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Synthesis of porous silica hollow spheres using sacrificial template for drug delivery applications

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A B S T R A C T

In this work, we report on the synthesis of SiO_2 hollow spheres using carbon nanospheres as the sacrificial template by hydrothermal method. The synthesized substrates are in a spherical morphology and uniform size distribution. The effects of hydrothermal process, concentration and the reaction temperature were optimized during synthesis of carbon nanospheres. Infrared spectroscopy (IR), and scanning electronic microscopy (SEM) methods were used for identification of the synthesized products. The synthesized SiO_2 nanospheres were used as drug carrier to investigate *in vitro* release behavior of monoterpenic phenol isomers, carvacrol and thymol, in simulated body fluid (SBF). Ultraviolet-visible spectroscopy (UV-vis) method was carried out to determine the amount of the drugs entrapped in the carrier. The results indicated that SiO_2 nanospheres have high ability to adsorb the drugs and there is no need for adjusting the pH during the adsorption process. The drug release profile shows a three stages pattern and indicates a delayed release action.

1. Introduction

Morphology of nanostructures plays an important role in determining their properties. Because of low density, high surface area, loading ability, encapsulation of guest molecules, high porosity, ease of production, and suitable biodegradability, hollow nanospheres are of great interest[1, 2]. Performance of SiO_2 nanospheres is strongly influenced by the size of their porosity and their surface area. SiO_2 nanospheres have many applications in medical sciences[3], biotechnology photovoltaic chromatography[4,5] and targeted drug delivery[6]. So far, many physical and chemical methods were used to synthesis the SiO_2 nanospheres, such as hydrolysis[7], hydrothermal, sol gel, polymerization[8], using sacrificial templates[9], and etc. Among these, sacrificial templates method has attracted much attentions due to its ability to control particle size[10]. By controlling template size and concentration, reaction time and temperature, desired morphology and size of SiO_2 nanospheres could be obtained[11]. In this research, SiO_2 nanospheres with uniform morphology and size distribution were synthesized

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using carbon sacrificial templates. In addition, the effects of temperature, concentration and reaction time were optimized. To create porosity in SiO_2 nanospheres, cetyltrimethylammonium bromide (CTAB) was used as surfactant. Exploring of drug loading on porous SiO_2 nanospheres showed that these particles have good potential to be a drug carrier with no need to pH adjustment.

2. Experimental

2.1 Materials and Methods

All the reagents were of analytical grade and were from Merck Company. Reagents were used without any further purification.

The FT-IR spectra were recorded using KBr disks on an FT-IR SHIMADZU 8400S infrared spectrometer and absorptions were reported as wave numbers (cm^{-1}). Ultraviolet-visible (UV-Vis) absorption spectrum was measured on a T80 spectrophotometer. The morphologies of particles were observed by scanning electron microscopy (SEM, LEO-1455 VP).

50 mL of glucose solution (0.4 M) was transferred into an autoclave receptacle and maintained at 180 °C for 12 h. The product was dispersed in water using ultrasonic bath, then centrifuged for 20 min at a speed of 6000 rpm, and finally washed with ethanol. The procedure of dispersing, centrifuging and washing repeated six more times. After solvent evaporation, carbon nanospheres were obtained.

To synthesize the SiO_2 hollow spheres, 0.06 g carbon nanospheres were dispersed in 100 mL ethanol, and 0.05 g CTAB was added to the mixture. The pH was adjusted at 10.5 by addition of 10 mL ammonia solution (25%). Then, while using an ultrasonic bath, 2 mL of tetraethylorthosilicate (TEOS) was added dropwise to the suspension. After 1h sonication, the product was centrifuged and washed with water and ethanol until pH 7 and let to dry. The obtained precipitate ($C@SiO_2$) was calcined at 600 °C for 3h to burn the carbon cores and obtain the SiO_2 hollow nanospheres as final product.

The loading of the monoterpenic phenol isomers (carvacrol and thymol) was carried out by the soaking of 0.01 g of SiO_2 hollow spheres in 5 ml ethanolic solution of drugs (6.5 mM). The suspension was stirred for 48h. After centrifugation of drug-loaded SiO_2 nanospheres, the amount of the drug loaded was measured using the absorption intensity of the drug remained in solution at 420 nm by means of UV-vis spectroscopy method. In addition, the in vitro release of the drug was performed by soaking the drug-loaded powder in simulated body fluid (SBF), with continuous stirring at 37°C in a water bath. The release ration of the drug from the carrier into the solution was measured by examining the concentration of the drug in SBF at different time intervals, by means of UV-vis spectroscopy.

