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# Preparation of Ibuprofen chitosan/montmorillonite microspheres by ionic cross-linking under microwave irradiation

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Ibuprofen chitosan (CS) /montmorillonite (MMT) microspheres have been produced by an ion cross-linking technique under microwave irradiation. The morphology and mechanical strength of the microspheres are significantly improved due to the use of chitosan as a drug carrier. Also, in comparison with other cross linker reagents, the effect of adsorption can be increased by the use of a small amount of sodium pyrophosphate. Furthermore, an orthogonal design method has been applied in order to obtain the optimal conditions for microsphere production, and the results are as follows: the reaction temperature is 60°C, the amount of montmorillonite added is 13%, the amount of ibuprofen added is 10%, the mole ratio of cation to anion is 50:1, and the entrapment efficiency is 49.70%. The structure, mechanical strength and characteristic infrared peaks of the microspheres have been examined by scanning electron microscopy (SEM), thermogravimetric analysis (TG) and Fourier transform infrared spectroscopy (FTIR), respectively.

**Keywords:** Ca-montmorillonite, CS/MMT microspheres, Ion cross-linking technique, Orthogonal design method, Sodium pyrophosphate

The use of natural, renewable resources as basic materials for drug carriers is of great interest because of the ecological benefits. The key advantages of these materials based on natural biopolymers, such as chitosan or cellulose, are that the products are non-toxic with a wide range of applications after degradation[1].

Chitosan (CS) is a natural linear biopolyaminosaccharide obtained from a deacetylated derivative of chitin which mainly consists of β-(1,4)-linked 2-deoxy-2-amino-D-glucopyranose units, and it is the second abundant natural polysaccharide in the world[2-4] and its structure is shown in Fig. 1. Its properties, such as its biocompatibility, biodegration, antimicrobial action, low toxicity, ability to chelate with heavy metals and form films, are well established[5,6]. Chitosan can be readily processed to form microspheres, scaffolds, nanoparticles, beads and nanofibers[7-11] due to these desirable characteristics. In addition, chitosan microspheres are also extensively used as a new drug delivery system. However, there are some disadvantages of chitosan microspheres, such as their hardness, and low mechanical and low thermal stability, which may be a barrier to pharmaceutical applications. For this reason, chitosan-based materials have attracted the attention of many researchers in the pharmaceutical field[12].

The better performance of clay mineral-based composites allowing the ability to load model drugs as drug delivery systems, compared with common minerals exhibiting the properties of a unique hybrid, ensures that clay mineral-based composites have a significant role to play in the field of health products[13].

Ca-montmorillonite (MMT) is a clay mineral belonging to the smectite group, and its crystalline structure consists of an alumina octahedron between two silica tetrahedral sheets[14-16] and its crystalline structure was first proposed by Pauling[17]. Ca-montmorillonite can be used not only to improve the mechanical properties of polymers, but also to reduce the cost of cross linker reagents because of its high capacity for interlayer reactions and exchangeable cations[18]. The properties of interlayer reactions, high cation exchange ability and zero toxicity allow Ca-montmorillonite to be widely used in pharmaceutical applications.

In the last few years, there has been growing interest in the development of hybrid microspheres made of clay minerals and biopolymers for pharmaceutical applications, such as MMT and CS[19]. The hybrid microspheres have some specific features

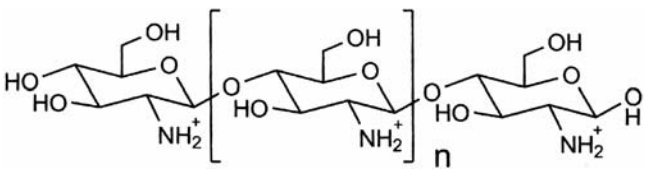


Fig. 1 — Structure of Chitosan

which cannot be found in chitosan microspheres, such as excellent mechanical characteristics and thermal behavior[20].

