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RESEARCH PAPER

Hydrophobic polymers modification of mesoporous silica with large pore size for drug release

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Abstract Mesostructure cellular foam (MCF) materials were modified with hydrophobic polyisoprene (PI) through free radical polymerization in the pores network, and the resulting materials (MCF-PI) were investigated as matrices for drug storage. The successful synthesis of PI inside MCF was characterized by Fourier transform infrared (FT-IR), hydrogen nuclear magnetic resonance (^{1}H NMR), X-ray diffraction patterns (XRD) and nitrogen adsorption/desorption measurements. It was interesting to find the resultant system held a relatively large pore size (19.5 nm) and pore volume (1.02 $cm^3\ g^{-1}$), which would benefit for drug storage. Ibuprofen (IBU) and vancomycin were selected as model drugs and loaded onto unmodified MCF and modified MCF (MCF-PI). The adsorption capacities of these model drugs on MCF-PI were observed increase as compared to that of on pure MCF, due to the trap effects induced by polyisoprene chains inside the pores. The delivery system of MCF-PI was found to be more favorable for the adsorption of IBU (31 wt%, IBU/silica), possibly attributing to the hydrophobic interaction between IBU and PI formed on the internal surface of MCF matrix. The release of drug through the porous network was investigated by measuring uptake and release of IBU.

Keywords Mesoporous silica · Hydrophobic polymers · Surface modification · Pore size · IBU · Nanomedicine

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Introduction

In recent years, there has been rapid growth in the fabrication of delivery systems for their promise applications in many fields including drug release (Song et al. 2005). Both organic and inorganic matrices have been investigated in various delivery processes (Nasongkla et al. 2004; Yang et al. 2005). Mesoporous silica materials with pore diameters of 2–50 nm and internal surface areas as high as 700–1,200 $m^2\ g^{-1}$, are suitable candidate for use as supports (Zhao et al. 1998a, b; Vallet-Regí et al. 2006). Generally, surface functionality is carried out to increase the storage capacity for its potential use as a delivery system. Maria et al. reported a carrier system based on octyltrimethoxysilane and octadecyltrimethoxysilane modified SBA-15 (Juan et al. 2006). Meanwhile, Sousa and his co-workers demonstrated a hybrid biological-inorganic material prepared by filling a mesoporous silica structure with collagen (Fagundes et al. 2006). Recently, hybrid

functional nanosystems based on silica and polymers have attracted much attention, for control of molecular transport in including drug release. Up to now, to the best of our knowledge, only one paper concerning about control of molecular transport based on poly (*N*-isopropyl acrylamide) (PNIPA) polymerized inside MCM-41 has been reported (Fu et al. 2003). Unfortunately, the systems based on mesoporous MCM-41 support with pore size of 2–4 nm, are not suitable for encapsulation drugs with large molecular weights involved, such as therapeutic protein or gene regulating medicines. In this case, Xiao presented that modified MCM-41 exhibited very low storage of vancomycin (6.9 wt%), due to the limitation of a relatively small mesopore size of 2.3 nm (Yang et al. 2005). Large mesopores are considered to be suitable host for the storage of bulky medical molecules, such as vancomycin. Mesostructure cellular foam materials (MCF) with large pore diameters of 17–42 nm and high surface areas are attractive to host large molecules (Schmidt-Winkel et al. 1999). Recently, our group reported grafting of hydrophilic polymrs PNIPA inside MCF using atom transfer radical polymerization (ATRP) (Zhou et al. 2007). The multilayer thermo-responsive polymers inside MCF would be expected to form internal cavity for drug molecules. However, a little research has been directed to fabricate hydrophobic polymers modified MCF channels for its potential application as delivery system of oil soluble drugs.

In this paper, we demonstrate a nanocomposite delivery system based on MCF with hydrophobic polyisoprene coating in the pore channels. How to introduce hydrophobic polyisoprene (PI) formed inside the mesopores with large pores is the key point, because of the easy effumability of the monomer isoprene. Here we develop a facile method to conduct free-radical polymerization of isoprene inside MCF through vapor adsorption then polymerization, and prepare successfully the delivery system of MCF-PI. It is interesting to find the resultant system still holds a relatively large pore size of about 19.5 nm and high pore volume of 1.02 $cm^3\ g^{-1}$, which will benefit it for drug storage with relatively large molecules. Ibuprofen (IBU) with small molecules and vancomycin with large molecules were selected as model drugs and loaded onto unmodified and PI functionalized MCF. The release of drug through the porous network was investigated by measuring uptake and release of IBU.

