Chitosan and Chitosan/β-Cyclodextrin Microspheres as Sustained-Release Drug Carriers

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ABSTRACT: The main aim of this study was to compare two microspheres, chitosan (CTS) and CTS/β-cyclodextrin (β-CD), made by spray-drying, as pulmonary sustained drug-delivery carriers. Theophylline (TH) was used as a model drug. The characteristics of the microspheres and *in vitro* release were studied. The yield of CTS/β-CD microspheres was 46.1%, which was higher than that of the CTS microspheres (36.5%). The drug loads of the CTS and CTS/β-CD microspheres were 22.7 and 21.1%, respectively, whereas the encapsulation efficiencies were 90.7 and 91.4%, respectively. The distribution of 50% [(diameter) *d* (0.5)] of the CTS microspheres was below 6.49 μm and that of the CTS/β-CD microspheres was below 4.90 μm. Scanning electron microscopy showed that both microspheres yielded a spherical shape with smooth or wrinkled surfaces. Fourier transform infrared spectroscopy demonstrated that the carbonyl group of TH formed hydrogen bonds with the amide group of CTS and the hydroxyl group of β-CD. The swelling ability of the two microspheres was more than three times their weight, and their humidity rates attained equilibrium within 24 h. The ciliary beat movement times of CTS and CTS/β-CD microspheres were 493.00 and 512.33 min, respectively, which indicated that the two microspheres effectively reduced the ciliotoxicity and possessed better adaptability. *In vitro* release of TH from CTS/β-CD microspheres was slower than that from CTS microspheres at pH 6.8 and provided a sustained release of 72.0% within 12 h. The results suggest that CTS/β-CD microspheres are a promising carrier for sustained release for pulmonary delivery. J Appl Polym Sci 103: 1183–1190, 2007

Key words: drug delivery systems; particle size distribution; chitosan

INTRODUCTION

Chitosan (CTS) is a cationic natural copolymer of glucosamine, obtained from the deacetylation of chitin, which is the second most abundant polysaccharide after cellulose in the world. It has been widely used in several pharmaceutical formulations as sustained release carrier systems, including beads,[1] gels,[2] films,[3] sponges,[4] and microspheres,[5,6] for its many unique properties, including low toxicity, biocompatibility, and biodegradability and mucoadhesive properties. Furthermore, CTS has been used as a component to build drug carriers to attain desirable drug release profiles and enhance the dissolution rate of low-water-soluble drugs.[7–9] It can bind with mucosal surfaces due to its cationic nature, which leads to bioadhesion and a reduced mucociliary clearance.[10] In addition, CTS has another dramatic effect in terms of improving drug absorption by opening the intercellular tight junctions of the lung epithelium.[11] Therefore, CTS has become a good candidate for application in pulmonary drug delivery,[12] and its microspheres were developed toward this aim.[7,8,13] Previous studies have examined the release of CTS-encapsulated theophylline (TH), which only lasted more than 1 h.[7] Cerchiara et al.[14] showed that β-cyclodextrin (β-CD) complexes combined with CTS provided the controlled release of progesterone by spray-drying. However, whether or not CTS/β-CD microspheres that are co-spray-dried possess a more sustained release remains to be determined.

Cyclodextrins (CDs), cyclic oligosaccharides with a hydrophobic central cavity, have played an important role in modern pharmaceutics due to their unique properties, such as an increase in drug absorption and solubility, minimization of irritation effects, and modulation of the release of the incorporated drug.[14–16] A previous study for pulmonary delivery showed that CDs could provide a wider therapeutic safety margin and could markedly improve the poor solubility of cyclosporine A.[17] Another study indicated that CDs could be used as an inhalation powder to improve the

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pharmaceutical and biopharmaceutical properties of drugs without lowering their pulmonary deposition.[18] The possibility of using CDs for pulmonary sustained release was investigated in the study of salbutamol as a model drug, which indicated that stoichiometric ratio of the complex was 1 : 1.[19] Despite the many possible advantages, the number of studies dealing with pulmonary applications of CDs has been very limited.