Based on these findings, this paper describes the intercalation of chitosan into a layered silicate structure to allow the production of CS-MMT microspheres prepared by an ion cross-linking technique under microwave irradiation. Intercalation of chitosan within the Ca-montomrillonite was shown in Fig. 2. Ibuprofen was used as a model drug and sodium pyrophosphate was used as the cross linker reagent, respectively. Sodium pyrophosphate has the added benefit of being nonpoisonous, so it can reduce the adverse effects of a chemical cross-linking reagent in the human body, as well as the cost of production. The novelty of the method described in this paper was that sodium pyrophosphate was used as the cross linker reagent. Moreover, microwave radiation was used instead of conventional heating methods, and these experimental combinations are rarely seen in studies involving microspheres. In this paper, the CS-MMT microspheres were prepared by the above method and the resulting hybrid microspheres were characterized by UV, FTIR, SEM, and TG analysis. The entrapment efficiency was used to evaluate the effect of different formulations and preparations to determine the optimal method for preparing CS-MMT hybrid microspheres.

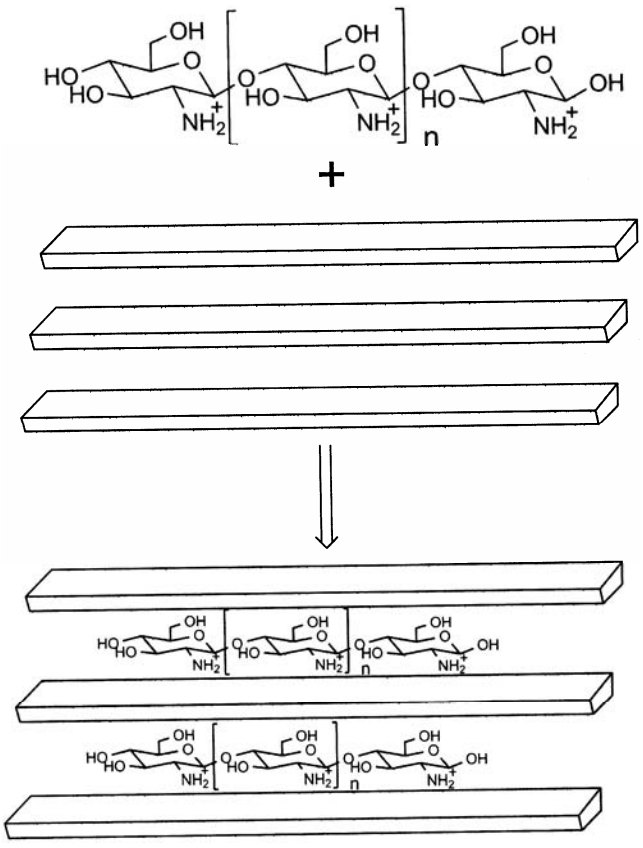

Fig. 2 — Intercalation of chitosan within the MMT in acidic acid medium

## Experimental Section

### Materials

The tablets were prepared using the following ingredients obtained from the sources indicated. Chitosan (deacetylation degree=80-95%) was purchased from Sinopharm Chemical Reagent Co., Ltd. China, while high purity Ca–montmorillonite (MMT, the content of montmorillonite was 98.8% as determined by XRD technology) was purchased from Zhejiang Sanding Technology Co., Ltd. China, and sodium pyrophosphate was purchased from Tianjin Bodi Chemical Co., Ltd. China. All solvents were of analytical grade.

### Methods

First of all, a clear aqueous chitosan solution was prepared by dissolving chitosan (CS) in a 2% (v/v) aqueous acetic acid solution at a concentration of 1wt% and stirring for 3 h. The suspension of Ca-montmorillonite (1wt %) was prepared by dispersing MMT powder in distilled water and then the suspension was stirred for 8h in distilled water prior to use. Finally, the suspension of MMT was added drop-wise to 50 mL chitosan solution. The reaction mixture was stirred at room temperature for 3 h and then a certain amount of ibuprofen was added to the reaction mixture followed by stirring at room temperature for another 3 h. Then, the reaction mixture was placed in a microwave reactor and the parameters of temperature, time, and stirring speed were set. Meanwhile, the solution of sodium pyrophosphate was added drop-wise to the reaction mixture during stirring. The hybrid microspheres were collected by centrifugation, washed three times with distilled water and lyophilized at -39°C in a freeze-drier for 24 h.