Experimental

Materials

Synthesis of MCF

The MCFs were prepared in aqueous hydrochloric acid using dilute solution of the nonionic block copolymer surfactant Pluronic P123 ($EO_{20}PO_{70}EO_{20}$) with 1,3,5-trimethylbenzene (TMB) as the organic swelling agent (Sauer et al. 2001). In a typical preparation, P123 (2.0 g, 0.4 mmol) was dissolved in 1.6 M HCl (75 mL, 120 mmol) at room temperature while being stirred in a beaker covered with a watch glass. TMB (0.6 g, 5.1 mmol) was then added, and the mixture was heated to 37–40 °C. Following 1 h of stirring, tetraethyl orthosilicate (TEOS, 4.4 g, 21 mmol) was added. After 20 h at 40 °C, the milky reaction mixture was transferred to an autoclave and aged at 100 °C for 24 h under static conditions. The mixture was then allowed to cool to room temperature, and the white precipitate was isolated by filtration, dried in air, and calcined at 500 °C for 8 h in air to produce the MCF materials.

Synthesis of MCF-PI

Typically, 0.2 g MCF in a glass plate was placed in isoprene bottle and sealed at 30 °C for 12 h. Then, 0.02 g free radical initiator azoisobutyronitrile in 2 mL toluene were added droplet into the above MCF powder with isoprene inside and then sealed with a rubber plug. The flask was evacuated and filled thrice with Ar. Then, PI nanocasting MCF (MCF-PI) can be obtained via in situ free-radical polymerization by increase the temperature to 80 °C under nitrogen. The mixture was subsequently diluted with $CHCl_3$ and thrice vacuum-filtered using a 0.22 μm polycarbonate membrane. To ensure that no polymers were fixed on the outside surface, the filtered mass was dispersed in $CHCl_3$, then filtered, and washed with $CHCl_3$. The MCF-PI was obtained by filtration and drying overnight under vacuum.

Loading of drug IBU

The loading of drug IBU (Aldrich) inside the sample MCF-PI was carried out as follow process: 0.3 g of the samples was added to 20 mL of ibuprofen–hexane solution (35 mg/ml) and soaked under stirring at 25 °C for 48 h until the concentration of the solution keeping steady; this was conducted by monitoring the ibuprofen concentration using Lambda 20 UV/Vis spectrometer at a wavelength of 272 nm. Then, the mixture was washed quickly and thoroughly with hexane and dried under vacuum at 40 °C. Finally, the precipitate was obtained through filtration, which was denoted as MCF-PI-IBU. The same procedure were used to sample unmodified MCF, the sample thus prepared was denoted as MCF-IBU.

The loading of vancomycin (Aldrich) inside MCF-PI pores network was carried out as follow process: A total of 0.5 g of sample MCF-PI in 10 mL of water was mixed with 0.5 g of vancomycin hydrochloride under stirring at ambient temperature for 24 h. After filtration, washing with water four times, and drying under vacuum at room temperature for 24 h, the vancomycin loaded sample was obtained, which was designated as MCF-PI-V. In comparison, the storage procedure of the unmodified MCF was similar to those of MCF-PI, which was designated as sample MCF-V.

In vitro drug release study

The release profiles of model drugs were determined by soaking 0.2 g of sample MCF-PI-IBU in 100 mL of Phosphate buffer (pH 7.4) under stirring at 100 rpm in a flask. 3.0 mL of the suspension was withdrawn at a predetermined time, replaced with the same volume of fresh medium, and analyzed by using a UV/Vis spectrometer at 272 nm.

Characterization

X-ray diffraction patterns (XRD) were recorded on Bruker-AXS X-ray diffractometer system with Cu Kα radiation. Nitrogen adsorption measurements at 77 K were performed on an ASAP2010 volumetric adsorption analyzer, samples were out-gassed for 8 h in the degas port. Transmission electron micrographs (TEM) measurements were carried out on a JEOL2010 microscope. Fourier transform–Infrared (FT-IR) measurements were recorded on KBr pellets with a PE Paragon 1,000 spectrophotometer. Hydrogen nuclear magnetic resonance (^{1}H NMR) spectra were measured with a Varian Mercury Plus 400 MHz spectrometer with $CDCl_3$ as solvent. Thermal gravimetric analysis (TGA) was conducted on a PE TGA-7 instrument with a heating rate of 20 °C/min in air.

