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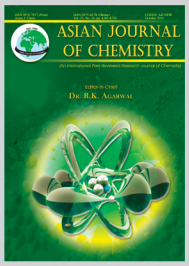

Study on Controlled Slow Release Action of Nitrendipine/MCM-41 Drug Loading System

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In the study, MCM-41 molecular sieves were modified with trimethylchlorosilane before calcination. Nitrendipine was doped inside the pores of the modified MCM-41 *via* liquid-phase grafting method and the prepared drugs kept the structures of mesoporous pore. The drug release process from the matrix into a simulated body fluid (SBF) solution has been studied. The results showed that the process was divided into four stages. It was observed that the samples showed a sharp initial release burst after 2 h for unmodified nm-MCM-41 as carrier (MN) sample and 1 h for modified nm-MCM-41 as carrier (MMN) sample. By the way of modified before calcination, the drug was doped inside the pores of molecular sieve mainly and made the release become slowly, respectively. For the unmodified MCM-41 sample, the release effect of nitrendipine was 51.4 % at 5 h and was 99.6 % at 30 h. For the modified MCM-41 sample, the release effect of nitrendipine was 51.4 % at 7 h and was 99.7 % at 34 h.

Key Words: Nitrendipine, MCM-41 molecular sieve carrier, Slow release.

INTRODUCTION

Drug release is to combine drug active molecules and polymer carriers by physical or chemical methods and drug active molecules are released continuously with appropriate concentration in human body by the way of diffusion and permeation control to achieve the purpose of bringing drug efficacy into full play[1]. Drug carriers are an important part of drug delivery system, also the main factor affecting drug efficacy. Drug delivery system plays an important role in maintaining plasma level, reducing times of drug administration, lowering toxicity of drug and improving drug efficacy. Therefore scholars have been active in the research of drug delivery carriers. An ideal drug carrier should have good biocompatibility, biodegradability, physico-chemical property, biological stability and low toxicity[2].

Mesoporous materials have regular pore texture, chemical homogeneous nature, larger specific surface area and pore volume of inorganic nano-particles, which have not pharmacological activity, non-toxic, can be recycled repeatedly and their surface can be functionalized. They can not only adjust drug loading, but also effectively control the release rate of drug molecules to achieve the purpose of slow-release drug[3]. MCM-41 mesoporous molecular sieves with one-dimensional uniform and hexagonal ordered pore channels and narrow pore size distribution, specific surface area (> 700 m^2/g), adsorption capacity (> 0.7 cm^3/g), conducive to the diffusion of organic molecules, are excellent catalyst carriers[4]. MCM-41 mesoporous molecular sieves have important applications in chemical, optical, environmental, biomedical and other industries[5-9]. Vallet-Regi[10] first used MCM-41 mesoporous molecular sieves as drug carriers in 2001, to load water-insoluble drug ibuprofen, overcoming the shortcoming of traditional slow-release polymer matrix mixed with drug unevenly and this system could also extend the cycle of drug release, which quickly attracted the attention of medicine, pharmacy and materials chemistry and has become the research focus of new drug carriers. Amila *et al.*[11] have successfully made ibuprofen loaded into mesoporous molecular sieves. Horcajada *et al.*[12] synthesized small-porous MCM-41 mesoporous molecular sieves by using two different trimethyl ammonium mixtures with 8-10 carbons as surfactants and big-porous MCM-41 mesoporous molecular sieves by using trimethyl ammonium with 12-16 carbons as surfactants, then made ibuprofen drug lead into channels of molecular sieves to investigate the effect of molecular sieve pore size on drug release by comparing release rates of the two molecular sieve drug. Cao *et al.*[13] synthesized MCM-41 mesoporous molecular sieve and aminopropyl modified MCM-41-$(CH_2)_3NH_2$ mesoporous molecular sieve, respectively by the means of microwave-assisted hydrothermal synthesis and co-condensation and made diuretic hydrochlorothiazide drug assembled in the two materials. The results showed that MCM-

