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Faculty of Chemical and Biopharmaceutical Technologies
Department of Industrial Pharmacy

Master's thesis

on the topic TECHNOLOGY OF PRODUCTION OF DRUGS WITH CONTROLLED RELEASE IN CAPSULES BASED ON NANOPOROUS SILICON DIOXIDE

Completed: student of the group MPhch-20

of the speciality 226 Pharmacy, industrial pharmacy
(code and title of the specialty)

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ASSIGNMENTS
FOR THE MASTER'S THESIS

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1. Thesis topic Technology of production of drugs with controlled release in capsules based on nanoporous silicon dioxide.

2. Scientific supervisor Olena Saliy, Associate Professor, PhD
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5. Content of the thesis (list of questions to be developed). *a review of the literature on nanoporous silicon dioxides and controlled release drug systems, the development of methods for the synthesis of nanoporous silica and drug-loading nanoporous silica, the study of drug release behavior of drug-loading nanoporous silica.*

6. Consultants of the master's thesis sections

Section	Surname, initials and position of the consultant	Signature	
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Execution schedule

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1	Introduction	20.09 –27.09.2021	Hongjuan Wang
2	Section 1 *Theoretical basis*	28.09. – 11.10.2021	Hongjuan Wang
3	Section 2 *production of drugs with controlled release in capsules*	12.10 – 25.10.2021	Hongjuan Wang
4	Section 3 *Study of drug release of Metoprolol tartrate*	26.10 - 08.11.2021	Hongjuan Wang
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7	Submission of master's thesis to the departmentfor review (*14 days before the defence*)	06.12.-14.12.2021	Hongjuan Wang Getalo
8	Checking the master's thesis for signs of plagiarism (*10 days before the defence*)	14.12-18.12.2021	Hongjuan Wang
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SUMMARY

Hongjuan Wang. Technology of production of drugs with controlled release in capsules based on nanoporous silicon dioxide.

Master's Thesis Specialty 226 Pharmacy, Industrial Pharmacy. - Kyiv National University of Technology and Design, Kyiv, 2021.

The master's thesis is devoted to study the synthesis technology of mesoporous silicon dioxide with solid and hollow structure based on the self-assemble between surfactants, co-structure directing agents and inorganic silica precursors. Well-defined spherical mesoporous silica displays interesting properties for biomedical applications such as uniform particle size, large surface area and tunable pore diameters and volumes, allowing the incorporation of large amounts of drugs and protecting them from deactivation and degradation processes acting as an excellent nanoplatform for drug delivery.

The hollow structure was templated by the ultrasonic cavitation (Sample of MS-Hollow) and high-pressure carbon dioxide bubbles (Sample of HMS-Bubbles). Especially, Hollow structured HMS-Bubbles with 200-400 nm in size and 20-30 nm in shell thickness was first prepared. The prepared robust hollow mesoporous silica could well-dispersed in aqueous or organic systems, showing high drug loading amounts and excellent metoprolol tartrate drug-controlled release as compared to solid mesoporous silica, which was expected a potential carrier for drug-controlled release.

Keywords: *mesoporous silica, hollow, self-assemble, bubble template, ultrasound, drug controlled release.*

АНОТАЦІЯ

ХУНЦЗЮАНЬ ВАН. Технологія виробництва лікарських засобів із контрольованим вивільненням у капсулах на основі нанопористого діоксиду кремнію.

Магістерська робота Спеціальність 226 Фармація, промислова фармація. – Київський національний університет технологій та дизайну, Київ, 2021.

Магістерська робота присвячена вивченню технології синтезу мезопористого діоксиду кремнію з твердою та порожнистою структурою на основі самостійного формування між поверхнево-активними речовинами, ко-структуронаправляючими агентами та неорганічними прекурсорами (попередниками) кремнезему. Добре визначений сферичний мезопористий діоксид кремнію демонструє цікаві властивості для біомедичних застосувань, такі як однорідний розмір частинок, велика площа поверхні та настроюванні діаметри та об'єми пор, що дозволяє вводити велику кількість ліків і захищає їх від процесів дезактивації та деградації, діючи як вімінна наноплатформа для доставка ліків.

Порожнью структуру формували за допомогою ультразвукової кавітації (зразок MS-Hollow) і бульбашок вуглекислого газу високого тиску (зразок HMS-Bubbles). Зокрема, спочатку були виготовлені порожнисті структуровані HMS-бульбашки з розміром 200-400 нм і товщиною оболонки 20-30 нм. Приготований міцний порожній мезопористий діоксид кремнію зміг добре диспергуватися у водних або органічних системах, демонструючи високу кількість завантаженого лікарського засобу та відмінне контрольоване вивільнення лікарського засобу метопрололу тартрату, порівняно з твердим мезопористим кремнеземом, який, як очікувалося, буде потенційним носієм для контрольованого вивільнення препарату.

Ключові слова: *мезопористий кремнезем, порожнина, самостійне формування, бульбашковий шаблон, ультразвук, контрольоване вивільнення лікарського засобу.*

CONTENT

ABBREVIATION LIST

APES - 3-aminopropyltrimethoxysilane

API – active pharmaceutical ingredient

BET - Brunauer-Emmett-Teller method

BJH - Barett-Joyner-Halenda method

CTAB - cetyltrimethylammonium bromide

MTP - metoprolol tartrate

MSNs - mesoporous silica nanoparticles

TEOS – tetraethyl orthosilicate

TEM - Transmission electron microscopy

Sar-Na - N-Lauroylsarcosine sodium

UPPS - ultra-fine particle process system

Introduction

The **relevance of the topic**. Hypertension is a leading cause of cardiovascular disease, stroke, and death. It affects a substantial proportion of the population worldwide, and remains underdiagnosed and undertreated [1]. The attack of hypertension usually begins in the morning when the patient wakes up from a situation of relative hypotension. Therefore, the development of controlled drug delivery is of great importance in chronopharmacology, for example, to minimize the risk of morning hypertension attack [2].

Beta-adrenoblocker metoprolol is wide used in arterial hypertension and ischemic heart disease. Metoprolol has salt such as tartrate (MPT) which is used for production of immediate release and may need to be taken multiple times per day.

In the last years many efforts have been devoted to the development of new formulations that can control both rate and period of drug delivery. Mesoporous silica carriers have a number of attractive features for enhancing drug dissolution, such as high surface area, large pore volume and ordered pore networks and they can also provide an adjustable drug release profile. Silica matrices show high biocompatibility and these materials are biodegradable to monosilicic acid (in the long run, in the intestine) and resistance to microbial attack. Moreover, physico-chemical and textural properties of silica can be modulated ad hoc by the choice of a tailored synthetic approach.

Mesoporous silica nanoparticles (MSNs) have been widely studied as drug carriers to get controlled release behaviors, however, their application in sustained release of MPT is limited. The possible reason is due to MPT molecule being bulky, while normal type MSNs like MCM-41 and SBA-15 have pore sizes of only 3–6 nm. Studies for the controlled release of MPT are described, which are aimed at both new approaches to synthesis and characterization of silica carriers: a one-time sol-gel approach and wetness impregnation method, where MPT is adsorbed on a silica support by wet impregnation after synthesis. MSNs with

MTP were synthesized through the reaction of tetraethyl orthosilicate (TEOS) in the water medium at 353 K, with introducing some cetyltrimethylammonium bromide (CTAB) as mesoporogens. A novel technique ultra-fine particle process system (UPPS) was employed to develop sustained-release MPT microspheres for oral administration [9].

Scientific interest is hollow structured mesoporous silica, which was usually prepared by hard templates or selective etching of solid spherical silica in a basic solution [84]. Mesoporous silica hollow spheres displayed excellent performance in drug-controlled release characteristics for a number of drugs and are promising for molecular modeling of the bulky MPT molecule delivery system.

Despite significant progress in the characterization and development of mesoporous drug delivery systems to improve drug dissolution, more research is needed such as dissolution test to establish the kinetic profile of drug release from mesoporous silica materials, the rate of release of the active ingredient (API) from the carrier, and the possibility of re-adsorption API on the surface of mesoporous silica. The interaction of dispersion medium with the drug-silica matrix and the release rate of the API are dependent on factors such as porosity, the initial drug load, the drug's solubility in the release medium and the diffusion coefficient of the drug molecules in the medium and importance of utilizing relevant and effective in vitro dissolution methods with discriminating dissolution media.

The **purpose of the study** is: Aim of our work is to produce a metoprolol tartrate drug-loading mesoporous silica capsule and to investigate the pore size effect and morphology of mesoporous silica on metoprolol tartrate release.

The **research objectives of the study:**

- to prepare mesoporous silicon dioxide solid nanoparticles;
- to prepare hollow structured mesoporous silicon dioxide spheres templated by cavitation bubble (vapor bubble) under ultrasound;
- to prepare hollow structured mesoporous silicon dioxide spheres

templated by CO_2 bubble under high pressure;

- to prepare drug loaded capsules based on mesoporous silica with different porosities and morphologies.

- to test the release behavior of drug loaded mesoporous silica.

The **object of MTh** research is the interaction of dispersion medium with the drug-silica matrix and the release rate of the active ingredient (API) at different influence factors such as porosity, the initial drug load, the drug's solubility in the release medium and the diffusion coefficient of the drug molecules in the medium and importance of utilizing relevant and effective in vitro dissolution methods with discriminating dissolution media.

The **subject of MTh** is the production a potential mesoporous silica carrier for MPT drug-controlled release, which do not need be taken multiple times per day for patients with hypertension and heart disease.

Research methods: Mesoporous silica drug carriers were synthesized by a hydrothermal method using a tetrafluoroethylene lined stainless steel autoclave. Transmission electron microscopy (TEM) was characterized by JEOL JEM-1400 TEM microscope working at 100 kV to observe the information of particle shape, particle size, hollow structure and porous channels, etc. Nitrogen adsorption experiments was used a Quantachrome IQ instrument to test the surface area, pore size and pore volume of mesoporous silicon dioxides，The samples were firstly degassed at 373 K under vacuum for 10 h before testing at 77 K. Specific surface area was evaluated by BET (Brunauer-Emmett-Teller) method, the pore size distribution was obtained from the adsorption branch using BJH (Barett-Joyner-Halenda), and total pore volume was calculated based of the adsorption amounts at relative pressure about 0.98. In drug release experiments, the concentration of metoprolol in the solution was determined by a UV-Vis spectrophotometer (Persee TU-190, Beijing, China) by use of quartz cuvettes with an optical path length of 1 cm at a maximum wavelength of 274 nm.

Practical value is the results of scientific research can be used to improve the technology for producting various drug release capsules based on nanoporous silica.

Elements of scientific novelty. Mesoporous silicon dioxide with solid and hollow structure was synthesized based on the self-assemble between surfactants, co-structure directing agents and inorganic silica precursors. The hollow structure templated and high-pressure carbon dioxide bubbles was first prepared, which was low-cost, robust and high-volume cavities. Importantly, it showed high drug loading amounts and excellent MPT drug-controlled release as compared to solid mesoporous silica, which was a potential mesoporous silica carrier for drug-controlled release.

Section 1 Theoretical basis

1.1 Hypertension

With the developments of society, cardiovascular disease has become one of the biggest killers of human life. Hypertension is a leading cause of cardiovascular disease. It affects a substantial proportion of the population worldwide, and remains underdiagnosed and undertreated [1]. The attack of hypertension usually begins in the morning when the patient wakes up from a situation of relative hypotension. Therefore, the development of controlled drug delivery is of great importance in chrono-pharmacology, for example, to minimize the risk of morning hypertension attack [2].

Metoprolol as a β1 receptor blocker is the first-line drug for the treatment of hypertension [3-8]. The solubility of metoprolol itself is poor in aqueous solution, which makes it normally to be used in the soluble salts form. Metoprolol has salt such as tartrate (MPT) which is widely used for production of immediate release. However, the elimination half-life of metoprolol tartrate is short, about 3-4 hours. So, it needs to take medicine 2-3 times per day. MPT sustained-release tablets/capsules can effectively overcome these shortcomings. They can reduce the "peak valley" phenomenon and adverse reactions of blood drug concentration to improve the treatment effect and enhance patient compliance. It will be very meaningful to make MPT into a sustained-release drug. But MPT drug is a bulky in molecular volume because one MPT molecule composed of two metoprolol molecules and one tartaric acid molecule.

At present, there are no reports on the research, development and marketing of such products, and there are few literatures on the preparation process [9-10].

1.2 Mesoporous silica

1.2.1 The development mesoporous materials

According to the definitions of the *International Union of Pure and Applied Chemistry*, mesoporous nanoparticles belong to a class of porous materials with a pore size between 2-50 nm. Mesoporous materials have the characteristics of

extremely high specific surface area, regular and ordered pore structure, narrow pore size distribution, and continuously adjustable pore size. It is mesoporous materials that play a significant role in catalytic reactions, photochemistry and biological simulation. Thereby, mesoporous materials have attracted interest in various research fields such as physics, chemistry, biology and materials since its appearance. Among all mesoporous materials, mesoporous silica is the most representative. Therefore, in this thesis, the study of mesoporous silica materials, especially those with complex morphology will be used as an example to specifically explain their development history and applications.

Before the discovery of mesoporous materials, crystalline aluminosilicate zeolite molecular sieve with uniform pore distribution and pore diameter, which is less than 2.0 nm, has been widely used in petroleum smelting and molecular adsorption separation. However, it has been found that in practical applications, zeolite molecular sieves are difficult to efficiently process some macromolecular substances, such as macromolecules in heavy fractions of base oil, because these macromolecules cannot pass through the small pore size of zeolite molecular sieve. At that time, in order to solve this problem, many attempts were made to obtain the zeolite molecular sieve materials with an increased pore size and an ordered meso-structure, and the macroporous materials that could be used at the same time had a wide pore size distribution, which was hard to ensure its ordered mesoscopic structure, making macroporous materials unsuitable for many applications. Therein, it was against the background that the mesoporous nanocomposites with ordered mesoscopic structure and pore diameters between 2-50 nm came into being.

An approach for synthesizing mesoporous solids from aluminosilicate gels was reported by Kresge et al. from Mobil Research and Development Corporation in the presence of surfactants, providing these materials uniform channels with regular arrays and dimensions which can be tailored by choosing surfactants, chemical reaction conditions and other auxiliary chemicals in the year of 1992 [11]. The most well-known representatives of this class ranges

from the silica solids MCM-41 (with mesopores in a hexagonal arrangement), to MCM-48 (with mesopores in a cubic arrangement,), and finally to MCM-50 (with a laminar structure,) which space groups are *p6mm*, *Ia3d* and *p*2 respectively, and the 3D structures are shown in Figure 1.1 below [12]. The M41S family of mesoporous materials similar to microporous crystalline zeolites, which exhibited a very large specific surface area, ordered pores in a uniform order and continuously tunable pore diameters ranging from 3 to 10 nm are synthesized by them. Beck et al [13] from Mobil described the synthesis, characterization, and suggested formation mechanism of M41S silicate aluminosilicate mesoporous molecular sieve family, and MCM-41 as an example of this family were arranged in the shape of a hexagon, with uniform mesopores, and its size can be designed in a range between 5 and 10 nm. Therefore, their discovery really attracted a large number of researchers to engage in the study of mesoporous materials, and the fields including catalysis, drug loading and molecular adsorption separation.

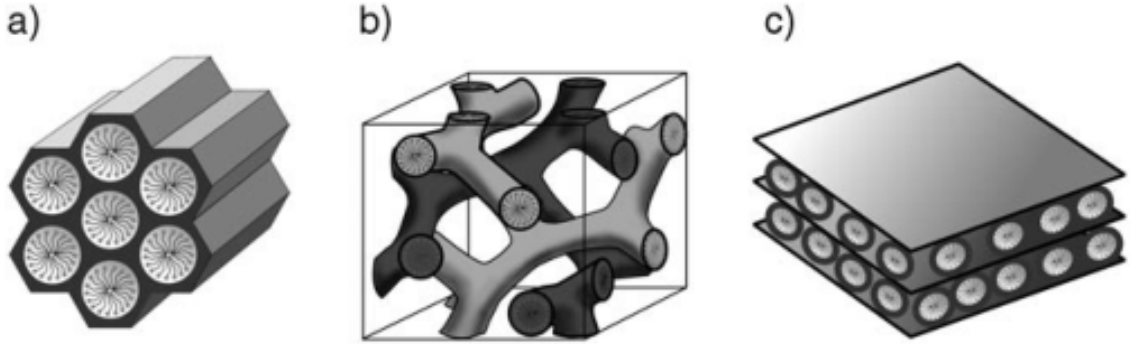


Figure 1.1. Structures of mesoporous M41S materials: a) MCM-41 b) MCM-48 and c) MCM-50. [2]

In the year of 1998, an ordered hexagonal mesoporous silica structure (SBA-15) has been prepared by Zhao et al [14] using an amphiphilic triblock copolymer to guide the organization of polymeric silica species, and resulting in a uniform pore size of approximately 30 nm. By the way, it was regarded as another important milestone in mesoporous materials research. The thick silica walls of SBA-15 (*p6mm*), in particular, ranging from 3.1 to 6.4 nm are different

from thinner walled MCM-41 structures which are synthesized with conventional cationic surfactants, providing SBA-15 with a greater hydrothermal stability. At present, polymer surfactants and other surfactants used for such macroporous materials are classified as soft templates. The advantage of using a soft template is that the mesoporous material can be prepared at a relatively low temperature, and the pore structure of the resulting material can be easily controlled by simply modifying the template molecules.

The templates, are classified as instance products, ranging from SBA-15 [15], SBA-1 [16] and even to MCM-48 [16] in the presence hard templates Besides, these templates were first utilized to synthesize the ordered mesoporous molecular sieves with carbon framework by Joo et al [15] and Ryoo et al [16], which is considered an important breakthrough in the history of mesoporous materials. The structure of the synthesized carbon referred as CMK family was by the composition of ordered nano-porous carbon, which was originally formed inside the cylindrical nanotubes of the SBA-15 template and the images of transmission electron microscopy and schematic model were presented in Figure 1.2 below.

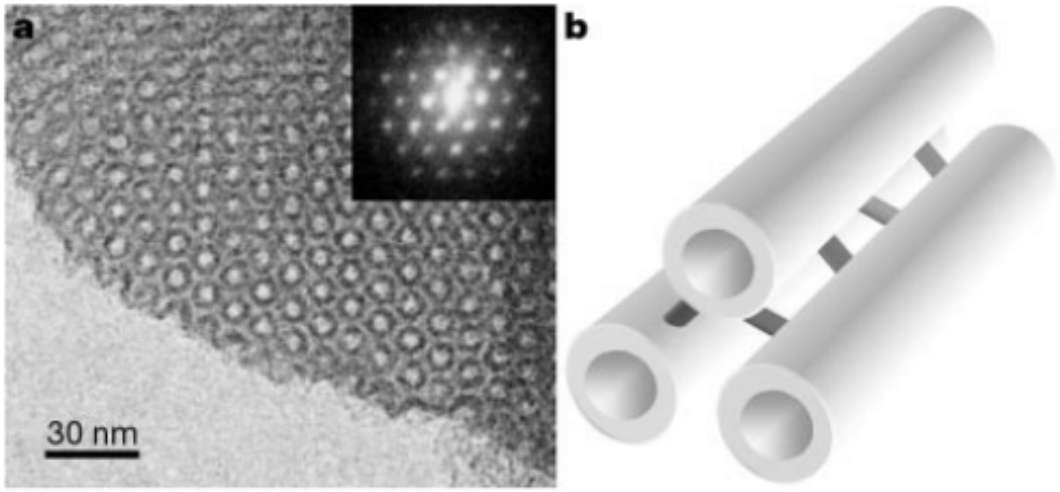


Figure 1.2. Ordered porous carbon prepared by template synthesis method using ordered mesoporous silica SBA-15. a) TEM image viewed along the direction of the ordered porous carbon. b) Schematic model for the carbon structure [15].