The model drug TH is one of the most important drugs in the treatment of asthma, and recent studies have indicated that it has anti-inflammatory effects.[20,21] Because of its short half-life (6 h), conventional dosage forms are administered three to four times a day to avoid large fluctuations in plasma concentrations,[22] which causes poor patient compliance. The large fluctuations of plasma TH levels lead to adverse gastrointestinal and cardiovascular effects. Moreover, its therapeutic index is narrow (10–20 μg/mL). The therapeutic effects require a plasma TH concentration of at least 5–10 μg/mL, and toxic effects are frequent above 20 μg/mL. Sustained-release dosage forms can overcome these drawbacks. Therefore, TH is the most suitable drug for the preparation of sustained release formulations in an attempt to increase pharmacological effects and minimize adverse systemic effects.

Therefore, the main objective of this study was to prepare CTS and CTS/β-CD microspheres made by the spray-drying method. The microspheres were characterized by a series of pharmaceutical properties to study them as pulmonary sustained-drug-delivery carriers.

EXPERIMENTAL

Materials

TH was freely supplied by Minsheng Pharmaceutical Factory (Hangzhou, China). CTS (molecular weight = 1300 KDa, deacetylation degree = 80%) was prepared in our laboratory by the method of acetic acid hydrolyzes reported by Chen et al.[23] All other chemicals and reagents used were analytical grade and were provided by Shanghai Chemical Reagent Co. (Sigma Co., St. Louis, MO).

Solubility studies

Solubility studies were performed according to the method reported by Cerchiara et al.[14] TH in amounts that exceeded its solubility (50 mg) was carefully weighted into 10-mL test tubes, to which 3 mL of aqueous solutions containing β-CD at various concentrations (0–0.007 mol/L) were added. The test tubes were sealed and equilibrated by shaking at 25 or 37°C. When equilibrium was reached (5 days), the samples were filtered through a 0.22-μm filter (Whatman International, Ltd., Middlesex, UK), and the concentration of TH was measured spectrophotometrically at 275 nm [Shimadzu UV-1700 ultraviolet–visible (UV–vis) spectrophotometer, Tokyo, Japan].

Preparation of the microspheres

Predetermined amounts of TH, CTS, and β-CD, dried *in vacuo* at room temperature, were dissolved in 200 mL of 1% acetic acid aqueous solution according to various formulation ratios: TH/CTS = 1 : 3 (w/w) and TH/CTS/β-CD = 1 : 3 : 1 (w/w/w); accordingly, the dry matter within the fluid was 1.3 and 1.7%, respectively. The aqueous solutions were spray-dried with a spray-dryer (Büchi mini spray-dryer, B-191, Flawil, Switzerland). Blank microspheres were made for comparison. The liquid formulations, which were concurrent with the direction of the inlet drying air (cocurrent flow type), were atomized by contact with compressed air via a two-fluid nozzle (diameter = 0.7 mm) into a hot-air stream. The small droplets were dried into particles and then collected via a high-efficiency cyclone. The operating parameters were as follows: feed rate = 6 mL/min, inlet temperature = 150 ± 2°C (which resulted in outlet temperatures of 81 ± 2°C). The airflow rate was constant at 600 L/h, and the aspirator was set 90%. The air pressure was 5 bar, and the volume of the heating chamber was 3.6 L. The spray-dried microspheres were collected and stored in a desiccator (with anhydrous $CaCl_2$) at room temperature. The production yield was calculated according to the following equation:

$$\text{Production yield} = [\text{Weight of the spray-dried microspheres} / \text{Weight of total solids (CTS + TH + β-CD) in the spray-dried solution}] \times 100\%$$

