Controlled Release of (SBA-15)-Carvedilol Drug

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In this paper, the SBA-15 molecular sieve was prepared by hydrothermal method. Carvedilol was loaded in the SBA-15 with impregnation method and the loading capacity of carvedilol is 443.50 mg/g. By means of chemical analysis, powder X-ray diffraction and low-temperature nitrogen adsorption-desorption technique at 77 K, the products were characterized. The results showed that carvedilol guest molecules had been successfully encapsulated into the channels of SBA-15. A research of the slow release effect of carvedilol encapsulated in SBA-15 mesoporous material was studied in simulated body fluid. The drug cumulative release is 19.6 % in 1 h and release 99.3 % after 32 h and tended to tranquilization. The drug release has tended to tranquilization to 19.2% after 4 h in simulated gastric fluid and to 63.2 % after 8 h in simulated intestinal fluid.

Key Words: SBA-15 mesoporous material, Carvedilol, Controlled release.

INTRODUCTION

Structure of mesoporous molecular sieve is intervenient between amorphous inorganic pore materials (such as amorphous aluminosilicate) and inorganic pore materials with crystal structure (such as zeolite)¹. Mobil company matter-41 (MCM-41) is the real sample of first mesoporous material^{2,3}. In 1992, researchers of Mobil company first used alkyl quaternary cation surfactant as template and under basic condition mesoporous silicate and aluminosilicate with single pore size was synthesized. Its structure is long-order ordered and specific surface area is above 700 m²/g. This kind of material family is called M41S, which includes hexagonal crystal system MCM-41, cubic crystal system MCM-48 and sandwich MCM-50 with a pore channel size of 2-10 nm. Therefore, as soon as M41S was come out, it caused researchers of relative subject area high regard. As people deeply studied, on the basis of M41S series some special structure mesoporous molecular sieves such as SBA-1, SBA-2, SBA-15, *etc.*^{4,5} have been synthesized. Breakthrough progress of silica mesoporous material synthesis is that under acidic condition amphi-affinitive non-ionic polymer surfactant was used as template to synthesize mesoporous material SBA-15 different from M41S type. By changing template and preparation conditions, SBA-15 with different pore diameter size and its series products could be prepared⁶. SBA-15 is highly ordered two-dimensionally arranged hexagonal phase. After calcination at 500-550 °C, the template is

removed and pore material can be obtained. The template can also be removed by organic solvent extraction. SBA-15 mesoporous size can be adjusted and controlled within the range of 4.6-30 nm. The silica pore wall thickness varies within the range of 3.1-6.0 nm. Specific surface area is between 500-1000 m²/g. After the template is removed for SBA-15, it has higher thermal stability and hydrothermal stability. Thermal stability of SBA-15 is higher than 900 °C and in its internal surface a great amount of silanol exist^{4,5}. Mesoporous molecular sieve has abundant structure type and arrangement way and connection way of pore channels is different from other type pore materials such as active carbon, zeolite, amorphous silica, alumina and clay. Thus, as a kind of full novel nanopore material it provided an expansive space for other many domains⁶⁻⁸. Due to SBA-15 characteristic, it has been extensively concerned by scientists in recent years. Especially, the aspect studies of catalysis, separation, purification of water, preparation of multifunctional parts of an apparatus, as well as drug loading caused scientists' great interests⁹⁻¹¹. Vallet-Regi *et al.*¹¹ first used MCM-41 mesoporous molecular sieve as drug carrier and loaded aqueous insoluble drug ibuprofen. Not only disadvantage that mix of traditional slow release matrices polymers and drug is not homogeneous was overcome, but also the system can prolong the release period of drug. Attention was caused by biological medicine, pharmacy and material chemistry and SBA-15 has already become research hotspot of new type drug carrier. Vallet-Ragi *et al.*¹² loaded amoxicillin

in SBA-15 molecular sieve channels and studied effect of SBA-15 molecular sieve shape on the loading amount of amoxicillin. The results revealed that the release speed of amoxicillin mainly depended the physical state of sample and the release speed of powder state is faster than that of patch. Lehto *et al.*¹³ loaded antipyrin and ibuprofen in thermal carbonifying mesoporous silica by liquid phase method and observed loading location of drug. Carvedilol is $(\pm)$ -[3-(9H-carbazol-4-yloxy)-2-hydroxypropyl] [2-(2-methoxyphenoxy) ethyl]amine having m.f. $C_{24}H_{26}N_2O_4$. Its structure is as follows (Fig. 1).

