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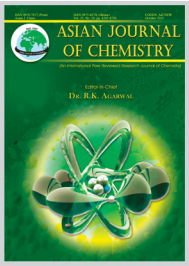

Preparation of Silica-Based Inorganic Capsule Shell *via* a Novel Emulsion-Sol-Gel Route

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NH_4OH was directly adopted as water phase and catalyst to prepare the silica shell, hexane and Span 80 were respectively adopted as oil phase and emulsifier to prepare water-in-oil emulsion. TEOS was adopted as the silica source, then the silica shell can be obtained through the sol-gel route at the interface of emulsion. Scanning electron microscope and X-ray diffraction were chosen to investigate the morphological and crystallized properties of samples. Results reveal that the morphology of capsule experienced the regular-irregular-regular-irregular transformation and hollow capsule can be obtained when the ratio of water phase to oil phase is 1:6. Furthermore, a schematic model of the experiment is proposed.

Key Words: Water-in-oil, Sol-gel, Inorganic medical capsule.

INTRODUCTION

Capsule is a kind of metallic, metalloid and organic enclave with a core-shell structure. According to its dimension, it can be divided into conventional capsule, microcapsule, nanocapsule and so on[1]. In contrast to the conventional capsule, the micro/nano capsule, with the dimension scale from several nanometers to tens of micrometers, instead of encapsulating drugs with a macroscopic protective shell, can encapsulate tiny drug molecules. In this way, not only the smell and the active constitute of drugs can be shield and protected from the outer environment owing to the micro pore of the shell, but also the activities and release of drugs can be altered obviously, *i.e.* both enhance the activity of the drugs and control the rate of its release by adjusting the dimension of the drugs and micro pore[2]. Furthermore, the micro/nano capsule for drugs is promising in drug targeting and controlled release owing to the versatility of shell materials and easily crossing blood brain barrier (BBB). Therefore, the investigation of micro/nano capsule for drugs is a hot issue both in the filed of material science and medical science.

Up to date, the shell material of micro/nano capsule has been widely investigated. Organic polymer is generally adopted in drug delivery system (DDS)[3,4], *i.e.* polymer is adopted as the carrier of active drug to realize the controlled drug release by gradually degradation of polymer. However, for most organic polymer, the mechanical strength, chemical stability and biocompatibility is poor, especially, some of polymer is toxic, which hindered the application of polymer shell *in vivo*. In contrast, inorganic material especially inorganic ceramic is considered as a promising candidate for medical capsule shell owing to its excellent mechanical and biological properties[5]. Silica, one of the well-known inorganic ceramics, is attractive and be applied in drug delivery system owing to its favourable mechanical stability, chemical stability and biocompatibility[6-10]. Till now, the investigation on silica-based drug delivery system is focus on the silica molecular sieves (SBA-15, MCM-41 and so on), silica hollow sphere as carriers. In this way, drug can be loaded through blending method and drug delivery system is obtained. Nevertheless, the pore size deeply restricts the dimension and loading rate of drug. As an alternative solution, conventional water-in-oil (W/O) emulsion can be adopted to prepare a core-shell structure, *i.e.* TEOS is adopted as silica source to prepare silica shell at the interface of water and oil, then the drug (core) can be encapsulate with shell (silica) and the dimension and loading rate of drug can be enhanced. For this solution, most catalyst to improve the hydrolysis of TEOS is difficult to aggregate at the interface of water and oil, which hinder the derivation of silica capsule shell. In order to solve this problem, Wang *et al.*[11] adopted hydrochloric acid as both water phase and catalyst, hexamethylene as oil phase, directly encapsulated the water soluble drugs into silica shell. However, hexamethylene is toxic, which is unfavourable to the preparation of drug delivery system.

In this paper, the distribution of catalyst in W/O emulsion and the toxicity of reagent is concerned. Ammonia water

(NH_4OH) was adopted as both template (water phase) and catalyst, hexane with lower toxicity was adopted as oil phase to prepare the silica hollow capsule. Furthermore, the formation mechanism of the system is investigated, which pave the way for the application of silica as medical capsule shell.