Characterization of microspheres

The sizes of the microspheres were measured by laser diffraction (Malvern MasterSizer, model MS 2000, Malvern Instruments, Ltd., Malvern, UK) to determine the volume mean diameter. A small amount of sample (ca. 10 mg) was dispersed in 10 mL of deionized water. Each sample was measured at least three times. The morphology was evaluated by scanning electron microscopy (SEM; KYKY2800B, KYKY Technology Development, Ltd., Beijing, China). The microspheres were sputter-coated with a thin layer of Au/Pd and photographed. Fourier transform infrared (FTIR) spectroscopy was carried out with an Avater-360 FTIR spectroscope (Nicolet, Madison, WI). The samples were prepared by the grinding of the dry blend microspheres (2 mg) with KBr powders (100 mg)

and then compression of the mixtures to form disks. The sample was scanned from 400 to 4000 cm^{-1}.

Swelling ability

Swelling behavior was established by measurement of the water uptake. Dried microspheres of known weight (W_d) were dispersed in 5-mL test tubes containing 4 mL of a phosphate buffer solution (pH = 6.8). The mixture, after thorough mixing with a vortex for 5 min, was incubated for 12 h to make the microspheres reach swelling equilibrium, and centrifuged; water on the surface was removed with filter paper, and the sample was weighed immediately on an electronic balance. The weight of the swollen microspheres (W_w) was recorded. The swelling ability was determined by calculation of the water content:

$$\text{Water content} = (W_w - W_d)/W_w$$

All experiments were carried out in triplicate.

Evaluation of humidity

Humidity was evaluated by the moisture sorption. About 100 mg of microspheres (W_d), which were dried to constant weight *in vacuo* before use, was packed into each polystyrene tube, which was stored in the chamber at 40°C and at a relative humidity of 75%. At the end of different predetermined intervals (4, 8, 12, 24, and 48 h), the weight of the microspheres (W_h) was recorded. The increase in weight represented the weight of moisture taken by the microspheres. The moisture uptake was calculated as a ratio of the weight of absorbed moisture to the weight of the dry microspheres at each period of time as follows:

$$[(W_h - W_d)/W_h] \times 100\%$$

All samples were analyzed in triplicate.

Determination of drug load

The drug contents of the microspheres were determined with a UV spectrophotometer (Shimadzu UV-1700 UV–vis spectrophotometer) at a wavelength of 275 nm. An equivalent of 30 mg of microspheres was crushed in a mortar with 2 mL of phosphate buffer solution (PBS) (pH = 6.8). Then, the solution was adjusted to 100 mL with PBS (pH = 6.8), sonicated for 3 min, and extracted after vigorous shaking for 3 h, which was sufficient to ensure TH release completely. Subsequently, the solution was filtered through a 0.45-μm filter. The concentration was calculated according to the standard curve equation

$$C = 18.228H + 0.1287$$

where (number of samples) $n = 3$, (regression modulus) $r = 0.9997$, C is the concentration of TH, and H is the absorbance at 275 nm. The actual drug content was calculated according to the concentration and volume of the microspheres dissolved, and the theoretical drug content was derived from the drug/excipient ratio in spray-drying feed. The drug load was calculated from the ratio of the actual drug content to the weight of the microspheres, and encapsulation efficiency was calculated from the ratio of actual to theoretical drug content. The drug load and encapsulation efficiency were expressed as a percentage. All tests were carried out in triplicate.

In vitro drug release

In vitro release of TH from microspheres was studied with a variation of the method of Corrigan et al.,[24] which was a dialysis system comprising a dialysis bag and receptor chamber. Specifically, microspheres (30 mg) were put into a dialysis bag, and 1 mL of the release medium (PBS at pH 6.8 or HCl at pH 1.2) was added. Then, the dialysis bag was put into a 250-mL flask containing 200 mL of the same medium. The whole apparatus was placed in a water-bath shaker with horizontal shaking at 100 rpm and thermostated at 37 ± 0.5°C. At set time intervals, 4-mL samples were withdrawn from the flask, and the same volume of blank medium with the same temperature as that of the tested medium was added immediately. The drug was spectrophotometrically determined in the receiving phase (Shimadzu UV-1700 UV–vis spectrophotometer) at 275 nm. All experiments were carried out with five samples, and the average values were plotted.

