*Drug Delivery*

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# Stimuli-Responsive Controlled Drug Release from a Hollow Mesoporous Silica Sphere/Polyelectrolyte Multilayer Core–Shell Structure**

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Recently, there has been increased interest in mesoporous silica materials for use as carriers in controlled drug release, to meet the need for prolonged and better control of drug administration. Amorphous mesoporous silica materials have been investigated as drug supports because of their nontoxic nature, adjustable pore diameter, and very high specific surface area with abundant Si–OH bonds on the pore surface.[1–10] Several research groups have investigated the conventional mesoporous silica materials (such as MCM-41 and SBA-15) used as drug-delivery systems.[1–8] These systems exhibit sustained-release properties, but their drug storage capacity is relatively low, and also the irregular bulk morphology is not perfect for drug delivery. To overcome these disadvantages, one strategy is to synthesize hollow mesoporous silica (HMS) spheres on the nanoscale with pore channels penetrating from the outside to the inner hollow core. Recently, our group has successfully synthesized HMS spheres with a 3D pore-network shell.[11,12] We also investigated the aspirin storage capacity and release properties of these spheres,[13] which indicated that they could store significantly more aspirin molecules than the conventional mesoporous silicas MCM-41 and MCM-48, and also have sustained-release properties.

Compared to the sustained-release system, the stimuli-responsive controlled-release system can achieve a site-selective, controlled-release pattern, which can improve the therapeutic efficacy. Up to now, only two reports have been published about stimuli-responsive controlled drug release from mesoporous silica MCM-41.[9,10] Lin and co-workers reported the stimuli-responsive controlled release of water-soluble drugs from MCM-41 by using chemically removable CdS nanoparticles as caps for mesoporous channels and disulfide bond-reducing molecules as release triggers.[9] Fujiwara and co-workers accomplished, for the first time, the photocontrolled reversible release of drug molecules from coumarin-modified MCM-41.[10] Therefore, it is still a challenge to find more convenient ways to achieve a fully controllable drug-release system under normal physiological pH and NaCl concentrations.

The properties and structure of polyelectrolyte multilayers (PEM) are sensitive to the various physical and chemical conditions of the surrounding medium. The polyelectrolyte pair, which comprises sodium polystyrene sulfonate (PSS) and the polycation poly(allylamine hydrochloride) (PAH), has been widely investigated for hollow microcapsules.[14–24] Möhwald and co-workers prepared hollow PAH/PSS capsules by colloid-templated assembly of polyelectrolytes (layer-by-layer technique),[15] and confirmed the controlled encapsulation and release of several kinds of molecules (such as dyes, enzymes, dextran, and DNA) from the capsules by changing the pH value (or ionic strength) of the release medium.[16–20] However, these hollow capsules are not mechanically strong and about 10% of them easily break in the course of drying and the removal of the colloid templates. In addition, reports on the storage and controlled release of drugs with the freestanding capsules are not found, probably as a result of the relatively low molecular weight of most drugs. Researchers have also tried to directly coat the polyelectrolyte multilayers onto certain drug microcrystals of low molecular weight.[22–24] These systems could prolong the release time to some extent, but unfortunately they did not show the stimuli-responsive controlled release of drug molecules.

It is known that the surface of mesoporous silica is negatively charged above the isoelectric point (pH 2–3),[25] which favors a first-layer coating of the positively charged polycation PAH, followed by the negatively charged PSS. Thus, polyelectrolyte multilayer coatings on mesoporous silica spheres can be prepared. The HMS spheres can be used as a container for drug molecules and the polyelectrolyte multilayer coatings as a stimuli-responsive switch. It is encouraging that with this system one can not only increase the drug-storage capacity, but also achieve stimuli-responsive controlled release of drug molecules and enhance the mechanical strength of the polyelectrolyte multilayers to prevent them from breaking.

Herein, we propose a strategy to combine the advantages of HMS spheres with a 3D pore network and polyelectrolyte multilayers with a stimuli-responsive property. We also report a stimuli-responsive controlled drug-delivery system, which consists of HMS spheres with an average sphere diameter of 300–400 nm and polyelectrolyte multilayer coatings (PAH/PSS) with an average thickness of 14 nm. Prior reports on such a controlled-release system have not been found. In addition, the uncoated HMS sphere drug-release system was used for comparison to investigate the release property.