Compared with surfactants, nano-casting strategy had brought forward incredible possibilities in synthesizing novel mesostructured materials, and finally resulted in a large amount of ordered nanowire arrays [17]. Therefore, mesoporous carbon has received much attention because its capacity of accommodating a large number of guest atoms, molecules or particles in the pores and its high conductivity, making it be used as an electrode material in the areas of supercapacitors, chemical sensors and batteries with high performance.

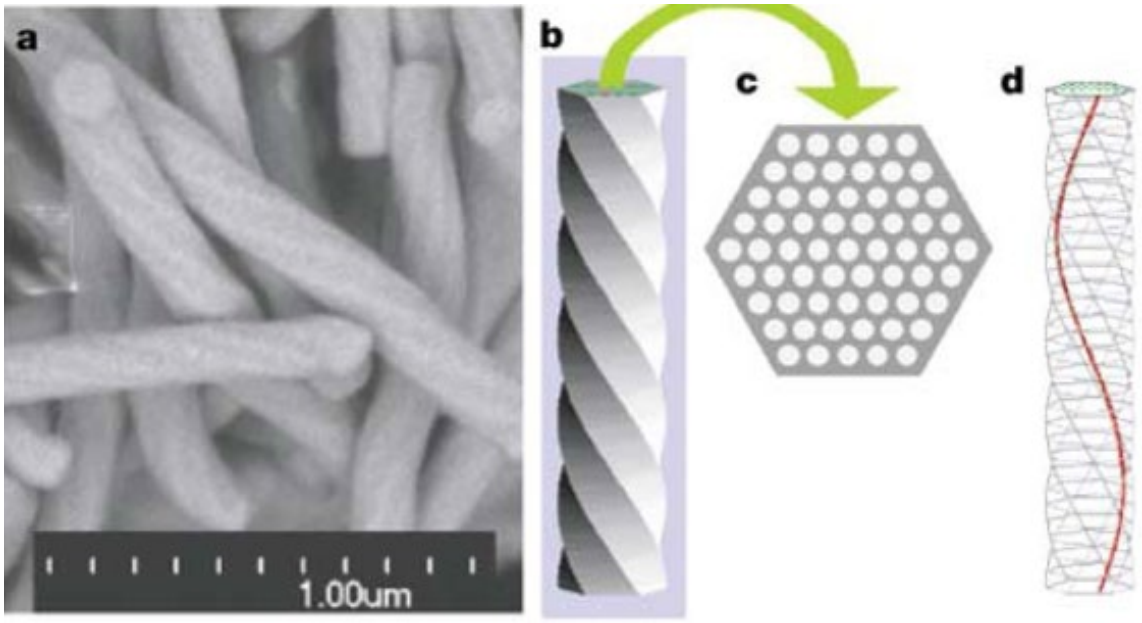


Figure 1.3. Chiral mesoporous silica [8].

Che and her colleagues [18] reported the surfactant-templated synthesis of the ordered chiral mesoporous silica, in the shape of a twisted hexagonal rod which diameter is 130-180 nm, and length 1-6 mm and a general method for the structural analysis of these chiral mesoporous crystals, as shown in Figure 1.3. In their previous study, they have reported the synthesis of highly ordered anionic surfactant templated mesoporous silica (AMS) materials with anionic surfactant and co-structure directing agent (CSDA) through a new $S^-N^+{\sim}I^-$ pathway, where S stands for surfactant, N stands for CSDA, and I stands for inorganic precursors [19]. In this pathway, aminosilane (e.g., 3-aminopropyltrimethoxysilane) or quaternizedaminosilane (e.g., N-trimethoxylsilylpropyl-N,N,N-tributylammonium) were used as CSDA. During the self-assembly process, the positively charged amine or ammonium

sites of CSDA interact electrostatically with the templating anionic surfactant micelles and the alkoxysilane sites of CSDA co-condense with the inorganic precursors. This new pathway has been proven a successful way to produce a series of novel mesostructured phases, such as lamellar, hexagonal, cubic, and disordered mesostructures, as well as well-defined morphologies.

1.2.2 Formation mechanism of mesoporous silica

Mesoporous silica was discovered in the 1990s [11]. They have been known for their special structural properties such as high specific surface area, large pore volume, and continuously adjustable mesoporous channels, which makes them widely used and popularized in the fields of catalysis, separation and optics, and so on.

Mesoporous silica materials are mainly synthesized by supramolecular templating self-assemble methods. The synthesis process can be summarized as the inorganic species to interact with organic supramolecular templates to form mesoporous materials follows under certain conditions, such as pH, temperature, concentration, etc. The formation processes of typical mesoporous material is mainly divided into two stages: (i) the formation of organic/inorganic liquid crystal phase (mesoscopic structure). Organic/inorganic complexes with mesoscopic structure were synthesized by self-assembly of amphiphilic surfactant organic molecules that contain hydrophilic and hydrophobic groups and polymerizable inorganic precursors under certain synthetic conditions. (ii) amphiphilic surfactant organic molecules are removed by calcination or solvent extraction, and the space left is to form mesopores. During the synthesis processes, four substances of template, inorganic precursor, solvent and solution ion are present. Among them, template plays a core role in the synthesis of mesoporous materials. The common templates are organic molecules with amphiphilic properties. According to whether it is charged and whether it is positive or negative, they can be divided into cationic, anionic and neutral surfactants. In addition, biological macromolecules, peptides, polysaccharides,

supramolecular aggregates, organic gels, etc. can also be used as template agents for the synthesis of mesoporous materials.

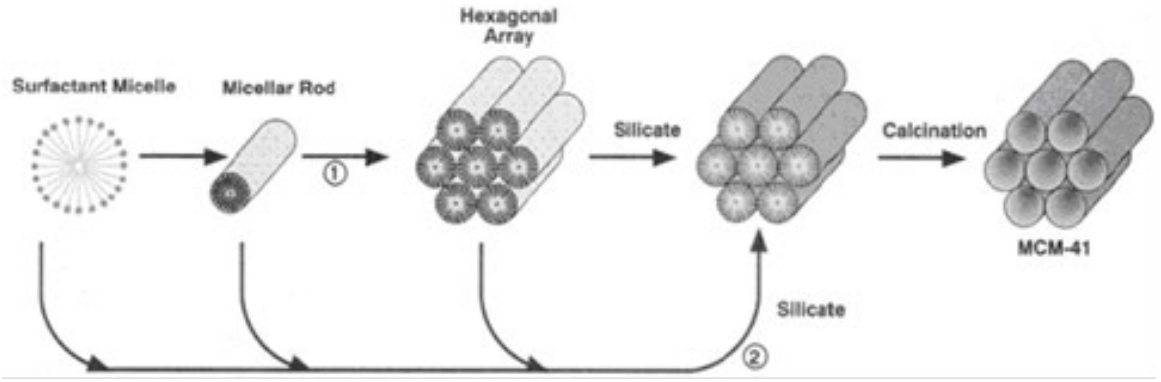


Figure 1.4 ① Liquid crystal templating mechanism (LCT) and ②Synergistic mechanism (CFM) [11].

Several models are proposed based on different synthesis systems to explain the formation mechanism of mesoporous materials. All models believe that surfactants play a structure oriented role. In order to explain the synthesis mechanism of MCM-41, Mobil first proposed the liquid crystal template mechanism and synergistic mechanism [11] (Figure 1.4).

As shown in Figure 1.4, the LCT mechanism is proposed based on the similar spatial symmetry between the synthetic mesoporous silica and the surfactant liquid crystal phase. It is mainly considered that the liquid crystal phase generated by the surfactant is used as the template for forming mesoscopic structure, and the liquid crystal phase of the surfactant is formed before adding inorganic reactants. Surfactants (organic templates) with hydrophilic and hydrophobic groups first form spherical/rod micelles in the water system. The outer surface of the micelles is composed of the hydrophilic end of the surfactant. The inorganic monomer or oligomer molecules precipitate in the pores between the micelles due to the interaction with the hydrophilic end. Subsequently, inorganic monomer or oligomer molecules polymerize and solidify to form the silica pore wall.

Cooperative formation mechanism (CFM) proposes to form surfactant mesophase due to the interaction between micelles and inorganic species. This

interaction accelerates the polycondensation process of inorganic species. At the same time, the polycondensation reaction of inorganic species promotes the formation of liquid crystal. CFM mechanism can explain the synthesis of new phase products different from liquid crystal structure, synthesis at low surfactant concentration and phase transition during the synthesis process.

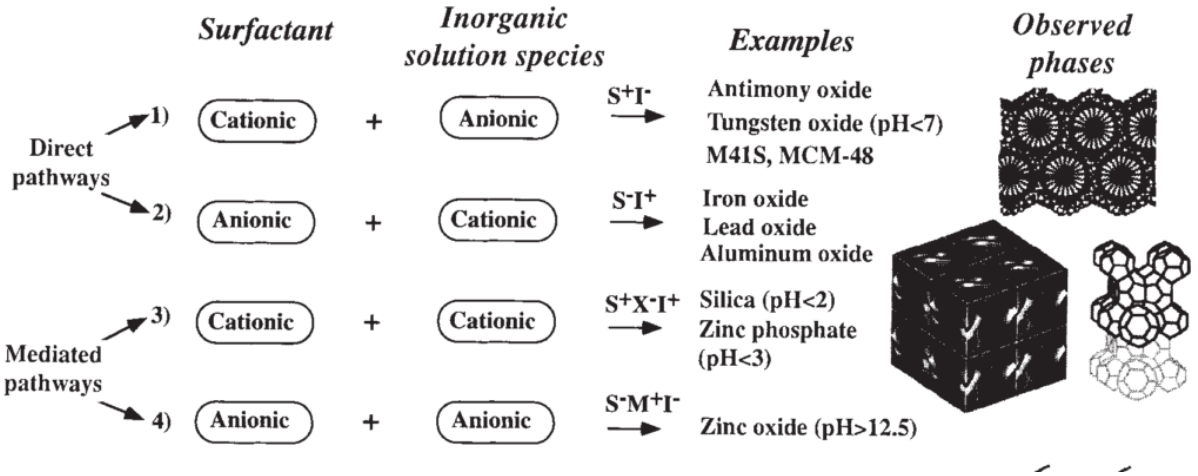


Figure 1.5 cooperative self-assembly mechanism [20].

At present, as shown in Figure 1.5, the "cooperative self-assembly mechanism" proposed by Stucky's group is widely accepted [20-21], which is considered that inorganic and organic molecular species finally form an ordered arrangement structure through cooperative assembly. During synthesis, the silica anions interact with surfactant cations, the silica monomer polymerization and the hydrophobic/hydrophobic interaction between the long chains of surfactants make the long chains of surfactants close to each other, and the charge matching between inorganic and organic species controls the arrangement of surfactants. The final meso-phase depends on the degree of the reaction, which is the degree of polymerization of the inorganic part. This mechanism emphasizes the synergy between inorganic and organic species. The interaction between inorganic and organic species, hydrophobic interaction between organic species and condensation between inorganic species will all affect the final mesoscopic structure.

1.2.3 Synthesis methods of mesoporous silica

With the proposal of the synthesis mechanism of mesoporous silica, another important topic is the exploration of the synthesis method of mesoporous materials. At present, the synthesis method of mesoporous silica also shows diversity, but mainly through Supra-molecular template method [11, 20] to synthesize. Nowadays the synthesis of mesoporous silica mainly has the following methods: hydrothermal synthesis method, evaporation induced self-assembly method, microwave radiation synthesis method and ultrasonic synthesis method [22-25]. The general process of hydrothermal synthesis is to use a surfactant as a templating agent, add an acid or a base to prepare a solution, and then slowly add the inorganic raw material, stir it for a period of time, put it into an autoclave. Next the precursor of the reaction can be obtained by hydrothermal treatment for a period of time. The mesoporous material is then obtained by centrifugation, cleaning, drying, etc. And finally removing the surfactant by calcination or extraction. Evaporation-induced self-assembly method as a new method for synthesizing mesoporous materials is a process of preparing a reaction in a non-aqueous medium, such as methanol, ethanol, acetone, etc. With this method of preparation, the concentration of the surfactant contained in the precursor solution needs to be lower than the critical micelle concentration. With the constant evaporation of the organic solvent, the concentration of the precursor solution will sustain to increase and it will make the concentration of the surfactant close to each other. Eventually greater than the critical micelle concentration until a composite liquid crystal phase of a surfactant□inorganic species is induced to form. This structure undergoes further polycondensation to ultimately result in an ordered mesoporous material. Compared with the traditional hydrothermal method, the evaporation-induced self-assembly method can achieve the perfect combination of sol gel method and template self-assembly efficiency. Thereby, a controlled mesoporous structure morphology is prepared, and the time taken for the synthesis is saved. The sol-gel method is a general method for synthesizing mesoporous materials. The

synthesis process can be mainly divided into two steps: first, the surfactant in the solution forms a supramolecular structure, and then it is followed by a sol-gel process in which the surfactant interacts with the inorganic species to direct self-assembly into an ordered mesostructured material. Surfactant as a template could be seen one of the most common methods for synthesizing mesoporous materials. Synergistic self-assembly between surfactants and inorganic substances forms a supramolecular liquid crystal structure, which is the key element in the synthesis of ordered mesoporous materials.

For the purpose of application, surface functionalization would be necessary. The functionalization of the surface of the mesopore has been achieved by direct co-condensation and post-synthesis grafting methods using organoalkoxysilanes [26]. A direct co-condensation method is based on the co-condensation of a tetraalkoxysilane and organoalkoxysilanes in the aqueous solution containing surfactant to produce inorganic-organic hybrid networks through sol-gel chemistry. On the other hand, a post-synthesis grafting method is based on the silylation of organoalkoxysilane with surface silanol groups on the mesopores of the pre-fabricated mesoporous silica. Organic-inorganic hybrid mesoporous materials have also been prepared by using the alkoxysilane monomer bridged by an organic group as silica source, as showed in Figure 1.6 [27].

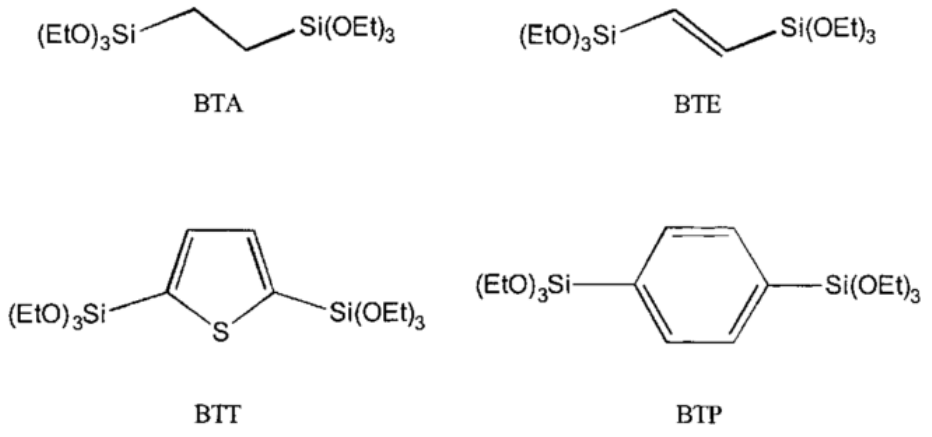


Figure 1.6. The molecular structure of alkoxysilane monomer bridged by an organic group [27].

Although this method leads to a homogeneous distribution of organic fragments within the framework, the variation of functional groups introduced as well as mesostructure of the materials is limited. So, I selected direct co-condensation method in my experience, because the direct co-condensation would result in a homogeneous distribution of amino-organic moieties on the silica wall. But in the post-synthesis grafting method, most amino-organic moieties would concentrate near the openings of channels and/or on the external surface.

1.3 Morphology of mesoporous silica

In terms of practical application, mesoporous silica material is not only related to their internal pore structure, but also closely related to their macro and micro morphology. Therefore, the morphology of mesoporous materials has become a hot spot in the field of mesoporous materials since the discovery of mesoporous materials. Mesoporous silica materials can be synthesized with surfactant molecular aggregates as templates under alkaline or acidic conditions. Acid mainly controls hydrolysis and condensation at the end of silicate ionic polymer to form silica, while alkali accelerates hydrolysis and condensation at the same time, so as to form a highly condensed compact structure. Therefore, acidic synthesis usually has rich morphology, and alkaline synthesis generally provides better stability and ordered meso-structures.

1.3.1 Spherical mesoporous silica

Spherical mesoporous silica has attracted much attention because of its wide application prospects in catalysis, chromatographic separation and optical devices. In 1968 [28], Stöber added silicon source to ethanol/alkali/water system to successfully prepare monodisperse spherical silica, which was called Stöber process. Then, a series of silica spheres with mesoporous structure were synthesized by introducing long-chain structure directing agent. This method is called modified Stöber method.

There are many reports on the synthesis of spherical mesoporous silica by improved Stöber method.

In 1998, Unger et al. synthesized mesoporous silica materials by adding long-chain alkyl silane or long-chain alkyl amine to ethanol/alkali/water system by Stöber process [29]. They also successfully synthesized MCM-48 spherical mesoporous material by adding cationic surfactant CTAB [30].

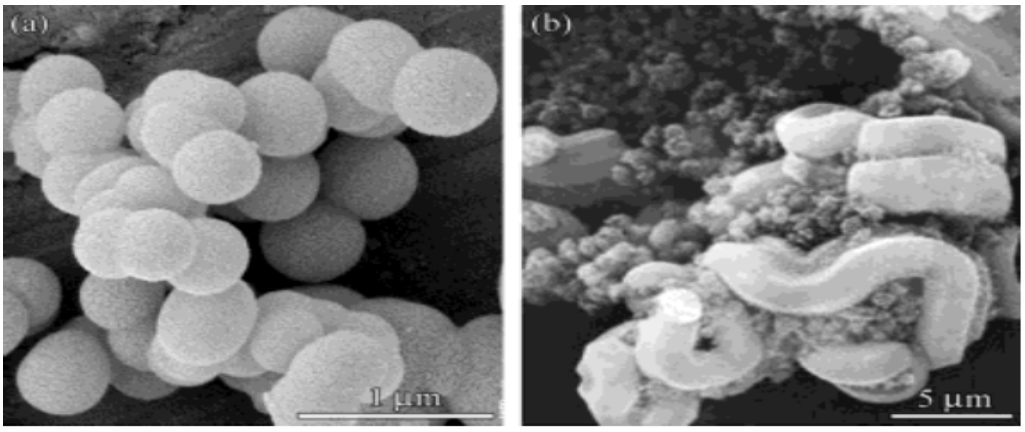


Figure 1.7 (a) spherical MCM-41 by using the improved Stöber method and (b) regular MCM-41 by traditional method [31].

Pauwels et al. synthesized MCM-41 mesoporous silica spheres by using the improved Stöber method, as shown in Figure 1.7 [31]. It was found that the mesoporous channels of MCM-41 spheres are arranged radially. In addition, spherical mesoporous materials with mixed mesoscopic phases of MCM-41 and MCM-48 were also synthesized by similar methods. Transmission electron microscopy (TEM) showed that the central region of the ball was MCM-48 mesoporous structure, and the edge of the ball was MCM-41 mesoporous arrangement [32]. By studying the growth process of radiation pore mesoporous silica spheres, Rankin et al. Found that the growth rate of spherical silica is very fast, the diameter of the sphere has been hundreds of nanometers in 70 seconds, and the mesoporous pores are always preferentially arranged in a direction perpendicular to the interface on the particle interface [33].