Results

Fourier transform–Infrared is known to provide surface information of materials for identification of chemical groups. Shown in Fig. 1 are the FT-IR spectra of the resultant MCF, PI, IBU, MCF-PI and MCF-PI-IBU. The delivery system MCF-PI was obtained after polymerization of PI in the channels of MCF, as evidenced by IR bands at 1,357, 1,454, and 1,645 cm^{-1} for the $–CH_3$, $–CH_2–$, and C=C groups, characteristic of the presence of PI in MCF-PI (Fig. 1). Further characteristics of thermogravimetric analysis (TGA) of the sample MCF-PI indicates a weight loss of 9 wt% when MCF-PI was heated up to 800 °C in air (Fig. 2).

The structure of the prepared MCF–PI was further investigated by ^{1}H NMR spectrum in $CDCl_3$ shown in Fig. 3. The aliphatic proton signals at 0.9 and 1.2 ppm are attributed to saturated $–CH_3$ and $–CH_2–$ groups. The resonance at 1.2–2.0 ppm is mainly due

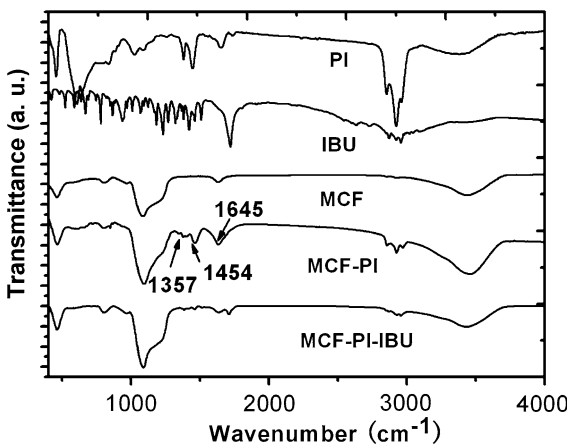


Fig. 1 FT-IR spectra of the samples polyisoprene (PI), IBU, MCF, MCF-PI and MCF-PI-IBU

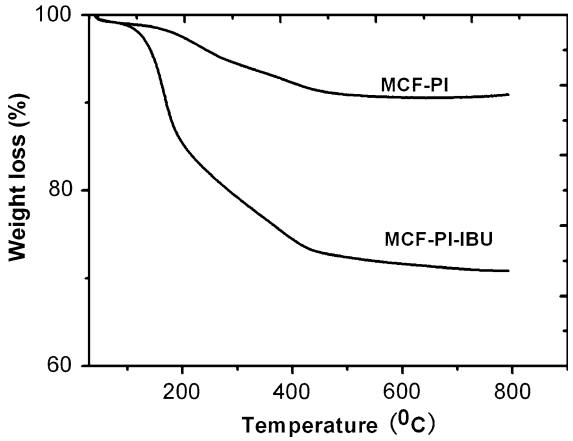


Fig. 2 TGA curves of the samples MCF–PI and MCF–PI–IBU

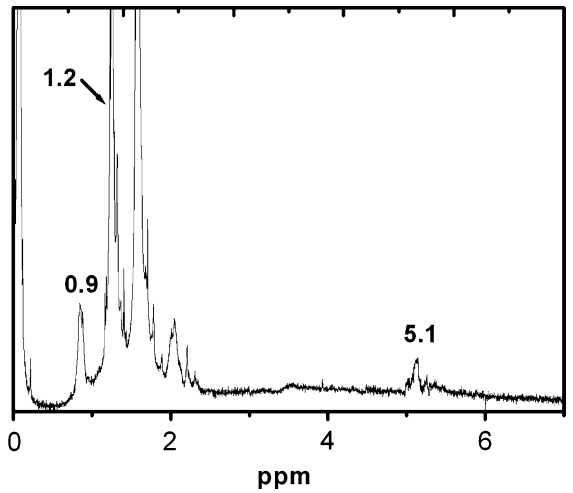


Fig. 3 ^{1}H NMR of MCF–PI in $CDCl_3$

to the backbone of PI. There is a small signal at 5.1 ppm, which confirms the existence of carbon–carbon double bond in PI.