Figure 1 schematically illustrates two drug-delivery systems, which were designed to demonstrate the stimuli-responsive controlled drug release from PAH/PSS polyelectrolyte multilayer coatings on HMS loaded with ibuprofen (IBU-HMS@PEM) or a simplex sustained-release pattern from the IBU-HMS system. In the former system, the key is to coat the PAH/PSS multilayers on IBU-HMS spheres, which could cap the mesopore channels. During the release process,

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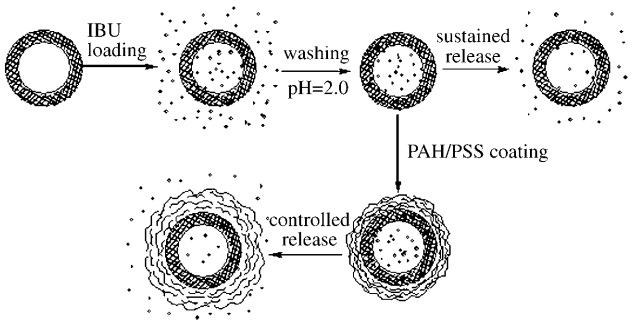


***Figure 1.*** Schematic illustration of two drug-delivery systems which give the different controlled-release patterns.

the loaded drugs need to diffuse subsequently through the mesoporous shell and the PAH/PSS multilayers into the release medium. That is, drug release is doubly controlled by the mesoporous shell and the PAH/PSS multilayers sequentially. The stimuli-responsive controlled drug-release pattern of this system is possible as a consequence of the pH sensitivity and salt-induced responsive property of the PAH/PSS multilayers. For the IBU-HMS system, only the mesoporous shells control drug diffusion, which results in the sustained-release behavior alone.

The detailed synthesis, characterization, and formation mechanism of HMS spheres with a 3D pore network can be found in our recent report.[11] Figure 2a and b show TEM micrographs of spherical mesoporous silica particles with an average diameter of 300–400 nm. The noticeable contrast between the core and the shell of the sphere implies a hollow-core structure. The highly ordered lattice array over the shell suggests that HMS products have a uniform, well-defined mesostructure. Figure 2c shows a TEM micrograph of the HMS sphere after adsorption of IBU molecules (IBU-HMS).

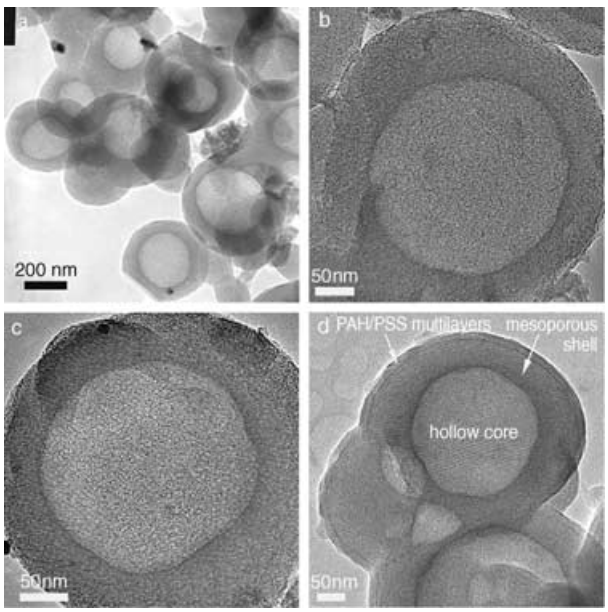


***Figure 2.*** TEM micrographs of HMS (a and b), the IBU-HMS system (c), and the IBU-HMS@PEM system (d).

No apparent difference can be observed compared to HMS, although IBU-HMS contains a large number of IBU molecules. One reason might be that the scattering effects of IBU molecules (which contain carbon, hydrogen, and oxygen) in the hollow core and the pore channels are not strong enough to show the contrast. Figure 2d shows a TEM micrograph of IBU-HMS after being coated with PAH/PSS multilayers (IBU-HMS@PEM). A uniform thin layer with a thickness of around 14 nm exists on the outer surface of the HMS sphere, and the thin layer has coated the whole sphere. Furthermore, the hollow core–mesoporous shell structure still remains intact. Therefore, two controlling layers (mesoporous shell and PAH/PSS multilayers) have been formed in the IBU-HMS@PEM system.