Fig. 1. Structure of carvedilol

Inside treatment dosage range carvedilol has functions of α_1 and non-selective β acceptor block and has no internal imitate interaction activity. The sample inhibits projecting touch back membrane α_1 acceptor and thus expands blood vessel to debase outside circumambience blood vessel resistance. β acceptor is blocked to restrain kidney to excrete adrenalin and adrenalin-blood vessel tension incretion-aldehyde fixation ketone system is prevented and blood pressure fall function is produced. The present study uses SBA-15 mesoporous molecular sieve as host and loads carvedilol into the molecular sieve. Characterizations for the products using chemical analysis, powder X-ray diffraction and low temperature N_2 adsorption-desorption technique were made. Slow release effects of the drug in (SBA-15)-carvedilol composite material in simulated body fluid, gastric juice, intestinal fluid were investigated. As SBA-15 is not-toxic and its specific surface area is big and homogeneous pore channel diameter distributes and pore diameter is adjustable and pore wall is thick and hydrothermal stability is very high, so it has a broad applied foreground in medical field, *etc.* Research results of the slow release showed that SBA-15 is suitable to be used as the slow release carrier of carvedilol.

EXPERIMENTAL

Carvedilol was obtained from Beijing Juneng Pharmacy Corporation, Ltd., China. Triethanolamine was purchased from Tianjin City Medicine Technique Research Institute, China.

Reagents used for the synthesis of SBA-15: Tricopolymer poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol) (EG₂₀PG₄₀EG₂₀, average molecular weight 5800) was obtained from Aldrich. Tetraethyl orthosilicate was the product of Shanghai Chemical Leechdom Corporation, Ltd., China. Hydrochloric acid procured from Beijing Chemical Plant, China. Reagents used for the preparation of human body simulated fluid (SBF): NaCl, NaHCO₃, K₂HPO₄·3H₂O, KCl, MgCl₂·6H₂O, CaCl₂, Na₂SO₄·10H₂O, hydrochloric acid and NH₂C(CH₂OH)₃ were obtained from Beijing Chemical Plant, China. Reagents used for the preparation of simulated gastric juice (SGJ): concentrated hydrochloric acid (Beijing Chemical Plant, China).

Reagents used for the preparation of simulated intestinal fluid (SIF): NaH₂PO₄·2H₂O and K₂HPO₄·3H₂O were purchased from Beijing Chemical Plant, China. All of the chemical reagents used in the experiments were of analytical grade. The experimentally used water was double deionized water.

Preparation of simulated fluid^{14,15}

Preparation of simulated body fluid: NaCl (7.996 g), NaHCO₃ (0.350 g), KCl (0.224 g), K₂HPO₄·3H₂O (0.228 g), MgCl₂·6H₂O (0.305 g), 1 mol·L⁻¹ HCl (40 mL), CaCl₂ (0.278 g), Na₂SO₄ (0.071 g) and NH₂C(CH₂OH)₃ (6.057 g) were dissolved in a small amount of water and then diluted to 1 L with water. During the experimental process, the experimental temperature should be kept at 37 °C.

Preparation of simulated gastric juice (pH = 1.3): 6.217 g of concentrated hydrochloric acid was placed into a 1 L volumetric flask and then water was added to dilute to 1 L.

Preparation of simulated intestinal fluid (pH = 7.4): Na₂HPO₄·2H₂O (5.9284 g) and KH₂PO₄·3H₂O (58.0187 g) were weighed, respectively and paced in a beaker and dissolved in water. The solution was transferred to a 1 L volumetric flask and diluted to the mark with water.

Sample preparation and drug slow release

Synthesis of SBA-15¹⁶: 2 g of the triblock copolymer poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol) was dissolved in 15 g of water and 60 g of 2 mol/L hydrochloric acid solution, stirred until complete dissolution. At 40 °C, 4.25 g of tetraethyl orthosilicate was added and stirred for 24 h and then transferred into autoclave. At 100 °C, crystallization was made for 48 h at the constant temperature. After the crystallization was finished, filtration was made and the product was washed using water. The product was dried at room temperature. The above-stated product was placed in a ceramic crucible, put into a muffle oven and calcined at 550 °C for 24 h to eliminate the template. A mesoporous SBA-15 molecular sieve white powder was obtained.

