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Fabrication of Hydrogel Beads Entrappted by Mesoporous Silicates Nanoparticles for pH-sensitive and Sustained Release of Indomethacin

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In this study, hydrophobic indomethacin was quantitative loaded onto various mesoporous silicates nanoparticles by the wetness impregnation. The DSC results of indomethacin-loaded mesoporous silicates nanoparticles exhibited the amorphous state of drugs and thus might increase its dissolution and bioavailability. The release assays of indomethacin from these mesoporous silicates nanoparticles indicated that both the pore size and the surface functionalization of mesoporous silicates nanoparticles could affect their release rate. Furthermore, these indomethacin-loaded mesoporous silicates nanoparticles were entrapped into chitosan/alginate hydrogels and formed a series of hydrogel beads. The swelling studies indicated that the incorporation of mesoporous silicates nanoparticles had no influence on the swelling behaviors of hydrogel beads. The resultant beads displayed pH-sensitive and sustained-release of hydrophobic indomethacin and thus the combination of chitosan/alginate hydrogels and mesoporous silicates nanoparticles might serve as a potential oral hydrophobic drug delivery system.

Keywords: Hydrogels, Mesoporous silicates, Indomethacin, pH-sensitive, Sustained release.

INTRODUCTION

Hydrogels made of polysaccharides, such as chitosan and alginate, have been proposed for many biomedical and pharmaceutical purposes in recent years[1,2]. Chitosan is a deacetylated form of chitin and alginate is a polyanionic copolymer of mannuronic and guluronic sugar residues extracted from brown algae. Both polymers are biodegradable and non toxic and form ionic complexes through hydrogen bonding or electrostatic interactions. Chitosan/alginate hydrogels swell or shrink in response to pH changes and thus yielding a variety of chitosan/alginate hydrogel-type pH-sensitive oral drug delivery systems in the last decade[3-9]. However, these systems were largely used for controlled release of hydrophilic drugs and little was used for the entrapment of hydrophobic drugs. To achieve the controlled release of hydrophobic drugs, it was proposed chitosan/alginate hydrogel systems with amphiphilic properties should be employed. For example, poly(ε-caprolactone) (PCL)-modified chitosan/alginate hydrogel system was successfully prepared for pH sensitive release of theophylline[10], in which hydrophobic cluster poly(ε-caprolactone) play an important role in improving encapsulation efficiency and reducing release rate of poorly soluble drug due to its hydrophobic interactions with the drug. The example gives us a hint that the graft/entrapment of any other ingredients with similar functions as those of poly(ε-caprolactone) onto/into the polymer backbone could also regulate the release profiles of hydrophobic drugs.

Due to several intrinsic advantages, such as non-toxic nature, high surface area, large pore volume, adjustable pore diameter and versatile surface chemistry, mesoporous silica nanoparticles have become an ideal host for various drugs payload[11-15]. Recently, mesoporous silicates nanoparticles were found to be a useful excipient in the increase of the solubility of hydrophobic drugs by holding back the formation of crystalline material and retaining drugs in amorphous form[16-18]. It is known that oral bioavailability of hydrophobic drug candidates constitutes one of the most challenging tasks over the last two decades. The finding of such a property of mesoporous silicates nanoparticles may offer unprecedented avenues for enhancing the oral bioavailability of these candidates in oral therapy. Indomethacin is a very effective anti-inflammatory drug. When taken orally against chronic inflammatory and pain conditions, indomethacin can result in serious gastrointestinal disturbance generally. In this study, indomethacin was chosen as a hydrophobic model drug and then loaded quantitatively onto different types of mesoporous silicates nanoparticles by incipient wetness procedure and then these indomethacin-loaded mesoporous silicates nanoparticles were encapsulated into chitosan/alginate hydrogels. Furthermore, the release kinetics of indomethacin

from these composites was evaluated. The aim of us is to construct a series of pH sensitive and sustained release systems for oral hydrophobic drugs delivery by combining the merits of two types of materials.

EXPERIMENTAL

Sodium alginate, chitosan (deacetylation degree, 85 %; viscosity average molecular weight, 40000) and indomethacin was purchased from Shanghai Chemical Reagent Company. Cetyltrimethylammoniumbromide, 3-aminopropyltriethoxysilane, Tetraethylorthosilicate, Triblock-copolymer Pluronic (P123), mesitylene was obtained from Sigma Aldrich. Other chemicals were used as received.