X-ray diffraction patterns (XRD) of the samples MCF, MCF–PI and MCF–PI–IBU were compared as depicted in Fig. 4. XRD experiments reveal a distinct broad peak at small angle for MCF, indicating certain ordered structures of MCF. After polymerization of PI inside the pores network, the peak is detected to be remained, illustrating that the relatively ordered structures have not been disturbed. The only reflection for sample MCF–PI–IBU is retained, which indicates that IBU storage did not result in the damage of the structure. The shift of the diffraction peaks to lower angle and the decrease of intensity are

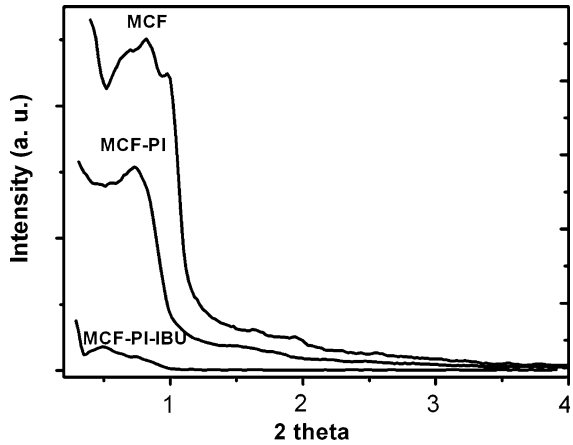


Fig. 4 Low-angle powder XRD patterns for the samples MCF, MCF–PI, and MCF–PI–IBU

owing to introducing polymers and loading IBU drugs inside the pores as described by others (Sauer et al. 2001).

Nitrogen adsorption/desorption measurement was conducted to illustrate the pore structures of the resultant samples. The isotherms show large hysteresis (Fig. 5), which is in conjunction with BdB pore size analyses possessing ink-bottle-type pores in which large cells are connected by narrower windows (Schmidt-Winkel et al. 2000). The sizes of the cells and windows of MCF have been determined from the adsorption and desorption branches of the nitrogen sorption isotherms, which are 22 nm and 7.0 nm, respectively. As it can be seen from Table 1, a Brunauer–Emmett–Teller (BET) surface area of 352.6 $m^2\ g^{-1}$ and a pore volume of 1.48 $cm^3\ g^{-1}$ are presented for unmodified MCF. After polymerization (MCF-PI), the resultant surface area and pore volume are found to be 276.7 $m^2\ g^{-1}$ and 1.02 $cm^3\ g^{-1}$, respectively, due to the formation of nanocasting PI inside the mesopores. Correspondingly, the cavity size is observed decrease from 22 nm to 19.5 nm determined by nitrogen adsorption, suggesting the increase of the wall thickness after PI formed inside MCF. These results suggest that the grafting of polymer chains on the internal surface of MCF has occurred, with the reduction of surface area as well as pore size. The local and less long-range order were confirmed by the pore size distributions obtained from desorption branches of the N_2 sorption isotherms in Fig. 6. It is worth mentioning, the delivery system still (MCF-PI) holds an average pore sizes of