Measurement of mucociliotoxicity

The ciliotoxicity of the microspheres was evaluated by the lasting time of ciliary movement with an *in situ* toad palate model. Briefly, Chinese toads, male and female, weighing 30–40 g, were divided into five groups (six toads in each group), the physiological saline group, the TH solution group, the blank microspheres group, the TH/CTS microspheres group, and the TH/CTS/β-CD group, and were secured on their backs on a board during experiments. After the toad palate was exposed, physiological saline solution (0.5 mL), 0.5% TH solution (0.5 mL), blank microspheres (20 mg), TH/CTS microspheres group (20 mg), and TH/CTS/β-CD microspheres group (20 mg) were placed on the palate surface, respectively. The tests lasted 4 h, during which the physiological saline solution was dropped to keep wetting. At the end of 4 h, a freshly cut 3 mm square piece of palate mucous membrane was obtained and cleaned by washing with physiological saline solution, placed on the slide. The ciliary beat movement was measured by light micros-

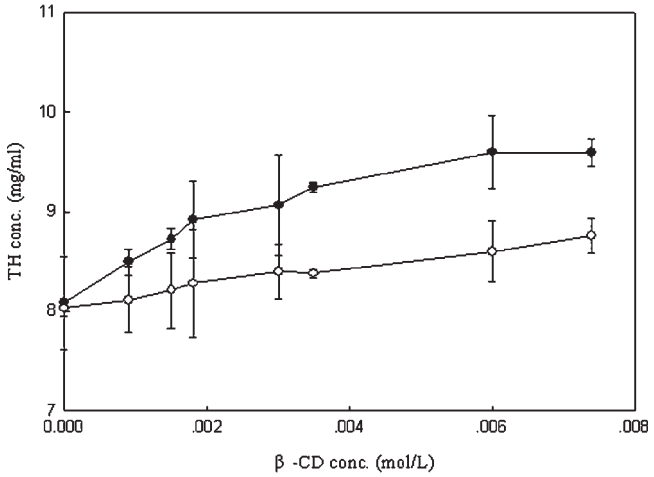

Figure 1 Solubility of TH in the presence of β-CD at (○) 25 and (●) 37°C.

copy. The slide was enclosed in an intrinsic chamber filled with distilled water at 20–25°C after observation. At set intervals, ciliary beat movement was observed until the ciliary movement stopped; then, the movement time was recorded.

Statistical analysis

All the data are the arithmetic mean plus or minus the standard deviation (SD), and statistical data were analyzed with SPSS13.0 (SPSS Inc., Chicago, IL), and differences were considered to be significant at a level of $p < 0.05$, with a two-tailed paired t test.

RESULTS AND DISCUSSION

Solubility

The solubility of TH was improved by the complex formation between TH and β-CD tested in this study, which was about 8.00 mg/mL in distilled water at 25°C. The solubility of TH increased with the concentration of β-CD, and the temperature increased. The result is presented in Figure 1.

Preparation of the microspheres

The drug load and encapsulation efficiency were important features of the microspheres. The drug loads, encapsulation efficiencies, and yields with two formulations are shown in Table I. The drug loads of TH/CTS microspheres and TH/CTS/β-CD microspheres were 22.7 and 21.1%, whereas encapsulation efficiencies were 90.7 and 91.4%, respectively. No significant difference was found between the two microspheres ($p > 0.05$), which indicated that β-CD had no effect on the drug loads and encapsulations. The yields of TH/CTS and TH/CTS/β-CD microspheres were 36.5 and 46.1%, which had significant differences ($p < 0.05$). The yield of TH/CTS microspheres was in accordance with Alpar et al.,[25] whose yield was around 40.0% because more products were deposited in the spray-drying chamber. However, the yield of TH/CTS/β-CD microspheres increased with the amount of β-CD incorporated, which was higher than what Alpar et al.[25] reported. This was probably because the viscosity of the solution decreased when β-CD was added[26] and little product was deposited in the chamber during the process of spray-drying. These results show that β-CD had an effect on the yields, and TH/CTS/β-CD microspheres were achieved to optimal results with a considerable yield and encapsulation efficiency and a high drug load.