Loading of carvedilol in SBA-15: 0.3 g of the SBA-15 was taken and placed in a 100 mL beaker. 40 mL of 2 mg/mL carvedilol triethanolamine solution was added. The mixture was stirred for 48 h at room temperature, filtrated, washed and dried at room temperature to obtain the loaded product. It was marked as (SBA-15)-carvedilol.

Slow release principle of carvedilol loaded SBA-15: At 37 °C, 0.3 g of the drug loaded SBA-15 was soaked in 50 mL of simulated gastric juice, simulated intestinal fluid, simulated body fluid, respectively and stirred. Every other 1 h the content of carvedilol drug in solution was spectrophotometrically determined¹⁷. After the solution was taken out each time, the same volume of simulated fluid was added.

Sample characterization: The content of carvedilol in the composite drug was determined by the spectrophotometric method¹⁷ with a 722S spectrophotometer (Shanghai Linggunag Technique Co. Ltd., China). For powder X-ray diffraction, powder samples, of 100 mg each, were evenly dispersed onto glass slides. Patterns were determined using a Siemens D5005 X-ray diffractometer with a diffractometer beam monochromator and CuK α radiation source with an X-ray wavelength of $\lambda = 1.5418$. The operating voltage (tube voltage) was 40

kV and the operating current (tube current) was 30 mA, respectively. The diffraction patterns were collected from 0.4° to 10° (2θ) for small angle and from 10° to 80° (2θ) for wide angle, respectively. The scan speed and scan step were 20/min and 0.020° , respectively. Low temperature nitrogen adsorption-desorption experiment was made at 77 K on a Micromeritics ASAP2010M adsorption analyzer (The American Mike Company) in order to determine pore channel structure of mesoporous molecular sieve material (pore diameter, pore volume, specific surface area, *etc.*). Specific surface area and pore size distribution were calculated by following BET (Brunner-Emmett-Teller)¹⁸ and BJH (Barrett-Joyner-Halenda)¹⁹ procedures, respectively. The BET specific surface area was estimated using adsorption data. The BJH mesopore size distribution was obtained by analyzing the adsorption data of the nitrogen isotherm.

RESULTS AND DISCUSSION

The spectrophotometric method was used for the determination of carvedilol content in (SBA-15)-carvedilol composite material and the determined result was 382.05 mg/g (carvedilol / SBA-15). It showed that carvedilol has already been loaded in SBA-15.

Fig. 2 is XRD patterns of SBA-15, composite material and carvedilol. It can be seen that in pattern (a) and (b), (100) diffraction peak of SBA-15 molecular sieve appeared and the intensity is very large. For curve (a) besides (100) peak another 2 clear diffraction peaks appeared too, which correspond (110) and (200) diffraction peaks. This illustrates that the quality of SBA-15 molecular sieve prepared was very good¹⁶. Compared curve (b) with curve (a) in the figure, (110) and (200) diffraction peaks disappeared, which shows that carvedilol molecules went into molecular sieve mesoporous channels, resulting in decrease in diffraction contrast degree between SBA-15 framework and pore channels. The existence of (100) shows existence of SBA-15 framework in the composite material. Fig. 3 reveals that the wide angle powder X-ray

Fig. 2. Small angle XRD patterns of the samples: a) SBA-15; b) (SBA-15)-carvedilol composite material; c) carvedilol

diffraction pattern of the (SBA-15)-carvedilol, SBA-15 and carvedilol. For (SBA-15)-carvedilol, SBA-15 diffraction peak emerged and no characteristic peaks of carvedilol appeared, suggesting that there was no collective carvedilol detected by XRD method on the outside surface of (SBA-15)-carvedilol and carvedilol might homogeneously locate in SBA-15 pore channels.