Syntheses of mesoporous silicates nanoparticles and amino-modified mesoporous silicates nanoparticles: MCM-41 and SBA-15 were synthesized according to the previous reports[19,20]. In brief, for MCM-41, 1 g of cetyltrimethylammoniumbromide was dissolved in 480 mL of water and 3.5 mL of 2 M NaOH solution. Mesitylene (7 mL, 48.8 mmol) was then added to the solution. The mixture was stirred vigorously at 80 ºC for 2 h. tetraethylorthosilicate (5 mL, 21.9 mmol) was then added. The mixture was stirred vigorously at 80 ºC for another 2 h and then collected. Cetyltrimethylammoniumbromide and mesitylene were removed at 50 ºC in a 100 mL methanolic solution with 0.75 mL HCl for 6 h. For SBA-15, 2 g of P123 was dissolved in 15 mL of water and 30 g of 2 M HCl solution at 35-40 ºC under stirring. Then, 4.4 g of tetraethylorthosilicate was added. After 24 h, the silica suspension was transferred into a Teflon-lined autoclave and placed in an oven for hydrothermal treatment at a temperature of 100 ºC for another 48 h. The solid products were filtered, washed and dried at room temperature. P123 was removed *via* three repeated ethanol extraction for 6 h at 70 ºC. The amine functionalization of mesoporous silicates nanoparticles was conducted as follows. 1 g of mesoporous silicates nanoparticles was added to 5 mL 3-aminopropyltriethoxysilane and 40 mL toluene mixed solution and then placed into a Teflon-lined stainless steel vessel at 120 ºC for 6 h. The obtained amino-modified mesoporous silicates nanoparticles (denoted as MCM41-NH_2 or SBA-NH_2) was isolated, washed with a mixture of CH_2Cl_2/Et_2O (1:1) and dried under vacuums at 60 ºC overnight.

Loading of indomethacin onto different mesoporous silicates nanoparticles: Indomethacin was loaded onto different mesoporous silicates nanoparticles according to the incipient wetness procedure. In order to obtain 20 % (w/w) of drug loading, 150 mg of the support materials was impregnated with 750 μL of drug solution (50 mg mL^{-1}) in methylene chloride. The moist powder was homogenized with stirring, after which it was dried at 40 ºC in a vacuum oven for 48 h to remove any residual methylene chloride. The drug content of the mesoporous silicates nanoparticles formulations was determined by suspending 5 mg of drug-loaded mesoporous silicates nanoparticles in 10 mL of an aqueous solution containing 3 % of sodium lauryl sulfate. These suspensions were sonicated for 0.5 h and subsequently put in a rotary mixer for 24 h. Preliminary tests had pointed out that a time span of 24 h was enough to remove the entire drug load from mesoporous silicates nanoparticles. The silica was separated from the drug solutions by centrifugation and then the supernatant was analyzed with UV-visible absorption spectroscopy at 320 nm.

Preparation of mesoporous silicates nanoparticles-doped chitosan/alginate hydrogel beads: Chitosan/alginate hydrogel beads were produced by the gelation method. In brief, chitosan was dissolved in 1 % (v/v) acetic acid to get a 0.3 % (w/v) solution and then $CaCl_2$ was added to the chitosan solution to get a 2 % solution. 200 mg sodium alginate was dissolved in 10 mL distilled water to get a 2 % solution (w/v) and then 3 mg of indomethacin or the moderate amounts of mesoporous silicates nanoparticles containing 3 mg of indomethacin was added. The solution was stirred thoroughly to ensure complete mixing. 4 mL of this viscous solution was introduced in a 5 mL syringe and extruded through a 0.7-mm-diameter needle using compressed air. The droplets were pulled off in 20 mL $CaCl_2$ stirred solution at a rate of 20 mL per hour and were hardened for 0.5 h and then filtrated and rinsed with deionized water until neutral. The capsules were dried in the oven at 60 °C. To determine the encapsulation efficiency of indomethacin in the hydrogel beads, the beads (0.2 g) were dissolved in 100 mL of PBS (pH 7.4) under stirring during 24 h. The amount of free indomethacin was determined in the clear supernatant by UV spectrophotometry at 320 nm. The encapsulation efficiency is defined as the weight percentage of loaded drug based on feed amount.