41 mesoporous molecular sieve modified by aminopropyl remained hexagonal pore structure and its pore size slightly reduced, activity points increased. The modified MCM-41 kept larger drug loading (38.23 %). Both MCM-41 mesoporous molecular sieve and MCM-41-$(CH_2)_3NH_2$ mesoporous molecular sieve drug carriers could achieve sustained release. The release rate slowed down further after modification and declined with an increasing amount of aminopropyl grafing, which indicated that could adjust release rate *via* the amount of modified aminopropyl. Munoaz *et al.*[14] used organic groups with amino to modify, respectively two different pore size MCM-41 and studied their effect of sustained release on ibuprofen. The results showed that small-porous molecular sieve had lower loading of ibuprofen. The molecular sieve modified with organic functional groups after calcination could make the release rate of ibuprofen slow down. Manzano *et al.*[15] studied the morphology of molecular sieve and the effect of amino modification on sustained release of ibuprofen with MCM-41 loading ibuprofen and found that the molecular sieve modified with amino as carriers could make the release rate of ibuprofen reduce.

Nitrendipine is the second-generation dihydropyridine calcium channel blocker, which is highly effective for the treatment of many kinds of hypertension and is an effective antihypertensive drug[16]. Hypertensive patients generally require long-term medication to maintain stable blood pressure. Therefore, antihypertensive drugs are more suitable for making sustained-release preparation to extend the duration of action of drug in the body, reduce the number of medication and the peak and valley phenomenon in order to reduce harmful side effects. In this study, MCM-41 molecular sieves were synthesized by hydrothermal synthesis method and modified, which then were used as carriers of nitrendipine drug to investigate the effect of unmodified MCM-41 molecular sieves and modified MCM-41 molecular sieves on nitrendipine drug release.

EXPERIMENTAL

Ethyl silicate (TEOS, A.R., China Medicine Group Ltd. Co., China); cetyltrimethylammonium bromide (CTMAB, A.R., Changzhou Xinhua Research Institute for Reagents, China); sodium hydroxide(A.R., Kaiyuan Kangyuan Chemical Reagent Factory, China); nitrendipine (NTD, Nanjing Pharmaceutical Factory, China); trimethylchlorosilane (Shanghai Chemical Company, China Pharmaceutical Group Corporation, China); the water for the experiment was deioned water.

The powder X-ray diffraction experiment (XRD) with the selected wavelength of X-ray was λ = 1.5418 Å, operating current (tube current) was 20 mA, operating voltage (tube voltage) was 30 kV and the experiment was conducted with the D5005 model X-ray diffraction analyzer (Siemens Company).

The powder sample in the experiment of Fourier transform infrared spectroscopy (FT-IR) was KBr (the proportion of the sample was 1 wt %, KBr was wt 99 wt %) pellet. FT-IR experiments were accomplished with BRUKER Vertex-70 FTIR Analyzer. The test temperature of the low-temperature nitrogen adsorption-desorption test was 77 K to determine the pore structure of molecular sieves (pore size, pore volume, specific surface area, *etc*.) and that was conducted on the Micromeritics ASAP2010M adsorption analyzer. Before test, the samples were degassed under vacuum at 573 K for 12 h. The scanning electron micrograph (SEM) was made with the JEOL JSM-5600L scanning electron microscope and transmission electron micrograph (TEM) was conducted with the JEOL 2010 transmission electron microscope. The determination of component content of nitrendipine in the prepared sample and the experiment on nitrendipine release process by spectrophotometry were accomplished with a U-2800 spectrophotometer (Japan Hitachi Company)[17].

Process of the experiment

Synthesis of MCM-41 molecular sieves: Add 1 g of CTMAB into 480 mL of deionzed water at 80 ºC under violent stirring until the solution became homogeneous. Then add 3.5 mL of 2 mol L^{-1}NaOH solution with stirring well and 5 mL of ethyl silicate was slowly added dropwise, reacted at 80 ºC for 2 h, then filtrated, washed with deionized water and dried at room temperature to get the sample. The original sample was placed in a muffle furnace, calcined at 500 ºC for 4 h to obtain MCM-41 sample[18], marked with M.

Treatment of MCM-41 with trimethylchlorosilane: Trimethylchlorosilane was used for modification treatment to the external surface of MCM-41 molecular sieves before calcination. 1 g of MCM-41 sample before calcination was taken in 50 mL of 1 % (v/v) of trimethylchlorosilane in anhydrous ethanol, stirred at room temperature for 24 h, then filtrated, washed with anhydrous ethanol to get the sample, dried in air at 50 ºC. Then the prepared sample was calcined at 500 ºC for 4 h to get methylation- MCM-41, marked with MM. In this study, the aim of modification treatment to the surface of MCM-41 molecular sieves was to make silanol on the surface of MCM-41 methylated, at the same time, silanol in the inner surface of pore channels could be saved, thus enabling the assembly of nitrendipine as much as possible to the channels of mesoporous channels.

