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PAA-grafted surface and fractal feature of dense nanosilica spheres for ibuprofen delivery

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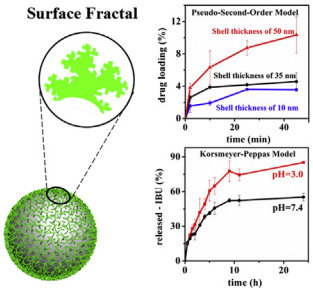
HIGHLIGHTS

- The microspherical P/SiO_2-MPS with core-shell feature was prepared.
- The surface effect of coated PAA on the IBU delivery was obvious.
- The surface fractal evolution of P/SiO_2-MPS was investigated via SAXS method.

GRAPHICAL ABSTRACT



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ABSTRACT

The polymer/SiO_2 hybrid material (P/SiO_2-MPS) with core-shell structure were synthesized using the dense nanosilica spheres (DNSS) as core and pH responsive poly(acrylic acid) (PAA) as a shell. Meanwhile, using ibuprofen (IBU) as a model drug, the structure and properties of obtained P/SiO_2-MPS were characterized by SEM, TEM, FT-IR, TGA, EDS, NMR, XRD, DLS and SAXS. The results elucidated that PAA was successfully incorporated onto the surface of DNSS, and thereafter the thickness of PAA shell could be controlled by adjusting the additive amount of AA. Particularly, SAXS patterns evidently exhibited that P/SiO_2-MPS before IBU-loading and after releasing possessed the surface fractal feature, which increased from 2.19 for SiO_2-MPS, to 2.41 for P/SiO_2-MPS, to 2.54 for IBU-loaded P/SiO_2-MPS, and to 2.65 for IBU-released P/SiO_2-MPS. Moreover, the IBU-releasing percentage of three samples (P/SiO_2-MPS-1, P/SiO_2-MPS-3 and P/SiO_2-MPS-5) increased gradually at both pH 3.0 and 7.4 with the enlarged thickness of PAA shells, while for P/SiO_2-MPS-7 with the thickest PAA layer, its release rate was not more than that of P/SiO_2-MPS-5. Therefore, IBU molecules were hindered from passing through PAA layer. Furthermore, the IBU loading of P/SiO_2-MPS was fitted into the pseudo-second-order model, while its drug-release kinetic profile was favorable to Korsmeyer-Peppas model. These observations evidently demonstrated that the surface effects of P/SiO_2-MPS on its surface fractal feature and the diffusion of IBU delivery were very important, and therefore its mechanism was essentially proposed.

1. Introduction

Recently, the polymer/inorganic hybrid materials have attracted a great deal of academic interest [1–3] and potential applications [4–6], due to combination of the advantages of inorganic materials

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(e.g. rigidity, thermal stability) and organic polymers (e.g. pH stability, chemical functionality, flexibility, ductility and processability). For example, Reddy et al. reported the synthesis of conducting polyaniline-functionalized multi-walled carbon nanotubes containing noble metal (Au and Ag) nanoparticles composites, which may be very useful in nanotechnology, gas sensing, and catalysis [7]. Moreover, in the field of controlled drug delivery, the polymer/inorganic hybrid materials have been playing an increasingly important role. Many strategies have been developed for the fabrication of the polymer/inorganic nanocomposites, including self-assembly [8], emulsion polymerization [9], surface initiated *in situ* chemical oxidative graft polymerization [6,7], microemulsion polymerization [10], *in situ* emulsion polymerization [11]. Besides, Reddy et al. [12] proposed a facile preparation for core-shell structural composites via the interactions between positive and negative charges on the surface of iron oxide nanoparticles.

The past decade has witnessed a rapid growth in the research of polymer/inorganic hybrid materials as drug carriers in controlled drug delivery. The ibuprofen (IBU) is a non-steroidal inflammatory drug used in treatment of pain and inflammation in rheumatic disease and other musculo skeletal disorders [13]. Besides, due to its poor water solubility and the short biological half-life time (2 h), IBU has become one of the most commonly used model drug in the drug delivery research [14–16].

