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Preparation of Cefalexin/MCM-41 Composite Material and Its Controlled Release Property

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MCM-41 mesoporous material was prepared by hydrothermal synthesis and a cefalexin/MCM-41 composite material was prepared by impregnation method. Tetrahydrated ammonium molybdate was used for to detect the concentration of drugs by the spectrophotometric method before and after loading. The detection of cefalexin loading capacity in the MCM-41 mesoporous material was 696.5 mg/g. Before and after the loading, MCM-41 molecular sieve and its composite material sample were characterized by chemical analysis, Fourier transform infrared spectroscopy, powder X-ray diffraction, scanning electron microscopy, transmission electron microscopy and 77 K low temperature N_2 adsorption-desorption. A diameter of the composite material was 333 ± 5 nm of fibrous grains. The release law of cefalexin/MCM-41 in the simulated body fluid, gastric and intestinal fluid was investigated. The maximum cumulative release in simulated body fluid was 99.2 % at 15 h. The maximum cumulative release in simulated gastric juice was 38.7 % at 6 h and in simulated intestinal fluid the maximum cumulative release rate of 47.9 % was achieved at 7 h.

Key Words: MCM-41 mesoporous material, Cephalexin, Controlled release effect.

INTRODUCTION

Since 1992 Beck *et al.*[1] exercised quaternary ammonium salt type surfactant as template for porous silicate with breakthough to synthesize pore size that can be in the range of 2 to 10 nm modulation mesoporous molecular sieves M41S. The synthesis and application of mesoporous molecular sieves were paid more and more attention and MCM-41 mesoporous molecular sieves is a typical representative in M41S family[1,2]. Compared to the old-fashioned zeolite molecular sieve material, the greatest advantage of MCM-41 mesoporous molecular sieves consists is followings. The pore size of MCM-41 mesoporous molecular sieve is more and more than that of the conventional zeolite molecular sieve (pore size is less than 1.5 mm pore size range) and MCM-41 mesoporous molecular sieve has features of uniform one-dimensional pore, hexagonal ordered arrangement and pore size distribution narrowing, *etc.* MCM-41 has higher specific surface area (1000 m^2/g) and large adsorption capacity (> 0.7 mL/g) and is conducive to the free diffusion of organic molecules and is an excellent catalyst carrier. MCM-41 can be widely applied to heterogeneous catalysis, adsorption and separation *etc.* in many fields[3-8]. As cephalexin is insoluble in most of the solvents, if MCM-41 is use as a carrier, it can be directly absorbed by human body by becoming cephalexin into nano-drugs, which can greatly improve the therapeutic efficacy and drug use rate. The ideal state of using this system to carry drugs is that the drug is totally introduced into mesopores pores of MCM-41 molecular sieve. According to our best of knowledge, the literature of cephalexin loaded into MCM-41 has not been reported. In this study, cephalexin is loaded into MCM-41. Finally characterized by chemical analysis, Fourier transform infrared spectroscopy, powder X-ray diffraction analysis, nitrogen adsorption-desorption technique, transmission electron microscopy images and scanning electron microscopy image. The results for various aspects of nature of the system show that cephalexin has been successfully loaded to MCM-41. In this study, cephalexin content was determined by the spectrophotometric method[9] and the release process of cephalexin in simulated body fluid was simulated. The results showed that the cephalexin/MCM-41 composite materials have controlled release effect, having potential applicable value.

EXPERIMENTAL

Tetraethoxysilane (TEOS, Shanghai Chemical Co. Ltd., Chinese Medicine Group, China), Cetyltrimethylammonium bromide (CTMAB, Beijing Beihua Fine Chemicals Co. Ltd., China); Cefalexin (Beijing Yongzheng Pharmaceutical Co. Ltd., China); $NaAlO_2$ (Beijing Chemical Plant, China); White carbon black (SiO_2, Beijing Chemical Plant, China); NaOH (Beijing Chemical Plant, China): 2 mol/L; ammonium molybdate tetrahydrate (Beijing Beihua Fine Chemicals Co.

Ltd., China): 10 g of ammonium molybdate was weighed and 100 mL of 9 mol/L sulfuric acid (Beijing Chemical Plant, China) solution was added. The solution can be stable for 10 days by close storage avoiding light. Absolute ethyl alcohol (Beijing Chemical Plant, China); NaCl (Beijing Chemical Plant, China); $NaHCO_3$ (Shanghai Chemical Co. Ltd., Chinese Medicine Group, China); KCl (Beijing Chemical Plant, China); $K_2HPO_4 \cdot 2H_2O$ (Tianjin Jinke Fine Chemical Reagent Development Center, China); $KH_2PO_4 \cdot 12H_2O$ (Tianjin Kemiou Center for Development of Chemical Reagents, China); Magnesium chloride ($MgCl_2 \cdot 6H_2O$, Liaoning Medicine Economic and Trade Company, China); Hydrochloric acid (Beijing Chemical Plant, China); $CaCl_2$ (Beijing Chemical Plant, China); Na_2SO_4 (Tianjin East China Reagent Factory, China); trihydroxymethyl aminomethane ($NH_2C(CH_2OH)_3$, Beijing Chemical Plant, China). Experiment reagents were of analytical purity and the water was deionized water.