Assembly of nitrendipine in MCM-41: The liquid phase method was used in this study for the assembly of nitrendipine drug into MCM-41 molecular sieves. The specific process of operation was as follows: (1) For the samples of M and MM, 0.5 g were placed into 250 mL beakers, then 100 mL of nitrendipine chloroform solution was added, respectively, stirred at room temperature for 48 h. (2) The above mixture was filtrated, washed, dried at room temperature and put in brown bottles, respectively, stored in a dryer. The drug of M carrier was marked as MN and MM carrier marked as MMN.

Simulation experiment on nitrendipine release process: A certain amount of the prepared drug powder was soaked in 50 mL simulated body fluid (SBF) at 37 ºC[19] with magnetic stirring. The spectrophotometry[17] was used to determine the content of nitrendipine at fixed time. In the process, great care was taken to add the same amount of SBF to supplement when the mixed liquor was removed to measure each time.

Composition of simulated body fluid: NaCl (7.996 g), $NaHCO_3$ (0.350 g), KCl (0.224 g), $K_2HPO_4{\cdot}3H_2O$ (0.228 g), $MgCl_2{\cdot}6H_2O$ (0.305 g), 1 mol L^{-1} HCl (40 mL), $CaCl_2$ (0.278 g), Na_2SO_4 (0.071 g), $NH_2C(CH_2OH)_3$ (6.057 g) were dissolved in distilled water in a 1000 mL volumetric flask diluted up to the mark[12].

RESULTS AND DISCUSSION

Fig. 1 showed small-angle XRD curves of the prepared M sample, MN sample, MM sample and MMN sample. It can be seen that both of M (Fig. 1a) and MM (Fig. 1c) samples showed three diffraction peaks, which were (100), (110) and (200) crystal face diffraction peak. That was consistent with the literature[18], which indicated that MCM-41 molecular sieves have been successfully synthesized and silane treatment did not destroy the structure of MCM-41. The prepared molecular sieves had higher crystalline degree with 2D hexagonal structure. MN (Fig. 1b) and MMN (Fig. 1d) samples showed two diffraction peaks, which were (100) and (110) crystal face diffraction peak, corresponding to characteristics diffraction of MCM-41. That showed the decrease of crystallization of carriers after the assembly of nitrendipine drug into the molecular sieves of M and MM samples. However, hexagonal structure was well-preserved and the prepared samples were still pore structure material.

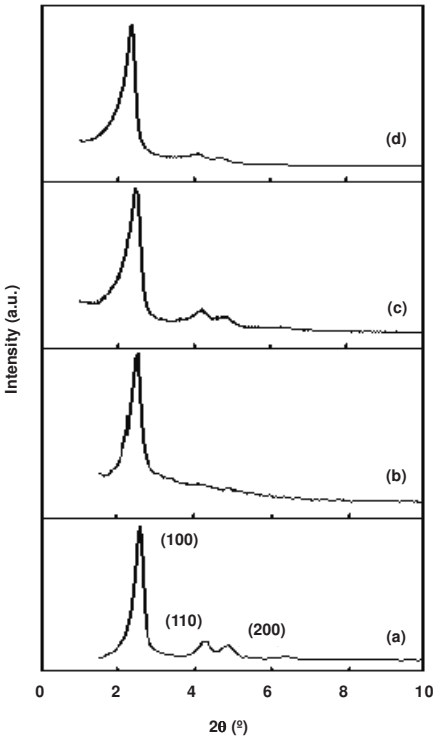


Fig. 1. Small-angle XRD patterns: (a) M; (b) MN; (c) MM; (d) MMN

Fig. 2 showed wide-angle XRD curves of nitrendipine powder of the prepared samples. Seen from this wide-angle XRD: MN sample (Fig. 2c) and MMN sample (Fig. 2e) did not show characteristic diffraction. In other words, there was no obvious characteristic peak of nitrendipine obtained in wide-angle XRD diffraction of the samples, which indicated that after the assembly, there was no nitrendipine drug gathered on the surface of molecular sieves and nitrendipine mainly distributed in the pore channels of MCM-41 molecular sieves.