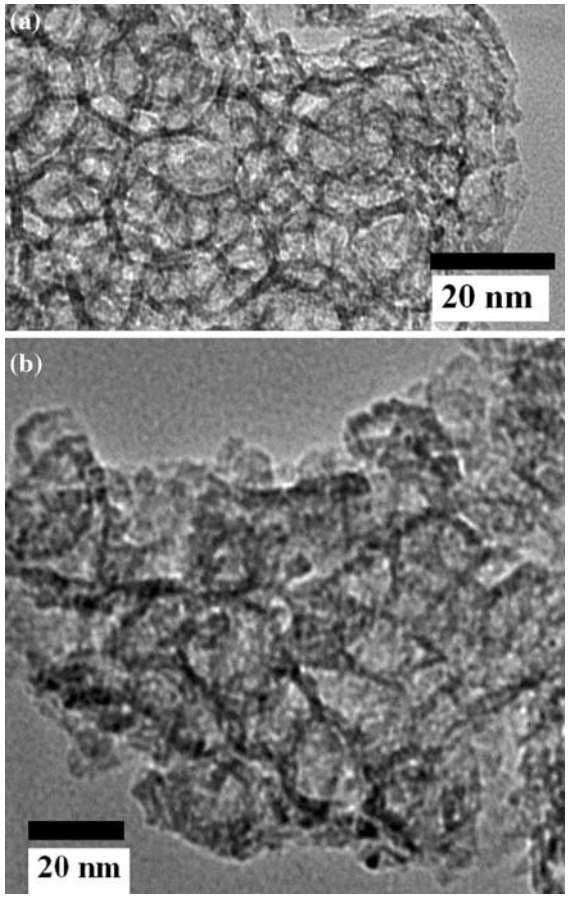


Fig. 5 TEM images of the samples MCF (**a**), MCF–PI–IBU (**b**)

19.5 nm and pore volume of 1.02 $cm^3\ g^{-1}$ with 9 wt% PI formed inside the pores, which may be superior for loading drugs. As an example, after loading of IBU into MCF-PI, the surface area is observed reduce from 276.7 $m^2\ g^{-1}$ to 133.3 $m^2\ g^{-1}$, with the corresponding decrease of pore volume to be 0.67 $cm^3\ g^{-1}$.

Transmission electron micrographs (TEM) of the MCF and MCF-PI-IBU are demonstrated in Fig. 5. Although the diameter of the white disks is not simply correlated to the pore size, the edge of the particle might be very thin, and the image contrast is dominated by mass contrast. Thus, the cell diameter of MCF is estimated to be around 22 nm in consistent with that calculated from N_2 sorption isotherms. A distinct local and less long-range ordered structure is observed from the image (Fig. 5a). As for MCF-PI-IBU, large spherical cells that are interconnected by windows to create a continuous 3-D pore system are maintained.

By anchoring hydrophobic polymers on the internal surfaces, the sorption capacity could be substantially altered. To detect the adsorption efficiency of the obtained system on drugs, IBU with small molecules and vancomycin with large molecules were selected as model drugs, and loaded onto MCF and modified MCF (MCF-PI). The sorption capacities are summarized in Table 2. It shows about 31 wt% (IBU/silica) drug ibuprofen can be anchored in the MCF-PI channels, similar results were observed by Yang et al. based on carboxylic acid and polyelectrolyte modified SBA-15 (Yang et al. 2005). As a contrast, the amount of IBU adsorbed on unmodified MCF was measured to be only 14.5 wt%. Similarly, the storage capacity of vancomycin on MCF-PI was observed increase a lot compared with that of on pure MCF. It is not difficult to understand that a certain amount of IBU (14.5 wt%) can be loaded onto MCF, since silanol groups on the pore wall are liable to form hydrogen bonding with the carboxyl group of IBU as described by many others (Song et al. 2005). However, the weak host/guest interactions are not strong enough to hold much more drugs. Therefore, only 14.5 wt% of IBU could be adsorbed on MCF. We are surprised to learn the amount of IBU stored in MCF-PI is up to 31 wt%, even though no distinct interaction between IBU and MCF-PI can be detected from analysis of FT-IR (Fig. 1).

Table 1 Textural parameters of the various samples

Sample	BET Surface area ($m^2\ g^{-1}$)	Pore volume ($cm^3\ g^{-1}$)	[a]Cavity size (nm)	[b]Entrance size (nm)
MCF	352.6	1.48	22	7.0
MCF-PI	276.7	1.02	19.5	8.1
MCF-PI-IBU	133.3	0.67	19.5	6.5

[a] Calculated from the adsorption branches of the N_2 sorption isotherms based on the BdB sphere model

[b] Calculated from the desorption branches of the N_2 sorption isotherms based on the BdB sphere model