Hydrothermal synthesis of MCM-41: In accordance with a molar ratio of 1.0: 1.9: 0.1: 4.0: 200, CTMAB, NaOH, $NaAlO_2$, SiO_2 and H_2O were mixed and stirred for 2 h. Then, the mixture was heated for 5 days in polytetrafluoroethylene lined stainless steel autoclaved at 373 K and the product obtained was washed with water and filtered, dried at room temperature. The as-synthesized MCM-41 was calcined for 6 h at 873 K to remove the surfactant CTMAB to obtain MCM-41 product[10].

Loading of cephalexin in MCM-41: 0.5 g of MCM-41 was weighed and placed into a 250 mL beaker and then 100 mL of 29.0981 mg/mL cefalexin were added. The mixture was stirred at room temperature for 48 h, filtered, quickly washed and dried at room temperature to become a powder to obtain the required cephalexin/MCM-41 composite material sample.

1 mL of filtrate was accurately taken and properly diluted. The drug residue amount in the filtrate was determined by the spectrophotometric method and then cephalexin content in the composite was calculated by subtraction method.

Preparation of work curve[9]: In 25 mL volumetric flasks, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8 mL of 1 mg/mL cefalexin standard solutions were respectively added and then 10 mL of the solution of ammonium molybdate in sulfuric acid was added. Distilled water was used to dilute the solutions to the constant volume mark. The solutions were heated for 15 min in a boiling water bath and then cooled for 10 min using flowing water. Compared with reagent blank, absorbance was measured with 1 cm cells at a wavelength of 670 nm. A regression equation between absorbance (A) and concentration C (mg/mL) was obtained: A = 17.588C-0.3217, with a regression coefficient of $\gamma = 0.9960$.

Preparation of simulated body fluid, simulated gastric fluid and simulated intestinal fluid[11]

Preparation of simulated body fluid: NaCl (17.996 g), $NaHCO_3$ (0.350 g), KCl (0.224 g), $K_2HPO_4 \cdot 2H_2O$ (0.228 g), $MgCl_2 \cdot 6H_2O$ (0.305 g), 40 mL of 1 mol/L HCl, $CaCl_2$ (0.278 g), Na_2SO_4 (0.071 g) and $NH_2C(CH_2OH)_3$ (6.057 g) were dissolved in distilled water and diluted to 1 L with water. In the experiment, the temperature was maintained at 37 ºC and the pH value of the environment was maintained at 7.3-7.4.

Preparation of simulated gastric juice: 6.217 g of concentrated hydrochloric acid were weighed and placed into a 1 L volumetric flask, then diluted with water to 1 L. Simulated gastric fluid was obtained.

Preparation of simulated intestinal fluid: The simulated intestinal fluid was prepared by mixing 0.2 mol/L Na_2HPO_4 and KH_2PO_4 in a suitable ratio (pH 7.4).

Release of cephalexin loaded MCM-41 in simulated human body fluid, simulated human gastric juice, simulated human intestinal fluid: At 37 ºC, 0.3 g of drug loaded MCM-41 powder was soaked in a 50 mL of simulated human body fluid (simulated human gastric juice, simulated human intestinal fluid) with magnetic stirring. Drug content in the simulated human body fluid (simulated human gastric juice, simulated human intestinal fluid) was determined by the spectrophotometric method at an interval of 1-2 h. Each time 4 mL of solution was taken out for the determination, while the same amount of simulated human body fluid (simulated human gastric juice, simulated human intestinal fluid) was added to the original solution. Finally, calculation was made and the sustained-release curve was drawn.