Particle size and morphology

The most important factor of an aerosol that deposits in the lung is its diameter. The aerodynamic diameters of particles for optimal lung administration should be approximately 1–5 μm;[27] particles larger than 6 μm are generally deposited in the upper respiratory tract, and particles smaller than 1 μm are exhaled without deposition. Therefore, the particle size must be 1–5 μm so that the drug may deeply penetrate the lungs. The distribution curves for both microspheres are shown in Figure 2. The particle size distribution of the TH/CTS microspheres was from 2.67 [d (0.1)] to 14.02 μm [d (0.9)], and for the TH/CTS/β-CD microspheres, the particle size distribution was from 2.36 to 8.81 μm (a more narrow particle size distribution). The volume

TABLE I
Production Yield, Drug Load, Encapsulation Efficiency, and Swelling Ratio of Spray-Dried Microspheres

Microspheres	Production yield (%)	Drug load (%)	Encapsulation efficiency (%)	Swelling ratio
TH/CTS	36.5 ± 1.1	22.7 ± 0.1	90.7 ± 0.5	4.11 ± 0.43
TH/CTS/β-CD	46.1 ± 0.1[a]	21.1 ± 0.6[b]	91.4 ± 2.7[b]	3.19 ± 0.21[b]

All values are given as mean plus or minus SD ($n = 3$).
[a] Compared with TH/CTS microspheres, $p < 0.05$.
[b] Compared with TH/CTS microspheres, $p > 0.05$.

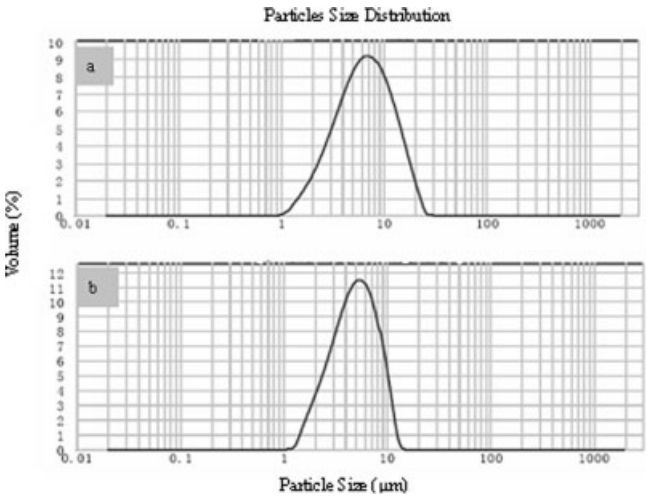

Figure 2 Particle size distributions of the microsphere systems: (a) TH/CTS and (b) TH/CTS/β-CD microspheres.

distribution of 50% [*d* (0.5)] of the TH/CTS microspheres was below 6.49 μm and, for the TH/CTS/β-CD microspheres, was below 4.90 μm, which indicated that the latter was more suitable for inhalation. This variation in size may have been due to the β-CD-encapsulated in the CTS microspheres. SEM photomicrographs of two microspheres are shown in Figure 3. The TH/CTS microspheres showed a regular spherical shape and a smooth surface; some part of the minute acicula particles and whiskers were found on the microspheres surface. This may have arisen because the whiskers of TH existed on the surfaces of the microspheres. The morphology suggested that the TH/CTS microspheres had the characteristic of agglomerates. A similar morphology was observed for the TH/CTS/β-CD microspheres. Furthermore, a slightly wrinkled surface was found in the TH/CTS/β-CD microspheres, which was similar to previous studies.[5,6] This phenomenon was probably due to the rapid drying process of spray-drying, the composition of the formulation, and so on.