3. Results and discussion

IR spectrum of carbon nanospheres shows that they contain carboxyl, ester and alcoholic functional groups on their surface. According to IR spectrum, the peaks at 875-750 cm^{-1}, 1460-1000 cm^{-1}, 1715-1700 cm^{-1}, 3000-2815 cm^{-1} and 3700-3000 cm^{-1} region are attributed to the out of plane aromatic C-H, C-O stretching, ester stretching, aliphatic C-H stretching, and carboxylic acid stretching vibrations, respectively. Comparing Fig. 1, a and b shows that with increasing the hydrothermal time (from 8 to 16h), glucose loses more water and finally polymerizes. Therefore by reducing the oxygen to carbon ratio, the intensity of the 3700-3000 cm^{-1} peaks are reduced[13]. As shown in IR spectra of glucose core and SiO_2 shell before and after calcination (Fig. 2), the functional groups attached to the carbon nanospheres are eliminated that could be due to the complete burning of carbon template. The peaks at 470 and 1110 cm^{-1} region are attributed to the Si-O bending and stretching vibrations, respectively. The peak around 3500 cm^{-1} could be due to the O-H stretching vibration of water.

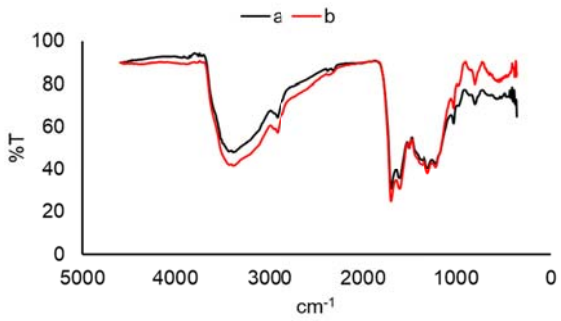

Fig. 1. IR Spectra of the glucose core (a) after 16h and (b) after 8h heating in a hydrothermal system

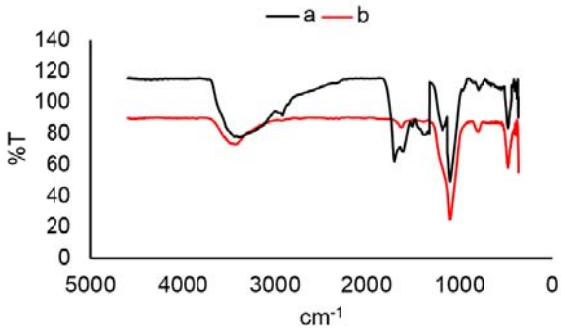

Fig 2. IR Spectra of C@ SiO_2 before (a) and after calcination (b) at 600 ◦C for 3 h

The SEM images (Fig. 3) confirm the morphology of carbon nanospheres. The SEM images show, the size of the carbon nanospheres at different hydrothermal reaction time (Fig 3 a –d). According to Fig. 3, to obtain the carbon nanospheres with the desired uniform morphology and size, the optimum time for hydrothermal process is 12h. Longer hydrothermal process is undesirable, because it causes an agglomeration of nanospheres[14].