Fig. 3 is the infrared spectra of prepared samples, from the figer it can be seen that in the measurement range for sample (M), (MM), (MN) and (MMN) four characteristic absorption peaks occurred and according to sample (M), (MM), (MN) and (MMN) order, they can belong to absorption peak which

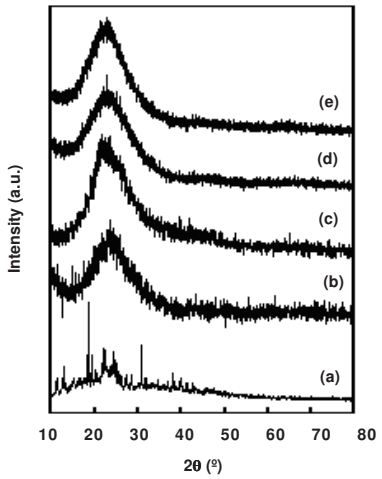


Fig. 2. Wide-angle XRD patterns: (a) Nitrendipine; (b) M; (c) MN; (d) MM; (e) MMN

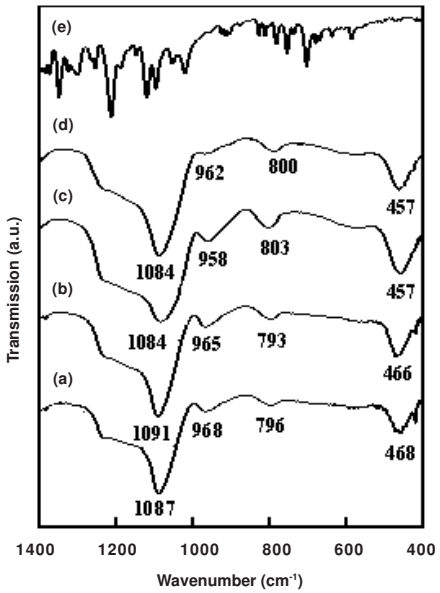


Fig. 3. Infrared spectra of samples: (a) M; (b) MN;(c) MM; (d) MMN; (e) nitrendipine

which located at 468, 466, 457 and 457 cm^{-1} and they can be attributed to T-O bending vibrations. Absorption peak which located at 796, 793, 803 and 800 cm^{-1} can be attributed to the Si-O-Si TO_4 symmetric stretching vibration. Absorption peak which located at 965, 968, 958 and 962 cm^{-1} and located at 1091, 1087, 1084 and 1084 cm^{-1} can be attributed to Si-O-Si TO_4 asymmetric stretching vibration absorption peak[20].

The existence of these absorption peaks can prove the existence of MCM-41 molecular sieve frameworks. Besides, absorption peak which was located at 968, 965, 958 and 962 cm^{-1} can also be attributed to Si-OH non-bridge oxygen atom's stretching vibration absorption peak.

Fig. 3 shows that MN (Fig. 3b) and MMN (Fig. 3d) samples had not presented the obvious nitrendipine characteristic absorption peak, their infrared absorption spectra and the relating MCM-41 molecular sieve source powder were basically consistent. That is to say, after MCM-41 molecular sieve loaded nitrendipine, prepared drugs were still mesoporous

pore structural materials, molecular sieve frameworks were preserved completely, the guest materials which were not accumulated distributed in the carrier outside surface, nitrendipine was mainly distributed in molecular sieve's pore channels or even dispersered in molecular sieve frameworks.