Swelling measurements: The preparation of drug-free and mesoporous silicates nanoparticles-doped chitosan/alginate hydrogel beads was performed as described in the former and the same amounts of mesoporous silicates nanoparticles as those of drug-loaded hydrogel beads were used. Swelling studies of these beads were carried out in simulated gastric fluid (SGF, pH 1.2) and simulated intestinal fluid (SIF, pH 7.4) at 37 ºC. In brief, accurately weighed amounts of beads were immersed in 40 mL of desired solution. At fixed time intervals, the beads were separated from the medium through filtration. Immediately, they were gently wiped with paper and weighed. The dynamic weight change of the beads with respect to time was calculated according to formula: % weight change = (Ws-Wd)/Wd, in which Ws and Wd are the weight of the swollen beads and that of the dried beads respectively.

Release of indomethacin from various mesoporous silicates nanoparticles and mesoporous silicates nanoparticles-doped hydrogel beads. The release profile of 3 mg of indomethacin was obtained by soaking different mesoporous silicates nanoparticles and mesoporous silicates nanoparticles-doped hydrogel beads in 50 mL of simulated gastric fluid (pH 1.2 HCl aqueous solutions containing 0.5 % tween-80) without pepsin and simulated intestinal fluid (pH 7.4 PBS solutions) at 37 ºC under stirring at a rate of 100 r/min. At given time intervals, 1.5 mL solution was removed using a syringe and replaced with the same volume of fresh solution. The withdrawn samples were centrifuged for 5 min and the supernatant was monitored by UV spectrophotometry at 320 nm.

Characterization: Transmission electron microscopy (TEM) analyses were conducted on a JEM-2100F electron microscope operating at 200 kV. Scanning electron microscopy (SEM) images were obtained on a field emission JEOL JSM-

6700F microscope. Nitrogen adsorption and desorption isotherms were measured with ASAP 2000 surface area and porosity analyzer (Micromeritics) at 77 K. The UV-visible absorption spectra were measured using a U-4100 spectrophotometer (Hitachi Inc). The differential scanning calorimetry (DSC) analysis was carried out with a DSC 6200 (Seiko Inc) using a heating rate of 10 ºC/min.

RESULTS AND DISCUSSION

Characterization of mesoporous silicates nanoparticles: As shown from TEM images (Fig. 1a, b), both MCM-41 and SBA-15 showed hexagonal arrays of cylindrical mesopores. The mesoporous characteristics were further demonstrated by N_2 adsorption-desorption isotherms, where type IV isotherm with a hysteresis loop was exhibited (Fig. 2). The pore size of MCM41/SBA-15 calculated using BJH method was 3.63/9.85 nm and the BET surface area and the total pore volume of MCM41/SBA-15 were 664.7/671 $m^2 g^{-1}$ and 0.78/1.08 $cm^3 g^{-1}$, respectively (Table-1). The grafting of amino groups onto mesoporous silicates nanoparticles was confirmed by XPS (Fig. 3), in which one N1s peak was found as compared to the XPS of the original mesoporous silicates nanoparticles. The modification of mesoporous silicates nanoparticles with amino-groups further led to the reduction of nitrogen adsorption parameters of the original materials (Table-1).

TABLE-1
STRUCTURE PARAMETERS OF VARIOUS MESOPOROUS SILICATES NANOPARTICLES

Sample	S_{BET} (m^2/g)	V_p (cm^3/g)	D_p (nm)
SBA-15	671.7	1.082	9.85
IDM-loaded SBA-15	351.4	0.706	8.59
SBA-15-NH_2	272.9	0.524	7.9
IDM-loaded SBA-15-NH_2	123.8	0.241	6.28
MCM-41	664.7	0.786	3.63
IDM-loaded MCM-41	348.9	0.431	3.32
MCM-41-NH_2	268.2	0.339	3.55
IDM-loaded MCM-41-NH_2	48.6	0.132	2.08

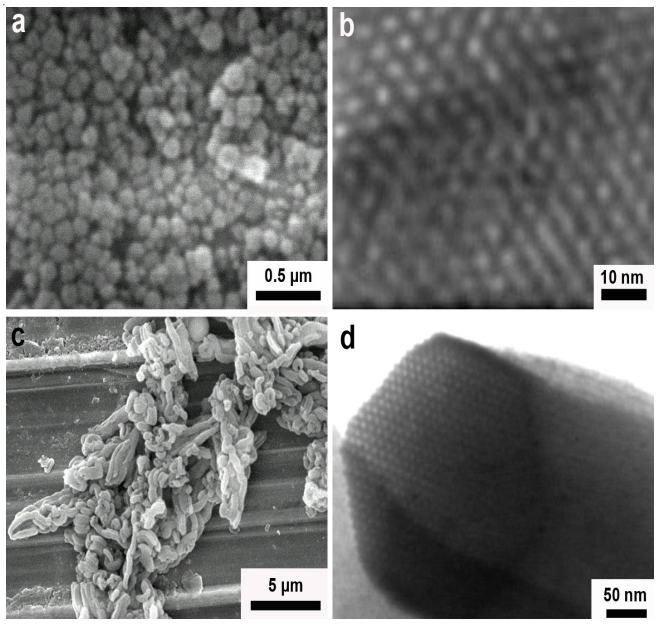

Fig. 1. SEM and TEM images of MCM-41 (a, b) and SBA-15 (c, d)

