A Facile Fabrication to Cellulose-based Nanoparticles with Thermo-responsivity and Carboxyl Functional Groups

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Cellulose-based nanoparticles having thermo-sensitivity and carboxyl functional groups were fabricated for the first time without using any surfactant and organic solvent. The nanoparticles exhibit rapid and reversible dispersion–aggregation changes in response to narrow range temperature alternation near our body temperature as demonstrated by dynamic light scattering, which may be utilized in biomedical fields.

In recent years, the synthesis of stimuli-responsive nanoparticles, especially those with thermoresponsivity, has attracted growing interest from both fundamental and applied fields of science.[1–4] Many synthetic polymers with lower critical solution temperature (LCST), such as poly(*N*-isopropylacrylamide) (PNIPAM) which exhibits LCST behavior at around 33 °C and poly(propylene oxide) (PPO) which has a LCST between 10 and 20 °C, has been selected to construct thermoresponsive nanoparticles.[3,4] However, the synthesis of block copolymers is usually inevitable in these reports and the complicated fabrication of resultant nanoparticles hindered their extensive application. Therefore, the exploration of fabricating thermoresponsive nanoparticles by more facile approach or from novel macromolecules seems much more promising in application.

As a water-soluble polysaccharide, hydroxypropyl cellulose (HPC) has been approved by the United States Food and Drug Administration (FDA) to be used in biomedical fields owing to its excellent bio-degradability and bio-compatibility (the chemical structure of HPC is shown in Figure 1a).[5] The temperature-sensitive self-association of HPC in water above its LCST and the synthesis of nanogel from HPC have been studied in detail,[6,7] but in this approach, the use of surfactant is necessary, and the absence of appropriate functional group in resultant nanogels make them difficult to be further modified.

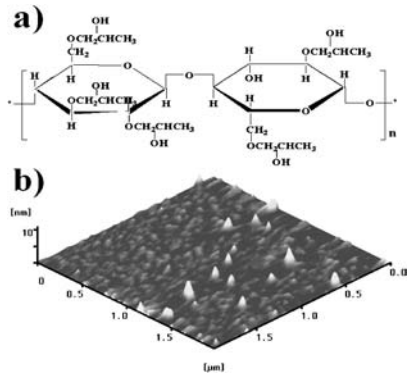


Figure 1. Chemical structure of HPC (a) and AFM micrograph (b) of HANP1 nanoparticles.

In previous report, we fabricated dextran-based nanoparticles with stable structure and carboxyl functional groups by a one-pot approach.[8] Herein, we choose the thermoresponsive HPC which possess a LCST nearing our body temperature as a original material, to fabricate stable thermoresponsive nanoparticles containing carboxy groups. Up to our knowledge, this is the first report about fabricating polysaccharide-based nanoparticles with stable structure, thermoresponsivity as well as functional groups without using any organic solvent and surfactant.

The preparation of HPC-based nanoparticles (denoted as HANP particles) is quite straightforward. An aqueous solution of cerium(IV) ammonium nitrate (CAN) in nitric acid and acrylic acid (AA) was successively added to 150 mL of 1.2% (Wt) aqueous solution of HPC ($M_w \approx 80000\,g\cdot mol^{-1}$) under gentle stirring and nitrogen bubbling, the concentration of nitric acid was maintained at ca. $0.0025\,mol\cdot L^{-1}$. Thirty minutes later, *N*,*N*′-methylene biacrylamide (MBA) was added and the reaction was kept at 30 °C and pH = 1–2 for 4 h, followed by adjusting pH to 7.0 with $1\,mol\cdot L^{-1}$ NaOH. A serial of HANP nanoparticles were fabricate at different feed compositions.

The three-dimensional morphology of HANP nanoparticles was studied by using Atom Force Microscopy (AFM). The typical AFM image of HANP1 nanoparticles (fabricated at M_{AGU}:M_{AA}:M_{Ce}:M_{MBA} = 1:5:0.04:0.5) is presented in Figure 1b. It is clear by AFM observation that the nanoparticles possess spherical morphology with a dimension of 80–120 nm. The diameter of nanoparticles observed by AFM is slightly smaller than the hydrodynamic diameter of 168 nm of HANP1 nanoparticles in water (pH = 6.7) determined by dynamic light scattering (DLS), this decrease of size should be caused by the shrinkage of nanoparticles during water evaporation in the sample preparation, and similar phenomenon was also observed in the morphology observation of other nanoparticles composed with hydrophilic components.[9]

FT-IR characterizations were conducted to study the composition of HANP nanoparticles. Figure 2 shows the FT-IR spectra of HPC, PAA, and HANP2 (synthesized at M_{AGU}:M_{AA}:M_{Ce}:M_{MBA} = 1:4.8:0.03:0.25) nanoparticles in water. Compared with pure HPC, a new absorption peak of HANP2 nanoparticles at $1556\,cm^{-1}$ could be assigned to the stretching vibration of COO^- groups.[10] Furthermore, the band at 1000–$1100\,cm^{-1}$ typical for ether linkages of HPC could also be found in the spectrum of HANP2 nanoparticles. By FT-IR measurements, the main compositions of HANP nanoparticles were confirmed as HPC and PAA.