Since the introduction of surfactant (CTAB) into the synthetic medium, the modified Stöber method has been widely used in the synthesis of spherical mesoporous silica. The synthesis did not require high concentration of surfactant.

The synthesis could be finished in a dilute solution under the condition of room temperature or slight heating with a suitable surfactant. The synthetic pH value could be adjusted with ammonia or sodium hydroxide. Tetraethyl orthosilicate (TEOS) was usually chosen as silicon source. The presence of surfactant could induce the deposition of silica oligomers, which was self-assemble with surfactant micelles to form an ordered mesostructure. The nanoparticles prepared by the improved Stöber method displayed a variety of mesoscopic structures and different particle size distribution. It is found that the particle size distribution of the final product is affected by many factors, including the pH value attributed to the concentration of sodium hydroxide or ammonia [34].

synthetic temperature, the presence of co-solvent, the category and concentration of surfactant and the type and amount of silicon source, and so on. [35-37] For example, the particle size of the final mesoporous silica spheres will increase with the increase of the added amount of NaOH/ammonia and silicon source (TEOS). The effects of reaction time, TEOS concentration and pH value on the particle size distribution of the synthesized mesoporous silica spheres during the synthesis were studied in detail by Chiang's group [38]. It was found that pH value of synthetic medium had the greatest influence on the results, followed by reaction time and silicon source concentration (TEOS amounts). If the swelling agent of trimethylene was added, the mesoporous diameter could be expanded to ca. 20 nm [39,40].

Although the above-mentioned modified Stöber method can prepare mesoporous silica spheres with ordered mesoscopic structure, there are still a lot of disadvantages for this method. If the silica concentration is low, the particle size distribution will be very wide. The introduction of triethanolamine replaced with ammonia or sodium hydroxide into the synthetic system could effectively solve this problem [41], which could obtain mesoporous silica spheres with narrow particle size distribution at the range of 50 nm to 100 nm. It was found that triethanolamine have the roles to catalyze the hydrolysis of TEOS instead of traditional sodium hydroxide or ammonia, meanwhile, it could prevent the

aggregation and growth of particles by interaction with silica oligomers. A similar synthetic method by adding triethanolamine to the synthetic medium, ordered mesoporous silica spheres with narrow particle size distribution could be accurately regulate by changing the type of silicon source, such as using silicon source with different long alkyl groups of tetraalkyl orthosilicate [42]. This was due to the different hydrolysis rate of different tetraalkyl orthosilicates. Yu and his coworkers [43] employed sodium acetate as additive, cationic surfactant as mesoporous template, TEOS as silicon source, to prepared mesoporous silica spheres with adjustable particle size in the range of 50-110 nm by changing the synthesis temperature in the range of 40 ℃ to 80 ℃. Tatsumi and his coworkers [44] firstly tried basic amino acids instead of sodium hydroxide or ammonia to achieve a low hydrolysis of TEOS silicon source to prepare mesoporous silica spheres with a wide range of 15-200 nm (Figure 1.8).

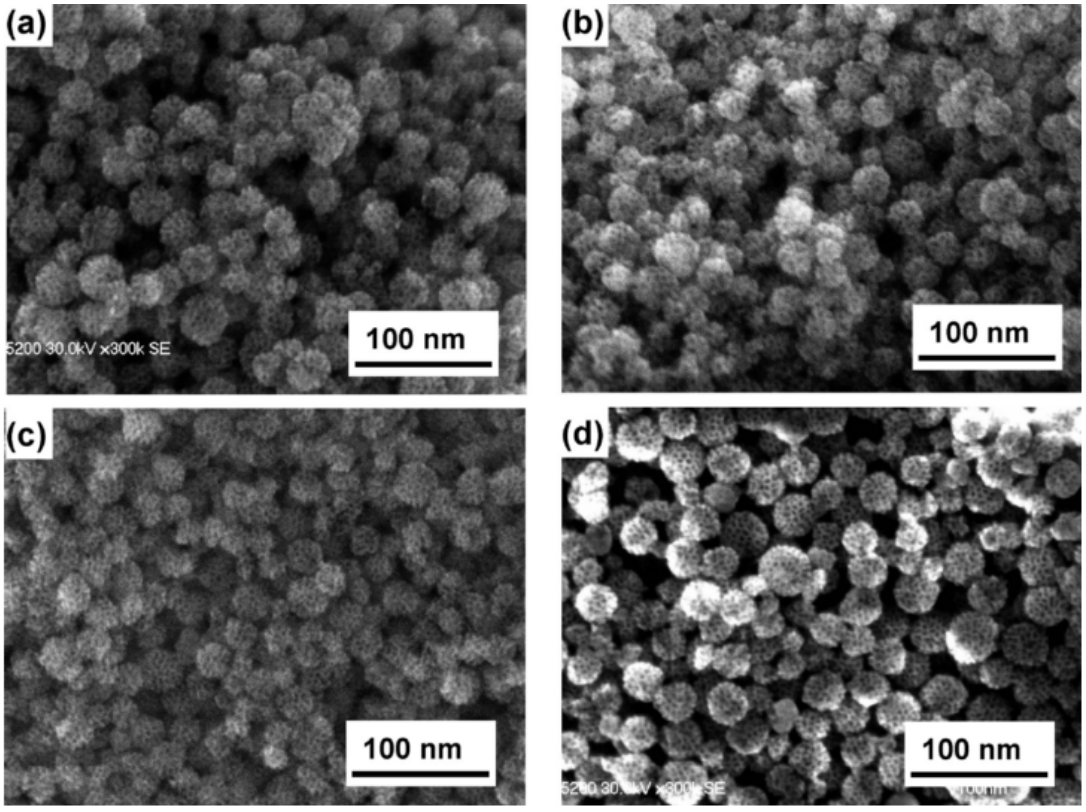


Figure 1.8. SEM images of the mesoporous silica nanospheres synthesized with different amounts of amino acid of arginine [44].

Wang's group [45] introduced weakly basic primary amines such as methylamine to catalyze the hydrolysis of TEOS silicon source to prepare

mesoporous silica nanospheres with a narrow particle size distribution. The synthesized mesoporous silica nanospheres possessed narrow particle size of 28-54 nm and good hydrothermal stability. So as to prepare smaller nanoparticles, Ma et al. [46] employed polymers to quench the rapid growth of silica nanoparticles during the starting stages. They prepared extremely small-sized nanoparticles with about 9 nm in diameter. Although not all the related works about the improved Stöber method is summarized here, we can deduce a conclusion from the above-mentioned experimental and results. It is found that mesoporous silica spheres can achieve the controlled synthesis by adjusting the component and concentration of starting materials in the synthetic system, temperature, or quenching treatments.

In 2008, Wang et al. [47] prepared monodispersed mesoporous silica spheres with radially oriented mesopores. They employed an anionic surfactant synthetic system and the formation process was relative lower than cationic surfactant system. The formation of mesopore have enough time (several hours) to minimize its micelle free energy to re-alignment self-assembly to form preferential ordered structure and spherical shape (Figure 1.9).

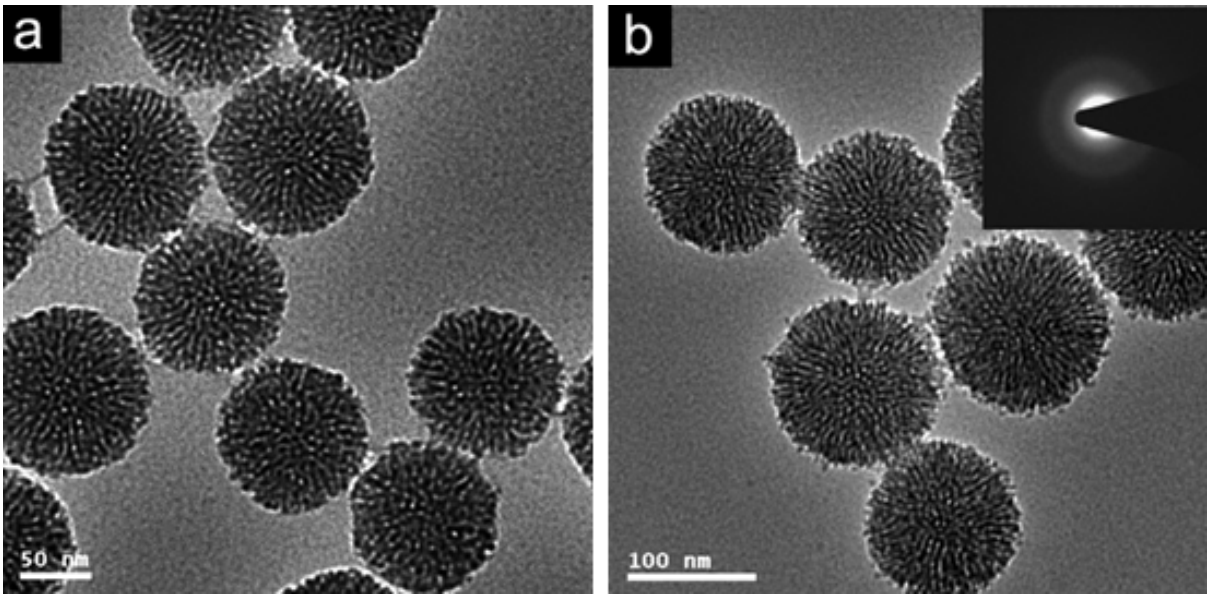


Figure 1.9 Monodispersed mesoporous silica spheres with radially oriented mesopores templated from an anionic surfactant synthetic system. [47].

Evaporation induced self-assembly (EISA) is to concentrate the system by evaporation of small molecular solvents. With the increase of species concentration, surfactants self-assembly into liquid crystal phase, so as to obtain mesoporous materials. Rao et al. synthesized the monodisperse mesoporous silica spheres by the EISA method of aerogel with cationic surfactant (CTAB) or non-ionic surfactant (Brij-58) [48].

1.3.2 Hollow structured mesoporous silica

Well-defined spherical mesoporous silica displays interesting properties for biomedical applications such as uniform particle size, large surface area and tunable pore diameters and volumes, allowing the incorporation of large amounts of drugs and protecting them from deactivation and degradation processes acting as an excellent nanoplatform for drug delivery. Figure 1.10 showed a series of hollow mesoporous silica with different morphology and nano-structure by using polystyrene microspheres as hollow templates and anionic surfactant as mesoporous templates [49].

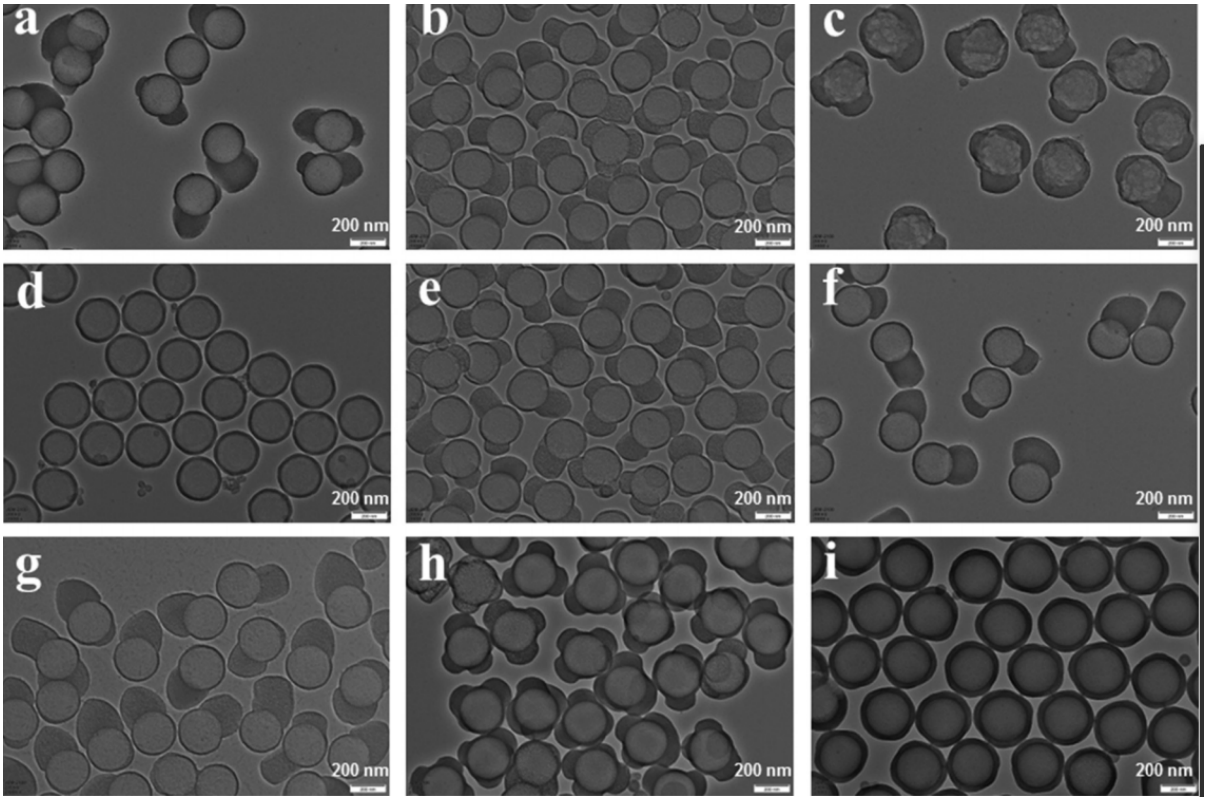


Figure 1.10 Hollow mesoporous silica with different morphology and nano-structure [49].

In addition, hollow structured mesoporous silica with low density, large hollow structure, and high specific surface area, make it show higher application value and better application prospects in biomedicine such as drug loading, delivery and controlled release. [50-54]

Various methods for preparing mesoporous materials with hollow structures have been developed one after another. And many nanomaterials were employed as templates to construct hollow structure, include vesicles, [55-57] bubbles, [58-59] and microemulsions, [60-62] metals, metal oxides, semiconductor materials, and polymer microspheres, [63-64] and so on [65-66].

1.3.3 Elliptical mesoporous silica

For preparing elliptical mesoporous silica, it was usually required the complex preparation procedures. Shen's group reported developed a facile method to prepare ellipsoidal particles with relatively less expensive experimental equipment and higher yields than other scientists and researcher had done previously [67]. They introduced the synthesis of silica ellipsoids with hexagonal meso-structure by organic-inorganic co-assembly in the presence of potassium chloride and ethanol, which are regarded as co-solvents. In addition, the aspect ratio of the ellipsoid will be systematically tunable if the concentration of ethanol is well controlled. In fact, their investigation filled the gap of the synthesis method of anisotropic ellipsoidal nanoparticles.

In their reported experimental procedures, the templates utilized during synthesis of non-spherical particles were poly (ethylene oxide) and poly (propylene oxide). In the meantime, tetraethyl orthosilicate as the silica precursor with the assistance of co-solvents (potassium chloride and ethanol) where the pH value is less than 7 at room temperature. The product had the shape of an ellipsoid, with a highly ordered 2D hexagonal mesoporous structure. Its pore channels are just parallel to the long axis of the ellipsoid. After calcination, the ellipsoidal mesoporous silica was observed by scanning electron microscopy (Figure 1.11)

Hao et al reported MCM-41 nanoparticles in the morphology of an ellipsoid, which were synthesized in the presence of surfactant-template cetyltrimethylammonium bromide (CTAB) and sodium dodecylbenzene sulfonate (SDBS) [68, 69]. The MCM-41 nanomaterials possess a diameter around 100 nm and a length 200 nm or so. Unlike the work of Shen et al, Hao's group obtained a non-spherical mesoporous silica which pore channels are parallel along the short axis.

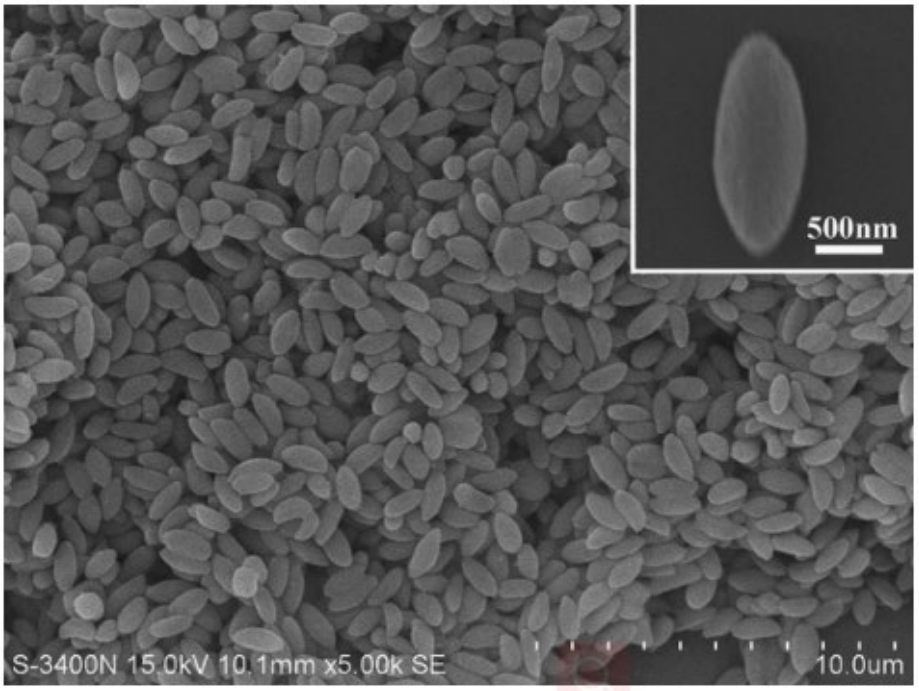


Figure 1.11. SEM image of the calcined ellipsoidal mesoporous silica. [67]

1.3.4 Mesoporous Silica with Complex Morphologies

Suteewong et al reported a one-pot approach to synthesize a kind of mesoporous silica nanomaterials which have multi-compartment of mesoporous silica nanomaterials [70]. Each particle is made up of a core in the shape of a cubic mesoporous morphology and normally less than four branches, where the mesopores with hexagonal cylinder morphology, growing outward from the apex of the cubic nucleus as indicated in Figure 1.12. At the same time, the growth degree of these classes of nanomaterials is easily controlled through adjusting the amount or concentration of addition agents.

To be more detailed, most of multicompartment mesoporous silica nanomaterials prepared in a dilute ethyl acetate (EtOAc) had short branches and which diameters were no longer than their size of core. Whereas, the nanomaterials synthesized under relatively high concentration EtOAc, normally had branches up to two micrometers and then turned to rods.

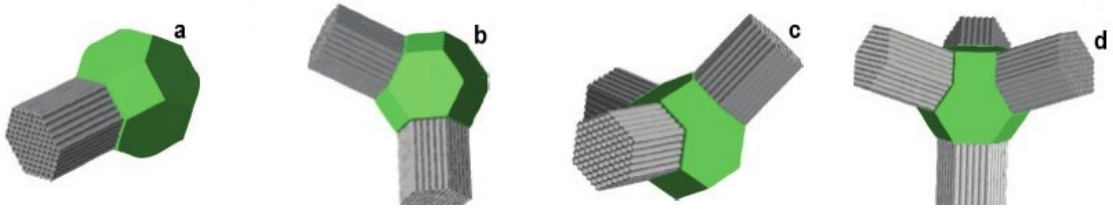


Figure 1.12. Schematic images of multicompartment mesoporous silica nanomaterials with (a) one arm, (b) two arms, (c) three arms, (d) four arms [70].