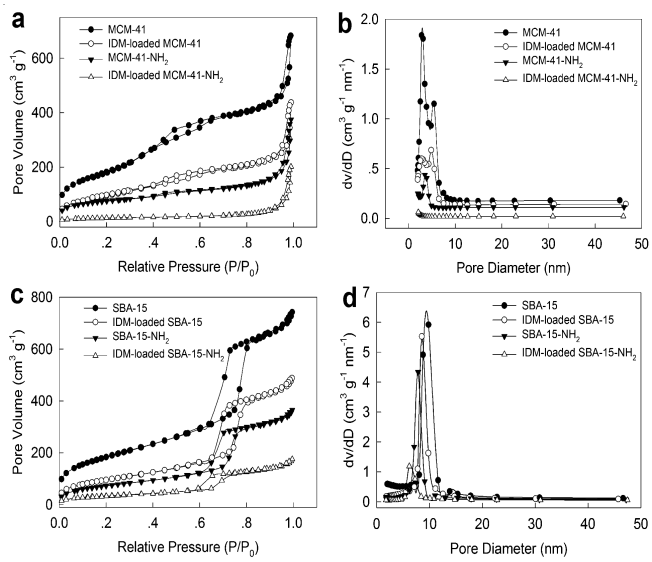

Fig. 2. N_2 adsorption-desorption isotherms (a, b) and the corresponding pore size distributions (c, d) of various mesoporous silicates nanoparticles

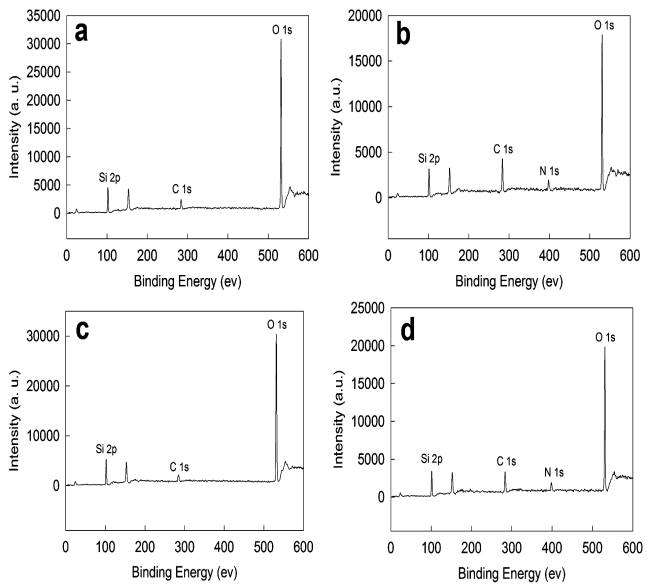

Fig. 3. XPS spectra of MCM-41 (a), MCM-41-NH_2 (b), SBA-15 (c) and SBA-15-NH_2 (d)

Characterization of indomethacin-loaded mesoporous silicates nanoparticles: The loading of indomethacin onto mesoporous silicates nanoparticles was *via* the incipient wetness impregnation, by which the void space of mesoporous silicates nanoparticles could be filled with a precise amount of highly concentrated drug solution and thus avoiding the time-consuming equilibration and filtration step that was necessary for the most common adsorption procedure. The actual loading of indomethacin onto mesoporous silicates nanoparticles was determined by TGA measurements and 24 h release experiments (data not shown), in which the uniform results were achieved. Furthermore, the loading of indomethacin also decreased the BET surface area, pore volume and pore size of the corresponding pure materials (Table-1). In addition, to elucidate the physical state of indomethacin, DSC measurements were performed. It can be seen from Fig. 4 that crystalline