Fig. 3. Wide-angle XRD patterns of the samples: a) SBA-15; b) (SBA-15)-carvedilol composite material; c) carvedilol

Fig. 4 is N_2 adsorption-desorption patterns of samples at 77 K. It can be seen that N_2 adsorption-desorption isotherms of SBA-15 and (SBA-15)-carvedilol samples belong to Langmuir IV type isotherm. From this it can be indicated that they have typical one-dimensional columniform pore channel mesoporous material characteristics. Typical mesoporous material has single pore diameter distribution. At low temperature for nitrogen gas adsorption three phases can be divided: in the first phase the pressure is smaller and nitrogen molecules are adsorbed in pore channels in the form of monolayer. This made the adsorption curve smoother. In the second phase, middle grade pressure range came. At this time, as nitrogen molecules are adsorbed in mesoporous pore channels from single layer to multilayer and capillary condensation phenomenon results in rapid increase of adsorption amount as relative pressure increases. In the third phase, adsorption gradually achieves saturation and therefore the adsorbed amount slowly increases as pressure increases. From Fig. 4 it can be known that low temperature N_2 adsorption-desorption isotherms types of (SBA-15)-carvedilol sample of post-loading carvedilol and SBA-15 sample accord, indicating that introduction of carvedilol did not destroy SBA-15 mesoporous pore channel structure. From the view of adsorption and desorption two branches, for the two samples three phases appeared and they tallied with mesoporous material adsorption characteristic. First, when relative partial pressure varied over the range of 0 to 0.62, adsorption curve is smoother. Then, at middle pressure section over the range of 0.62 to 0.80 N_2 adsorption-desorption curve happened to break and the slope is large, which suggests

TABLE-1
PORE STRUCTURE PARAMETERS OF SAMPLES

Sample	Interplanar spacing, d_{100} (nm)	Unit cell parameter, a_0^a (nm)	BET specific surface area (m^2/g)	Pore volume ^b (cm^3/g)	Pore size ^c (nm)	Pore wall thickness ^d (nm)	Content of medicine (carvedilol/molecular sieve) (mg/g)
SBA-15	10.50	12.12	594.7	1.059	8.14	3.98	0
(SBA-15)-carvedilol composite material	7.35	8.49	411.1	0.687	6.43	2.06	443.50

a) Unit cell parameter, $a_0 = \frac{2}{\sqrt{3}} d_{100}$; b) BJH adsorption cumulative volume of pores; c) Pore size calculated from the adsorption branch;
d) Wall thickness calculated by (a_0 - pore size)

Fig. 4. Low temperature nitrogen adsorption-desorption isotherms of the samples: a) SBA-15; b) (SBA-15)-carvedilol sample

that the samples have regular pore channel structure. Finally, over the range of a relative partial pressure of 0.80 to 1.00 the adsorbed amount increase tended to be gentle as relative pressure increased. This shows that adsorption of sample gradually attained saturation state. Fig. 5 is distribution pattern of sample pore diameter. It can be seen that pore diameter pattern of SBA-15 sample and (SBA-15)-carvedilol sample is narrow and homogeneous. Compared with SBA-15, pore diameter of the composite material sample of post-loading drug decreased and pore volume decreased (Table-1). This further shows that carvedilol guest molecules have entered in SBA-15 pore channels. Table-1 gives the physical and chemical characteristics of SBA-15 before and after loading of carvedilol.

Fig. 6 is the slow release curve of drug carvedilol in the composite material in simulated gastric juice. From the figure it can be known that the release of carvedilol in the composite

Fig. 5. Pore size distribution patterns of the samples: a) SBA-15; b) (SBA-15)-carvedilol sample

Fig. 6. Slow release curve of carvedilol in the (SBA-15)-carvedilol composite material sample in simulated gastric fluid