Analysis of nitrogen adsorption-desorption: Fig. 4 refered to nitrogen adsorption-desorption isothermal lines of prepared materials. From the figure it can seen that nitrogen adsorption and desorption isothermal lines were IV-shape. For samples (M), (MN), (MM) and (MMN), at the relative pressure 0.29, 0.20, 0.25 and 0.18 the adsorption branching and desorption branching jumped suddenly and a H1-shape hystersis loop turned up. This was mainly due to under a relative lower partial pressure, nitrogen adsorption in the molecular sieve pore channels was monolayer adsorption and this precedure was reversible, the adsorption branching and desorption branching didn't jump and there was not hystersis loop. However, when the relative partial pressure reached a certain degree, there would be capillary condensation and for the adsorption branching and desorption branching the second jump occured, there was also a hysteresis phenomenon. When relative differential partial pressure of sample (M), (MN), (MM) and (MMN) achieved 0.45, 0.25, 0.34 and 0.24, the hysteresis vanished. This was because the pore channels were filled with gas. When continued to pressurize, gas was mainly adsorpted in sample's outside surface and this precedure was also reversible and there was not a hysteresis phenomenon. When (M), (MN), (MM) and (MMN) relative partial pressure achieved 0.90, 0.93, 0.95 and 0.94, for the adsorption branching and desorption branching the second jump occurred, at the same time, there was also a hysteresis phenomenon. This was because the microbore formed between molecular sieves pellet. When the relative pressure reached a certain degree, there would be the second agglomeration phenomenon of capillary vessel. Genreally speaking, differenetial pressure of the agglomeration phenomenon of capillary vessel was related to aperture size. The bigger of the aperture, the bigger of differential pressure of the agglomeration phenomenon of capillary vessel. Sample MN and MMN's differential pressure of the agglomeration phenomenon of capillary vessel were very small. This was because in molecular sieve pore channels the drug was assembled and their aperture reduced (Fig. 5).

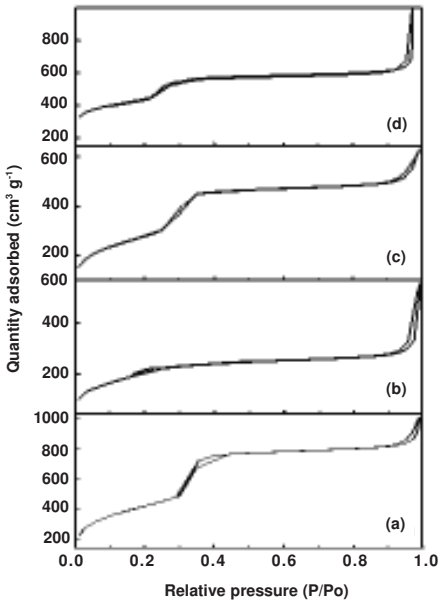


Fig. 4. Nitrogen adsorption-desorption isotherms: (a) M; (b) MN; (c) MM; (d) MMN

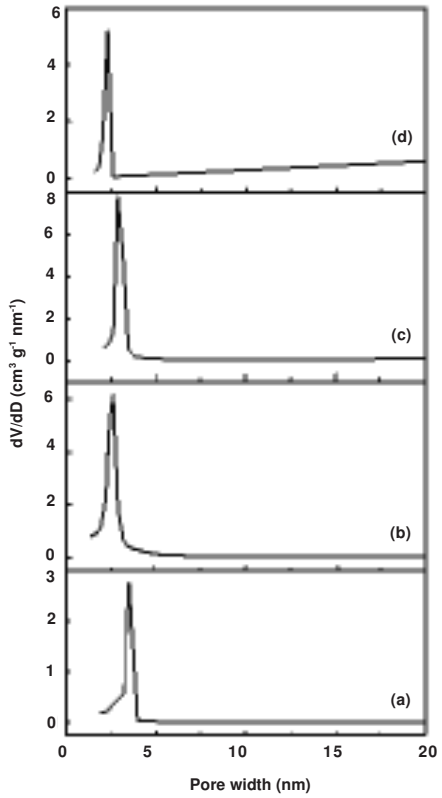
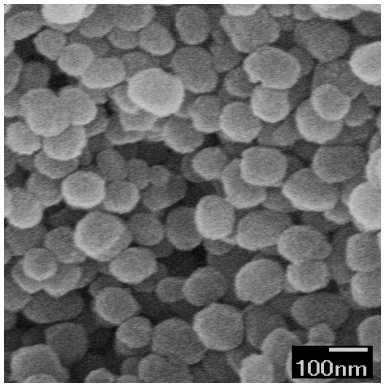


Fig. 5. Pore size distribution patterns of samples: (a) M; (b) MN; (c) MM; (d) MMN