Material characterization: Cephalexin component content determination and cephalexin release process determination were accomplished by the spectrophotometric method[9] with a 722 S type spectrophotometer (Shanghai Lengguang Technology Co. Ltd., China). Fourier transform infrared (FT-IR) spectra were accomplished with a Bruker Vertex-70 Fourier transform infrared spectrometer, the samples being pressed into disks with KBr. The ordered structure of the mesoporous molecular sieves was analyzed on a D5005 X-ray diffractometer (Siemens, Germany) using CuK_α radiation ($\lambda = 1.5418$ Å), an operating voltage (tube voltage) of 30 kV and an operating current (tube current) of 20 mA. The scans were taken from $2\theta = 0.4^\circ$ to 10° for small angle and $2\theta = 10^\circ$ to 80° for wide angle, respectively. Low-temperature nitrogen adsorption-desorption experiments were conducted with Micromeritic SASAP2010 M sorption analyzer and the test temperature was 77 K. The sample was processed under vacuum for 12 h at 573 K. Surface areas were calculated by the BET (Brunner-Emunett-Teller) method and pore size distributions were evaluated from the desorption branches of the nitrogen isotherms using the BJH (Barrett-Joyner-Halenda) method. Scanning electron micrograph was determined with a JEOL JSM-5600 L scanning electron microscope for observing the morphologies of the samples. For a typical sample preparation, 5 mg of the sample were placed into a plastic bottle to which 20 mL of ethanol was added. The bottle was subject to ultrasonic treatment for 20 min. After the treatment, 1-2 drops of this suspension were quickly transferred onto the surface of the SEM sample holder. The sample was allowed to dry overnight to accomplish the sample preparation. A JEOL 2010 transmission electron microscope was used to record the TEM micrographs of MCM-41 and (MCM-41)-cephalexin materials operated at 200 kV. The sample was dispersed in ethanol, deposited on a Cu grid and dried.

RESULTS AND DISCUSSION

Spectrophotometric determination of cephalexin in cefalexin/MCM-41 composite material sample was made and

the content of object cephalexin in cephalexin/MCM-41 composite was determined to be 696.5 mg/g (drug/molecular sieve). The analytical results show that the cephalexin has already been assembled and entered into the MCM-41.

Fig. 1 presents the FT-IR spectra of the prepared MCM-41 molecular sieve and drug loaded sample and cephalexin powder. Absorption peaks of MCM-41 sample and composite material samples located at 468 cm^{-1} can be assigned to the absorption peak caused by T-O bending vibration. Absorption peak of composite material at 550 cm^{-1} can be assigned to the absorption peak caused by double ring vibration. Absorption peaks of MCM-41 and the composite material at 796 cm^{-1} can be assigned to the Si-O-Si symmetric stretching vibration. Absorption peaks at 960 cm^{-1} and at 1085 cm^{-1} can be assigned to the TO_4 asymmetric stretching vibration of Si-O-Si. Absorption peak at 1643 cm^{-1} can be assigned to the stretching vibration of the hydrogen on the benzene ring. The drug absorption peaks of composite material occur at 2364 cm^{-1} and 3055 cm^{-1}. Absorption band at 3448 cm^{-1} is assigned to the asymmetric stretching vibrations of adsorbed water molecules and surface hydroxyl groups. The presence of these peaks shows that cefalexin has been successfully assembled into the MCM-41.

Overlay of the infrared spectrum of each sample shows that the main channel skeleton of molecular sieve did not collapse, due to object cephalexin assembly, in the process of object cephalexin assembly by the test methods. It shows that cephalexin object material and intermediate products did not damage to molecular sieve skeleton.

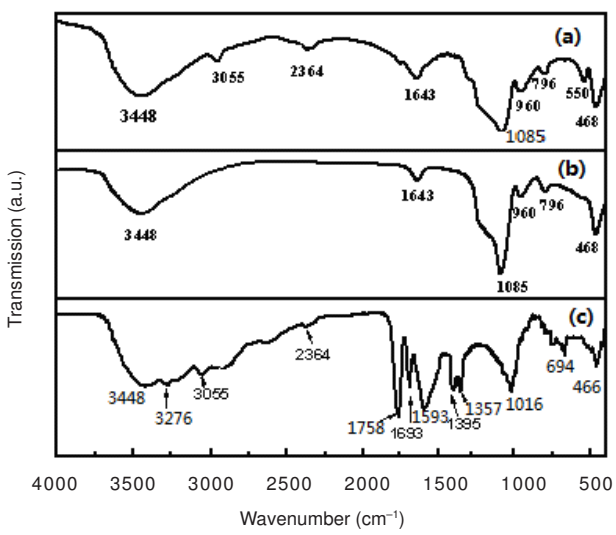

Fig. 1. IR spectra: a) composite material; b) MCM-41; c) cefalexin

From Fig. 2 it is known that on the XRD spectrum of MCM-41 at $2\theta = 2.2^{\circ}$ a major diffraction peak (100) appeared. Besides this peak, between $3^{\circ} < 2\theta < 6^{\circ}$ the three weak diffraction peaks are clearly visible, *i.e.* the sample showed three weaker diffraction peaks at (110), (200), (210) crystal faces. They are the typical MCM-41 mesoporous phase diffraction pattern, showing that ordered degree of the inside of sample was higher and the sample belonged to the hexagonal dense stack crystalline phase structure. Cephalexin has not any obvious peak, indicating that cephalexin internal part is neither ordered structure nor belongs to hexagonal dense pile crystalline structure. Compared composite material with unassembled molecular sieve it can be seen that the composite material was still long-range ordered and hexagonal dense pile crystalline phase structure, but its orderly degree declined. Fig. 3 is the wide-angle XRD patterns of samples. Under the wide-angle X-ray diffraction conditions, the diffraction pattern had not sharp peak shape, indicating that for unassembled MCM-41 crystal structure did not exist. MCM-41 is an amorphous material and behaves long-range disorder. The diffraction pattern of composite material prepared showed the characteristic peak of cephalexin, indicating that cephalexin had already been encapsulated in the composite material.