Thermogravimetric analysis (TGA) curves of the IBU-HMS and IBU-HMS@PEM systems are shown in Figure 3,

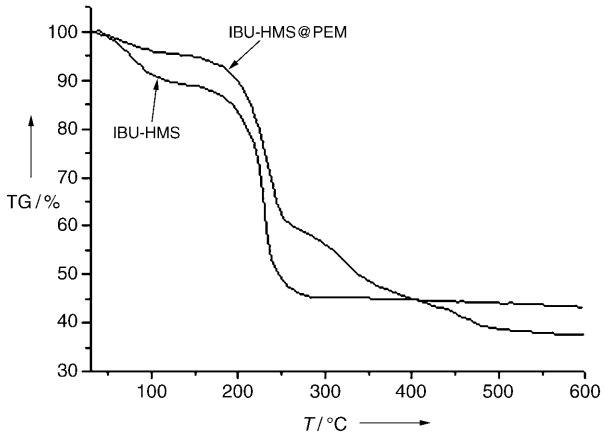


***Figure 3.*** TGA curves of the IBU-HMS and IBU-HMS@PEM systems.

and the results are summarized in Table 1. Both systems showed weight losses below 180 °C that resulted from the physical loss of water. For the IBU-HMS system, another

***Table 1:*** TGA results for the two drug-delivery systems.

| | 30–180 °C (wt %) | 180–280 °C (wt %) | 280–500 °C (wt %) | $SiO_2$ [wt %] | Storage capacity [$mg_{IBU}/g_{SiO_2}$] |
|---|---|---|---|---|---|
| IBU-HMS | 13.03 | 41.64 | – | 45.33 | 918.6 |
| IBU-HMS@PEM | 7.1 | 34.60 | 19.65 | 39.65 | 872.6 |

weight loss (about 41.64 %) occurred between 180 and 280 °C, which demonstrates that the IBU storage capacity of the IBU-HMS system is 41.64 % (918.6 $mg_{IBU}/g_{SiO_2}$). In the IBU-HMS@PEM system, three weight losses were detected from 180 to 600 °C. The loss of 34.60 % (872.6 $mg_{IBU}/g_{SiO_2}$) between 180 and 280 °C is attributed to the removal of IBU from the IBU-HMS@PEM system, while the other two weight losses occur by the removal of the PAH/PSS multilayers. Here, the IBU storage capacity in the IBU-HMS@PEM system is a little

  

lower than that in the IBU-HMS system, which may have resulted from the loss of some IBU molecules during the PAH/PSS multilayer coating process. However, this drug storage capacity is almost three times higher than that of the conventional mesoporous material MCM-41.[1–4]

Figure 4 shows the cumulative drug release from the two systems in release media of pH 1.4 (a simulated gastric fluid)

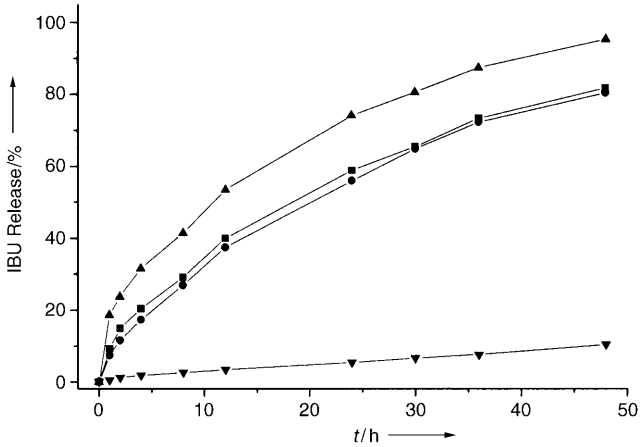


***Figure 4.*** Cumulative drug release from the two systems in release media of different pH values. ■: pH 1.4 from IBU-HMS, ●: pH 1.4 from IBU-HMS@PEM, ▲: pH 8.0 from IBU-HMS, ▼: pH 8.0 from IBU-HMS@PEM.