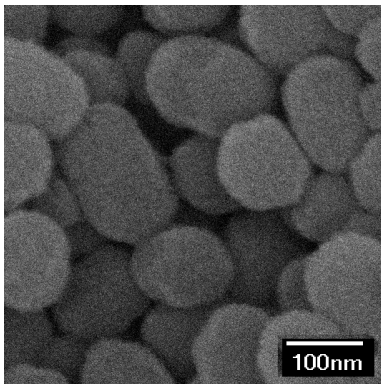
The specific surface area of prepared samples was calculated by BET (Brunner-Emmett-Teller)[21] and the distribution of aperture size was calculated by BJH (Barrett-Joyner-Halenda)[22]. The correlation data involved in each parameter's calculation were based on the adsorption branching of nitrogen adsorption and desorption isothermal line. Comparing sample MMN and MN with corresponding sample MM and M, the specific surface area, pore volume and pore size both reduced greatly and this was mainly because the guest materials entered the host pore channels (Table-1). From this we may draw the conclusion that the guest materials of nitrendipine had already entered into pore channels of molecular sieves.

Scanning electron micrograph: Fig. 6 refered to the scanning electron micrograph of sample (M), (MN), (MM) and (MMN). The prepared sample in this research was all micro sphere. Through the calculation, the diameter of sample (M) was 123 nm, the diameter of sample (MN) was 122 nm, the diameter of sample (MM) was 122 nm and the diameter of sample (MMN) was 121 nm.

Transmission electron micrograph: Fig. 7 showed the transmission electron micrograph of each sample. Sample (M), (MN), (MM) and (MMN) was perpendicular to the pores with highly ordered mesopore pore channel and it was transverse to the pores with orderly parallel joint. Every sample had mesopore pore channel structure, after assembling guest



(a)



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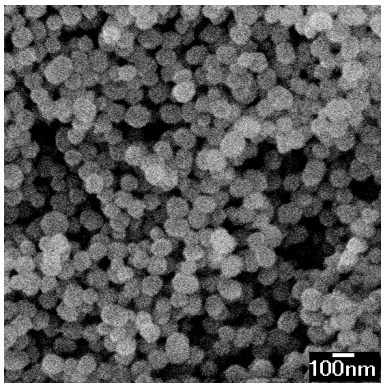
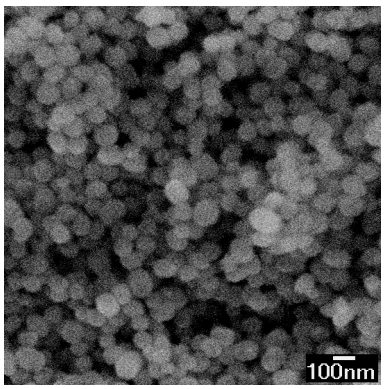


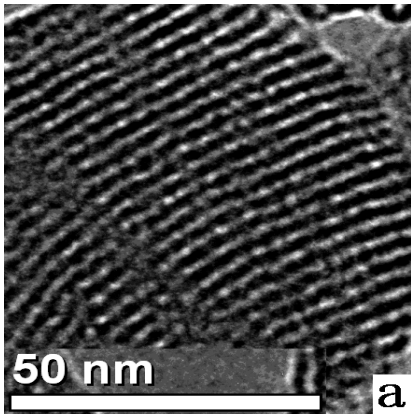
(c)

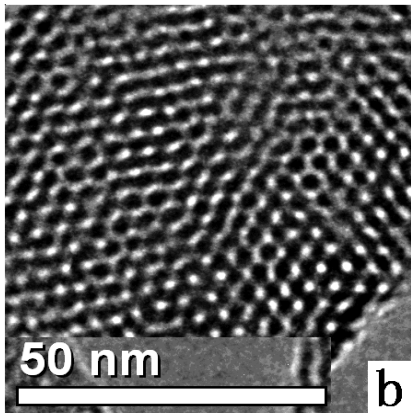


(d)

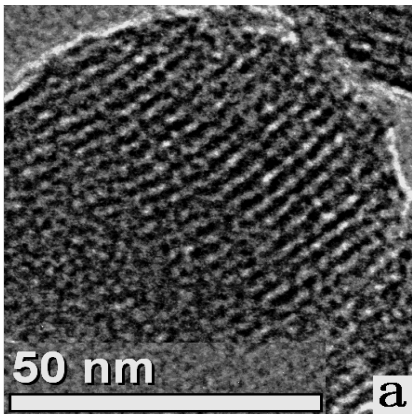
Fig. 6. SEM image of the samples:(a) M; (b) MN; (c) MM; (d) MMN