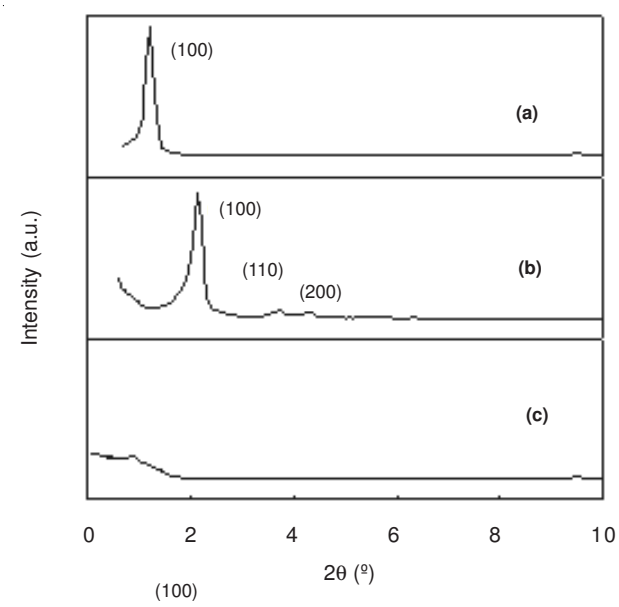

Fig. 2. Small angle XRD patterns: a) composite material; b) MCM-41; c) cefalexin

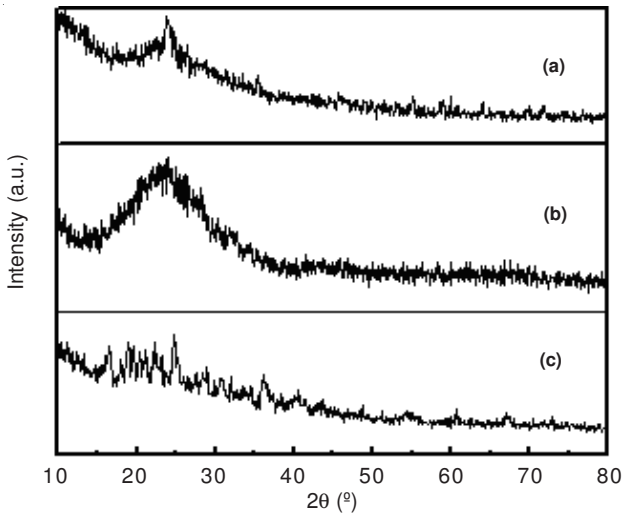

Fig. 3. Wide angle XRD patterns:a) composite material; b)MCM-41; c) cefalexin

Nitrogen adsorption-desorption isotherms at 77 K and pore size distribution of the samples are shown in Figs. 4 and 5. Table-1 shows the structure parameters of MCM-41 molecular sieve. It can be seen from Fig. 4 that jump point of N_2

adsorption-desorption isotherm of the assembled drug MCM-41 advances than that before the assembly. It can be seen from Fig. 5 that the pore size distribution of the drug assembled MCM-41 is narrower than that before the assembled MCM-41. But for both the overall change trend has not been altered.

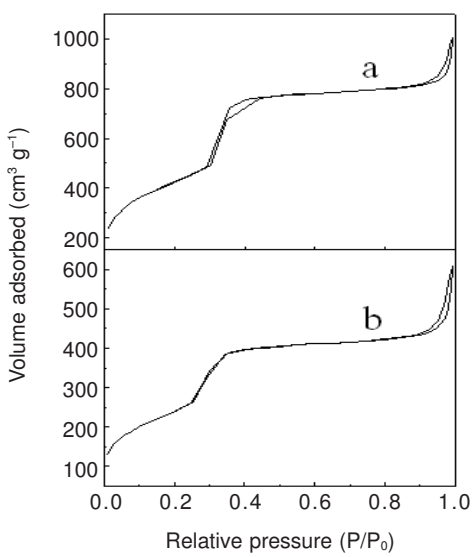

Fig. 4. Low temperature N_2 adsorption-desorption curves of the samples: a) MCM-41; b) (MCM-41)-cefalexin composite material