and pH 8.0 (a simulated intestinal fluid). This diagram clearly proves that both systems exhibit sustained-release properties and that the drug release rates from both systems are very close to each other in the medium of pH 1.4. The amounts released from the two systems reach about 80% in 48 h. This result implies that the PAH/PSS multilayers are incompact and have open pathways in the release medium of pH 1.4, and the incompact wall of the PAH/PSS multilayers could not cap the openings of the mesoporous channels. Therefore, the drug molecules can easily diffuse into the release medium through the mesoporous channels and PAH/PSS multilayers, that is, this system only exhibits the sustained-release property with the IBU-HMS system in acid media. When the pH value of the release medium increases to 8.0, the drug release rates from both systems become apparently different. The IBU-HMS system also exhibits the sustained-release property and the amount released reaches 95% in 48 h; the release rate in the pH 8.0 release medium is higher than that in the pH 1.4 medium. This difference in release rates should mainly be attributed to the different solubility of IBU in release media of different pH values. IBU has limited solubility in low-pH ($<7$) solutions but is readily soluble in high-pH ($>7$) solutions. For the IBU-HMS@PEM system the release rate is very low, and the released amount only reaches 10% over a period of 48 h. This finding indicates the good storage and sealing effect of the PAH/PSS multilayer coating on HMS spheres in pH 8.0 solution; that is, the PAH/PSS multilayers are compact and have decreased permeability at the increased pH value, and the compact multilayers could easily cap the openings of the mesoporous channels. It can be concluded that the IBU-HMS@PEM system has a much better controlled drug-release property than the IBU-HMS system and the reported polyelectrolyte multilayer capsule system.[22–24] That is, the IBU-HMS@PEM system can achieve a pH-responsive controlled drug-release pattern by changing the pH value of the release medium.

As we know, the structure and properties of PAH/PSS multilayers are sensitive to the NaCl concentration.[17,26] Therefore, we investigated drug release from the two systems in release media of different NaCl concentration. Sustained releases from both systems are obtained in 10 mM NaCl media (Figure 5) and the release rates are very close to each other,

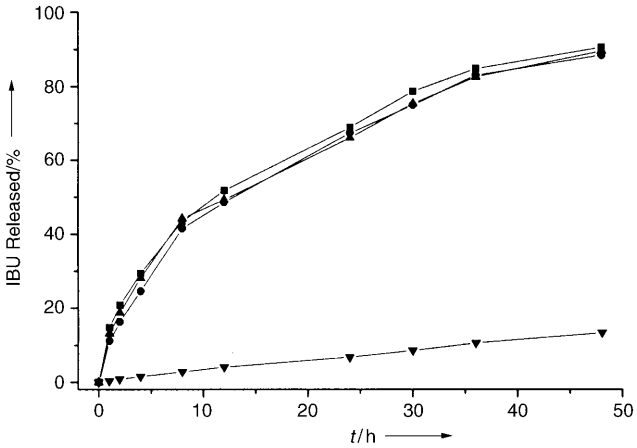


***Figure 5.*** Cumulative drug release from the two systems in release media of different NaCl concentration. ■: 10 mM NaCl from IBU-HMS, ●: 10 mM NaCl from IBU-HMS@PEM, ▲: 0.5 mM NaCl from IBU-HMS, ▼: 0.5 mM NaCl from IBU-HMS@PEM.

which is similar to the result in release media of pH 1.4. In 0.5 mM NaCl media, the amount of drug released from the IBU-HMS system reaches about 90% in 48 h, which is also close to the release rate in 10 mM NaCl media. However, the amount released from the IBU-HMS@PEM system only reaches 13% in 48 h. Therefore, a salt-induced controlled drug-release pattern can be achieved from the IBU-HMS@PEM system. The PAH/PSS multilayers play an important role during the controlled-release process. At the higher salt concentration, the high ionic strength weakens the electrostatic binding between the oppositely charged layers, which results in incompact PAH/PSS multilayers. The multilayers can no longer cap the openings of the mesoporous channels and provide the pathways for drug molecules to diffuse into the release medium. At the lower salt concentration, the electrostatic binding between the oppositely charged layers becomes stronger and the openings of the mesoporous channels are more easily capped by the compact PAH/PSS multilayers. Therefore, the multilayers can play a switch role between the lower and the higher salt concentrations.

In addition, the drug storage and release process does not damage the pore structure (see the Supporting Information). The low-angle XRD patterns show a diffraction peak at $2\theta = 2.2$–$2.5°$ ($\theta$ is the Bragg angle) which is unaffected by the drug

  

loading and release. The pore size becomes smaller after drug loading; however, the size distribution and pore volume can mostly recover after drug release from the two systems (see the Supporting Information). Therefore, the two controlled drug-release systems show good stability.