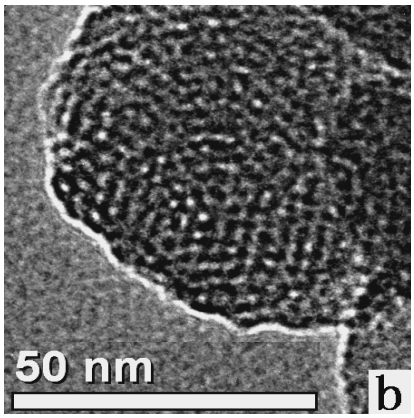
materials of the drug in molecular sieve pore. The mesopore pore channel of molecular sieve has been preserved well, so the existance of agminate pellets of guest materials from the picture can not be seen.





(A)





(B)

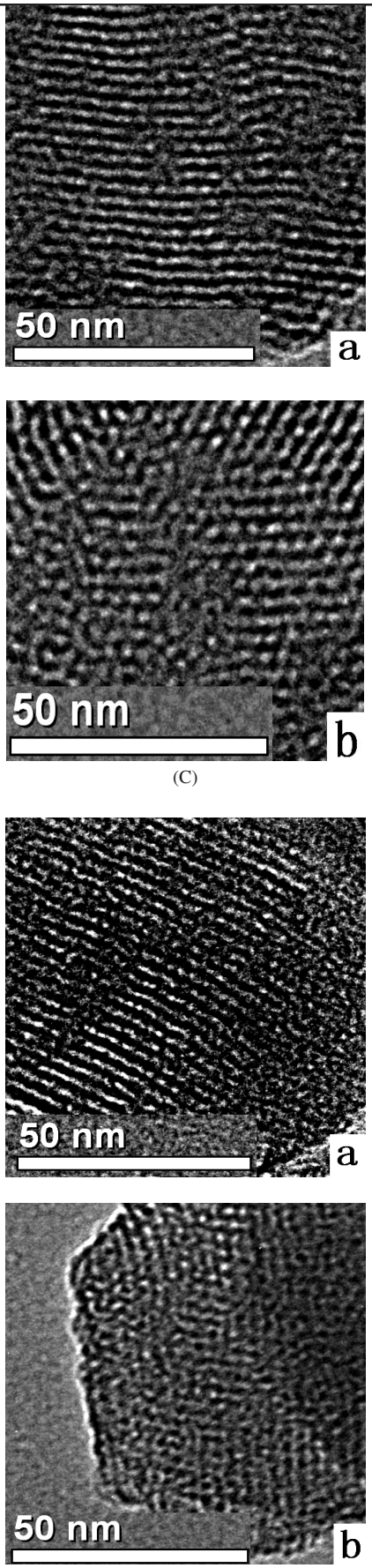


Fig. 7. TEM images of the samples:(a) taken with the beam direction perpendicular to the pores ; (b) taken with the beam direction parallel to the pores. (A) M; (B) MN; (C) MM; (D) MMN

Release curve of nitrendipine: In this research, we first used the spectrophotometry to measure the content of nitrendipine in the solution before assembling and then measured the content of nitrendipine in the solution after assembing. The difference in values of them was the drug assembly quantity of the sample. Through calculation, the content of nitrendipine in sample MN was 35.4 %, the content of nitrendipine in sample MMN was 33.3 %. As the surface of sample (M) had a large amount of silanol, which can form hydrogen bond with nitrendipine molecules, therefore, the assembly drug quantity of sample MN was larger than sample (MMN)'s. Fig. 8 showed the release curve of nitrendipine in the simulated body fluid. From the figure it can be seen that the release process of prepared drug could be divided into four stages. First stage: sample (MN) was rapidly released from the carrier during the first 2 h from the beginning and sample (MMN) was rapidly released from the carrier in the 1st h. This was mainly because the drug absorbed on the surface of carrier rapidly dissolved in the body fluid at the very beginning of release. As the silanol on the surface of sample MMN has been oxidized, it lead to the decrease in the drug adsorbed on the surface. Camparing with sample MN, release of the drug on the outside surface was rapidly over. Second stage: the drug release rate was slower than preceding stage, but quicker than latter stage when sample MN released in 2 - 8 h and sample (MMN) released in 1 - 7 h, this was because the drug absorbed in carrier hole released rapidly. Third stage: the drug release rate was much slower when sample (MN) released in 8-30 h and sample (MMN) released in 7-34 h. This was because the drug absorbed in the carrier mesopore hole slowly dissolved in the body fluid. Fourth stage: the density of drug in the body fluid was reduced after releasing for 30 h of sample (MN) and 34 h of sample(MMN), this was because the drug absorbed in carrier has completely released and continued to take out solution from the system, then added the body fluid to make the solute reduced, solvent inventory increased, so it resulted in the reduction of drug concentration.