Croissant et al reported a one-pot two-step synthesis of meso-crystalline periodic mesoporous organosilica (PMO) nanoparticles with multipods [71]. The synthetic procedures consist of two steps ranging from the condensation of benzene-based silane sphere-shaped PMO cores, to the condensation of ethylene-based silane rodlike PMO pods on the cores. First of all, the PMO nanospheres were obtained, and then these spheres turned to nanorods after the addition of 1,2-bis(triethoxysilyl)ethylene silane. The formation of final products was processed with a consistent stir, which is considered as a crucial parameter to control the morphology of the mixed nanoparticles.

Li and his coworkers synthesized a class of asymmetric single-pore mesoporous silica nanocages with the eccentric hollow spheres in a novel approach known as the anisotropic encapsulation method [72]. Besides, these kinds of nanoparticles were successfully synthesized from capsules in nanometer scale that was fabricated by the open pores on the surface of mesoporous shell and which uniform particle size ranged from 100 to 240 nm (Figure 1.13). This unique nanocarrier, the eccentric hollow cavity and big hole around 25 nm were observed, serving as a storage space and channel for large guest molecules. At

the same time, the size of these uniform mesopores range from 2 to 10 nm, which are able to effectively provide storage space for some small guest molecules. The preparation procedure consists of three steps: anisotropic encapsulation, hydrothermal treatment and HF etching, and the flow chart was presented below in Figure 1.14.

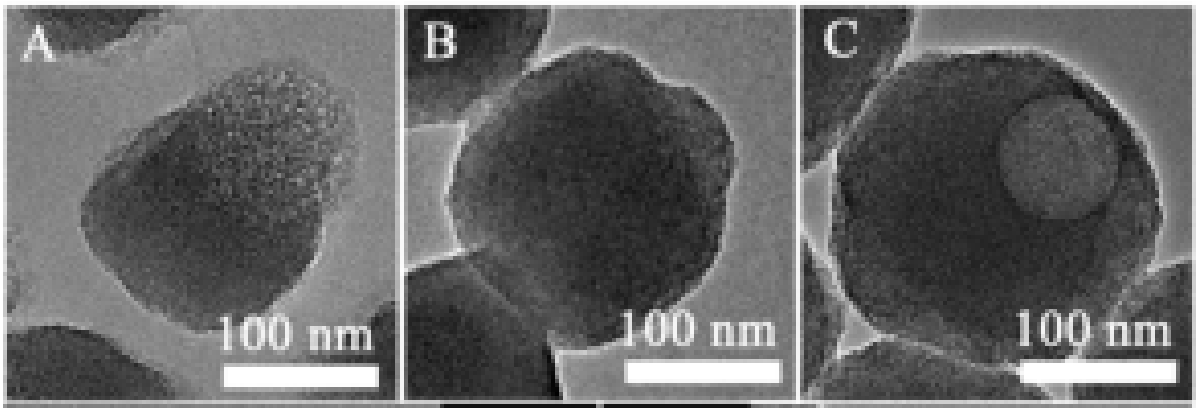


Figure 1.13. The TEM images demonstrating the morphology evolution of the eccentric nanocomposites [72].

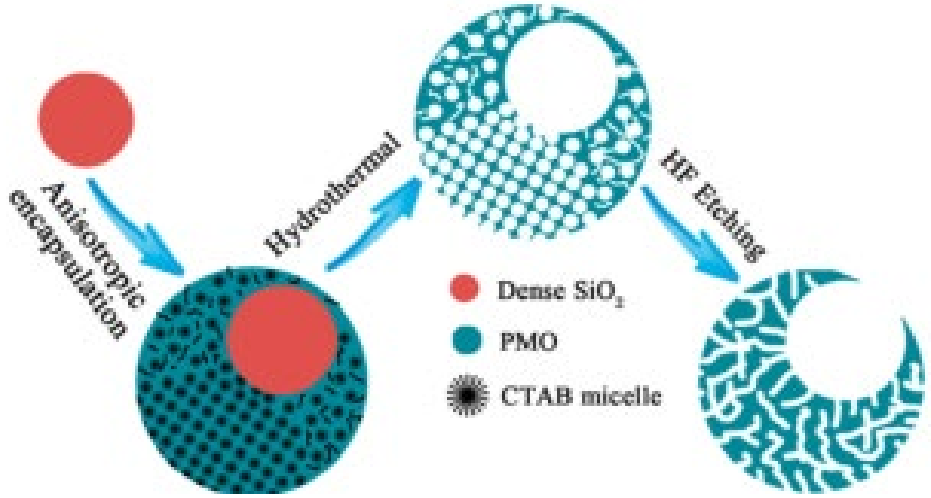


Figure 1.14. Preparing procedure for the asymmetric single-hole mesoporous nanocages [72]

During the first step, the template in the shape of a mesostructured, hexadecyltrimethylammonium bromide (CTAB) and the silica precursor, 1,2-bis(triethoxysilyl) ethane (BTEE), were used along with the addition of periodic mesoporous organosilica (PMO) resulting in the formation of the eccentric SiO_2@PMOcore@shell nanocomposites. Subsequently, the

nanocomposites underwent the twelve-hour hydrothermal treatment at 60 °C, and finally the etching of the dense SiO_2 nanoparticles and the fabrication of the eccentric hollow PMO nanoparticles were achieved. In the last step, it was the hydrogen fluoride solution that was utilized to get hollow PMO nanoparticles etched.

By adjusting the surface dynamics to control the number of nucleation sites, a series of mesoporous nanoparticles with precise and controllable surface topology were formed. Zhao et al [73] described several surface topological structures, and several pods from one to four, appeared on the surface of these mesoporous nanomaterials enhancing the capacity of bacterial adhesion due to their complex structure.

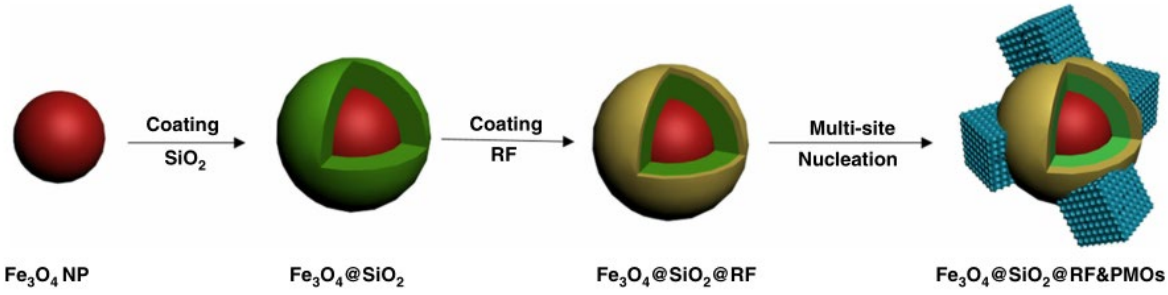


Figure 1.15. Illumination of complex mesoporous silica particles by adjusting the surface dynamics. [73]

1.3.5 Characterization of mesoporous silica nanoparticles

The composition and pore structures of the formed mesoporous silica nanoparticles were characterized by the following methods:

The content of inorganic elements, such as silicon, sodium, aluminum, etc. was tested by an inductively coupled plasma optical emission spectrometer (ICP-OES). The amount of organic element including nitrogen, oxygen, sulfur, etc., was characterized by an elemental analyzer.

The morphology and particle size can be characterized by using the scanning electron microscope (SEM) and transmission electron microscopy (TEM). The morphology and particle size can be found from the images.

The porosity of mesoporous silica nanoparticles can be characterized by nitrogen adsorption-desorption instruments tested at 77 K in a liquid nitrogen. The samples were firstly degassed at 373-573 K under vacuum for 10 h before testing. Specific surface area was calculated by the BET (Brunauer-Emmett-Teller) method and the pore size distribution was calculated from the adsorption data using BJH (Barett-Joyner-Halenda) method.

The meso-structure can be characterized by using powder X-ray diffraction (XRD) at the range of less than 10 degree. TEM and SEM technique can help to characterize the direction of mesoporous channels and hollow structure, and so on.

The presence of organic groups in the mesoporous silica can be characterized by using diffuse reflectance ultraviolet-visible spectrophotometer (DRUV/vis), Fourier Transform Infrared spectrophotometer (FTIR).

1.4 Mesoporous silica for drug controlled release

The widely distributed and abundant silica in nature not only has a wide variety of morphologies and mesoscopic structures but also has good biocompatibility, ensuring that it can be used as a carrier for drug release and can achieve spontaneous degradation in vivo.

Therefore, porous silica, especially, mesoporous silica with nano-sized pores was widely chosen to construct drug delivery system. Drug delivery system based on mesoporous silica were expected to solve the limitations of traditional organic carriers that were low drug loading capacity and high production cost.

Main advantages of mesoporous silica with nano-sized pores for drug delivery system:

- their simple synthesis;
- uniform morphology, high surface area and pore volume;
- tunable mesopore size and pore shape;
- controllable diameter pore;
- favourable chemical properties;

- thermal stability;
- good biocompatibility;
- opportunity modified by different functional groups through the silane chemistry;
- safety when circulating into the blood;
- realize on-command drug delivery;
- limitation of premature drug release before arriving at the target sites;
- targeting to specific tissue sites [86].

The pioneer application of mesoporous silica in drug delivery system was Vallet-Regí's group. They reported an ibuprofen loaded MCM-41 mesoporous materials as an anti-inflammatory drug in 2001, which achieved high drug loading amount, excellent controlled release of ibuprofen [74].

Naproxen, the well-known nonsteroidal anti-inflammatory drug (NSAID), was loaded into the pores of SBA-15 silica modified with aminopropyl groups. The released amount of naproxen represented 90.7% from the unmodified SBA-15 in 72h, while from the sample A-SBA-15/napro the released amount represented about 80.9% [75].

Subsequently, various drug delivery system based on mesoporous materials are developed from the aspects of mesostructure, pore size, particle size, morphology and functionalized modification [76-83].

Studies for the controlled release of MPT are described, which are aimed at both new approaches to synthesis and characterization of silica carriers: a one-time sol-gel approach and wetness impregnation method, where MPT is adsorbed on a silica support by wet impregnation after synthesis [9]. MSNs with MTP were synthesized through the reaction of tetraethyl orthosilicate (TEOS) in the water medium at 353 K, with introducing some cetyltrimethylammonium bromide (CTAB) as porogens [84, 85].

Mesoporous silica nanoparticles (MSNs) have been explored extensively as carriers for various drugs like Atorvastatin, telmisartan, methylprednisolone, prednisolone, quercetin, resveratrol, captopril, metoprolol succinate, Ibuprofen,

Ketoprofen, Bisphosphonates, Alendronate, Erythromycin, Amikacin, Cefuroxime, Vancomycin, Griseofulvin, Budesonide, lomefloxacin, Atenolol and so on [10 , 79].

There were represented synthesis of amino-decorated mesoporous silica nanoparticles (MSNs) for sustained delivery and enhanced bioavailability of sofosbuvir (active against hepatitis C virus). MSNs were synthesized using modified sol-gel method and the surface was decorated with amino functionalization. Was reached a 2-fold higher bioavailability of sofosbuvir in Sprague-Dawley rats in comparison with sofosbuvir alone, and the Tmax was delayed 3-times indicating a sustained release of sofosbuvir [87].

However, for an effective targeted drug delivery, the mesoporous silica nanoparticles can offer numerous problems such as, toxicity, bio-toxicity, tissue responses and cellular uptakes of the MSNs. Also, advancement in the production of novel specialized MSNs, particularly for drug delivery purposes, demands progress in analytical techniques suited for their characterization. The translation of MSNs laboratory results to human clinical trials is still limited, mostly due to the issues with a precise characterization of nanosystems in vivo [88].

Therefore, hollow silica particles (HSPs) are a promising scientific direction for controlled drug delivery.

Section 2 Production of drugs with controlled release in capsules

2.1 Mesoporous silicon dioxide with solid and hollow structure

2.1.1 Experimental sections

2.1.1.1 Chemicals

N-Lauroylsarcosine sodium (Sar-Na) was purchased from Sigma-Aldrich, and 3-aminopropyltrimethoxysilane (APMS), tetraethyl orthosilicate (TEOS) and hydrogen chloride (HCl) was from Shanghai Macklin Biochemical Co., Ltd. All the chemical agents were used without further purification.

2.1.1.2 Synthesis of mesoporous silicon dioxide with solid and hollow structure.

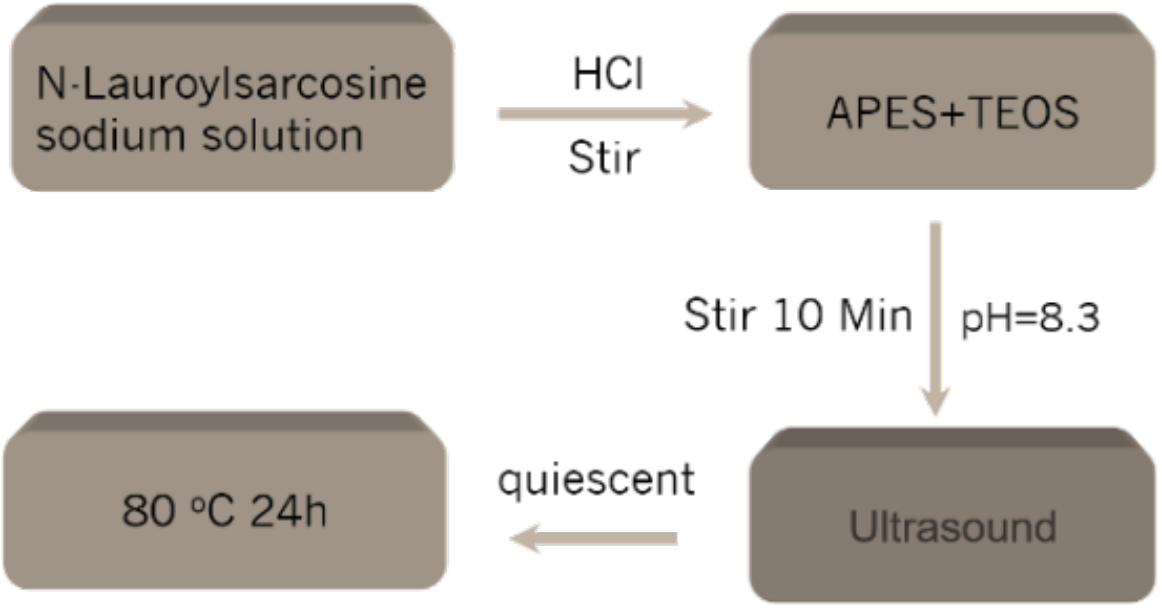


Figure 2.1 synthetic procedure of mesoporous silica.

As shown in Figure 2.1, 1.0 mmol of N-lauroylsarcosine sodium (Sar-Na) was dissolved in 30 mL of deionized water at room temperature. Then 4.0 mL of HCl (0.1 mol/L) was added. Next, a mixture of 1.5 mL Tetraethyl orthosilicate (TEOS) and 0.12 mL 3-aminopropyltriethoxysilane (APES) were added under stirring. After 10 minutes, the solution was treated under ultrasound (100 W) for 60 seconds. Then, it was placed at 80 °C for 24 h. The resulting powder was filtrated, dried at 100 °C. Surfactants of Sar-Na were removed from sample by a method of solvent extraction with 10 wt. % hydrochloric acid in acetonitrile at room temperature for 24 h. The product was filtered, washed, and dried overnight

at 80 °C, named as **MS-Hollow**. If no treatment of ultrasounds, the obtained product was solid mesoporous silica spheres, named as **MS-Solid**.

2.1.1.3 Metoprolol tartrate (MPT) drug loading experiments

Typically, 50 mg of MPT was fully dissolved in 2 mL of ethanol. Next, 50 mg hollow silica of HMS-Bubble was added and dispersed under sonication. The mixture was placed in a 50 °C oven to evaporate ethanol for 24 h. Subsequently, 2 mL of ethanol was used to wash the unabsorbed drug on the surface of the hollow sphere. The resulting mixture was centrifuged, and dried at 50 °C.

2.1.1.4 Materials characterization

Transmission electron microscopy (TEM) was characterized by JEOL JEM-1400 TEM microscope working at 100 kV to observe the information of particle shape, particle size, hollow structure and porous channels, etc.

Nitrogen adsorption experiments was used a Quantachrome IQ instrument to test the surface area, pore size and pore volume of mesoporous silicon dioxides. The samples were firstly degassed at 373 K under vacuum for 10 h before testing at 77 K.

Specific surface area was evaluated by BET (Brunauer-Emmett-Teller) method, the pore size distribution was obtained from the adsorption branch using BJH (Barett-Joyner-Halenda), and total pore volume was calculated based of the adsorption amounts at relative pressure about 0.98.

Particle size distribution was tested on a Malvern Zetasizer Nano ZS90 equipment. The nitrogen elemental content was obtained on a Vario EL Cube elemental analyzer.

2.2.2 Results and discussion

TEM images (Figure 2.2) showed MS-Hollow sample was a hollow sphere. The hollow sphere was 100-400 nm in size. The shell thickness was about 50 nm. There were a lot of mesoporous channels with a diameter of 3-4 nm in the shell,

which were perpendicular to the surface (as indicated by the blue double arrows).

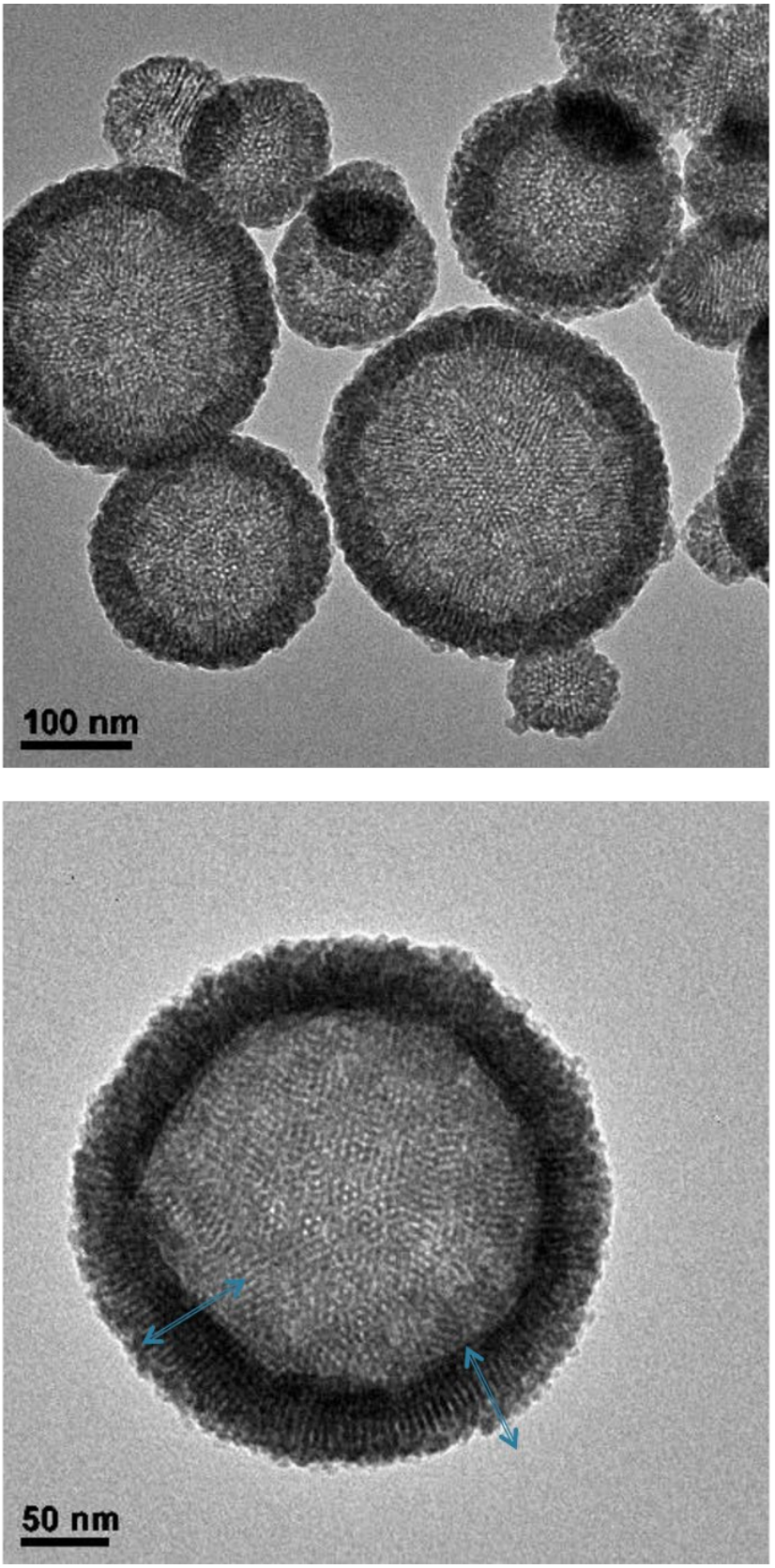


Figure 2.2 TEM images of mesoporous silicon dioxide of MS-Hollow with a hollow structure.