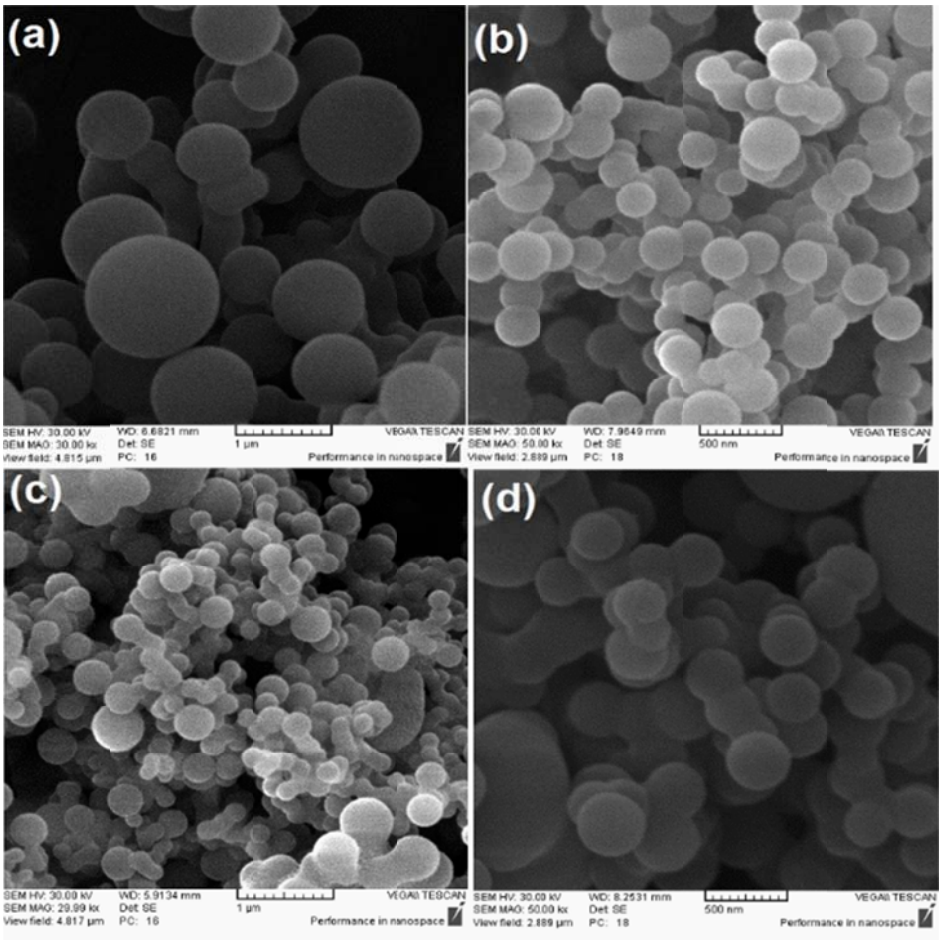

Fig 3. SEM images of glucose spheres after (a) 8, (b) 12, (c) 14 and (d) 16 h heating in a hydrothermal system

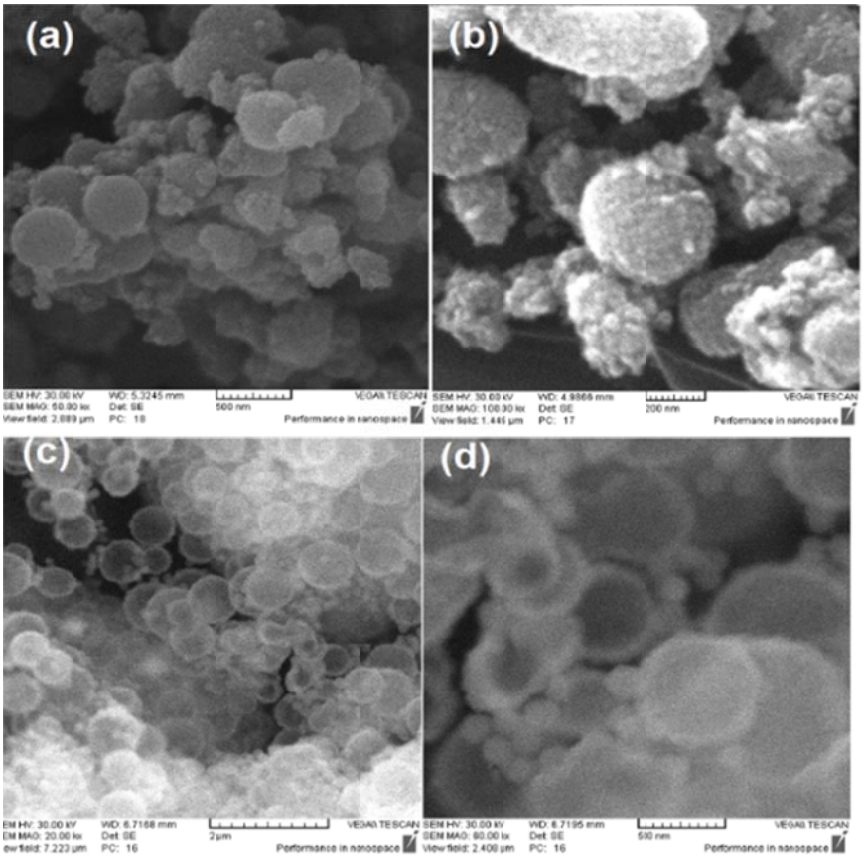

Fig 4. SEM images of C@SiO_2 shell before calcination (a,b) and SiO_2 hallow shells remained after calcination of C@SiO_2 (c,d)

The SEM images of C@SiO_2 nanospheres before calcination are shown in Fig 4 (a,b). The SiO_2 particles around the C cores are clearly obvious. SEM images in Fig 4 (c,d) show the hollow silica shells and it is obvious that after calcination, carbonaceous materials were burned out completely and SiO_2 hollow spheres were remained. Results of SEM images are in good agreement with IR data.