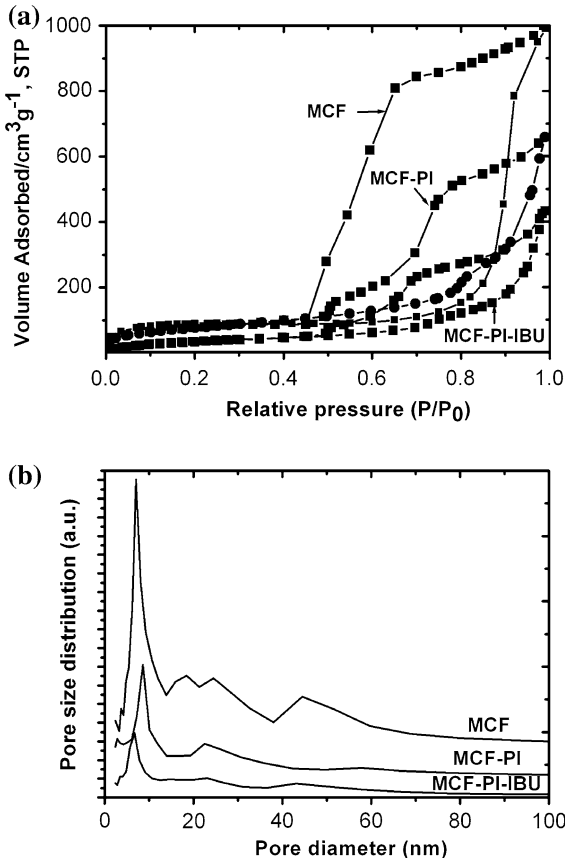


Fig. 6 Nitrogen adsorption/desorption isotherms of the samples MCF, MCF-PI and MCF-PI-IBU (**a**), pore size distributions measured from the desorption branches (**b**)

As a typical guest molecule, vancomycin with the size of 2.3 nm is used to study the efficiency of this carrier system on drugs with large molecular weights. Notably, the amount of vancomycin stored in the pores of MCF-PI is up to 21 wt% (vancomycin/silica, w/w). On the contrary, sample MCF based on pure MCF exhibits very low storage of vancomycin (5.6 wt%). It has been reported that the carrier system constructed by oppositely charged ionic interaction between polycations and anionic SBA-15 demonstrate of a high vancomycin capacities of 36.4%. However, no interaction evidence was detected between vancomycin and mesoporous matrixes from FT-IR spectra (Fig. 6), since FT-IR spectra of MCF-V and MCF-PI-V are very similar except for the intense peak at 1,393, 1,496 cm^{-1} for MCF-PI, characteristics of vancomycin. These adsorption behaviors are suggested that polymer chains on the internal surface of MCF would play an important role in influencing the adsorption amount of drugs. Xiao et al. found it is difficult to uptake vancomycin using unmodified SBA-15 as the host with relatively large pore size of 7.2 nm (Yang et al. 2005). Long and extended polymer chains are considered to act as a holder to retain drugs inside the pores in investigation of a delivery system based on PNIPA grafted MCF (Zhou et al. 2007). Herein, PI is hydrophobic without the presence of functional groups, thus it is impossible for them to form interaction with the model drugs. The reason for the improved loading amount of IBU or vancomycin on MCF-PI as compared to that of on pure MCF would possibly be explained to drug molecules encapsulation in the polymer chains as described in Scheme 1.

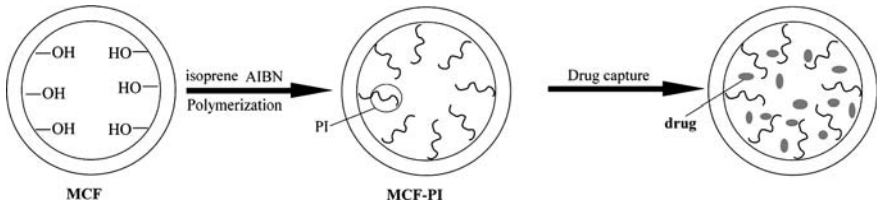
Table 2 Loading amount of model drugs on MCF and MCF-PI

Sample	Loading amt of IBU (wt%)	Loading amt of vancomycin (wt%)
MCF	14.5	5.6
MCF–PI	31	21

As it can be seen from Table 2, the amount of vancomycin adsorbed in MCF-PI is almost four times than that of on MCF. It is reasonable to conclude that PI modified MCF with large pore sizes is benefit its storage of large molecules. However, the delivery system of MCF-PI is found to be more favorable for the adsorption of IBU because the adsorption capacity can reach 31 wt%. It is well known that small adsorbate sizes result in high adsorption because the small molecules can enter micropores or small mesopores, as a result the loading amount is lower as the adsorbate becoming larger (Yiu et al. 2001). Apart from this, the polar-polar interaction between IBU and MCF-PI would partly contribute to the observations. IBU is hydrophobic, whereas vancomycin is a kind of water soluble drug (Fig. 7).