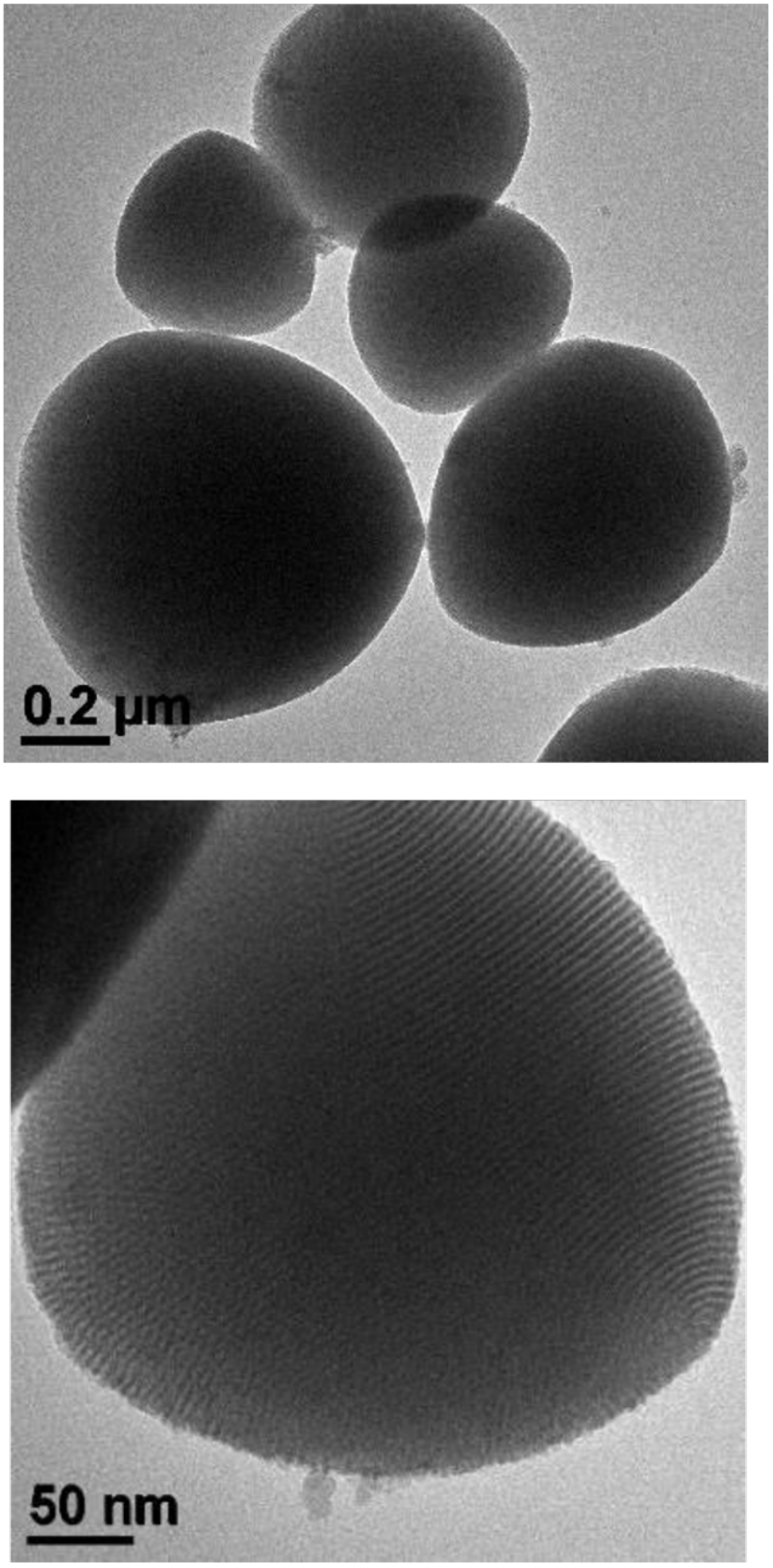


Figure 2.3 TEM images of mesoporous silicon dioxide of MS-Solid sample.

TEM images (Figure 2.3) showed MS-Solid sample was a solid nanoparticle with a size of 400-800 nm. There were a lot of mesoporous channels with a diameter of 3-4 nm present in the nanoparticles.

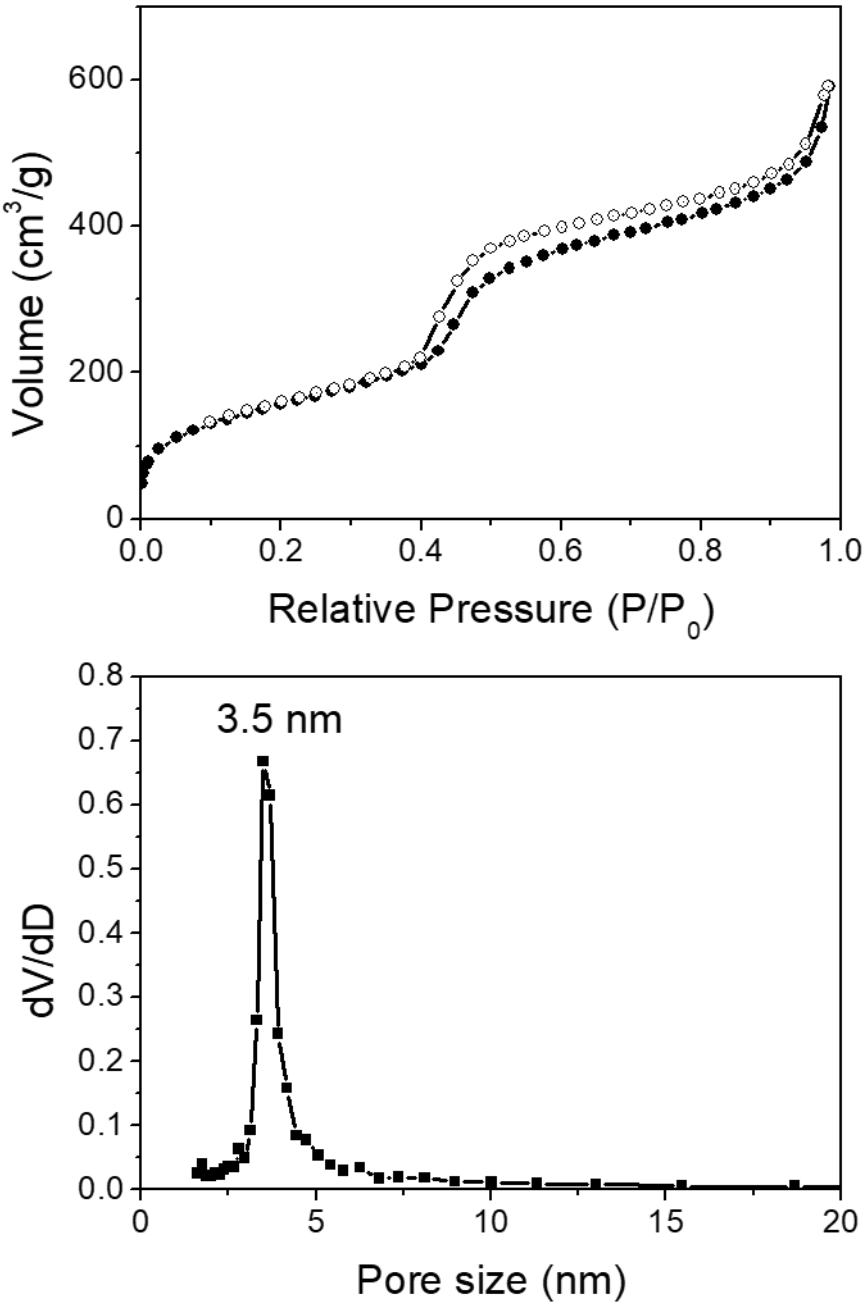


Figure 2.4 (Up) Nitrogen adsorption-desorption isotherms and (Down) pore size distribution of MS-Hollow sample.

The nitrogen adsorption-desorption isotherms of MS-Hollow sample gave a type-IV isotherm with an adsorption step at relative pressure between 0.4-0.5 due to the capillary condensation of the filling nitrogen in the mesopores (Figure 2.4).

The pore size distribution was very narrow with a peak centered at 3.5 nm, indicating the uniform sizes of the mesopores. The BET specific surface area was 445 $m^2 \cdot g^{-1}$, and the total pore volume was 0.71 $cm^3 \cdot g^{-1}$. The presence of a hysteresis loop at relative pressures of 0.5-0.9 indicated a hollow structure with mesoporous walls.

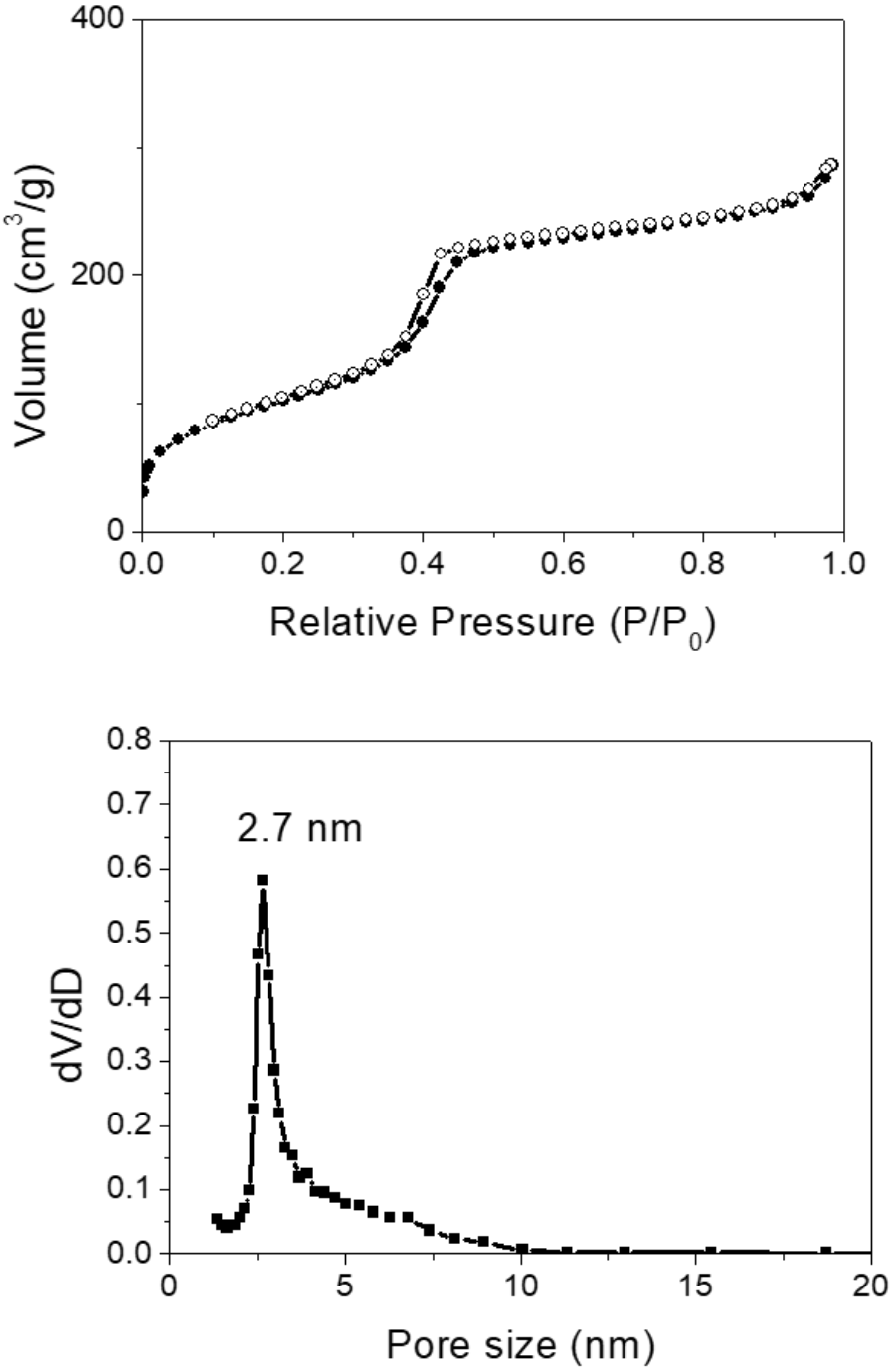


Figure 2.5 (Up) Nitrogen adsorption-desorption isotherms and (Down) pore size distribution of MS-solid sample.

The nitrogen adsorption-desorption isotherms of MS-solid sample showed a typical type-IV isotherm with an adsorption step at relative pressure between 0.3-0.5(Figure 2.5), indicating a mesoporous material. The pore size distribution was very narrow with a peak centered at 2.7 nm. The BET specific surface area was 379 $m^2 \cdot g^{-1}$, and the total pore volume was 0.44 $cm^3 \cdot g^{-1}$. As compared with MS-Hollow sample, sample MS-solid had smaller pore size, lower BET specific surface area and lower pore volume.

2.2 Hollow structured mesoporous silicon dioxide templated by CO_2 bubbles

2.2.1. Experimental section

2.2.1.1. Synthesis of amino-functionalized mesoporous silica hollow spheres templated by CO_2 bubbles

In a typical synthesis, 1.0 mmol of N-Lauroylsarcosine sodium (as anionic surfactant) was completely dissolved in 30 mL of deionized water at room temperature. Next, a mixture of 1.5 ml ethyl orthosilicate (as inorganic silica source) and 0.12 mL 3-aminopropyltriethoxysilane (as co-structure directing agent) was added under vigorous stirring. The total solution was transferred to a tetrafluoroethylene lined stainless steel autoclave. Next, CO_2 gas was introduced to a pressure of 1.0 MPa. The mixture was stirred at room temperature for 24 hours, and then placed in an oven at 80 °C for another 4 h. The resulting product was extracted with 10 wt.% hydrochloric acid in acetonitrile at room temperature for 24 h to remove surfactants. The final product was filtered, washed with distilled water, and dried overnight at 80 °C, named as **HMS-Bubble**.

2.2.1.2 Metoprolol tartrate (MPT) drug loading and release experiments

Typically, 50 mg of MPT was fully dissolved in 2 mL of ethanol. Next, 50 mg hollow silica of HMS-Bubble was added and dispersed under sonication. The mixture was placed in a 50 °C oven to evaporate ethanol for 24 h. Subsequently, 10 mL of ethanol was added and stirring for 10 minutes. The resulting mixture was centrifuged, and dried at 50 °C.

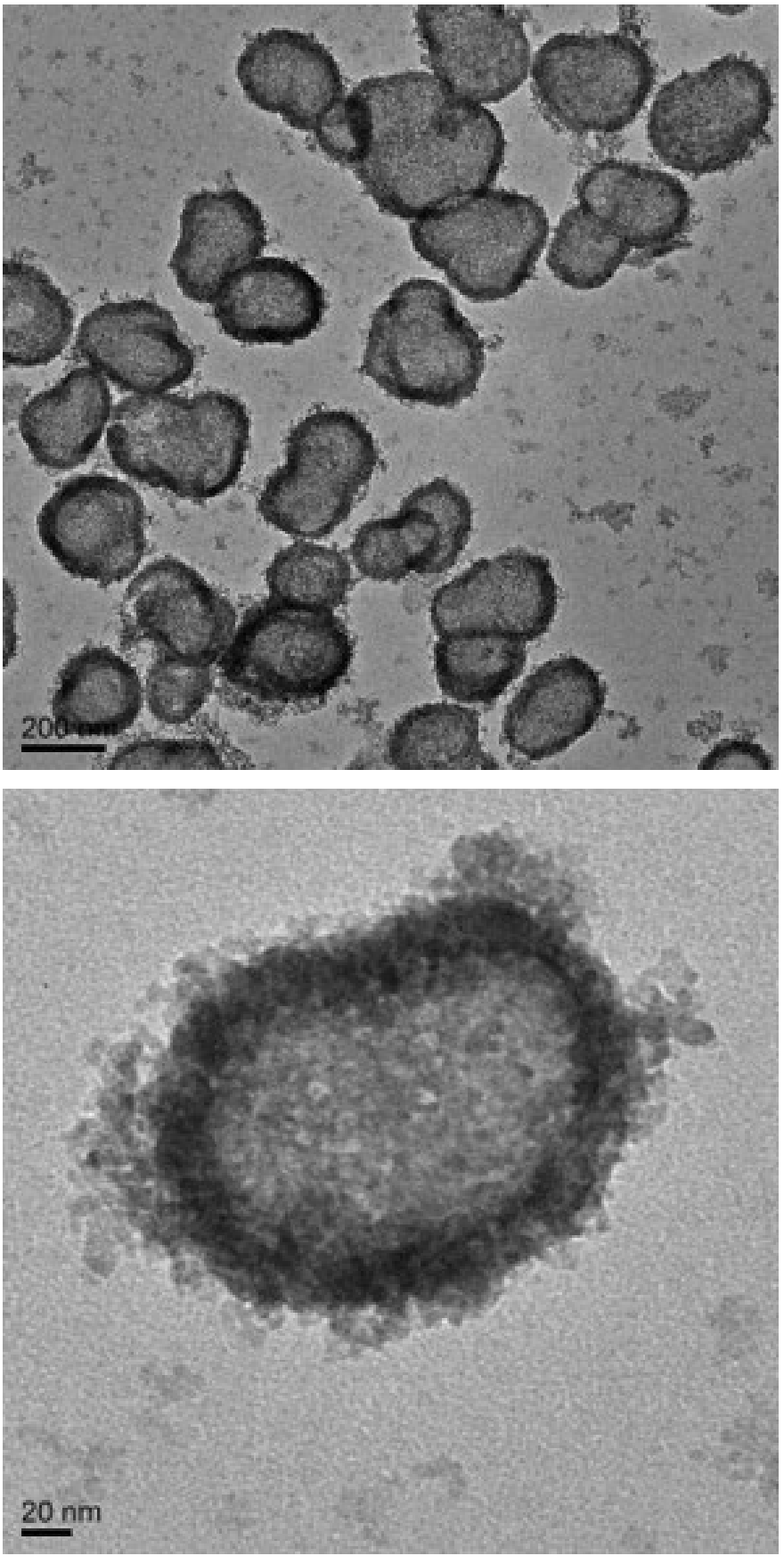


Figure 2.6 TEM images of the hollow structured mesoporous silica templated by CO_2 bubbles.