It is known that HPC polymer chains in water have a LCST at ca. 41 °C.[11] With the HPC chains being included as a main composition, HANP nanoparticles should be anticipated to have thermosensitivity. We measured the average hydrodynamic diameter D_h of HANP1 nanoparticles in water at a series of tem-

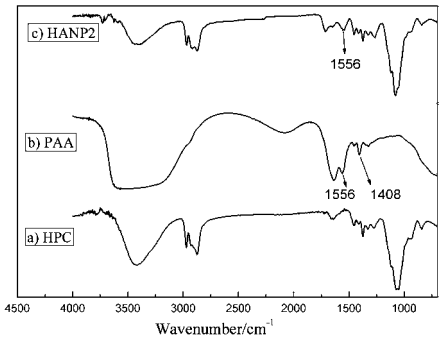


Figure 2. FT-IR spectra of HPC, PAA, and HANP2 nanoparticles.

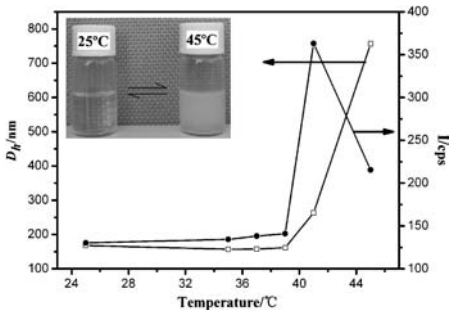
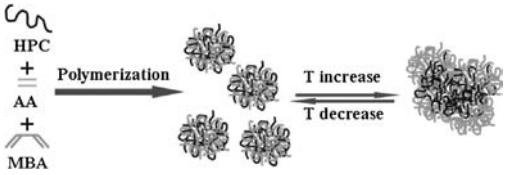


Figure 3. The variation of D_h and I of HANP1 nanoparticles in water with the increase of temperature (pH = 6.7), the inset is the aqueous solutions of HANP1 nanoparticles at different temperatures. The concentration of the particles is 1 mg/mL.

peratures by DLS. Figure 3 shows the D_h and scattering intensity I of the nanoparticles in water as a function of temperature. It is clear that over the broad temperature ranging from 25 to 39 °C, the diameter of about 160–170 nm almost does not change. As the temperature increased from 39 to 41 °C, D_h jumps to 263 nm, and accordingly, I also shows an abrupt increase in the same temperature range after a stable stage. The abrupt increase of D_h and I reflects the re-aggregation of HANP1 nanoparticles owing to the hydrophilicity to hydrophobicity transition of thermosensitive HPC chains in the nanoparticles. In addition, as shown in the inset of Figure 3, the solution shows much more distinct opalescence at 45 °C than at 25 °C, which also demonstrate that the existence of bigger particles in the solution at higher temperature. Moreover, this temperature-responsive transition is reversible as verified by not only the reversible clarity–opalescence transition of the solution but also the reversible D_h variation with the temperature as monitored by DLS.

The mechanism of the synthesis and thermosensitive re-aggregation of HANP nanoparticles could be proposed as illustrated in Scheme 1. After initiation of graft copolymerization of AA from HPC, the "micelle"-like nanoaggregates form attributed to the complexation between HPC and PAA.[12] Subsequently, participation of bifunctional monomer—MBA leads to further fixation of the structure. Thanks to the shielding effect of the HPC segments in periphery, the inter-particle crosslinking was prevented. The stability of the nanoparticles is confirmed by the fact that they still hold the integral structure at pH 7 in which



Scheme 1. The scheme of the synthesis and thermosensitivity of HANP nanoparticles.

the hydrogen bond between HPC and PAA has been destroyed because of the deprotonation of carboxy groups in PAA.[12] As temperature increases to higher than 40 °C, some segments of HPC chains in the nanoparticles transform from hydrophilic to hydrophobic due to their thermosensitivity, hence induce the re-aggregation of the nanoparticles. The thermosensitive aggregation and subsequent increase of diameter of HANP nanoparticles may be of potential in biomedical fields because of the transition point is near to our body temperature.

In summary, here we presented the first one-pot fabrication of polysaccharide-based nanoparticles with both carboxyl functional groups and thermosensitivity, without using any organic solvent and surfactant. The use of renewable material as the central material, HPC, as well as a benign solvent medium, offer numerous benefits ranging from environmental safety to applications in biologically relevant systems. In addition, the carboxy groups in the nanoparticles make them are promising in the delivery of cationic target species.

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