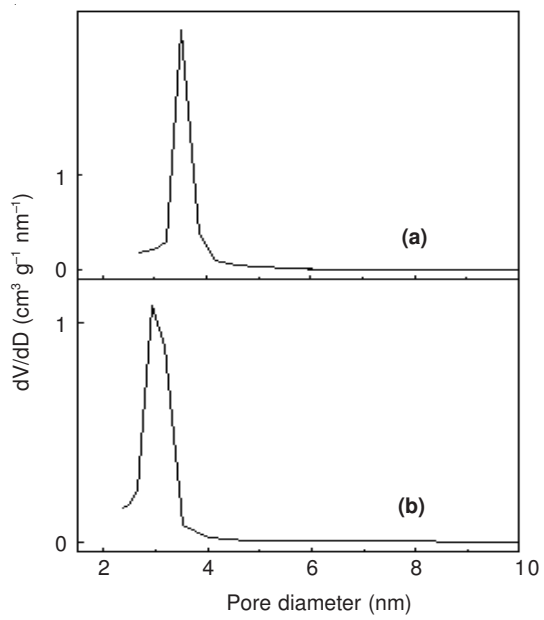

Fig. 5. Pore size distribution patterns of the samples: a) MCM-41; b) (MCM - 41) -cefalexin composite material

TABLE-1
PORE STRUCTURE PARAMETERS OF SAMPLES

Sample	d_{100} (nm)	a_0[a] (nm)	BET surface area (m^2/g)	Pore volume[b] (cm^3/g)	Pore size[c] (nm)
MCM-41	4.20	4.85	1120	1.60	2.75
Composite material	5.13	5.92	994	0.71	2.61

[a] $a_0 = \frac{2}{\sqrt{3}} d_{100}$; [b] BJH adsorption cumulative volume of pores

[c] Pore size calculated from the adsorption branch

Fig. 4 shows that the shape of N_2 adsorption-desorption isotherms of MCM-41 and its composite drug exhibits the typical IV isotherm characteristics. At the low pressure stage, the adsorption capacity gently increased and at this time N_2 molecules of the inner surface of MCM-41 molecular sieve pore channels are adsorbed from a single layer to multilayer. Adsorption capacity suddenly increased at P/P_0 = 0.3-0.45, which is because due to capillary condensation N_2 molecules fill fully in the mesoporous hole. When P/P_0 further increased, N_2 molecules were adsorbed from monolayer to multilayer on the surface of the mesoporous pores, so the location of the segment determined the pore size of the sample. And width of the change is the basis of a measure of the mesoporous holes uniformity. In addition, hysteresis loop near the saturation pressure is normal and is related to capillary condensation produced between the grain gap. And before P/P_0 = 0.4 low-pressure hysteresis loop is due to capillary condensation within the MCM-41 mesoporous channels. It can be known from Fig. 5 that pore size distribution of the MCM-41 and composite drug is very narrow, which indicates that both synthesized materials have regular single mesoporous skeleton structure.

The scanning electron microscopy images of samples are shown in Figs. 6 and 7. The surface shape (Fig. 6) of the MCM-41 was spherical, pore distribution was uniform and the average particle diameter was 170 nm. From Fig. 7 it can be known that the drug assembled molecular sieve sample average particle diameter was 180 nm and the shape was spherical. The transmission electron microscopy images of samples are shown in Figs. 8 and 9. It can be seen from Fig. 8 that distribution of MCM-41 pore channels is homogeneous and pore structure is of long-range order with a highly ordered hexagonal straight pore structure. It can be seen from Fig. 9 that compared drug assembled MCM-41 with the MCM-41 before the assembly of drug, the orderly degree decreased, which is mainly because inside the pore channels the drug was encapsulated. Although the degree of order was declined, the composite material was still of the hexagonal straight pore channel structure, showing drug encapsulated MCM-41 pore structure had not showed a collapse phenomenon and the drug was very well encapsulated in the molecular sieve pore channels.