2.2.1.3 Characterization

TEM image of the product is characterized by a JEOL JEM-2100 TEM microscope working at 200 kV.

Nitrogen adsorption isotherms were conducted by a TrisStar II 3020 sorption analyzer at 77 K.

Specific surface area and pore volume were analyzed by BET (Brunauer-Emmett-Teller) method and the pore-size distribution was analyzed from the adsorption data using BJH (Barett-Joyner-Halenda).

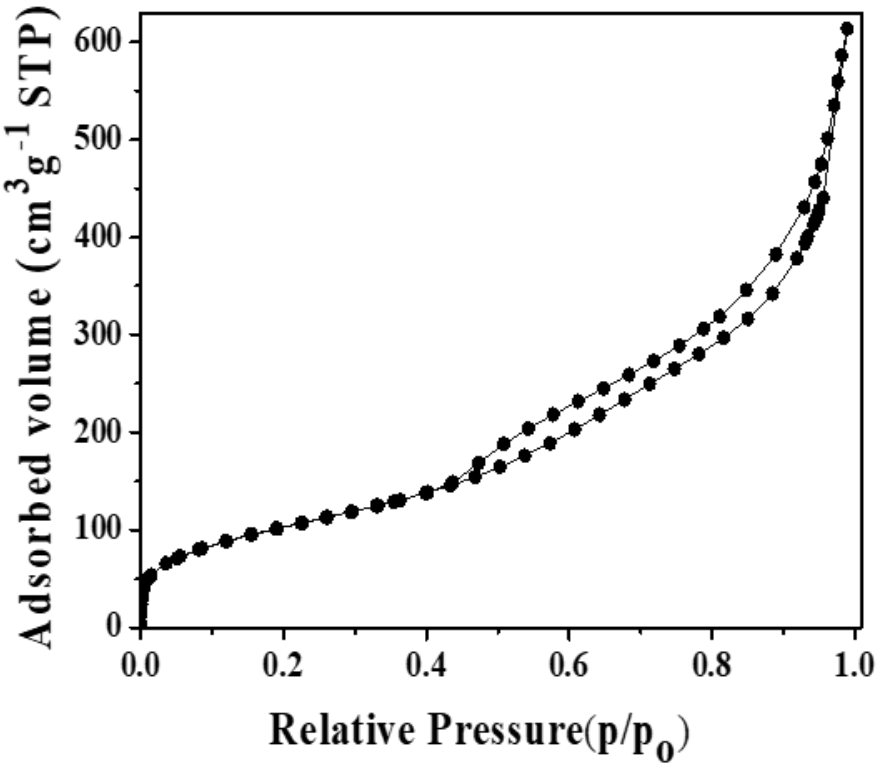
Particle size distribution was tested on a Malvern Zetasizer Nano ZS90 equipment.

2.2.2 Results and discussion

As shown in Figure 2.6, the obtained HMS-Bubble sample had a hollow structure and smooth spherical surface. The hollow sphere was 200-400 nm in size. The shell thickness was 20-30 nm. There were a lot of mesopores in the shell. Some hollow spheres were composed of several smaller hollow spheres, which was only one cavity without barriers at the junction. This was due to the CO_2 bubble template was always dynamic and not stable during the wrapping processes. The phenomenon of bubble merging is also an evidence of bubble template.

Figure 2.7a showed that the nitrogen adsorption-desorption isotherms of the obtained mesoporous silica hollow spheres gave a type-IV isotherms with an adsorption step at relative pressure between 0.4 and 0.8 due to the capillary condensation of the filling nitrogen in the mesopores. The presence of a sharp increase of adsorption amounts of nitrogen at the higher relative pressure (>0.95) indicated the small size of the synthesized mesoporous silica, which was consistent with the results of TEM testing. The pore size distribution curve (Figure 2.7b) showed that the obtained mesoporous silica hollow spheres had a single peak centered at 4.0 nm. The BET specific surface area was 361 $m^2 \cdot g^{-1}$, and the total pore volume was 0.95 $cm^3 \cdot g^{-1}$. The presence of a hysteresis loop at

relative pressures of 0.45-0.95 indicated a hollow structure with mesoporous walls.



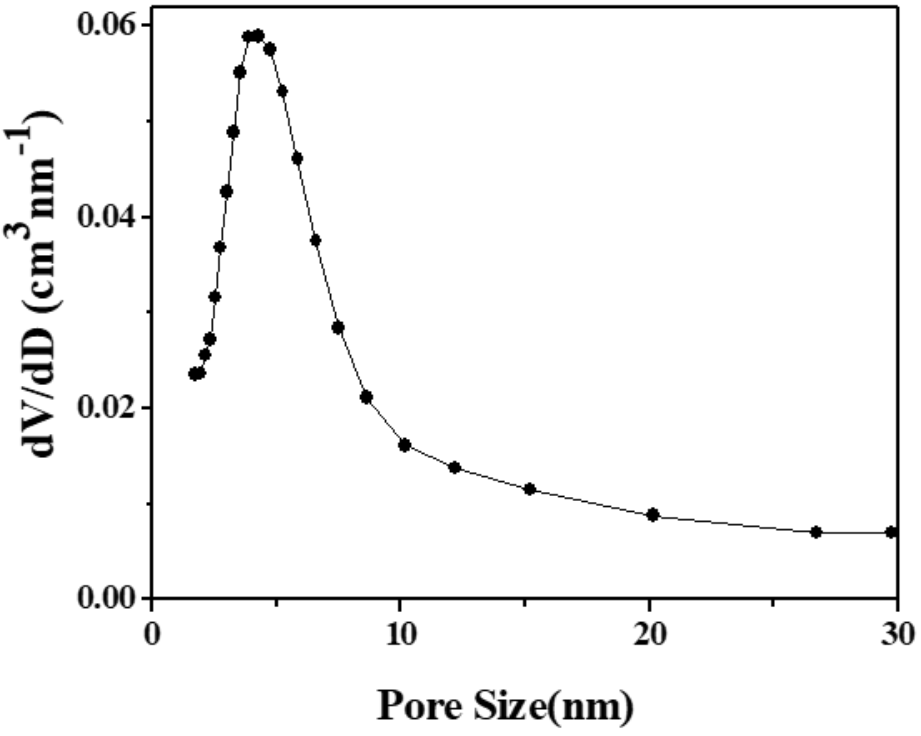


Figure 2.7 (Up) Nitrogen adsorption-desorption isotherms and (Down) the pore size distribution curves of Hollow structured mesoporous silicon dioxide templated by CO_2 bubbles

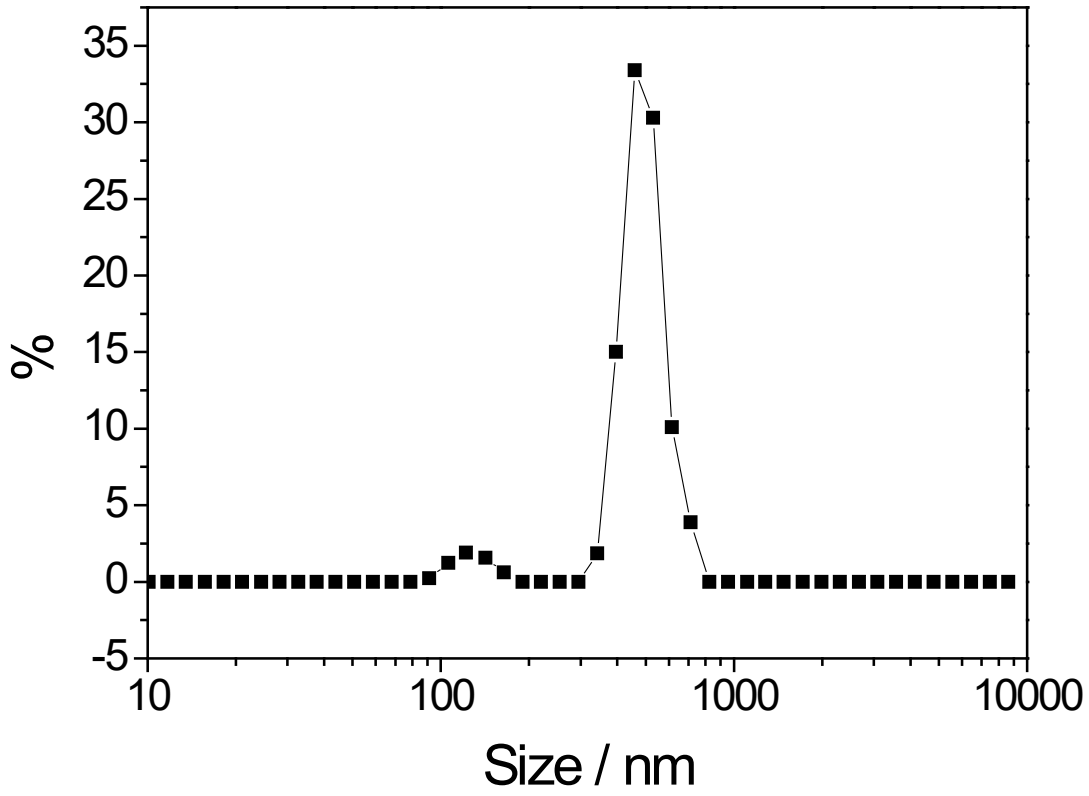


Figure 2.8. The particle size distribution of synthesized hollow spheres dispersed in DI water.

The particle size distribution of synthesized hollow spheres was shown in Figure 2.8. The peak was about 500 nm, the distribution of particle size was in the range of 300-600 nm. This observation was consistent with the results of TEM images.

We have done the experiments to test their dispersed properties. The synthesized hollow spheres could be well-dispersed in DI water and ethanol (as following Figure 2.9). There was no any deposition formed for several hours.

Figure 2.9. The photos of synthesized hollow spheres dispersed in (1) DI water and (2) ethanol.

Conclusion

In this work, mesoporous silicon dioxide with solid and hollow structure was synthesized based on the self-assemble between surfactants, co-structure directing agents and inorganic silica precursors. The hollow structure was templated by the ultrasonic cavitation (Sample of MS-Hollow) and high-pressure carbon dioxide bubbles (Sample of HMS-Bubbles). Especially, Hollow structured HMS-Bubbles with 200-400 nm in size and 20-30 nm in shell thickness was first prepared.

The prepared robust hollow mesoporous silica could well-dispersed in aqueous or organic systems, showing the possible applications in adsorption, and drug delivery in aqueous system and in catalysis in organic solvents.

Section 3 Study of drug release of metoprolol tartrate

3.1 Metoprolol tartrate (MPT) drug release experiments

Despite significant progress in the characterization and development of mesoporous drug delivery systems to improve drug dissolution, more research is needed such as Dissolution test to establish the kinetic profile of drug release from mesoporous silica materials, the rate of release of the active ingredient (API) from the carrier, and the possibility of re-adsorption API on the surface of mesoporous silica [46]. The interaction of dispersion medium with the drug-silica matrix and the release rate of the API are dependent on factors such as porosity, the initial drug load, the drug's solubility in the release medium and the diffusion coefficient of the drug molecules in the medium and importance of utilizing relevant and effective in vitro dissolution methods with discriminating dissolution media

Studies of the release profiles of the active substance MPT were performed under the following conditions:

- Device with stirrer;
- volume of dissolution medium: 100 mL;
- dissolution temperature: 25.0 ± 0.5ºC;
- dissolution medium: buffer solution with a pH of 7.4 (phosphate buffer);
- speed of rotation of the stirrer: 100 rpm;
- sampling time: 0.5 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h,3.5 h, 4 h, 5 h, 6 h, 8 h, 10 h, 18 h.

Drug release experiments: First, 10.0 mg of MPT-loaded mesoporous silica as powder was added in 100 mL of phosphate buffer with a stirring speed at 100 rpm at certain temperature. Extraction solution of 2.0 mL was taken out at different time to monitor the concentration of metoprolol in the solution by a UV-Vis spectrophotometer (Persee TU-190, Beijing, China) by use of quartz cuvettes with an optical path length of 1 cm at a maximum wavelength of 274 nm. After every extraction 2.0 mL fresh phosphate buffer was replenished. The

reference solution was prepared by dissolving a standard sample of metoprolol tartrate in a phosphate buffer as dissolution medium.

3.2 Methods to quantify the released drug from mesoporous silica

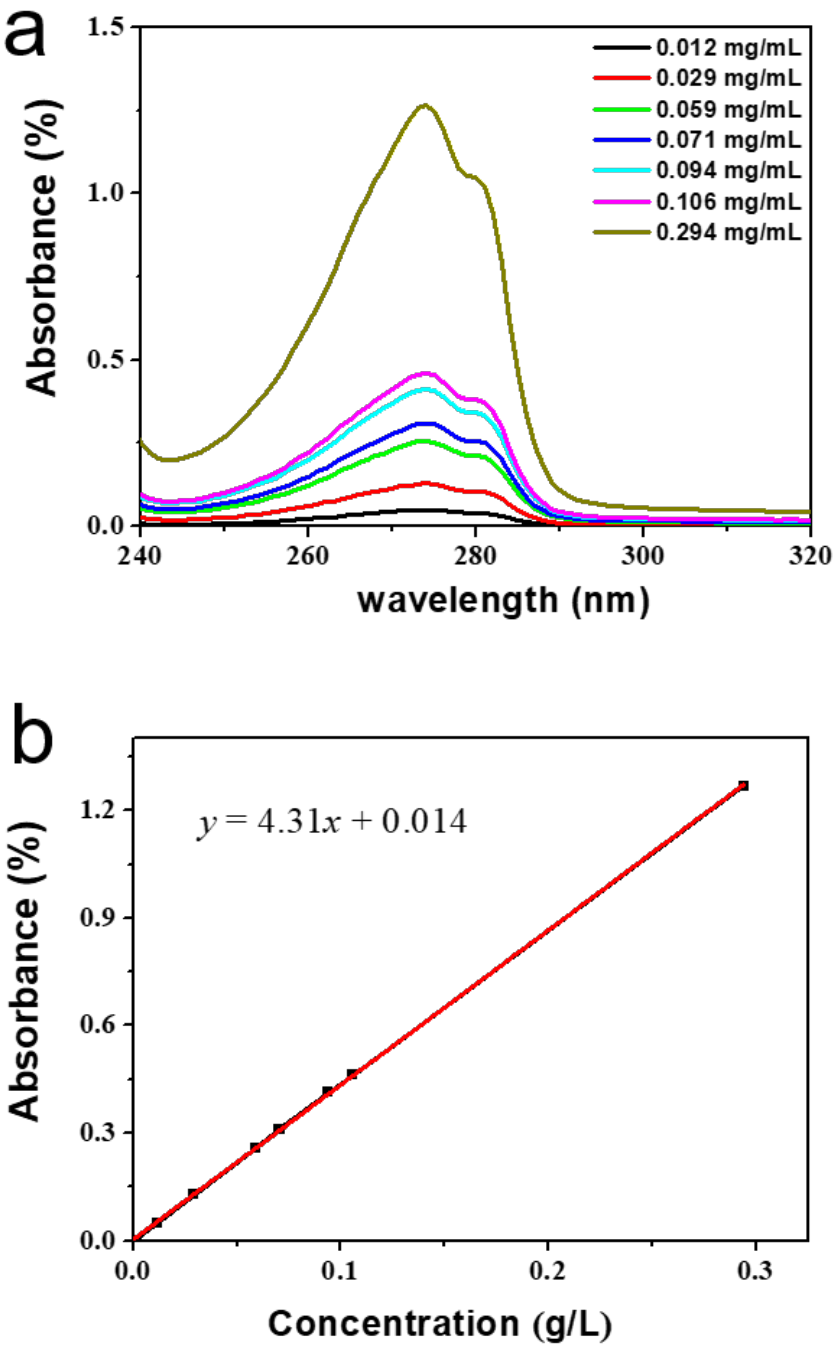


Figure 3.1 (a) UV-visible absorption spectra of different concentration of MPT solution and (b) calibration curve of the absorption peak to quantify the concentration of drug MPT in the solution.

Calibration curve of metoprolol was determined by taking absorbance vs. metoprolol concentration between 10 and 300 ppm. Figure 3.1a showed calibration curve of the strongest absorption peak at 274 nm to quantify the concentration of drug molecules in the solution. There was a good linear relationship between concentration of MPT and absorbance at 274 nm, as indicated by Figure 3.1b. The detected limitation was lower than 0.012 mg/mL, implying the MPT drug release could be well detected by UV-visible spectroscopy.

The effective concentration in solution was calculated on the basis of the following equation (1) [5, 14]:

$$C_{eff} = C_{app} + \frac{v}{V}\sum_{1}^{t-1} C_{app} \quad (1), \text{ where}$$

C_{eff} - is the corrected concentration at time, t;

C_{app} - is the apparent concentration at time, t;

v - is the volume of sample taken;

V - is the total volume of the dissolution medium.

$C_{eff} = C_{app} + 0.02 \times \sum_{1}^{n} C_{app}$

The test was performed thrice. We have obtained the same drug concentration value of that calculated on the basis of the formula for a drug release test, studied and concludes that the release of metoprolol is controlled.

3.3 MPT drug release behavior

3.3.1 Mesoporous silicon dioxide with solid and hollow structure

Figure 3.2 displayed the MPT drug release behavior of sample MS-Solid and sample MS-Hollow. The drug released amounts of two samples were similar to each other within 80 minutes. After 80 minutes, the MPT released amounts of MS-Hollow still increased. However, MS-Hollow showed lower increase of drug amounts. This was due to the loading amounts of MS-Hollow (52.0 wt. %) higher than that (44.0 wt. %) of MS-Solid. Both of MS-Solid and MS-Hollow samples

showed a 50% release amounts within 20 minutes and >80% within 80 minutes, indicating that the synthesized mesoporous hollow sphere could achieve controlled drug release.