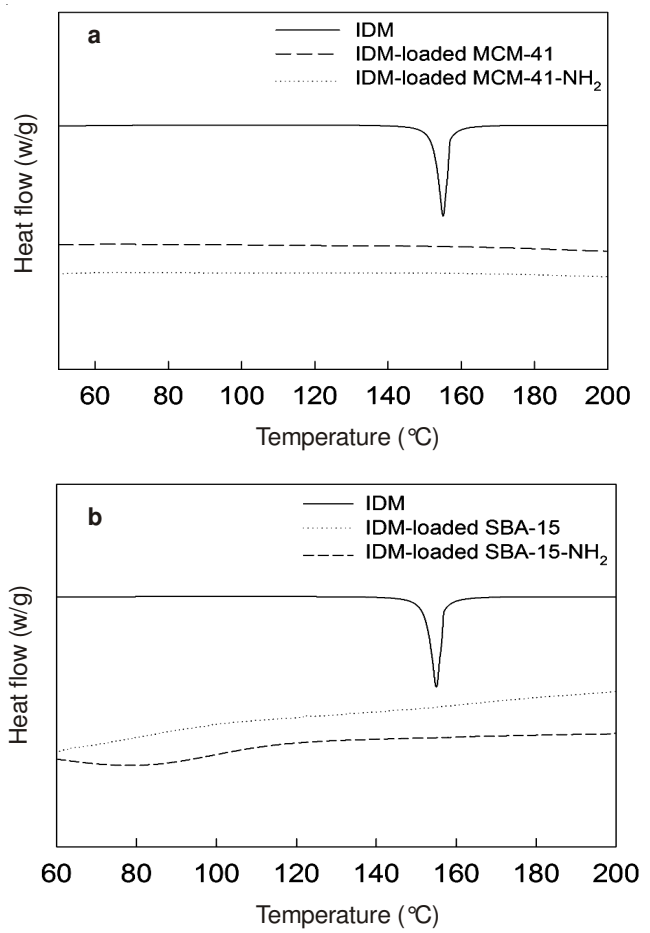

Fig. 4. Differential scanning calorimetry curves of various mesoporous silicates nanoparticles

indomethacin melted at 168 °C, whereas indomethacin formulated with mesoporous silicates nanoparticles showed no thermograms signs of melting whether at the bulk melting point or at depressed temperatures, suggesting their noncrystalline properties. Although the exact physical nature of indomethacin confined to mesopores is not yet fully understood, it is clear that the thermodynamic properties of molecules confined to porous solids alter significantly when compared to those of the bulk phase. The results are in agreement with the prior reports[15], suggesting the enhanced dissolution of hydrophobic drugs when formulated with mesoporous silicates nanoparticles.

***in vitro* Release of indomethacin from mesoporous silicates nanoparticles:** Generally, drug release process from mesoporous silicates nanoparticles accompany with a series of events, including the imbibition of release medium into matrices, which is driven by osmotic pressure arising from concentration gradients, drug dissolution and drug diffusion from matrices to the release medium. In this process, several factors could affect the release profile of the hosted molecule, such as the nature of the host-guest chemical interaction and the pore size of mesoporous silicates nanoparticles. Fig. 5 showed the *in vitro* release profiles of indomethacin from mesoporous silicates nanoparticles. It can be seen that indomethacin exhibited slower release rate from mesoporous silicates nanoparticles in simulated gastric fluid after the initial burst release than that of release rate in simulated intestinal fluid, which may caused by the low aqueous solubility of carboxylic indomethacin at acidic condition. indomethacin also exhibited slower release rate whether in simulated gastric fluid or in simulated intestinal fluid from the small pore sized MCM-41 than from the large pore sized SBA-15, indicating the reduction of the drug release rate with the decreasing pore size of mesoporous silicates nanoparticles. Furthermore, functionlization of mesoporous materials can also affect the release profiles of indomethacin due to changed pore size and surface property. Taking the release of indomethacin from the MCM41-type matrices as an example, 70 % of indomethacin was released from MCM41 original materials in simulated gastric fluid within 6 h. But for MCM41-NH_2, only 50 % of release were achieved. The prolonged release pattern of indomethacin from MCM41-NH_2 is mainly caused by the reduced pore size and the interaction between amine groups in the surface of the matrices and carboxylate groups of indomethacin. Thus, the different release mediums, the pore size and the functionlization of mesoporous silicates nanoparticles could affect the release profiles of indomethacin. The sequence of the release rate of indomethacin both in simulated gastric fluid and in simulated intestinal fluid from high to low is from MCM41-NH_2, SBA-NH_2, MCM-41 and SBA-15.