EXPERIMENTAL

Ammonia water (mass fraction: 25 %-28 %) and chemical pure *n*-hexane was adopted as water phase and oil phase, respectively. Span 80 was adopted as emulsifier to prepare W/O emulsion, the detail of experiment is as follows: 0.5 g Span80 was added into 30 mL *n*-hexane, after ultrasonic agitation for about 3 min, a homogenous solution can be formed. Afterwards, the solution was stirred (10000 rpm/5 min) with XHF-D high speed dispersator. In the meanwhile, different volume of ammonia water (1 mL, 3 mL, 5 mL and 7 mL, respectively) was dropwise added into the solution (volume ratio of water phase to oil phase is 1:30, 1:10, 1:6, 1:4.3, respectively), then the four groups of homogenous emulsion to prepare samples 1#-4# can be obtained. The emulsion was magnetic stirred at room temperature and a blended solution of 5 g TEOS and 6 g *n*-hexane was dropwised added into the emulsion. After magnetic stirring for 24 h, the precursor silica capsule was separated by centifugation and washed for 3 times. Finally, the samples with different ratio of water phase to oil phase (1#-4#) were treated under vacuum drying at room temperature for 10 h. The flow chart of experiment is shown in Fig.1. F-SEM (S4800, Hitachi) was adopted to observe the morphology of the capsule; XRD (D/max 2000, Rigaku) was adopted to investigate the crystallinity of sample.

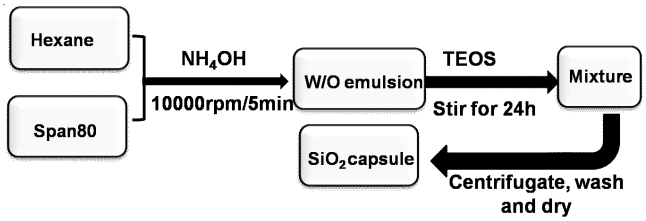

Fig. 1. Flowchart of the experiment

RESULTS AND DISCUSSION

Morphology of powders derived from different ratio of water phase to oil phase is shown in Fig.2. Fig.2(a)-(d) represent the volume of ammonia water is 1 mL, 3 mL, 5 mL and 7 mL (sample 1#-4#). When the volume of ammonia water is 1 mL, diameter of silica capsule is in the range of 100 nm-300 nm. In addition, no breakage can be observed, which hints the sample is solid sphere; if the volume of ammonia water increases to 3 mL, sample is composed of bulks and large solid sphere and the surface of sample is rough; if the volume increases to 5 mL, the size of silica spheres is in range of 2000-5000 nm and the surface is smooth. Furthermore, it seems that there is breakage on the surface of sphere; and if the volume increases to 7 mL, irregular structure of sample can be found. Therefore, with the increase of water phase, morphology of sample experience changes of regular-irregular-regular-irregular.

In order to further observe the morphology of sample 3#, local amplification SEM image of Fig. 2(c) is shown in Fig. 3. The breakage can be clearly observed and the hollow sphere is obtained. It should be noted that the capsule size is large (about 5000 nm) and the size can be change to fit the detail clinical demand by changing the emulsion condition (speed and time) and the related work is in progress.