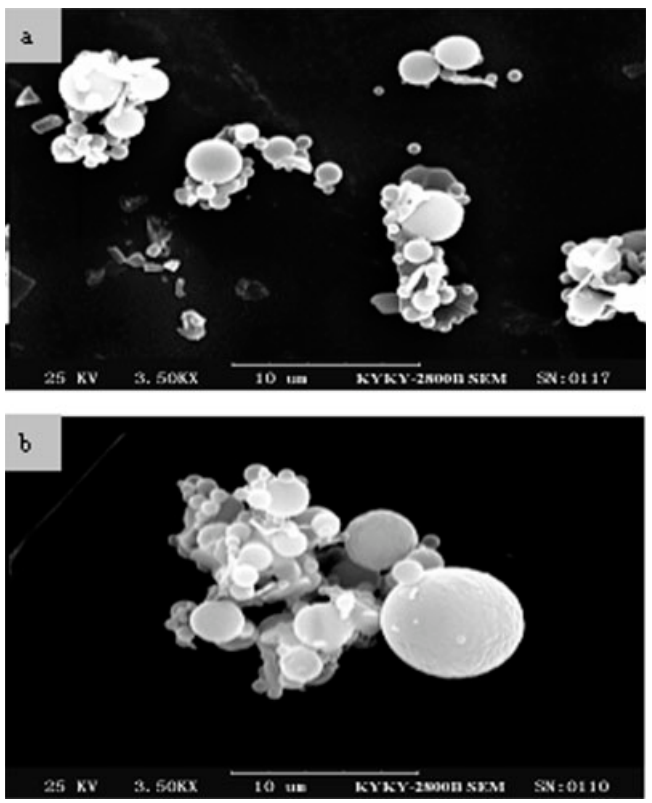

Figure 3 SEM of the spray-dried microspheres: (a) TH/CTS and (b) TH/CTS/β-CD microspheres.

Figure 4 shows the FTIR spectra of TH, CTS, β-CD, TH/CTS microspheres, and TH/CTS/β-CD microspheres. Compared with the spectra of TH [Fig. 4(a)], CTS [Fig. 4(c)], and TH/CTS microspheres [Fig. 4(d)], no significant shifts or reductions in the intensity of the 1 carbonyl of TH were observed (1716 → 1714 cm^{-1}), whereas the 2 carbonyl band was less intense, with a shift to lower frequency at about 21 cm^{-1} (1688 → 1667 cm^{-1}). The stretching vibration of the amide of CTS shifted to about 34 cm^{-1} (3414 → 3380 cm^{-1}) with a lower frequency side, which was indicative of the formation of intermolecular hydrogen bonds between this amide and the 2 carbonyl group of TH. The spectrum of β-CD [Fig. 4(b)] showed the hydroxyl group vibration appearing at 3381 cm^{-1}. When the TH/CTS microspheres compared with the TH/CTS/β-CD microspheres, this band was shifted to a lower frequency (3380 → 3355 cm^{-1}) by about 25 cm^{-1}, whereas when TH was compared with TH/CTS/β-CD microspheres, the 1 carbonyl vibration was shifted from 1716 to 1706 cm^{-1}, with a lower frequency about 10 cm^{-1}. In this case, CTS and β-CD did not have carbonyl vibrations (1706 cm^{-1}); we suggest that intermolecular hydrogen bonds were formed between the