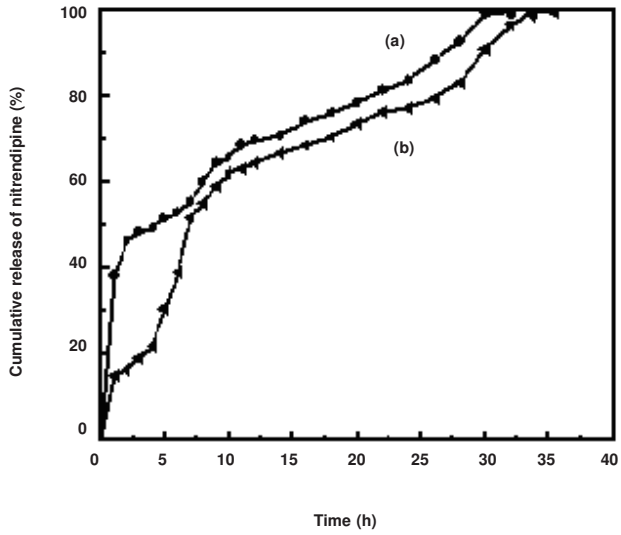


Fig. 8. Release curve of nitrendipine: (a) MN; (b) MMN

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^{-1})	Pore size[c] (nm)
M	3.34	3.85	1329.1	1.331	3.55
MN	3.46	4.00	1074.2	1.038	2.59
MM	3.59	4.15	1014.4	1.0952	3.28
MMN	3.74	4.32	867.3	0.961	2.49

[a] $a_0 = \frac{2}{\sqrt{3}} d_{100}$. [b]BJH adsorption cumulative volume of pores. [c]Pore size calculated from the adsorption branch.

Comparing the release process of sample (MN) with sample (MMN) it is find that the release rate of unmodified MCM-41 as a carrier was quicker than that of modified sample in the first 15 h, this was due to the outside surface of MCM-41 absorbed drug. Because the usage of modified MCM-41, the silanol on the outside surface of molecular sieve was eliminated. This made the drug absorbed on the surface of sample (MMN) be reduced, then caused the drug mainly be assembled to molecular sieve pore channels and made the release process of the drug become relatively slow. For the sample (MN), the release rate reached 51.4 % at 5 h and was 99.6 % at 30 h. For the sample (MMN), the release rate was 51.4 % at 7 h and was 99.7 % at 34 h.

Conclusion

In this study, MCM-41 molecular sieve was synthesized by hydrothermal synthesis. It used trimethylchlorosilane to make silane treatment to the surface of non-remove template's MCM-41 molecular sieve. After high temperature calcine to eliminate template and in the meantime, it also eliminated the silanol on the outside surface of molecular sieve in order to assemble the drug to molecular sieve pore channel as much as possible. It was used as a carrier, then assemble the nitrendipine to molecular sieves pore which experienced silane treatment by liquid-phase grafting method. It was used to follow-up the release processes of prepared drugs in the simulated body fluid. Through a series of characterizations it was found that liquid phase grafting method could successfully assemble nitrendipine to MCM-41 molecular sieve pore and assembling drug kept the features of mesoporous pore. Through the simulated release process, it was found that the release process could be divided into four stage. The drug release rate was very rapid during the first 2 h of sample (MN) and the first 1 h of sample (MMN). After molecular sieve carrier modification, the drug was much more assembled to molecular sieve pore to make the drug release process relatively slow. The release rate of sample (MN) was 51.4 % at 5 h and was 99.6 % at 30 h; and the release rate of sample (MMN) was 51.4 % at 7 h and was 99.7 % at 34 h.

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