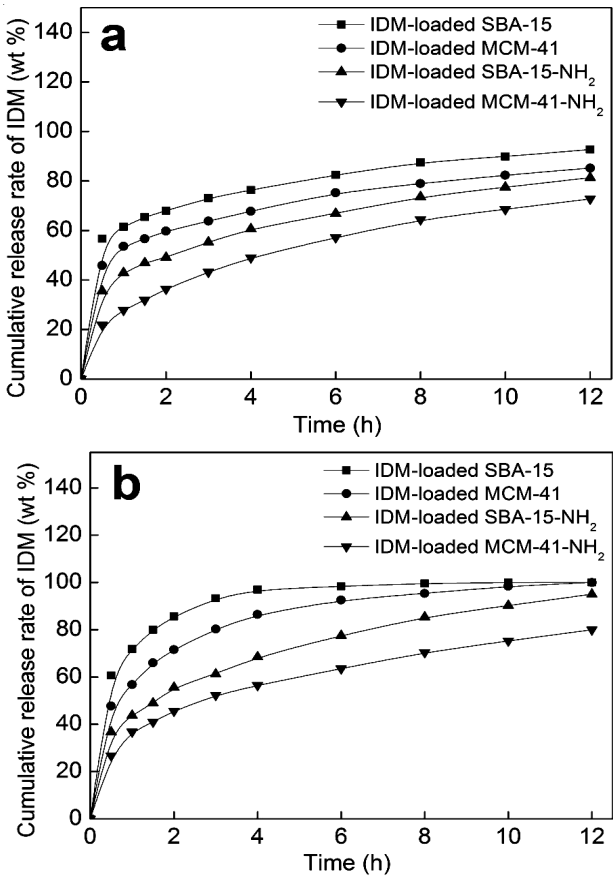

Fig. 5. Release profiles of indomethacin from various mesoporous silicates nanoparticles in SGF (a) and SIF (b)

Loading efficiency of indomethacin in chitosan/alginate beads Although the release rate of indomethacin can be tuned by using different mesoporous silicates nanoparticles, mesoporous silicates nanoparticles alone as the carriers of indomethacin is not enough to prevent its serious gastrointestinal

stimulation when oral delivery. To achieve a site-selective, controlled-release of indomethacin and reduce its side effects, indomethacin-loaded mesoporous silicates nanoparticles were further encapsulated into chitosan/alginate hydrogel. Fig. 6 showed the wet spherical chitosan/alginate beads containing the indomethacin-loaded mesoporous silicates nanoparticles or not. The loading efficiency of indomethacin in mesoporous silicates nanoparticles-doped chitosan/alginate beads was higher than that of indomethacin in chitosan/alginate beads (Table-2). In general, fewer host molecules leaked out during the capsule formation stage because the viscous properties of the droplet and the fast gelation reaction could be helpful for confining the host molecules within the capsules. The leakage of the host molecules mainly occurred during the capsule hardening stage. The combination of the carboxylate groups of guluronate monomers with Ca^{2+} reduced the space occupied by alginate and led to the shrinkage of the membrane as well as the inner size of the capsule. Therefore, a certain amount of water extruded out of the capsules carrying more or less host molecules out. Due to high surface area, large pore volume and functionalized surface of mesoporous silicates nanoparticles, more water molecules were adsorbed on their surface and thus more host molecules were confined within the mesoporous silicates nanoparticles-doped chitosan/alginate beads.