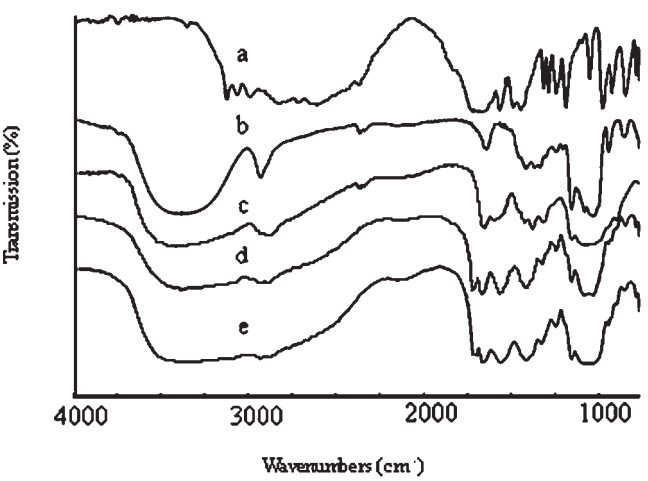

Figure 4 IR spectra of the TH/CTS/β-CD systems: (a) TH, (b) β-CD, (c) CTS, (d) TH/CTS microspheres, and (e) TH/CTS/β-CD microspheres.

TABLE II
Moisture Absorption Rate (%) of the Microspheres

	Microspheres	
Time (h)	TH/CTS	TH/CTS/β-CD
4	2.7 ± 1.2	4.1 ± 0.8[a]
8	4.8 ± 1.2	6.6 ± 0.3[a]
12	7.0 ± 1.0	8.1 ± 0.2[b]
24	13.2 ± 1.3	13.2 ± 1.0[a]
48	14.4 ± 1.7	13.5 ± 0.8[a]

All values are given as mean plus or minus SD ($n = 3$).
[a] Compared with TH/CTS microspheres, $p > 0.05$.
[b] Compared with TH/CTS microspheres, $p < 0.05$.

1 carbonyl group of TH and the hydroxyl group of β-CD. In short, for TH/CTS microspheres, the 2 carbonyl group of the TH combined with the amide group of CTS. For the TH/CTS/β-CD microspheres, the 2 carbonyl group of the TH combined with the amide group of CTS, and the 1 carbonyl group of the TH formed intermolecular action with the hydroxyl group of β-CD.

Swelling ability

Table I shows the result of the swelling studies of the TH/CTS and TH/CTS/β-CD microspheres at pH 6.8. The two microspheres attained equilibrium within 12 h, and their swelling abilities were more than three times their weight. Differences in swelling ability were not observed between the two microspheres ($p > 0.05$) because the mount of CTS in the two microspheres was no different. This could have been because the factors influencing the swelling ability of these two microspheres mainly depended on CTS.

Evaluation of humidity

Table II shows the humidity rates of the two microspheres. The humidity rates of the TH/CTS and TH/CTS/β-CD microspheres were 2.7 and 4.1%, respectively, within 4 h. No significance was found between the two microspheres ($p > 0.05$). With prolonged time, the humidity rates increased and attained equilibrium in 24 h; therefore, they increased little up to 48 h and were 14.4 and 13.5%, respectively. This result suggests that microspheres could absorb an amount of moisture at 40°C and at a relative humidity of 75%, but this would not be the case if they were stored inside inhalers. Because the humidity rate of microspheres affects lung deposition, this result indicates that microspheres should be kept away from humidity when they are stored.

Evaluation of ciliotoxicity

The results of ciliary movement for the TH/CTS and TH/CTS/β-CD microspheres are shown in Table III. The frog palate has been widely used as a model to investigate ciliotoxicity to the respiratory tract. The beat frequency *in vitro* is considered to be a very accurate, reproducible, and sensitive test of ciliotoxicity because the ciliated tissue is directly exposed to the compounds investigated.[28] The ciliary movement time of the TH solution was decreased (430.00 min), and the ciliary beat frequencies were 80.6% compared with the physiological saline solution (533.67 min; $p < 0.05$). This result shows that the TH solution had a significant toxicity on the palate mucosa. The ciliary movement time of the blank microspheres (510.00 min) was not significantly different than that of physiological saline solution ($p > 0.05$), and the ciliary beat frequency was 95.6%, whereas the ciliary movement times of the TH/CTS and TH/CTS/β-CD microspheres were 493.00 and 512.33 min ($p > 0.05$), and the ciliary beat frequencies were 92.4 and 96.0%, respectively. This result suggests that the two microspheres could effectively reduce the ciliotoxicity and possessed better adaptability.