material was rapider within 0-1 h. This resulted from the release of drug adsorbed outside surface of SBA-15. The release of carvedilol in the composite material was slower within 1 to 4 h, which resulted majorly from that the drug loaded inside carrier mesoporous channels slowly released into gastric juice. Up to 4 h, the release basically reached equilibrium and a moderate state. The cumulative release ratio was 19.2 %. Fig. 7 is release curve of carvedilol in composite material in simulated intestinal fluid. From the figure it can be known that within 1-2 h the release was quite rapid. This mostly is because release of the drug adsorbed near mouth of carrier pore channels was fast. Within 2-8 h, the release was slower. This mainly resulted from the slow dissolution of the drug adsorbed inside carrier mesoporous pore channels into intestinal fluid. After 8 h, the release basically finished and reached equilibrium. The cumulative release ratio was 63.2 %. Fig. 8 shows the release curve of carvedilol in the composite material in simulated body fluid. The drug inside molecular sieve channels formed congeries due to molecular inner hydrogen bond. This part could rapidly release under the action of simulated fluid. In addition, the drug inside molecular sieve pore channels took an action of silanol of molecular sieve inner surface and was not easy to break away from molecular sieve mesoporous channels. Thereby, it released out in a slow speed. From the figure it can be known that the release process can be divided into four stages. In the first stage, within 1 h of release for the sample, released speed of drug was rapid. This mostly is because the drug adsorbed on carrier outside surface was rapidly dissolved

Fig. 7. Slow release curve of carvedilol in the (SBA-15)-carvedilol composite material sample in simulated intestinal fluid

Fig. 8. Slow release curve of carvedilol in the (SBA-15)-carvedilol composite material sample in simulated body fluid

into body fluid. In the second stage, within 1 to 12 h of sample release, drug release speed was slower than that of previous stage but faster than that of latter stage. This is mostly because release of the drug adsorbed near mouth of carrier pore channels was also faster. In the third stage, within 12-32 h of sample release, the release of drug was very slow. This is mostly because that the drug adsorbed inside carrier mesoporous channels was slowly dissolved into body fluid resulted in. In the fourth stage, the release was basically not variational after the sample released for 32 h. This is because the drug loaded on the carrier has already basically released and done with. At this time, the cumulative release ratio was 99.3 %. It can be known from the structure of carvedilol (Fig. 1) that carvedilol has a definite alkaline property. More lower pH value of solution is more advantageous it is that the $-NH_2$ in carvedilol molecules forms $-NH_3^+$ and more faster the speed of drug release. The lower pH of the solution of simulated gastric juice leads to the faster dissolution rate of carvedilol in the composite drug, due to the alkaline property of carvedilol. Due to higher alkalinity of simulated intestinal fluid and simulated body fluid, their release

complete times are longer relative to that of simulated gastric juice. The properties of carvedilol and the properties of the above-stated three body fluids resulted in the above release results.

Carvedilol drug released into simulated fluid by diffusion action from SBA-15 channels. It was slowly dissolved into the simulated fluid and the drug gradually diffused from SBA-15 capillary channels according to a dissolution-filling way²⁰⁻²². The released fraction of drug (M_t/M_∞) can be expressed as a power function of time t:

$$M_t/M_\infty = kt^n \quad (1)$$

where M_t and M_∞ denote the cumulative mass of drug released at time t and at infinite time t_∞ , respectively, k is a characteristic constant of the system and n can decide the release mechanism obeyed by the system. For $n = 0.5$, the release kinetics follows the conventional Higuchi relationship²³. For $n > 0.5$, it follows anomalous diffusion release mechanism. When $n = 1$, zero-order ordered release mechanism is met^{24,25}. Fassihi *et al.* ever discussed this aspect²⁶. Based on the above-stated principle, we calculated to obtain released fraction of drug (M_t/M_∞) of the composite drug samples²⁷.

Release equation in simulated gastric juice: Within 0-1 h, $M_t/M_\infty = 9.2$ t. Within 1-3 h, $M_t/M_\infty = 6.57$ t. This release process meets zero order ordered kinetic process.

Release equation in simulated intestinal fluid: Within 0-6 h, $M_t/M_\infty = 8.50$ t. Within 6-8 h, $M_t/M_\infty = 8.19$ t. This release process meets zero order ordered kinetic process.

Release equation in simulated body fluid: Within 0-1 h, $M_t/M_\infty = 19.6$ t. Within 1-5 h, $M_t/M_\infty = 8.15$ t. Within 5-15 h, $M_t/M_\infty = 5.92$ t. This release process meets zero order kinetic process.

Conclusion

The present study used SBA-15 as carrier and carvedilol was successfully loaded in SBA-15 by impregnation method to prepare (SBA-15)-carvedilol composite drug. At the slow release 32 h of the composite drug in simulated body fluid, the cumulative released drug was 99.3 % and the slow release result was good, illuminating that SBA-15 has an applied potential as the carrier of drug.