In summary, we have demonstrated a concept to design a novel stimuli-responsive controlled drug-release system by using PAH/PSS multilayers as a coating to cap the mesopore openings of drug-loaded hollow mesoporous silica spheres. The drug storage capacity of this system is three times higher than that of the reported MCM-41 system. Compared with the system without a polyelectrolyte multilayer coating, the reported system can give stimuli-responsive controlled release; for example, it can be designed to release into the stomach instead of the intestine. The drug release rate from the IBU-HMS@PEM system can be well-controlled by changing the pH value (or the salt concentration) of the release medium. Therefore, this system combines the advantages of both high drug storage capacity and the property of stimuli-responsive controlled release, and has potential for applications in drug delivery.

## Experimental Section

Materials: Tetrapropylammonium hydroxide (TPAOH, 25% in water) was from Acros. Poly(allylamine hydrochloride) (PAH, $M_w = 15000$) and sodium polystyrene sulfonate (PSS, $M_w = 70000$) were from Aldrich and used without further purification. Ibuprofen (IBU, 99%) was from Shanghai Yuanji Chem. Co. and used as received. Cetyltrimethylammonium bromide (CTAB, 99%), tetraethyl orthosilicate (TEOS, 98%), hydrogen chloride (36–38%), hexane, sodium hydroxide, and aluminum sulfate ($Al_2(SO_4)_3{\cdot}18H_2O$) were purchased from Shanghai Chem. Agents Co. and used without further purification.

Preparation of hollow mesoporous silica spheres and drug-delivery system: HMS spheres were prepared by our method as described in the literature.[11] The drug-storage profile was taken as previously reported.[1–4] IBU was dissolved in hexane at a concentration of 60 mg mL$^{-1}$. HMS (1.0 g) was added to this solution (50 mL) at room temperature. The vials were sealed to prevent the evaporation of hexane, then the mixture was stirred for 24 h. The HMS with adsorbed IBU was separated by centrifugation and washed several times with a solution of pH 1.4. Finally, the sample was dried under vacuum at 60 °C. This sample is denoted as IBU-HMS.

Preparation of polyelectrolyte multilayer coating: PAH (5 mL) with a monomer concentration of 5 mg mL$^{-1}$ in 0.5 M NaCl was added to a suspension of IBU-HMS (1.0 wt%, 20 mL, pH 6.0). After stirring for 20 min, the suspension was centrifuged three times in water. Gentle shaking followed by ultrasonic treatment for 1 min was used to disperse the particles after centrifugation. Then, oppositely charged PSS (5 mg mL$^{-1}$ in 0.5 M NaCl) was coated on the particles. This coating process was repeated for eight layers and finally a composite of IBU-HMS coated with PAH/PSS multilayers was obtained. This sample is denoted as IBU-HMS@PEM.

In vitro drug-release study: The IBU-HMS (or IBU-HMS@PEM) sample was immersed in release media of different pH values (pH 1.4 and 8.0) or different ionic strength (0.5 and 10 mM NaCl solution) at room temperature, with stirring at a rate of 100 rpm. The release medium (2.0 mL) was removed for analysis at given time intervals with a syringe, and replaced with the same volume of fresh release medium. The extracted medium was diluted to a desired concentration (0.01–0.5 mg mL$^{-1}$) with release medium, and analyzed by UV/Vis spectroscopy at a wavelength of 264 nm. The samples with released IBU are denoted as IBU-HMS$_R$ and IBU-HMS@PEM$_R$.

Characterization methods: Powder XRD patterns were obtained on a Rigaku D/MAX-2550V diffractometer at 40 kV and 40 mA ($Cu_{K\alpha}$ radiation). TEM analysis was performed using a JEOL 2100F electron microscope operated at 200 kV. The UV/Vis absorbance spectra were measured with a Shimadzu UV-3101PC spectrophotometer. $N_2$ adsorption–desorption isotherms were obtained on a Micromeritics Tristar 3000 pore analyzer at 77 K under continuous adsorption conditions. Brunauer, Emmett, and Teller (BET) and Barrett, Joyner, and Halenda (BJH) analyses were used to determine the surface area, pore size, and pore volume. Thermogravimetric analysis (TGA) was recorded on an STA-449C thermal analyzer at 10 °C min$^{-1}$ in an $N_2$ atmosphere.

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