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Poly(NIPAM-co-MPS)-grafted multimodal porous silica nanoparticles as reverse thermoresponsive drug delivery system

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ABSTRACT

Hybrid drug delivery systems (DDS) have been prepared by grafting poly(NIPAM-*co*-MPS) chains on multimodal porous silica nanoparticles having an inner mesoporous structure and an outer thin layer of micropores. The hybrid thermoresponsive DDS were fully characterized and loaded with a model drug. The *in vitro* drug release tests are carried out at below and above the lower critical solution temperature (LCST) of the copolymer. The results have revealed that due to the presence of small diameter (~1.3 nm) micropores at the periphery of the particles, the collapsed globules of the thermoresponsive copolymer above its LCST hinders the complete release of the drug which resulted in a reverse thermoresponsive drug release profile by the hybrid DDS.

1. Introduction

Mesoporous silica nanoparticles (MSNs) have emerged as one of the most efficient drug delivery systems for the delivery of various drug molecules [1–4]. Easy synthesis and surface modification methods, good stability and biocompatibility are the characteristic properties that make MSNs versatile material in drug delivery applications [5]. The transformation of bare MSNs into controlled thermosensitive drug delivery systems (DDS) is carried out by grafting of thermoresponsive polymers such as poly(*N*-isopropylacrylamide) or its various copolymers on the particle outer surface or/and on the inner pore walls [6–8]. Poly(*N*-isopropylacrylamide) (PNIPAM) is a water

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soluble thermoresponsive polymer which shows a typical coil-to-globule transition at its lower critical solution temperature (LCST) which is around 32 °C [9,10]. The LCST of the polymer can be tuned toward higher values by preparing various co-polymers of PNIPAM [11]. Above LCST, the water soluble extended chains of the polymer collapse to form compact insoluble globules. As the volume occupied by the polymer in its hydrated coil form is much higher than the collapsed globules, this transition applies a pore opening–pore closing mechanism to the MSNs [6–8].

If the transition of the thermoresponsive polymer occurs inside the pores of the MSNs, at temperatures below the LCST the hydrated extended chains of the polymer block the pores, which prevent the release of the drug molecules loaded inside the MSNs. Instead upon heating above the LCST, the polymer chains collapse toward the pore walls which opens the pores and completely releases the drug. Thus a normal drug release profile of such thermosensitive DDS shows reduced or no release of the drug at temperatures below the LCST of the polymer and higher or complete release of the drug above the LCST of the polymer. However, the pore size can also play an important role in the pore opening/closing mechanism. This role of microporosity in thermoresponsive DDS needs to be investigated. Related to this in the present work we report about the influence of pore size in designing thermoresponsive DDS where the presence of micropores on the surface of MSNs can result in a reverse thermoresponsive drug release profile. This occurs due to the full or partial blockage of the micropores by the collapsed globules of the thermoresponsive copolymer. This work therefore points out an important consideration about the proper choice of MSNs and diameter of the pores present on them for their use for preparation of thermoresponsive DDS.

2. Materials and methods

2.1. Materials

Porous silica particles (particle size 200 nm, pore size 4 nm), N-isopropylacrylamide (NIPAM), azobisisobutyronitrile (AIBN), 3-(methacryloxypropyl) trimethoxysilane (MPS), ibuprofen (standard RS α-methyl-4-(isobutyl)phenylacetic acid, (±)-2-(4-isobutylphenyl) propanoic acid) were purchased from Sigma-Aldrich, Italy. All the solvents mentioned in the synthesis procedure were of high purity and used as received. Ethanol was kept on molecular sieves overnight before using for polymerization reaction.

2.2. Instruments and methods

High resolution transmission electron microscopy (HRTEM) images were obtained with a JEOL 2010 instrument (300 kV) equipped with a LaB6 filament. For specimen preparation powdery samples were supported onto holed carbon coated copper grids by dry deposition.

Fourier transform infrared spectroscopy (FTIR) spectra were collected with a Perkin Elmer FTIR Nexus instrument equipped with an attenuated total reflectance (ATR) devise (Thermo Nicolet Smart Endurance) and with a DTGS detector. The spectra were collected in the spectral range of 4000–670 cm^{-1} and with a resolution of 4 cm^{-1}.

Gas-volumetric analysis, specific surface area (SSA), pore volume and size were measured by N_2 adsorption–desorption isotherms at 77 K using an ASAP 2020 (Micromeritics) gas-volumetric analyzer. SSA was calculated using the Brunauer–Emmett–Teller (BET) method. Porosity distribution, allowing one

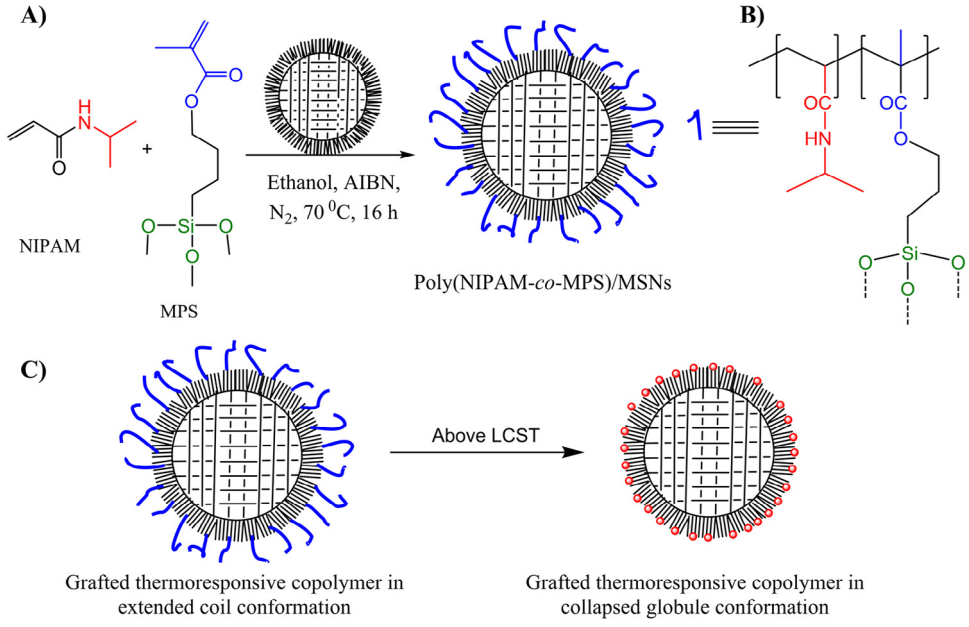

Fig. 1 – (A) Grafting of the copolymer on MSNs, (B) structure of the copolymer and (C) coil-to-globule transition of the grafted copolymer on the surface of MSNs.