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REFERENCES

1. Y. Han and D. Zhang, *Curr. Opin. Chem. Eng.*, **1**, 129 (2012).
2. C.T. Kresge, M.E. Leonowicz, W.J. Roth, J.C. Vartuli and J.S. Beck, *Nature*, **359**, 710 (1992).
3. J.S. Beck, J.C. Vartuli, W.J. Roth, M.E. Leonowicz, C.T. Kresge, K.D. Schmitt and T.W. Chu, *J. Am. Chem. Soc.*, **114**, 10834 (1992).
4. D.Y. Zhao, Q.S. Huo, J.L. Feng, B.F. Chmelka and G.D. Stucky, *J. Am. Chem. Soc.*, **120**, 6024 (1998).
5. D.Y. Zhao, J.L. Feng, Q.S. Huo, N. Melosh, G.H. Fredrickson, B.F. Chmelka and G.D. Stucky, *Science*, **279**, 548 (1998).
6. S. Ajitha and S. Sugunan, *J. Porous Mater.*, **17**, 341 (2010).
7. J. Ma, J. Chu, L.S. Qiang and J.Q. Xue, *Bull. Chin. Ceram. Soc.*, **31**, 301 (2012).
8. J.Q. Jiang and S.M. Ashekuzzaman, *Curr. Opin. Chem. Eng.*, **1**, 191 (2012).

9. A. Corma, *Chem. Rev.*, **97**, 2373 (1997).
10. E.D. Davis, *Nature*, **417**, 813 (2002).
11. M. Vallet-Regi, A. Ramila, R. del Real and P. Perez-Pariente, *Chem. Mater.*, **13**, 308 (2001).
12. M. Vallet-Regi, J.C. Doadrio and A.L. Doadrio, *Solid State Ionics*, **172**, 435 (2004).
13. V.P. Lehto, K.V. Heikkila and J.J. Paski, *Therm. Anal. Calorimet.*, **80**, 393 (2005).
14. P. Horcajada, A. Ramila, J. Perez-Pariente and M. Vallet-Regi, *Micropor. Mesopor. Mater.*, **68**, 105 (2004).
15. T. Kokubo, H. Kushitani, S. Sakka, T. Kitsugi and T. Yamamuro, *J. Biomed. Mater. Res.*, **24**, 721 (1990).
16. Z.H. Luan, M. Hartmann, D.Y. Zhao and L. Kevan, *Chem. Mater.*, **11**, 1621 (1999).
17. T.V. Sreevidya and B. Narayana, *Indian J. Chem. Technol.*, **16**, 74 (2009).
18. S. Brunauer, P.H. Emmett and E. Teller, *J. Am. Chem. Soc.*, **60**, 309 (1938).
19. E. Barrett, L.G. Joyner and P.P. Halenda, *J. Am. Chem. Soc.*, **73**, 373 (1951).
20. J.C. Doadrio, E.M.B. Sousa, B. Izquierdo-Barba, A.L. Doadrio, J. Perez-Pariente and M. Vallet-Regi, *J. Mater. Chem.*, **16**, 462 (2006).
21. M. Vallet-Regi, J.C. Doadrio, A. Doadrio, L. Izquierdo-Barba and J. Perez-Pariente, *Solid State Ionics*, **172**, 435 (2004).
22. A.L. Doadrio, E.M.B. Sousa, J.C. Doadrio, J. Perez-Pariente, I. Izquierdo-Barba and M. Vallet-Regi, *J. Control. Rel.*, **97**, 125 (2004).
23. T. Higuchi, *J. Pharm. Sci.*, **52**, 1145 (1963).
24. L.B. Yang and A.R. Fassihix, *J. Pharm. Sci.*, **85**, 170 (1996).
25. H.J. Kim, J.E. Ahn, S.J. Haam, Y.G. Shul, S.Y. Song and T.S. Tatsumi, *J. Mater. Chem.*, **16**, 1617 (2006).
26. A.R. Fassihix and W.A. Ritschel, *J. Pharm. Sci.*, **82**, 750 (1993).
27. S.M. Song, Z.L. Wang and W.B. Li, *Physical Chemistry*, Beijing: Higher Education Publishing House, p. 219 (1993).