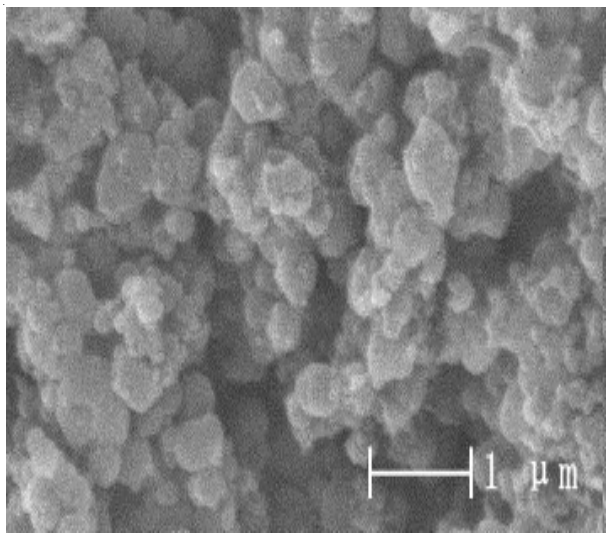

Fig. 6. SEM images of MCM-41

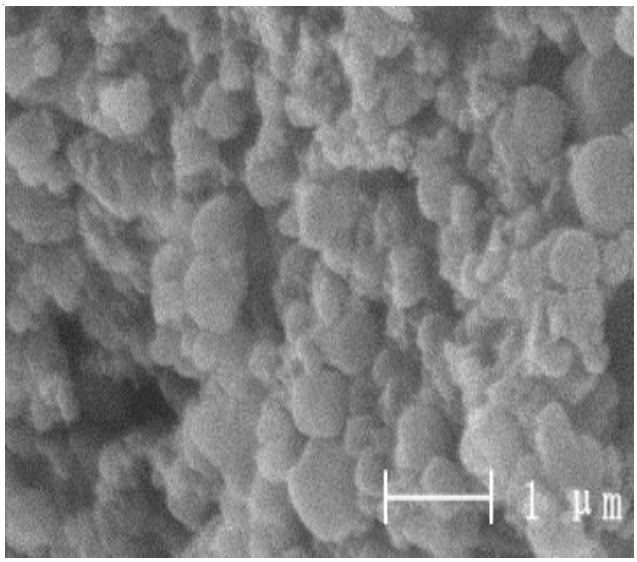

Fig. 7. SEM images of(MCM-41)-cefalexin composite material

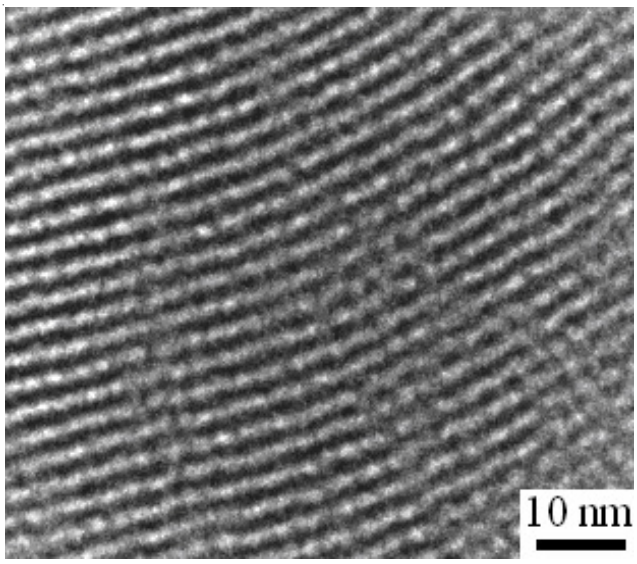

Fig. 8. TEM images of MCM-41

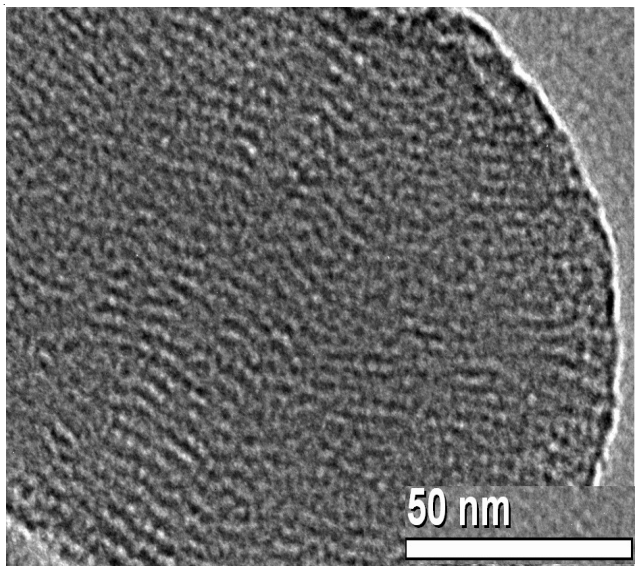

Fig. 9. TEM images of (MCM-41)- cefalexin composite material

Sustained-release of the composite material in simulated body fluid: Fig. 10 is a drug-loaded MCM-41 release profiles in simulated body fluid. The drug loading of mesoporous molecular sieve MCM-41 was 696.5 mg/g (drug/molecular sieve) by the experimental calculation. From the release curve it can be seen that cumulative release drug rate of this composite material was 78.5 % in simulated body fluid at 7 h, after 32 h the sustained release was basically stable and the maximum cummulative release rate reached 99.22 %. Within the first 7 h, the release profile of drug-loaded MCM-41 is very steep. This is the primarily drug release process on outer surface and outer channel. During this time, cephalexin release rate was very fast. This is because the contact area of the cephalexin adsorbed on the external surface of MCM-41 by physical and chemical adsorptive process and of the cephalexin distributed at the pore channel mouth of MCM-41 molecular sieve was bigger. When the cephalexin contacted with simulated body fluid, it began to be dissolved and release, so dissolution and release rate is also faster. After 7 h, cephalexin release rate in composite material has some declined and the release rate became slightly flat. This gentle release is related to the role between cephalexin drug and MCM-41 molecular sieve. The assembly process of cefalexin in MCM-41 is that some organic functional groups replaced silanol of mesoporous molecular sieve surface, so that the cephalexin was grafted into MCM-41 molecular sieve. The hydroxyl and amino groups of cefalexin and silanol groups of mesoporous silica were combined together by hydrogen bond and this interaction is relatively not very stable. Under the action of body fluid, hydrogen bond was broken, so that cephalexin drug was released into body fluid. In addition, as the sustained-release system was stirred, the flow character of body fluids was high, thus it could enter into the channels of mesoporous molecular sieves delivery drug system and make the drug in the channels normally be released. However, as the mesoporous material pore diameter is very small, it made the resistance change become larger for body fluid go into the channels. The drug must first be dissolved in body fluid and gradually spread out from capillary-like channels of the drug delivery system, which makes the cephalexin release become gentler,

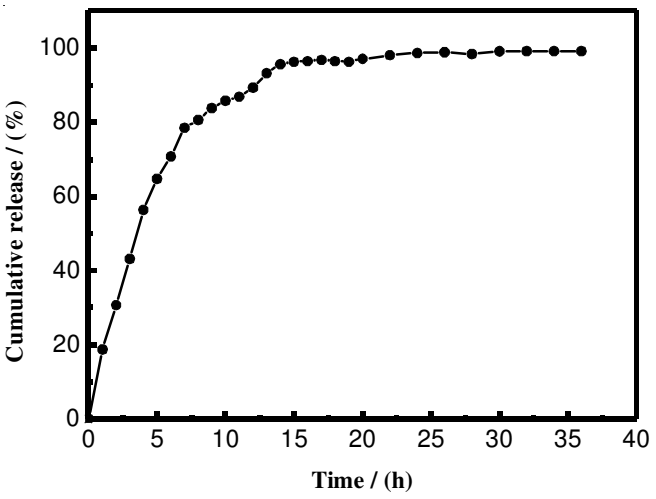