Mesoporous silica nanoparticles (MSNs) are suggested as potential carriers for drug delivery because of their unique features, such as uniform particle size, tunable pore size, controllable morphology with high surface area and pore volume, as well as facile surface functionalization, etc [17–20], especially, when imparted the controlled release performance by grafting the functional polymers on the surface, such as pH, temperature, fluorescent, photo and magnetic sensitive polymers [21–26]. Due to above-mentioned features, their studies for biomedical applications have experienced outstanding improvements. In 2001, it was the first time that Vallet-Regi and co-workers [27] used MCM-41 for controlled release of IBU under *in vitro* assays, and thereafter demonstrated the feasibility of controlling the drug delivery rate via mesoporous surface modification with aminopropyl groups [28,29]. Zhu et al. [30] reported a new type of well-ordered mesoporous bioactive glass microspheres (MBG-MSs) with high storage capacities and sustained release profiles. In our previous work, we have demonstrated the successful application of functionalized bimodal mesoporous materials (BMMs) [31] in controllable drug delivery system with high drug loadings [32–35]. Afterwards, much work has been carried out to design and prepare functionalized mesoporous drug carriers with high drug loading capacity and low drug release rate. For example, Zha *et al*. [28] prepared for the first time temperature-responsive microcapsules using poly (*N*-isopropylacrylamide) (PNIPAM) hydrogel with core-shell structures, which can be used for temperature-controlled drug release. Hong et al. [22] developed pH-responsive composite microspheres, which had the mesoporous silica core and the polymer outer shell. In addition, the storage-release performance could be effectively controlled after grafting a photo-responsive coumarin derivative on the pore outlet of Si-MCM-41 [24]. In our group, Zhang et al. [36] prepared a smart pH-controlled drug delivery system via surface-grafting of the preformed silane modified [poly(methylacrylic acid)] PMAA onto the mesoporous surface of BMMs, which further demonstrated that the obtained hybrid silicas presented a flexible control over drug release. More recently, our group have developed smart pH-dependent [poly (methacrylic acid)]-silica hybrid nanoparticles (P/NN-BMMs), using BMMs as a container and pH-responsive PMAA as a smart nano-valve via "graft to" method [37].

Obviously, most researchers just concentrated on the influences of various parameters involving functionalized groups, mesopores size distributions, and morphologies in drug loading and releasing behaviors. Only few reports documented the "confinement effects" and "surface effects" of inside mesoporous channels and outer surface in the drug delivery. Although both of the above mentioned effects based on diffusion and adsorption phenomenon of drug molecules play a very important role, their essential mechanism is still ambiguous. In this case, this work aimed at exploring the "surface effects" of outer polymer on the drug delivery, in which pH-responsive poly(acrylic acid) (PAA) was grafted onto the vinyl-modified dense nanosilica spheres (DNSS) to obtain the spherical P/SiO_2-MPS with core-shell feature. It was emphasized that DNSS were used as core instead of mesoporous MSN to remove the pore effects. Particularly, small angle X-ray scattering (SAXS) technique was employed to further describe surface fractal of P/SiO_2-MPS during the IBU delivery so as to demonstrate the essential mechanism of surface effects. Furthermore, we systematically evaluated the influences of the shell thickness of core-shell structural P/SiO_2-MPS on the IBU loading and release behaviors, and therefore the surface effect of P/SiO_2-MPS on its fractal evolution was proposed. In fact, some researchers have used the fractal theory to provide the deeper understanding for surface and structural effects of the obtained solid [38] having the fractal dimensions (D_s) between 2 and 3, which is actually a measure of their particle surface roughness and structural irregularities [39]. In 1997, Boukari et al. [40] investigated the formation and growth of silica nanostructure, and then found that the fractal structure characteristics of silica nanostructure were changed through various dynamics-controlled stages from mass fractals to surface fractals, even to non-fractal particles with smooth interface. Subsequently, Varga et al. [41] also applied the variation from mass fractal to surface fractal using SAXS characterization to explain the successful grafting of poly(ethylenimine) and poly(sodium-4-styrene-sulphonate) onto the mesoporous silica for the drug delivery applications.

In the present study, the DNSS were used with a particle size of around 130 nm. In comparison with our previous results [36,37], this work aimed the grafting of pH-responsive PAA onto 3-(methacryloxy) propyl trimethoxysilane (MPS) modified DNSS to obtain the spherical P/SiO_2-MPS with core-shell feature by investigating the surface effects of DNSS on the drug delivery system. Furthermore, using IBU as a model drug, the structure and properties of obtained core-shell P/SiO_2-MPS were characterized using various analytical methods, such as scanning electron microscopy (SEM), transmission electron microscopy (TEM), fourier transform infrared (FT-IR), thermogravimetric analysis (TGA), energy dispersive spectrometer (EDS), ^{13}C solid-state nuclear magnetic resonance (NMR), X-ray diffraction (XRD), dynamic laser scattering (DLS) and SAXS. In particular, SAXS as an analytical method offered robust characterization to describe surface fractal of all nanocomposite particles, and therefore the essence of surface from a new point of view has been elucidated. The related mechanism of surface effects is discussed in detail, which is expected to offer further understanding, oriented design and controlled synthesis of the organic-inorganic nanocomposites with high drug loading and controllable releasing.

2. Experimental section

2.1. Chemicals and characterization

Tetraethyl orthosilicate (TEOS), acetonitrile, and 2, 2'-azodiisobutyronitrile (AIBN) were purchased from Tianjin Fuchen chemical reagents factory. Ammonium hydroxide (25%, $NH_3 \cdot H_2O$) was obtained from Beijing chemical works. MPS and N, N'-methylenebisacrylamide (MBA) was obtained from Aladdin. Acrylic acid (AA) was provided by Sinopharm Chemical Reagent Co., Ltd. AIBN was purified with recrystallization before using. Ethanol, disodium