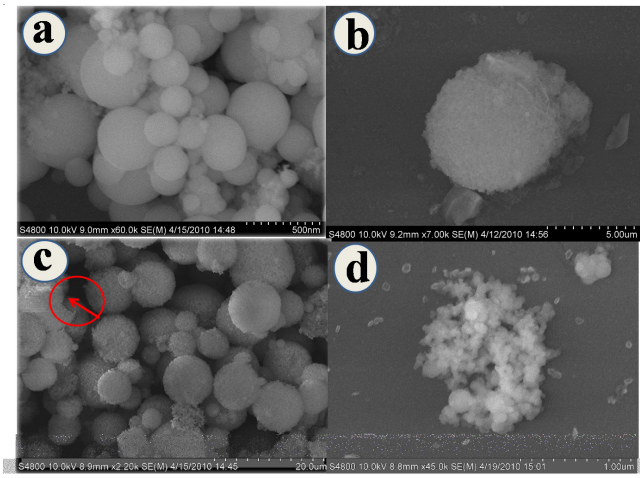

Fig. 2. Morphology of samples with different ratio of water phase to oil phase

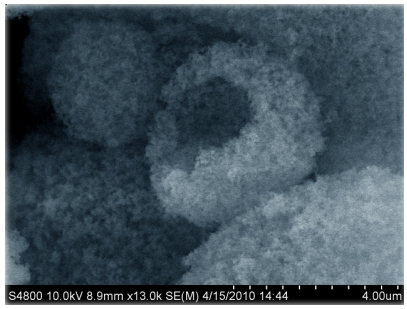

Fig. 3. Local amplicaiton image of sample 3#

XRD pattern of sample 3# is shown in Fig. 4. There is a dispersion diffraction peak in the range of 15°-30°, which hints amorphous structure of the capsule shell, *i.e.* there is no crystallization process during the sol-gel transformation and there is no reaction among water phase, oil phase, emulsifier and silica source to produce crystallized impurities.

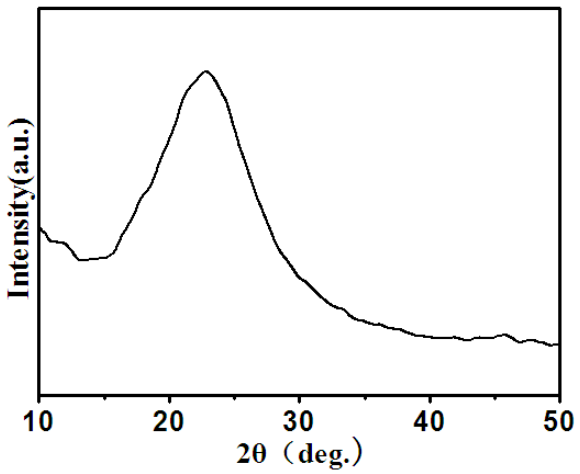

Fig. 4. XRD patteren of sample 3#

In order to further explore the reason for samples with different ratio of water phase to oil phase experiencing different morphology change, mechanism model of emulsion formation is proposed according to the experimental results, as shown in Fig. 5. Fig.5(a)-(d) represent sample1#-4#. When ammonia water is 1 mL, size of W/O droplet is low owing to the little water phase. In the meanwhile, hydrolysis of TEOS also consume some water, so the solid silica sphere is derived; with the increase ammonia water to 3 mL, micro W/O droplet is also formed owing to the low ratio of water phase to oil phase and the surface energy of the system is large. During the magnetic stirring, micro droplets tend to aggregate to form large droplet and irregular shape owing to its instability. Then the stability of the system improved owing to the decrease of surface area; if volume of ammonia water is 5 mL, it tends to form large W/O droplet because lower specific surface area corresponds to more stability. In the meanwhile, since the volume of water phase is greater, there is still water phase in spite of the consumption owing to TEOS. Then the hollow silica sphere can be obtained; if the volume of ammonia water increased further, large droplet tend to aggregate to form irregular silica bulk. Investigation on the thermodynamic stability of the system is in progress.

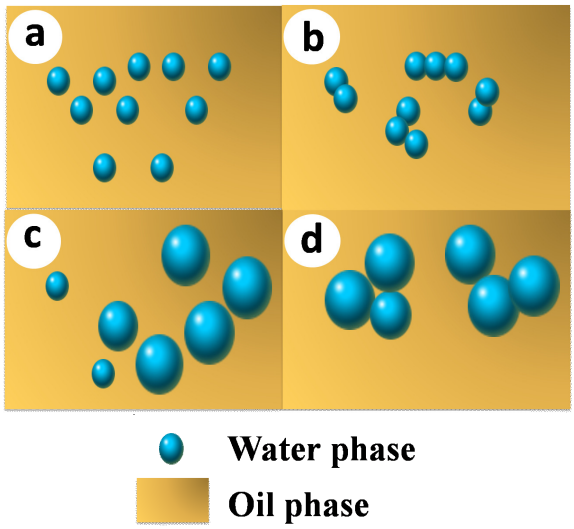

Fig. 5. Schematic figures for emulsion formation

Conclusion

Novel direct emulsion-sol-gel route is adopted to prepare hollow silica capsule shell, which can be applied in delivery system for water-soluble drug. Morphology of samples with different ratio of water phase to oil phase can experience the change of regular-irregular-regular-irregular. Hollow capsule can be obtained if the ratio is 1:6, the reason lies in the spontaneous transformation of droplets to stable state for emulsion system.

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