Fig. 10. Controlled release pattern of cefalexin/MCM-41 in simulated body fluid

thereby prolonging release time of cephalexin. At this time of the last sustained release, maximum cumulative amount of the cephalexin drug sustained release in simulated body fluid has reached 99.22 % and drug concentration in body fluids was higher and the role of hydrogen bond between the drug and the molecular sieve hindered the drug release, making cephalexin release more slowly. Thus, the time of drug action was improved and the efficacy of drug will be improved.

Sustained-release of the composite material in simulated gastric juice: Fig. 11 is the sustained-release curve of composite in a simulated gastric juice. From this curve it can be seen that the largest sustained release of the composite material in simulated gastric fluid was 38.7 %. Within the initial 3 h of drug release, the release rate reached 35.6 %. After 6 h, the release basically reached balance. During 1-3 h, the release curve was very steep, and which is a process of the release of a membrane (mainly the drug release process on the outer surface). During this time, the release speed of cefalexin was very fast and this is because the contact area of the cephalexin adsorbed on the external surface of MCM-41 by physical and chemical adsorptive process and of the cephalexin distributed at the pore channel mouth of MCM-41 molecular sieve with gastric juice was bigger. When the cephalexin contacted with simulated gastric fluid, it began to be dissolved and release, so dissolution and release rate is also faster. After 3 h, cephalexin release rate began to decline and the release rate became flat until the release of 38.7 %. This gentle release process has something to do with the existence way of cephalexin drug. The assembly process of cefalexin in MCM-41 is that some organic functional groups replaced silanol of mesoporous molecular sieve surface, so that the cephalexin was grafted into MCM-41 molecular sieve. The hydroxyl and amino groups of cefalexin and silanol groups of mesoporous silica were combined together by hydrogen bond and this interaction is relatively not very stable. Under the action of gastric juice, hydrogen bonds were broken, so that cephalexin drug was released into gastric juice. However, due to the small pore diameter of mesoporous materials, it made the resistance of the gastric juice going into the pore become larger. The drug must first be dissolve slowly in the gastric juice and then diffused slowly from capillary-like channels of the drug delivery system, it also made cephalexin drug release become sluggish, thus extending the release period of cephalexin, slowing down drug release, improving drug action time, thereby enhancing the drug release.

