hollow spheres were obtained from nanosphere NH7.5-2-5 with shells crosslinked by MBA and were denoted as HH7.5-2-5.

Transmission electron microscopy (TEM) was used to observe the morphology of core-shell PCL/PHPMA nanospheres and the corresponding crosslinked PMAA hollow spheres (Fig. 3). From Fig. 3(a) one can see that at a low magnification, nanospheres NH7.5-2-5 display small dark spheres with clear contours and even dimensions. Different from PCL/PNIPAM nanospheres [23], the TEM size (128−161 nm) of nanospheres NH7.5-2-5 is very close to its DLS result (131.9 nm). Both PCL and PHPMA are water-insoluble, the shell structure and core structure in water are both fairly dense. Therefore, the shrinkage in volume caused by drying during sample preparation is very small.

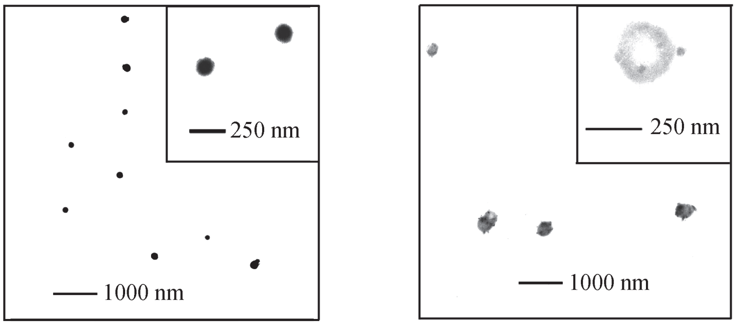


Fig. 3 TEM micrographs of (a) nanosphere NH7.5-2-5 and (b) hollow sphere HH7.5-2-5

From the TEM micrograph at a high magnification (inset, Fig. 3(a)), we can see that the typical core-shell structure with a clear contrast between the center and periphery. After degradation with lipase, the size and PDI of hollow spheres HH7.5-2-5 increase greatly to 473.1 nm and 0.10, respectively. This is because the degradation not only removes the restriction of the PCL core, but also makes the original hydrophobic crosslinked PHPMA shell convert to hydrophilic crosslinked PMAA, which can swell perfectly in water. The TEM micrograph of HH7.5-2-5 (Fig. 3(b)) presents typical hollow sphere morphology, and the hollow spheres on the whole are spherical and with a size (300−400 nm) smaller than that of DLS result. This is obviously caused by the contraction of PMAA shells during sample preparation.

Similar to nanospheres NH7.5-2-5, the size (165.9 nm) of nanospheres NV7.5-2-5 was also larger than that (116.9 nm) of the template PCL nanoparticles. Furthermore, in the TEM micrograph (Fig. 4) of naonospheres NV7.5-2-5 one can see dark spheres with a size (132−174 nm) close to its DLS result (165.7 nm). However, no distinct core-shell structure is observed. This is probably because PVAc is more hydrophobic than PHPMA, leading to formation of a shell layer with a packing density similar to that of the PCL core.

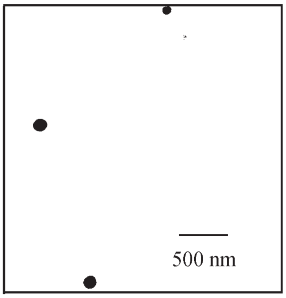


Fig. 4 TEM micrograph of nanosphere NV7.5-2-5

Using lipase degradation, the crosslinked poly(vinyl alcohol)(PVA) hollow spheres (denoted as HV7.5-2-5) were obtained from nanospheres NV7.5-2-5. Their size distributions determined by DLS were shown in Fig. 5. The size distributions of both NV7.5-2-5 and HV7.5-2-5 are very narrow, while the difference in the average diameter between the two is substantial. The <D_h> and PDI of NV7.5-2-5 and HV7.5-2-5 is 165.7 nm, 0.04 and 528.1 nm, 0.05, respectively. The remarkable increase in size of the nanosphere after degradation is obviously also due to the removal of PCL core and the conversion of crosslinked PVAc shell layer to water-swelling crosslinked PVA.

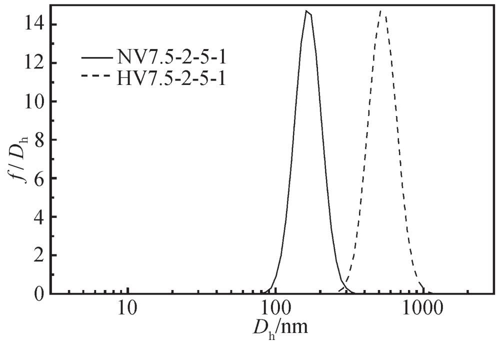


Fig. 5 Hydrodynamic diameter distributions of nanosphere NV7.5-2-5 dispersion and hollow sphere HV7.5-2-5 dispersion

We also studied the *in-situ* polymerization of 2-(diethylamino)ethyl methacrylate (DEA), which is water-soluble at a whole pH range from acid to base, whereas the corresponding polymer poly(2-(diethylamino)ethyl methacrylate)(PDEA) is water-insolube in basic medium due to de-protonation of amino groups. The *in-situ* polymerization of DEA in a NaOH aqueous solution of 0.01 mol/L was performed; however, no core-shell polymeric nanosphere was obtained, and precipitation of PDEA in water was observed instead. This is possibly because the surface of the PCL nanoparticles prepared in basic medium carries more negative charges, leading to a large repulsion on the particle surface. As a result, the produced PDEA in basic medium could not adhere to the surface of PCL nanoparticles, and just turned to precipitate from the water phase. One also cannot obtain core-shell polymeric nanospheres via *in-situ* polymerization in an acid medium as the protonation of the carboxyl ends of the template PCL nanoparticles makes the particles unstable.

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