To explore the amount of drug loading on the porous SiO_2 nanospheres, UV/Vis spectrophotometry was used. Fig. 5 shows the UV/Vis spectra of the ethanolic solution of the drugs (6.5 mM) in presence of SiO_2 hollow spheres after 6, 12, 24 and 48 h. As it is obvious due to the porosity of SiO_2 nanospheres, the drug molecules have adsorbed completely after 48 h. The SiO_2-drug conjugation methods include silanization and electrostatic attractions. The monoterpenic phenol isomers (carvacrol and thymol) contain hydroxyl groups, which can interact with silanol groups in silica via hydrogen bonding.

The drug release *in vitro* has been investigated also by means of UV-Vis spectroscopy. The spectra of a suspension of the SiO_2 loaded with drugs have been taken at the beginning of making the suspension, after 30 min, 1, 2, 5h and then every 3 h for a total of 26 h. Fig. 6 shows the release profile of the drugs from the hollow carrier. As can be seen, by the passage of time, the drug release % in solution increases which is due to the increment of the drugs concentration in the simulated body fluid (SBF). The drug release has happened in three stages. At the first stage, about 43% of the drug has been discharged within 125 min, which is probably due to the rapid release of the drug loosely adsorbed on the surface of the nanoshells or free drug molecules. However, this type of fast release is not probably favorable for the practical controlled release of drugs. The second stage has lasted to about 650 min (□ 11 h) in which 37% of the drug released from the nanoshells and in the third stage, which has lasted up to 26 h, 8% of the drug released. This last stage could be related to the release of the drug trap inside the hallow spheres of the carrier that causes a slow releasing to the target cells[12]. In addition, it is probable that slow release is pertained to the strong chemical

adsorption of some drug molecules in the silica pores. Lack of too many functional groups in carvacrol and thymol for interaction with SiO_2 nanospheres, results in encapsulation that could be very important for their slow releasing[10]. So counting on the last two stages, it can be concluded that the porous hollow silica nanospheres, as drug carrier, markedly delayed the release of the carvacrol and thymol drugs and can be used in drug delivery applications.

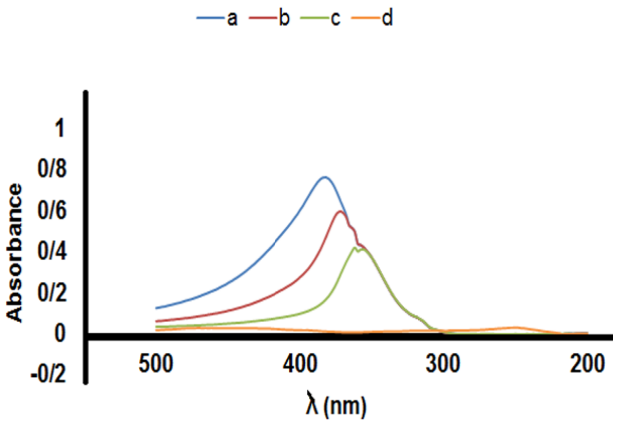

Fig. 5. UV/Vis spectra of the ethanolic solution of the drugs (6.5 mM) in presence of SiO_2 hollow spheres after (a) 6, (b)12, (c) 24 and (d) 48 h

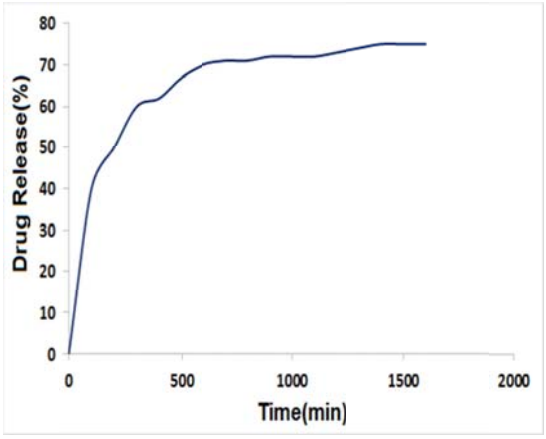

Fig 6. The release profile of the drugs from the hollow carrier into SBF

4. Conclusion

In summary, SiO_2 hollow spheres were successfully synthesized using carbon nanospheres as sacrificial template by hydrothermal method. The SEM images show that SiO_2 hollow spheres with uniform morphology and size distribution were synthesized. Also by controlling the hydrothermal process conditions like concentration and the reaction time and temperature, a tunable controlled size of SiO_2 can be prepared using carbon sacrificial templates, which have potential applications in drug delivery. The SiO_2 nanospheres have high ability for adsorbing drug and there is no need to adjust pH during adsorption. The results have also shown that SiO_2 nanospheres can release drugs at different rates.

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