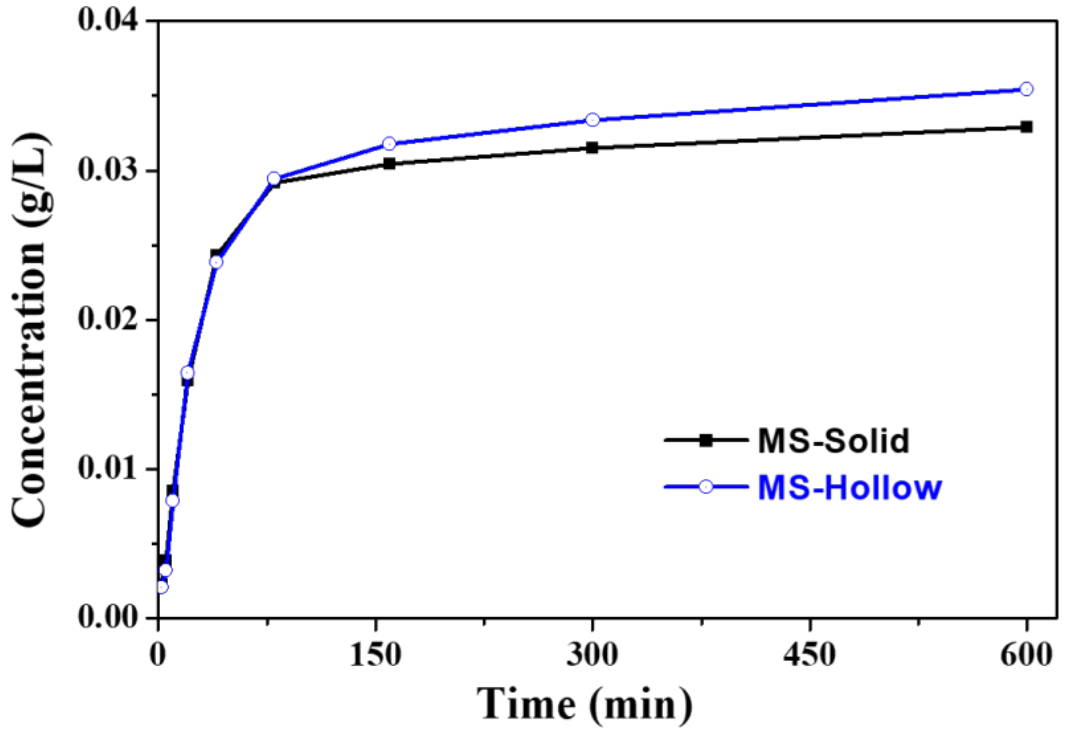


Figure 3.2 Metoprolol tartrate (MPT) drug release of sample MS-solid and sample MS-Hollow.

3.3.2 Hollow structured mesoporous silicon dioxide templated by CO_2 bubbles

Figure 3.3 showed the MPT drug release curve. The MPT loading amounts was 13.0 wt. %. The drug release amount could achieve a 50% release amounts within 1 hour and 90% within 5 hours, indicating that the synthesized mesoporous hollow sphere could achieve controlled drug release, which showed potential in

stimulus-response release and targeted therapy.

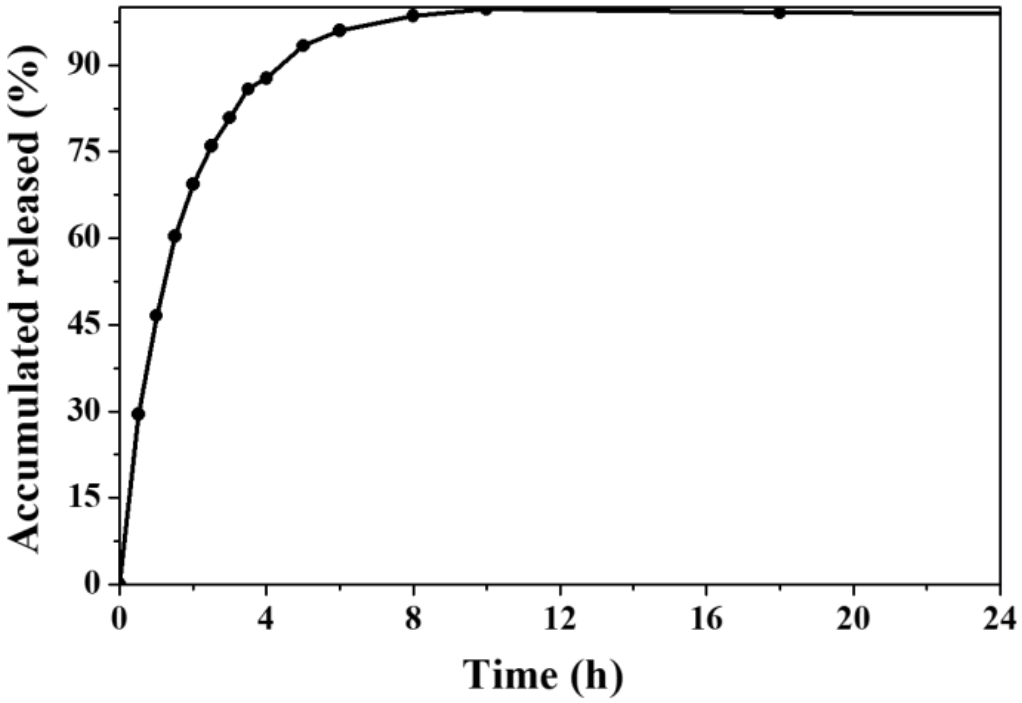


Figure 3.3 Metoprolol tartrate (MPT) drug release of hollow structured mesoporous silica.

Conclusion

In this work we have studied hollow mesoporous silica as possible carrier to the controlled release of metoprolol tartrate (MPT), a drug used in the treatment of several diseases of the cardiovascular system. MPT drug is a kind of bulky in molecular volume therefore porous structure and relatively large pore size was proper carrier for MPT to achieve desirable controlled release behaviors. Amino-functionalized hollow mesoporous silica with 200-400 nm in size and 20-30 nm in shell thickness was showed excellent metoprolol tartrate drug-controlled release. It is obtained the same drug metoprolol concentration value of that calculated on the basis of the formula for a drug release test, and concludes that the release of metoprolol is controlled.

Conclusions and research prospect

A literature review was conducted and the problem studied that the last two decades have seen a growing interest among scientists and the pharmaceutical engineering in mesoporous silica nanoparticles (MSNs) as drug delivery systems (DDS).

In this work we have studied hollow mesoporous silica as possible carrier to the controlled release of metoprolol tartrate (MPT), a drug used in the treatment of several diseases of the cardiovascular system. MPT drug is a kind of bulky in molecular volume therefore porous structure and relatively large pore size was proper carrier for MPT to achieve desirable controlled release behaviors.

Hollow mesoporous silica with large cavies and thin shell was showed high drug loading amounts and excellent metoprolol tartrate drug-controlled release as compared with solid mesoporous silica nanoparticles.

It is obtained the same drug metoprolol concentration value of that calculated on the basis of the formula for a drug release test, and concludes that the release of metoprolol is controlled.

The developed methods to prepare hollow structured mesoporous silica nanospheres by using gaseous/vapor bubbles was simple and low-cost. The surface functionalization of amine was directly achieved by one-pot synthesis. There is no requirement of the post treatment to modify amine groups. The generation of mesoporous channels was used a solvent extraction method under room temperature. Different from the traditional method by calcination to form toxic nitrogen oxides gas, there is no the calcination processes in our synthesis, which was environmentally benign.

The developed mesoporous silica hollow spheres were robust, nanometer size, high specific surface area and thin shell. There advantages endow this novel material a wide application in catalysis, adsorption, and drug delivery system. Especially, hollow structured mesoporous silica have a large cavity to load drugs and a mesoporous shell for drug controlled release, which is one of the best candidates for construction of a variety of controlled release system of

various of drugs. Furthermore, stimulus-response system based on our novel hollow mesoporous silica could be achieve by modification functional molecular “switch” for target drug release.

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Annex 1

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MDPI

Communication

Robust amino-functionalized mesoporous silica hollow spheres templated by CO_2 bubbles

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Abstract: Hollow structured mesoporous silica has wide applications in catalysis and drug delivery due to its high surface area, large hollow space and short diffusion mesochannels. However, the synthesis of hollow structure was usually required sacrificial templates, leading to the increase of production cost and environmental problems. Here, for the first time, amino-functionalized mesoporous silica hollow spheres were synthesized by using CO_2 gaseous bubbles as templates. The assembly of anionic surfactants, co-structure directing agents and inorganic silica precursors around CO_2 bubbles formed the mesoporous silica shells. The hollow silica spheres with 200-400 nm in size and 20-30 nm spherical shell in thickness had abundant amine groups on the surface of the mesopores, which showed excellent applications in the CO_2 capture, Knoevenagel condensation reaction, as well as controlled release of drugs.

Keywords: hollow; mesoporous silica; amino-functionalized; bubble template; CO_2 capture; drug controlled release

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1. Introduction

Since the discovery of mesoporous materials in the 1990s [1], they have been known for their high specific surface areas, large pore volumes, and continuously adjustable mesoporous channels, which makes them widely used and in the fields of catalysis, separation and biomedicine [2-6]. Hollow structured mesoporous silica shows better application prospects in catalysis and drug delivery, attributed to its large hollow space, low density, and short diffusion mesoporous channels. Various methods for preparing mesoporous materials with hollow structures have been developed. And many nanomaterials were employed as templates to construct hollow structure, including vesicles [7-9], bubbles [6,10,11], and microemulsions [12-14], metals, metal oxides, semiconductor materials, and polymer microspheres [15,16], and so on. However, most of the templates used were sacrificial and required to remove for making a hollow cavity, which led to many problems such as complicated preparation processes, high preparation cost, and environmental pollution. Among these methods, gaseous bubbles as templates were attractive due to low-cost and environmentally benign. However, the direct wrapping of the gaseous bubbles was not easy due to the bubbles were always dynamic.

Herein, hollow structured amino-functionalized mesoporous silica was prepared by using CO_2 bubbles as templates. The self-assemble of anionic surfactant, silane coupling agent, and inorganic precursor to form mesoporous silica shell to wrap the gaseous

bubbles generated by high-pressure CO_2. Here, CO_2 bubbles were employed as templates for hollow structure and anionic surfactants as templates for mesopores, respectively. The synthesized hollow mesoporous silica was robust. The hollow templates of CO_2 bubbles did not require further treatment to remove, which was economical and environmentally friendly. The obtained hollow mesoporous silica showed good CO_2 capture amounts and high performance in Knoevenagel reaction due to the presence of abundant amine groups. In addition, mesoporous silica hollow spheres displayed excellent performance in drug-controlled release.

2. Results and Discussion

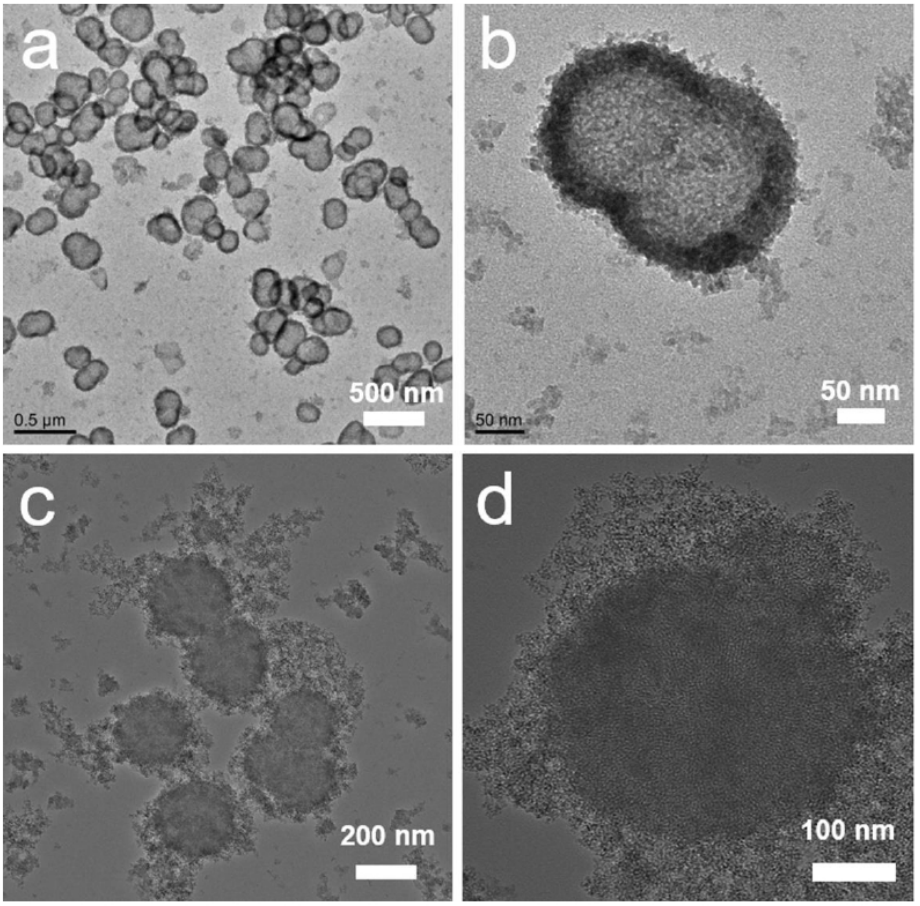

Figure 1. TEM images of the amino-functionalized mesoporous silica synthesized under different CO_2 pressure. (a, b) 1.0 MPa, (c, d) 0.2 MPa.

As shown in Figure 1a and 1b, when the pressure of CO_2 gas was 1.0 MPa during synthesis, the obtained sample had a hollow structure and smooth spherical surface. The hollow sphere was 200-400 nm in size. The shell thickness was 20-30 nm. There were a lot of mesopores in the shell. Some hollow spheres were composed of several smaller hollow spheres, which was only one cavity without barriers at the junction. This was due to the CO_2 bubble template was always dynamic and not stable during the wrapping processes. The phenomenon of bubble merging is also an evidence of bubble template. If the CO_2 pressure was lower, disordered amorphous silica nanoparticles and/or solid mesoporous silica particles would formed (Figure 1c, 1d). This suggested that the wrapping of a dynamic gas bubble by mesoporous silica should be precisely controlled.

Figure 2a showed that the nitrogen adsorption-desorption isotherms of the obtained amino-functionalized mesoporous silica hollow spheres gave a type-IV isotherms with an adsorption step at relative pressure between 0.4 and 0.8 due to the capillary condensation of the filling nitrogen in the mesopores. The presence of a sharp increase of adsorption amounts of nitrogen at the higher relative pressure (>0.95) indicated the small size of the synthesized mesoporous silica, which was consistent with the results of TEM testing. The pore size distribution curve (Inset of Figure 1a) showed that the obtained amino-functionalized mesoporous silica hollow spheres had a single peak centered at 4.0 nm. The BET specific surface area was 361 $m^2 \cdot g^{-1}$, and the total pore volume was 0.95 $cm^3 \cdot g^{-1}$. The presence of a hysteresis loop at relative pressures of 0.45-0.95 indicated a hollow structure with mesoporous walls. In addition, the content of amine moiety was 1.13 $mmol \cdot g^{-1}$.

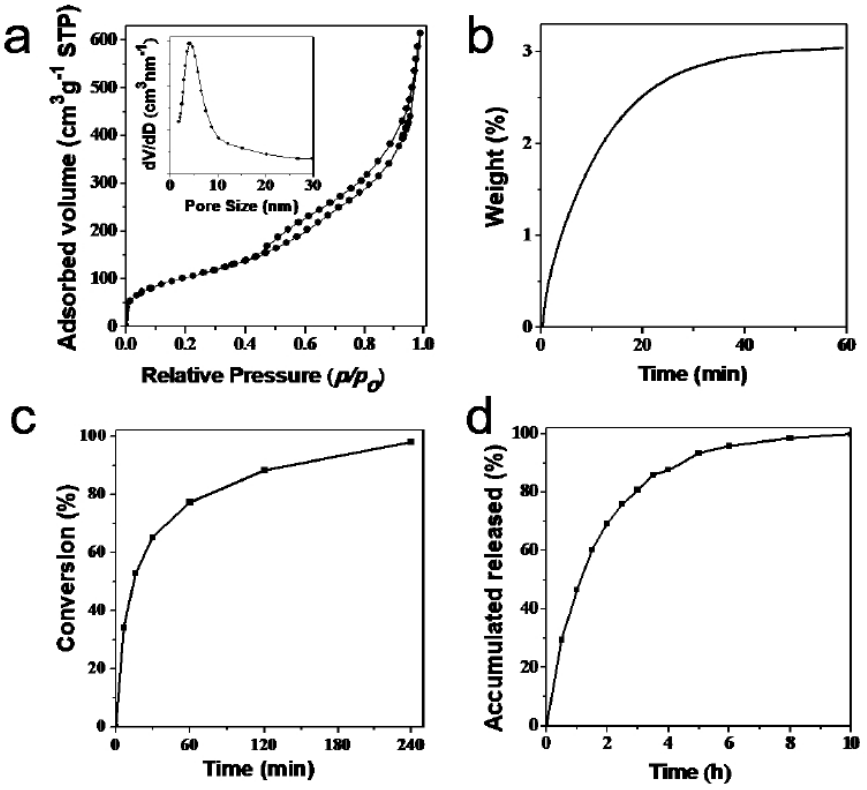

Figure 2. (a) Nitrogen adsorption-desorption isotherms and (inset) the pore size distribution curves, (b) CO_2 adsorption curve, (c) Knoevenagel reaction curve and (d) metoprolol tartrate (MPT) drug release of amino-functionalized mesoporous silica hollow spheres.

Based on the hollow structure and amino-functionalized characteristics of the synthesized materials, it was applied to CO_2 capture, Knoevenagel reaction and MPT drug controlled-release testing. Figure 2b showed that the CO_2 adsorption curve had an upward trend throughout the process, and gradually tended to equilibrium at 60 minutes. The maximal adsorption amount could reach 0.69 $mmol \cdot g^{-1}$, suggesting that each amine could capture about 0.6 CO_2 molecule. It implied that there was a certain physical adsorption in addition to chemical adsorption based on the quantitative reaction that one carbon dioxide molecule required two amines.

Amino-functionalized mesoporous has been proved to have catalytic activity in Knoevenagel reaction. Amine moieties were present on the inner surface of the mesochannels. So, the more the amine exposed, the better the catalytic activity was. As shown in Figure 2c, the conversion gradually increased with time, reaching about 80% conversion

within 1 h and about 100% at 4 hours, indicating a good catalyst for Knoevenagel reaction. This is due to abundant exposed amine groups and the short mesopores in the thin shell, which was beneficial to the reactant transport to contact the catalytic active sites of amines.

Figure 2d showed the MPB drug release curve. The drug release amount could achieve a 50% release amounts within 1 hour and 90% within 5 hours, indicating that the synthesized mesoporous hollow sphere could achieve controlled drug release, which showed potential in stimulus-response release and targeted therapy.

3. Materials and Methods

3.1. Synthesis of amino-functionalized mesoporous silica hollow spheres

All chemicals were all purchased from Macklin and used as received. In a typical synthesis, 1.0 mmol of N-Lauroylsarcosine sodium (as anionic surfactant) was completely dissolved in 30 mL of deionized water at room temperature. Next, a mixture of 1.5 ml ethyl orthosilicate (as inorganic silica source) and 0.12 mL 3-aminopropyltriethoxysilane (as co-structure directing agent) was added under vigorous stirring. The total solution was transferred to a Tetrafluoroethylene lined stainless steel autoclave. Next, CO_2 gas was introduced to a pressure of 1.0 MPa. The mixture was stirred at room temperature for 24 hours, and then placed in an oven at 80 °C for another 4 h. The resulting product was extracted with 10 wt.% hydrochloric acid in acetonitrile at room temperature for 24 h to remove surfactant so as to expose the amino groups on the surface of the mesopores. The final product was washed/exchanged with 1.0 wt.% ammonia solution, filtered, washed with distilled water, and dried overnight at 80 °C.

3.2 Carbon dioxide capture experiment

The CO_2 performance test is carried out in a thermogravimetric analyzer. In the pre-treatment stage, 5.0 mg of sample was put into a small crucible and heated from room temperature to 150 °C at a heating rate of 10 ℃/min in a nitrogen atmosphere for 30 min. When the sample naturally cooled to 30 °C, pure CO_2 was introduced at 100 $mL \cdot min^{-1}$ for 60 min. The change of mass was recorded by the balance provided with the instrument.