### Analysis

The resulting CS-MMT hybrid microspheres were characterized using an FTIR spectrometer (NEXUS470NEXUS470.Thermo Company) over the range 4000-400 $cm^{-1}$ using KBr pellets. The surface morphology was examined using a scanning electron microscope (SEM) (SNE3200m, Korea SNE Company) after coating the samples with gold film at

an acceleration voltage of 30 kV. The thermal stability of the chitosan-montmorillonite microspheres and pure chitosan microspheres was examined by thermogravimetric analysis (Netzsch Instrument Manufacturing Co., Ltd., Germany) from room temperature to 800°C at a heating rate of 10°C /min in an ambient atmosphere. In order to identify the optimal conditions for the production of ibuprofen CS-MMT microspheres, an orthogonal design was used to examine the optimal conditions with the reaction temperature (A), added amount of MMT (B), added amount of ibuprofen (C), mole ratio of cation and anion (D) and encapsulation efficiency being used as indicators. These factors have a critical effect on the particle formation and encapsulation efficiency (1). The factors and results of the orthogonal experiment are shown in Table 1.

Encapsulation efficiency =Weight of drug in microspheres/Weight of initial drug×100% (1)

According to the orthogonal method, the four parameters, A, B, C and D, are considered at 3 levels.

## Results and Discussion

### Infrared spectrum characterization

Figure 3 shows the intense characteristic bands of ibuprofen CS-MMT microspheres at 466 $cm^{-1}$, which corresponds to the coupled vibration of Si-O-M (metal cations) and M-O from MMT. Also,the characteristic bending vibrations of Si-O-Si were exhibited at 1042 $cm^{-1}$. The peaks at 2925 $cm^{-1}$ and 1578 $cm^{-1}$ reflected the absorption of the -OH groups in ibuprofen and the -$NH_3^+$groups in chitosan, respectively. Chitosan exhibits broad peaks at 3423 $cm^{-1}$ and 3419 $cm^{-1}$ which are due to the C-H stretching vibrations. The results obtained show that chitosan was successfully intercalated into Ca-montmorillonite and the loading of the model drug, ibuprofen, was also successful.

Table 1 — Factors and levels for orthogonal experiment

| Levels | Factors | | | |
|---|---|---|---|---|
| | A(%) | B(%) | C(%) | D |
| 1 | 80 | 13 | 22 | 40:1 |
| 2 | 60 | 17 | 10 | 50:1 |
| 3 | 70 | 9 | 16 | 60:1 |

### Scanning electron microscope characterization

Figure 4 shows SEM micrographs of pure chitosan microspheres (a) and chitosan/montmorillonite microspheres (b). The microspheres of pure chitosan were found to be spherical and smooth, suggesting that the pure microspheres without MMT resulted in a uniform rate of water loss from their surface. However, the surface of the chitosan-montmorillonite microspheres was uneven and had a crumpled shape, so it is possible that MMT markedly affected the structure of the microspheres, which affected the morphology. The addition of MMT provides physical

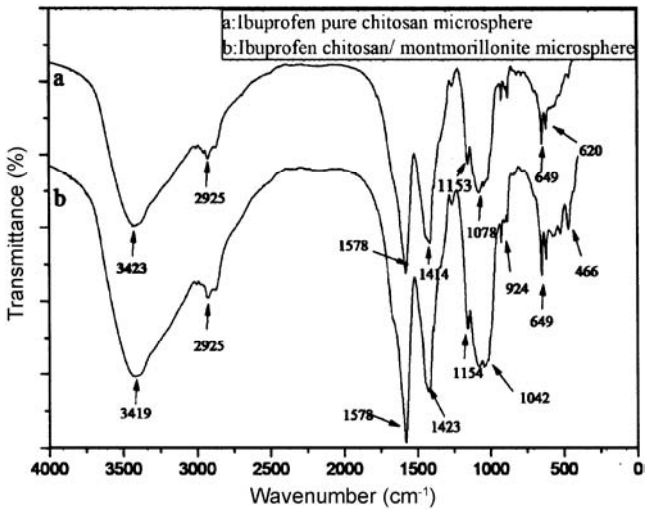


Fig.3 — FTIR spectra of ibuprofen pure chitosan microsphere and ibuprofen chitosan/montmorillonite microsphere