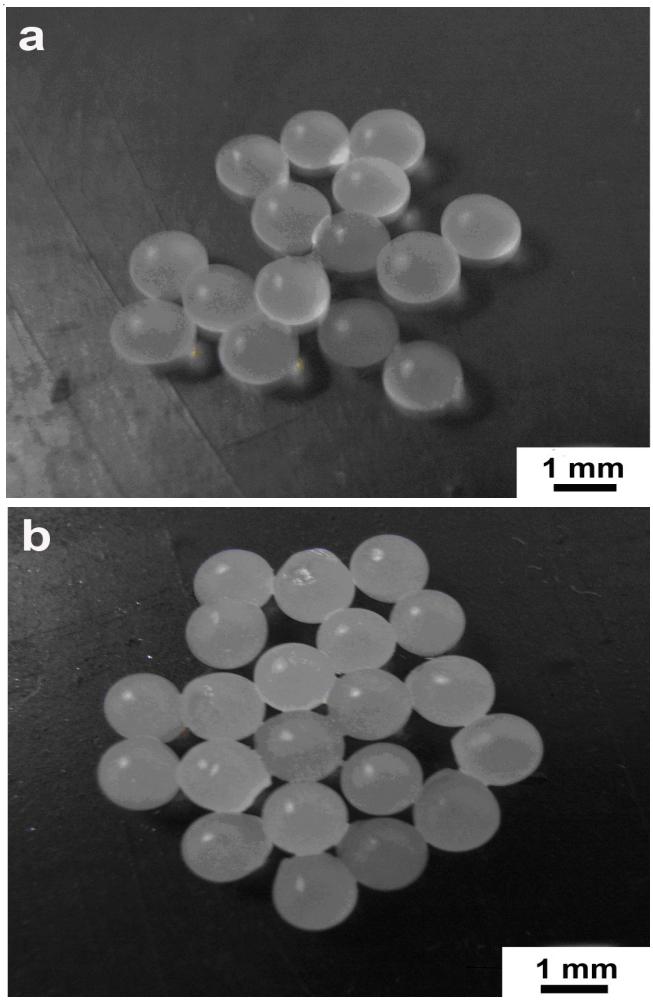

Fig. 6. Photographs of chitosan/alginate hydrogel beads (a) and mesoporous silicates nanoparticles-contained chitosan/alginate hydrogel beads (b)

TABLE-2
ENCAPSULATION EFFICIENCIES OF INDOMETHACIN IN THE VARIOUS HYDROGEL BEADS

Samples	Encapsulation efficiency (%)
IDM-loaded CHI/ALG hydrogel beads	78.18
Hydrogel beads containing IDM-loaded MCM-41	92.06
Hydrogel beads containing IDM-loaded MCM-41-NH_2	83.53
Hydrogel beads containing IDM-loaded SBA-15	90.78
Hydrogel beads containing IDM-loaded SBA-15-NH_2	80.39

Swelling studies of chitosan/alginate beads: To further evaluate the effects of mesoporous silicates nanoparticles on the swelling behaviors of chitosan/alginate beads in different medium, the swelling tests of hydrogel beads in simulated gastric fluid and in simulated intestinal fluid were performed by weight ratio method. As shown in Fig. 7a, and 7b, the swelling degrees of hydrogel beads in simulated gastric fluid had no clear change within 3 h, but in simulated intestinal fluid, the swelling degrees of hydrogels increased up to 1400 %. Mesoporous silicates nanoparticles-contained beads showed the similar swelling behaviors as those of blank beads. Herein, it should be emphasized that all the beads showed swelling and floating both in simulated gastric fluid and in simulated intestinal fluid without any sign of disintegration within 3 h. The results indicated that the incorporation of mesoporous silicates nanoparticles had no influence on the swelling behaviours of chitosan/alginate beads and these new systems still remained the pH sensitive nature of hydrogels.

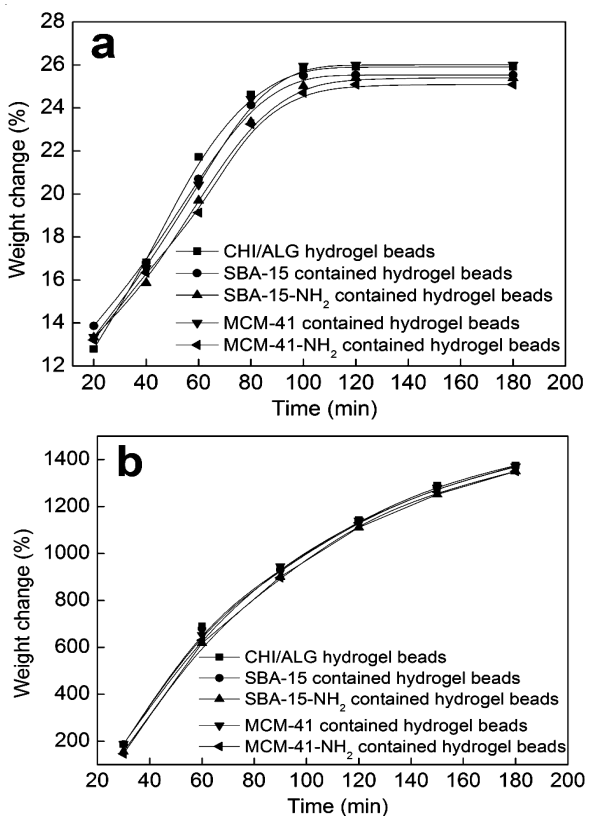

Fig. 7. Swelling profiles of various hydrogel beads in SGF (a) and SIF (b)