Control of drug release through the porous network was investigated by measuring uptake and release of ibuprofen (IBU, an analgesia and anti-inflammatory drug) in Phosphate buffer at 37 °C as monitored by UV spectroscopy and thermogravimetry (TG). The in vitro delivery of the drug was performed by soaking the samples in a solution simulating body fluid composition (SBF), maintaining pH at 7.4. In order to avoid limitation of the delivering rate by external diffusion constraints, continuous stirring is

Scheme 1 Schematic representation of drug delivery system based on PI modified MCF



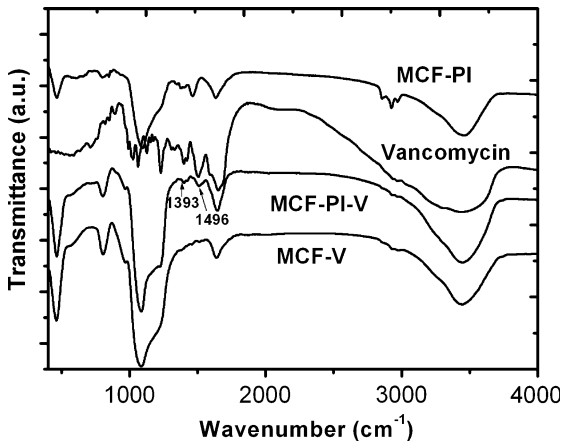


Fig. 7 FT-IR spectra of the samples MCF-PI, vancomycin, MCF-V and MCF-PI-V

maintained during the assays. The cumulative percentage release of IBU from MCF-PI was depicted in Fig. 8. The initial burst release from MCF-PI may be due to the excessive drugs which were loosely entrapped inside the mesopores or located at the outer surface of MCF. The total cumulative percentage release amount is up to 94% in 180 min owing to the large pore size of the matrix MCF.

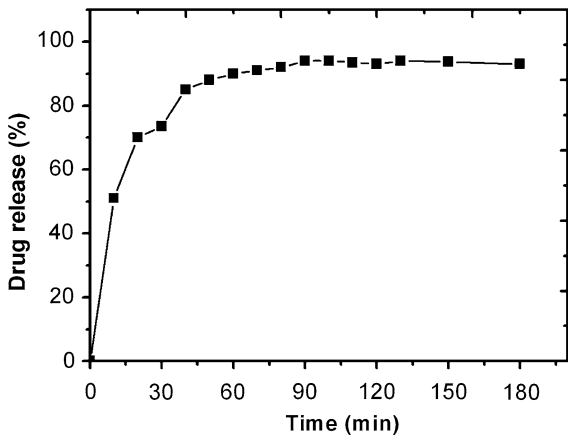


Fig. 8 The dependence of release amounts of IBU from MCF-PI-IBU on time in a solution simulating body fluid composition (SBF), maintaining pH at 7.4

Conclusions

In summary, a novel delivery carrier system has been successfully synthesized based on the MCF with hydrophobic polyisoprene coating inside the pores. It is interesting to find the result system holds a relatively large pore size (19.5 nm) and pore volume (1.02 $cm^3 g^{-1}$), which would benefit for drug storage with relatively large molecules. The delivery system of MCF-PI demonstrated a IBU storage capacity of 31 wt% (IBU/silica) and vancomycin of 21 wt% (vancomycin/silica), due to the capsulation effects of PI chains inside the pores. That is to say this system is efficient for storage of drugs with small and large molecules. The adsorption behaviors show PI modified MCF is more favorable for adsorption of IBU, possibly attributing to the hydrophobic interaction between IBU and PI on the inner surface of MCF pores. The dependence of release amounts of IBU on time through hydrophobic polymers inside MCF in a solution simulating body fluid composition (SBF) was investigated. The large pore size of the support and the hydrophobic inner surface can be expected to the potential use as carrier system for the oil soluble drugs with large molecular weights.

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