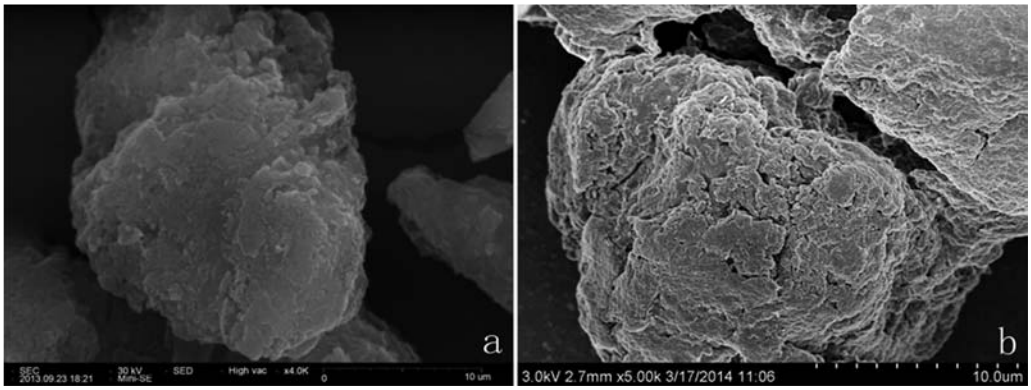


Fig. 4 — The SEM images of pure chitosan microspheres and chitosan/montmorillonite microspheres

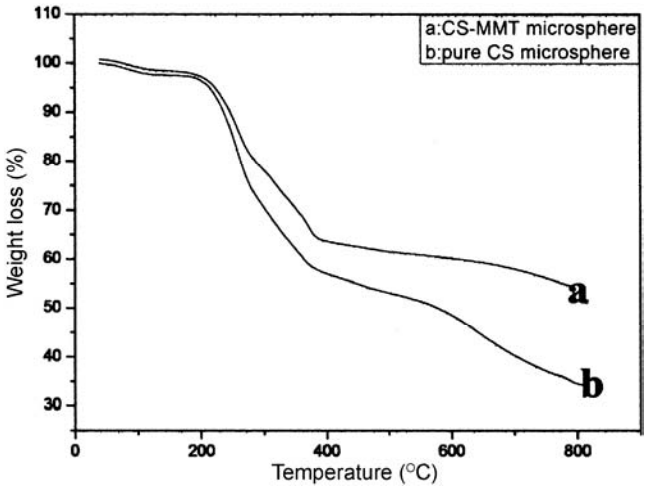


Fig. 5 — TGA curves of chitosan-montmorillonite microsphere and pure chitosan microsphere

cross-linking points, which may increase the stability of the chitosan microspheres[21]. Moreover, the existence of the MMT sheets plays a role in increasing the surface area of the microspheres and the model drug could be easily taken up by the microspheres. Therefore, this chitosan-montmorillonite microspheres offer a higher entrapment efficiency than pure chitosan microspheres.

#### Thermal characterization

The TG curves of chitosan-montmorillonite microspheres (b) and pure chitosan microspheres (a) are presented in Fig. 5 in order to allow a comparison of their thermal stabilities. The first weight loss of the two curves below 200°C is related to interlayer or adsorbed water molecules and the curve of Fig. 5(a) is almost the same as the curve of Fig. 5 (b). The second step from 200°C to 600°C reflects the degradation and deacetylation of chitosan. At this step, the curve of Fig. 5(b) exhibits a significant delay in weight loss compared with the curve of Fig. 5(a) since MMT can significantly improve the thermal stability of chitosan microspheres. As a result, the CS-MMT microspheres exhibited high thermal stability.

## Conclusion

In this study, the natural biopolymer chitosan has been successfully intercalated into Ca-montmorillonite through a cationic exchange process and sodium pyrophosphate is used as a cross linker. Moreover, ibuprofen has been selected as a model drug to prepare ibuprofen chitosan/montmorillonite microspheres by the ionic cross-linking method using microwave irradiation.

TG shows that the thermal stability of chitosan/montmorillonite microspheres is superior to that of pure chitosan microspheres. This suggests that Ca-montmorillonite can be used to improve the thermal stability of chitosan microspheres. The microspheres with MMT have a higher entrapment efficiency than those without MMT. They provide anions and, thus, reduce the amount of cross-linking agent required. The reaction time for ionic cross-linking was at least 20 min using conventional heating methods but, in our study, the reaction time was 6 min using the microwave radiation heating process. The high temperatures obtained by the microwave radiation heating process allow reactions to take place faster than under conventional thermal conditions. What is more, this novel heating process makes the production process more efficient and more economical to carry out.

The optimal conditions obtained from the orthogonal experiment were as follows: the reaction temperature was 60°C, the added amount of MMT was 13%, the added amount of ibuprofen was 10%, and the molar ratio of cation and anion was 50:1. Under these optimal conditions, an entrapment efficiency of 49.70% was obtained.

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