Release of indomethacin from chitosan/alginate beads containing mesoporous silicates nanoparticles: To investigate the effects of the combination of chitosan/alginate hydrogels and mesoporous silicates nanoparticles on the release of indomethacin, the release assays were performed. As shown in Figs. 8a and 8b, the release of indomethacin by chitosan/alginate beads within 6 h in SGF or in SIF was about 25 or 95 %, respectively, exhibiting the pH-sensitive nature of hydrogel. Compared to the release by chitosan/alginate beads alone, the release by hydrogel beads containing MCM41-NH_2, SBA-NH_2, MCM-41 and SBA-15 was reduced to 8, 9, 10 and 12 % in SGF and 40, 50, 60 and 70 % in SIF, respectively, indicating that the incorporation of mesoporous silicates nanoparticles clearly sustained the release of indomethacin from hydrogel beads regardless of release medium. Moreover, the release rate of indomethacin from hydrogel beads could be tuned by incorporating different mesoporous silicates nanoparticles and the sequence of the release from these formulations was in agreement with that of the release from mesoporous silicates nanoparticles. Meanwhile, the coating of mesoporous silicates nanoparticles by chitosan/alginate hydrogels also exerted the effects on the release of indomethacin from mesoporous silicates nanoparticles (Fig. 8). For example, the release by MCM-41 within 6 h was about 70 % in SGF and 90 % in SIF, respectively, but the release by chitosan/alginate-coated MCM-41 was reduced to less than 10 and 60 %, respectively (Fig. 8a).

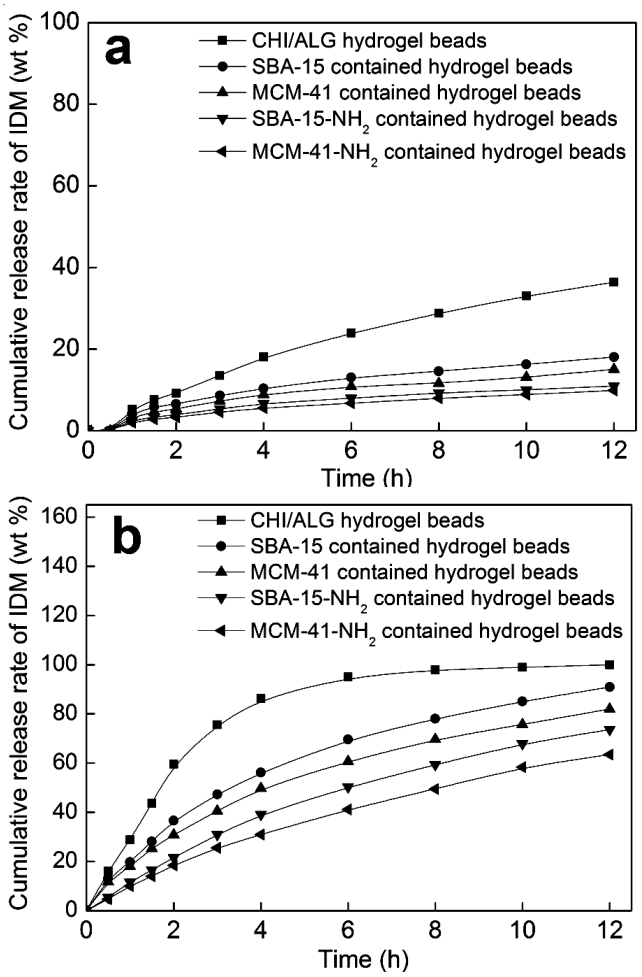

Fig. 8. Release profiles of indomethacin from various hydrogel beads in SGF (a) and SIF (b)

The lower release rate of indomethacin from chitosan/alginate-coated mesoporous silicates nanoparticles in SGF should be attributed to the lower swelling of outside hydrogels, which allowed drugs to be protected almost completely from acid in gastric juice. The results indicated that the coating of hydrogels endowed mesoporous silicates nanoparticles materials with pH-sensitive nature. Thus, the combination of chitosan/alginate hydrogels and various mesoporous silicates nanoparticles yielded a series of oral drug delivery systems that could achieved pH-sensitive and sustained-release of indomethacin.

Conclusion

In this study, various indomethacin-loaded mesoporous silicates nanoparticles were entrapped into chitosan/alginate hydrogels. The resultant beads displayed pH-sensitive and sustained-release of hydrophobic indomethacin and thus the combination of chitosan/alginate hydrogels and mesoporous silicates nanoparticles might serve as a potential oral hydrophobic drug delivery system, in which the use of mesoporous silicates nanoparticles is to increase the dissolution and bioavailability of hydrophobic drugs and regulate their release rate by the tuned pore size and the surface functionalization of mesoporous silicates nanoparticles and the use of chitosan/alginate hydrogels can endow the system with pH-sensitive nature.

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