3.3 Knoevenagel reaction

Typical, 50 mg of the catalyst was placed in a reaction vessel and then 1.4 mL of toluene, 0.02 g of naphthalene (internal standard), 133 μL of benzaldehyde, and 136 μL of ethyl cyanoacetate were added. The mixture was heated at 30 ° C in an oil bath under stirring. Small amounts of reaction mixture were taken out at different time and were analyzed by gas chromatography (Shimadzu GC-2014 equipped with a 30 m TC-1 capillary column and a flame ionization detector).

3.4 Metoprolol tartrate (MPT) drug loading and release experiments

Typically, 5 mg of MPT was fully dissolved in 2 mL of ethanol. Next, 50 mg hollow silica spheres were added and dispersed under sonication. The mixture was placed in a 50 °C oven to evaporate ethanol for 24 h. Subsequently, 2 mL of ethanol was used to wash the unabsorbed drug on the surface of the hollow sphere. The resulting mixture was centrifuged, and dried at 50 °C.

Next, drug-loaded mesoporous silica hollow spheres were used for drug release experiments. Typical, 10.0 mg of sample was added in 100 mL of phosphate buffer with a stirring speed of 100 rpm at room temperature and 2 mL of extraction solution was taken out each time. The absorbance of the sample was measured with a UV-Vis spectrophotometer (Persee TU-1901) at a wavelength of 274 nm.

3.5 Characterization

TEM image of the product is characterized by a JEOL JEM-2100 TEM microscope working at 200 kV. Nitrogen adsorption isotherms were conducted by a TrisStar II 3020 sorption analyzer at 77 K. Specific surface area and pore volume were analyzed by BET (Brunauer-Emmett-Teller) method and the pore-size distribution was analyzed from the adsorption data using BJH (Barett-Joyner-Halenda). CO_2 adsorption was tested by an SDT

Q600 simultaneous thermal analyzer. The flow rate of CO_2 is set to 100 mL·min^{-1}. The nitrogen elemental content was evaluated on a Vario EL Cube elemental analyzer.

4. Conclusions

Amino-functionalized hollow mesoporous silica with 200-400 nm in size and 20-30 nm in shell thickness was first prepared by using carbon dioxide bubbles as a template. The prepared hollow spheres possessed 1.13 mmol·g^{-1} amine moiety, which could capture 0.69 mmol·g^{-1} CO_2 molecules within 60 minutes. In addition, the robust hollow mesoporous silica could well-dispersed in aqueous or organic systems, showing good catalytic activity in Knoevenagel reaction and excellent MPB drug-controlled release.

Author Contributions: Conceptualization, H.W., X.L. and W.H.; methodology, H.W. and X.L.; validation, H.W. and X.L.; data curation, H.W. and X.L.; writing—original draft preparation, H.W., X.L. and J.W.; writing—review and editing, W.H. and O.S.; supervision, W.H. and O.S.; project administration, W.H. and J.W.; funding acquisition, J.W. and W.H. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the amino-functionalized mesoporous silica hollow spheres are available from the authors.

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Annex 2

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PORE SIZE EFFECT AND MORPHOLOGY OF MESOPOROUS SILICA ON METOPROLOL TARTRATE RELEASE

Purpose. *Study pore size effect and morphology of mesoporous silica on metoprolol tartrate release.*

Methodology. *A sample of hollow mesoporous silicon dioxide with amino-functional groups containing 12.7 wt. % metoprolol tartrate has been investigated as potential carriers for the controlled release of active substance. Studies of the release profiles of metoprolol tartrate were performed under the following conditions: dissolution medium was buffer solution with a pH of 7.4 (phosphate buffer); sampling time: from 0.5 h before 18 h. The metoprolol concentration in the liquid phase was evaluated by a UV-Vis spectrophotometer (Persee TU-190, Beijing, China) by use of quartz cuvettes with an optical path length of 1 cm at a maximum wavelength of 274 nm.*

Findings. *In this work we have studied mesoporous silica as possible carrier to controlled release of metoprolol tartrate, a drug used in the treatment of some diseases of the cardiovascular system. The material for research was a sample of hollow mesoporous silicon dioxide with amino-functional groups 200–400 nm in size and 20–30 nm in shell thickness. A calibrated curve to determine the amount of metoprolol was constructed by determining the absorption dependence of the concentration of metoprolol in the range from 10 to 300 ppm. The same drug concentration was obtained as calculated from the drug release test formula, which concludes that the release of metoprolol is controlled.*

Originality. *The controlled release of a sample of hollow spheres of mesoporous silicon dioxide filled with metoprolol tartrate was studied, which was synthesized by the School of Chemistry and Chemical Engineering, Qilu University of Technology, using a new technology, where hollow spheres of mesoporous silicon dioxide with amino groups were synthesized using CO_2 gas bubbles as templates.*

Practical value. *The metoprolol release amount could achieve a 50% release amounts within 1 hour and 90% within 5 hours, indicating that the synthesized mesoporous hollow sphere could achieve controlled drug release, and shows the potential of carriers with stimulus response and targeted therapy.*

Keywords: *hollow mesoporous silica; metoprolol tartrate; drug controlled release; dissolution.*

Introduction. Hypertension is a leading cause of cardiovascular disease, stroke, and death. It affects a substantial proportion of the population worldwide, and remains underdiagnosed and undertreated [1]. The attack of hypertension usually begins in the morning when the patient wakes up from a situation of relative hypotension. Therefore, the development of controlled drug delivery is of great importance in chronopharmacology, for example, to minimize the risk of morning hypertension attack [2].

Beta-adrenoblocker metoprolol is wide used in arterial hypertension and ischemic heart disease. Metoprolol has salt such as tartrate (MPT) which is used for production of immediate release (IR) and may need to be taken multiple times per day [3].

In the last years many efforts have been devoted to the development of new formulations that can control both rate and period of drug delivery. Mesoporous silica carriers have a number of attractive features for enhancing drug dissolution, such as high surface area, large pore volume and ordered pore networks and they can also provide an adjustable drug release profile [4]. Silica matrices show high biocompatibility and these materials are biodegradable to monosilicic acid (in the long run, in the intestine) and resistance to microbial attack. Moreover, physico-chemical and textural properties of silica can be modulated ad hoc by the choice of a tailored synthetic approach [5, 6]. Mesoporous silica nanoparticles (MSNs) have been widely studied as drug carriers to get controlled

release behaviors, however, their application in sustained release of MPT is limited. The possible reason is due to MPT molecule being bulky, while normal type MSNs like MCM-41 and SBA-15 have pore sizes of only 3–6 nm [7]. Studies for the controlled release of MPT are described, which are aimed at both new approaches to synthesis and characterization of silica carriers: a one-time sol-gel approach and wetness impregnation method, where MPT is adsorbed on a silica support by wet impregnation after synthesis [5]. MSNs with MTP were synthesized through the reaction of tetraethyl orthosilicate (TEOS) in the water medium at 353 K, with introducing some cetyltrimethylammonium bromide (CTAB) as porogens [8]. A novel technique ultra-fine particle process system (UPPS) was employed to develop sustained-release MPT microspheres for oral administration [9]. Scientific interest is hollow structured amino-functionalized mesoporous silica, which was usually prepared by hard templates or selective etching of solid spherical silica in a basic solution [10]. The obtained hollow mesoporous silica showed good CO_2 capture amounts and high performance in Knoevenagel reaction due to the presence of abundant amine groups. In addition, mesoporous silica hollow spheres displayed excellent performance in drug-controlled release characteristics for a number of drugs and are promising for molecular modeling of the bulky MPT molecule delivery system [7, 11].

Despite significant progress in the characterization and development of mesoporous drug delivery systems to improve drug dissolution, more research is needed such as Dissolution test to establish the kinetic profile of drug release from mesoporous silica materials, the rate of release of the active ingredient (API) from the carrier, and the possibility of re-adsorption API on the surface of mesoporous silica [12]. The interaction of dispersion medium with the drug-silica matrix and the release rate of the API are dependent on factors such as porosity, the initial drug load, the drug's solubility in the release medium and the diffusion coefficient of the drug molecules in the medium and importance of utilizing relevant and effective in vitro dissolution methods with discriminating dissolution media [13].

Statement of the problem. Aim of our work has been the investigation pore size effect and morphology of mesoporous silica on metoprolol tartrate release. The solubility of metoprolol (tartrate form) in water is >1000 (mg/ml) at 25°C (freely soluble in water). Metoprolol can quickly disperse into phosphate buffer solution system once it diffuse from nanopores of mesoporous silica. Samples of MPT drug-loaded mesoporous silica hollow spheres were previously synthesized by the School of Chemistry and Chemical Engineering, Qilu University of Technology, using the novel technology, where amino-functionalized mesoporous silica hollow spheres were synthesized by using CO_2 gaseous bubbles as templates.

Research results. The material for research was a sample of hollow mesoporous silicon dioxide with amino-functional groups 200–400 nm in size and 20–30 nm in shell thickness, containing 12.7 wt. % MPT. In addition, the robust hollow mesoporous silica could well-dispersed in aqueous systems, showing excellent drug-controlled release. The morphology of the amino-functionalized mesoporous silica with loaded MPT used in the present study is shown in Fig. 1.

Studies of the release profiles of the active substance MPT were performed under the following conditions:

- device with stirrer;
- volume of dissolution medium: 100 mL;
- dissolution temperature: 25.0 ± 0.5°C;
- dissolution medium: buffer solution with a pH of 7.4 (phosphate buffer);
- speed of rotation of the stirrer: 100 rpm;
- sampling time: 0.5 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h,3.5 h, 4 h, 5 h, 6 h, 8 h, 10 h, 18 h.

Drug release experiments: First, 10.0 mg of MPT-loaded mesoporous silica as powder was added in 100 mL of phosphate buffer with a stirring speed at 100 rpm at certain temperature. Extraction solution of 2.0 mL was taken out at different time to monitor the concentration of metoprolol in the solution by a UV-Vis spectrophotometer (Persee TU-190, Beijing, China) by use

of quartz cuvettes with an optical path length of 1 cm at a maximum wavelength of 274 nm. After every extraction 2.0 mL fresh phosphate buffer was replenished. The reference solution was prepared by dissolving a standard sample of metoprolol tartrate in a phosphate buffer as dissolution medium.

Calibration curve of metoprolol was determined by taking absorbance vs. metoprolol concentration between 10 and 300 ppm. Figure 2 showed calibration curve of the strongest absorption peak at 274 nm to quantify the concentration of drug molecules in the solution.

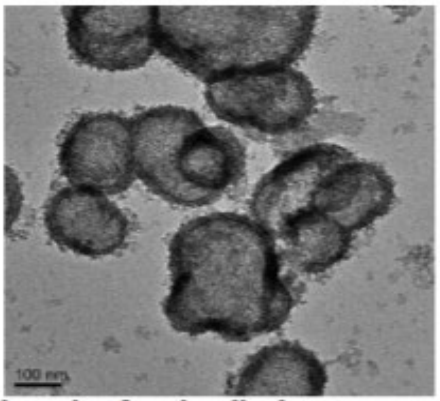

Fig. 1. **TEM images of the amino-functionalized mesoporous silica with loaded MPT**

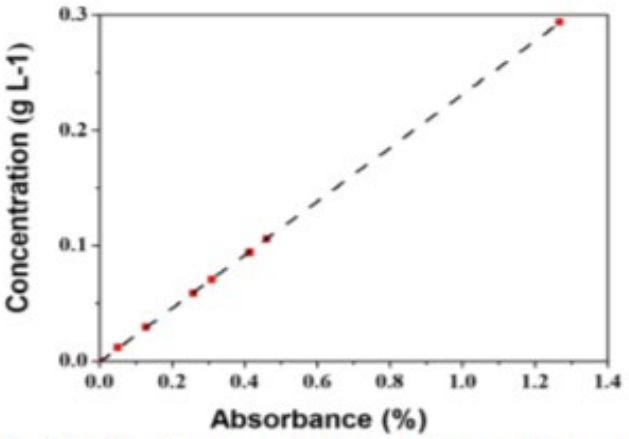

Fig. 2. **Calibration curve of the absorption peak to quantify the concentration of drug MPT in the solution**

The effective concentration in solution was calculated on the basis of the following equation (1) [5, 14]:

$$C_{eff} = C_{app} + \frac{v}{V}\sum_{1}^{t-1} C_{app} \qquad (1)$$

where C_{eff} – is the corrected concentration at time, t;
C_{app} – is the apparent concentration at time, t;

v – is the volume of sample taken;
V – is the total volume of the dissolution medium.

In relation to our conditions, the formula has the form: $C_{eff} = C_{app} + 0.02 \times \sum_1^n C_{app}$.

The test was performed thrice. We have obtained the same drug concentration value of that calculated on the basis of the formula for a drug release test, studied and concludes that the release of metoprolol is controlled.

Figure 3 showed the MPB drug release curve.

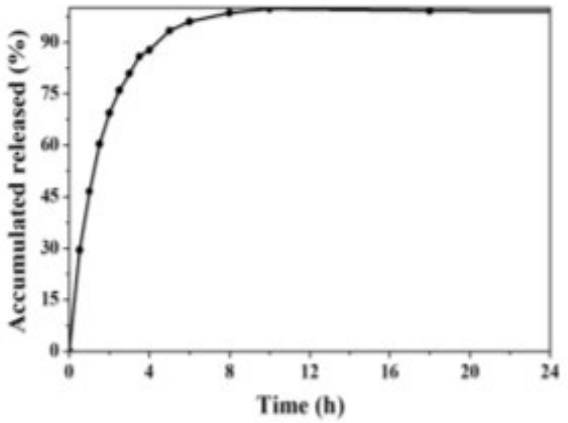

Fig. 3. **Metoprolol tartrate (%) release from amino-functionalized mesoporous silica hollow spheres (n = 3)**

The drug release amount could achieve a 50% release amounts within 1 hour and 90% within 5 hours, indicating that the synthesized mesoporous hollow sphere could achieve controlled drug release, which showed potential in carriers with stimulus response and targeted therapy.

Conclusions. In this work we have studied hollow mesoporous silica as possible carrier to the controlled release of metoprolol tartrate (MPT), a drug used in the treatment of several diseases of the cardiovascular system. MPT drug is a kind of bulky in molecular volume therefore porous structure and relatively large pore size was proper carrier for MPT to achieve desirable controlled release behaviors. Amino-functionalized hollow mesoporous silica with 200–400 nm in size and 20–30 nm in shell thickness was showed excellent metoprolol tartrate drug-controlled release. It is obtained the same drug metoprolol concentration value of that calculated on the basis of the formula for a drug release test, and concludes that the release of metoprolol is controlled.

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ВПЛИВ РОЗМІРУ ПОР ТА МОРФОЛОГІЇ МЕЗОПОРИСТОГО КРЕМНІЮ НА ВИВІЛЬНЕННЯ МЕТОПРОЛОЛУ ТАРТРАТУ

Мета. *Вивчити вплив розміру пор та морфології мезопористого кремнезему на вивільнення метопрололу тартрату.*

Методика. *Зразок порожнього мезопористого діоксиду кремнію з амінофункціональними групами, що містить 12,7 мас. % метопрололу тартрату досліджено як потенційний носій для*

контрольованого вивільнення активної речовини. Дослідження профілів вивільнення тартрату метопрололу проводили за таких умов: середовище розчинення - буферний розчин з pH 7,4 (фосфатний буфер); час відбору: від 0,5 год до 18 год. Концентрацію метопрололу в рідкій фазі визначали на спектрофотометрі UV-Vis (Persee TU-190, Пекін, Китай) з використанням кварцових кювет з товщиною шару 1 см при максимумі довжини хвилі 274 нм.

Результати. *У цій роботі ми вивчили мезопористий діоксид кремнію як можливий носій для контрольованого вивільнення метопрололу тартрату, препарату, який використовується при лікуванні деяких захворювань серцево-судинної системи. Матеріалом для дослідження був зразок порожнього мезопористого діоксиду кремнію з розміром аміно-функціональних груп 200–400 нм і товщиною оболонки 20–30 нм. Калібровану криву для визначення кількості метопрололу будували шляхом визначення залежності абсорбції від концентрації метопрололу в діапазоні від 10 до 300 ppm. Отримано таке саме значення концентрації лікарського засобу, яке було розраховано на основі формули для тесту на вивільнення лікарського засобу, що дозволяє зробити висновок про те, що вивільнення метопрололу знаходиться є контрольованим.*

Наукова новизна. *Досліджено контрольоване вивільнення зразку порожніх сфер мезопористого діоксиду кремнію, заповненого метопрололу тартратом, що синтезований Школою хімії та хімічної інженерії Технологічного університету Цілу, з використанням найновітньої технології, де порожні сфери мезопористого діоксиду кремнію з аміногрупами були синтезовані з використанням бульбашок газу CO_2 у якості темплатів.*

Практична значимість. *Кількість вивільнення метопрололу може досягати 50% вивільнення протягом 1 години та 90% протягом 5 годин, що вказує на те, що синтезована порожниста мезопориста сфера може досягати контрольованого вивільнення лікарського засобу, і показує потенціал носіїв зі стимул-реакцією та таргетною терапією.*

Ключові слова: *порожній мезопористий діоксид кремнію; метопрололу тартрат; контрольоване вивільнення препарату; розчинення.*

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ВЛИЯНИЕ РАЗМЕРА ПОР И МОРФОЛОГИИ МЕЗОПОРИСТОГО КРЕМНИЯ НА ВЫСВОБОЖДЕНИЕ МЕТОПРОЛОЛА ТАРТРАТА

Цель. *Изучить влияние размера пор и морфологии мезопористого кремнезема на высвобождение метопролола тартрата.*

Методики. *Образец полого мезопористого диоксида кремния с амино-функциональными группами, содержащий 12,7 мас. % метопролола тартрата, был исследован как потенциальный носитель для контролируемого высвобождения активного вещества. Исследования профилей высвобождения тартрата метопролола проводили при следующих условиях: среда растворения – буферный раствор с pH 7,4 (фосфатный буфер); время отбора: на протяжении от 0,5 ч до 18 ч. Концентрацию метопролола в жидкой фазе опрееделяли на спектрофотометре UV-Vis (Persee TU-190, Пекин, Китай) с использованием кварцевых кювет с толщиной слоя 1 см при максимуме длине волны 274 нм.*

Результаты. *В этой работе мы изучили мезопористый диоксид кремния как возможный носитель для контролируемого высвобождения метопролола тартрата, препарата, используемого при лечении некоторых заболеваний сердечно-сосудистой системы. Материалом для исследования служил образец полого мезопористого диоксида кремния с размером амино-функциональных групп 200–400 нм и толщиной оболочки 20–30 нм. Калиброванную кривую для определения количества метопролола строили путем определения зависимости абсорбции от концентрации метопролола в диапазоне от 10 до 300 ppm. Получено такое же значение концентрации лекарственного средства,*

какое было рассчитано на основе формулы для теста на высвобождение лекарственного средства, что позволяет сделать вывод о том, что высвобождение метопролола контролируемое.

Научная новизна. *Исследовано контролируемое высвобождение образца полых сфер из мезопористого диоксида кремния, заполненного метопролола тартратом, который синтезирован Школой химии и химической инженерии Технологического университета Цилу с использованием новейшей технологии, где полые сферы из мезопористого диоксида кремния с аминогруппами были синтезированы с использованием пузырьков газа CO_2 в качестве темплатов.*

Практическая значимость. *Количество высвобождения метопролола может достигать 50% высвобождения в течение 1 часа и 90% в течение 5 часов, что указывает на то, что синтезированная полая мезопористая сфера может достигать контролируемого высвобождения лекарственного средства, и показывает потенциал носителей со стимул-реакцией и таргетной терапией.*

Ключевые слова: *полый мезопористый диоксид кремния; метопролола тартрат; контролируемое высвобождение препарата; растворение.*