Sustained-release of composite material in simulated intestinal fluid: Fig. 12 is the sustained-release curve of composite material in simulated intestinal fluid. From this curve it can be seen that the largest sustained release of the composite material in simulated intestinal fluid was 47.9 %. Within the initial 4 h of drug release, the release rate reached 40.7 %. After 7 h the release basically reached balance. Within 1-4 h, the release curve was steep, showing that this process was the release of a membrane (mainly the drug release process on the outer surface). During this time, the cephalexin release speed was quick. This is because the contact area of the cephalexin adsorbed on the external surface of MCM-41 by physical and chemical adsorptive process and of the cephalexin distributed at the pore channel mouth of MCM-41 molecular sieve with intestinal fluid was bigger, so dissolution and release rate is also faster. After 4 h, the release rate of cephalexin began to decline and the release rate became flat until the release of 47.9 %. This gentle release process is related to the existence way of cephalexin drug. The assembly process of cefalexin in MCM-41 is that some organic functional groups replaced silanol of mesoporous molecular sieve surface, so that the cephalexin was grafted into MCM-41 molecular sieve. The hydroxyl and amino groups of cefalexin and silanol groups of mesoporous silica were combined together by hydrogen bond and this interaction is relatively not very stable. Under the action of intestinal fluid, hydrogen bonds were broken, so that cephalexin drug was released into intestinal fluid. However, due to the small pore diameter of mesoporous materials, it made the resistance of the intestinal fluid going into the pore become larger. The drug must first be dissolve slowly in the intestinal fluid and then diffused slowly from capillary-like channels of the drug delivery system, it also made cephalexin drug release become sluggish, thus extending the release period of cephalexin, slowing down drug release, enhancing drug action time, consequently improving the drug release.

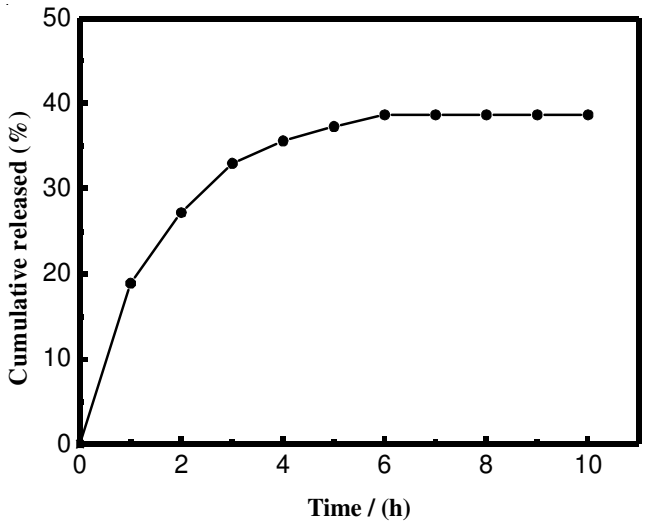

Fig. 11. Controlled release pattern of cefalexin/MCM-41 in simulated gastric juice

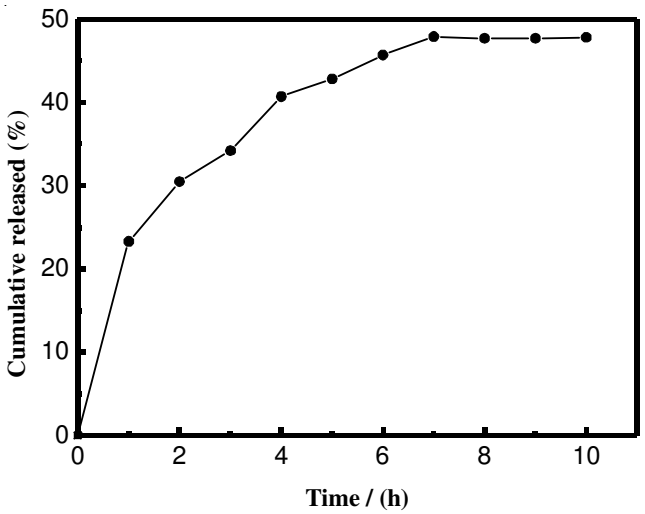

Fig. 12. Controlled release pattern of cefalexin/MCM-41 in simulated intestinal fluid

Conclusion

MCM-41 was synthesized by hydrothermal synthesis and cefalexin/MCM-41 composite material was prepared by impregnation method. Characterization of composite materials by chemical analysis, IR, XRD, SEM, TEM showed that the synthesis of cephalexin/MCM-41 molecular sieve composite material was successful and its average particle size was 180 nm.

Cephalexin/MCM-41 composite release principles in the simulated body fluid, gastric juice and intestinal juice were studied. The composite material releases particularly rapidly in simulated body fluid in the first 7 h, the maximum cumulative sustained release is up to 78.5 % and then the sustained release speed began to decrease, at 15 h the sustained release is basically in balance and the cumulative sustained release reaches 99.2 %. In simulated gastric fluid the release rate is 38.7 % and after 6h the release basically reached balance. Cumulative release rate in simulated intestinal fluid is higher than that in simulated gastric fluid, up to 47.9 %, after 7h up to the balance.

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