In vitro release

The release of TH from the TH/CTS and TH/CTS/β-CD microspheres is shown in Figures 5 and 6. The

TABLE III
Effect of the Spray-Dried Microspheres on Ciliary Movement (*In Situ*)

Sample	Lasting time of ciliary movement after drug administration (min)	Percentage versus physiological saline (%)
Physiological saline	533.67 ± 13.05	—
TH solution (0.5%)	430.00 ± 23.00[a]	80.6
Blank microspheres	510.00 ± 32.50[b]	95.6
TH/CTS microspheres	493.00 ± 46.51[b]	92.4
TH/CTS/β-CD microspheres	512.33 ± 7.64[b]	96.0

Values in column 2 are given as mean plus or minus SD. $n = 6$.
[a] Compared with the physiological saline solution, $p < 0.05$.
[b] Compared with the physiological saline solution, $p > 0.05$.

drug release from the two microspheres depended on the pH of the release media. Faster drug release from the TH/CTS microspheres was found at both pH 1.2 and 6.8, whereas drug release from the TH/CTS/β-CD microspheres was slower. At pH 1.2 (Fig. 5), the drug released rapidly from the TH/CTS microspheres and reached 89.0% within 12 h. When compared with the TH/CTS/β-CD microspheres, it was clear that the release profile from the TH/CTS microspheres consisted of a slow release in the first stage (up to 2 h) and a fast release in the second stage. For the TH/CTS/β-CD microspheres, the mount of drug released from only reached 72.0% during 12 h. An obvious burst release, which attained more than 70.0%, was observed in both the TH/CTS and TH/CTS/β-CD microspheres. This was because the release of TH adsorbed on the surface of the two microspheres. The rapid release from the TH/CTS microspheres might have been due to the fast dissolution of CTS in the acid medium, whereas the release action of TH from the TH/CTS/β-CD microspheres was probably due to the TH/β-CD interaction with the spectrum of IR shown.

As found at pH 1.2, the drug release from the two microspheres had the same tendency at pH 6.8. In this case, the drug release from the TH/CTS microspheres was rapid, with an initial release of about 75.0% and was almost complete within 12 h. The initial drug release of the TH/CTS/β-CD microspheres was 39.0%, which was relatively low; they released 72.0% within 12 h. The reason might have been that CTS was insoluble and only swelled at pH 6.8. Furthermore, the result showed that the drug release decreased with incorporated β-CD. This was possibly because TH diffusion became slower through the more hydrophilic CTS/β-CD matrix layer, which indicated that β-CD could prolong drug release.

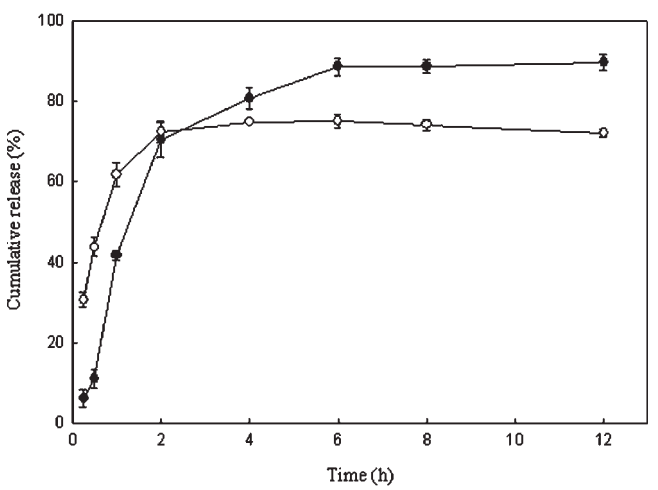

Figure 5 Release profile of TH from the spray-dried microspheres at pH 1.2 (Mean ± SD, $n = 5$): (●) TH/CTS and (○) TH/CTS/β-CD microspheres.

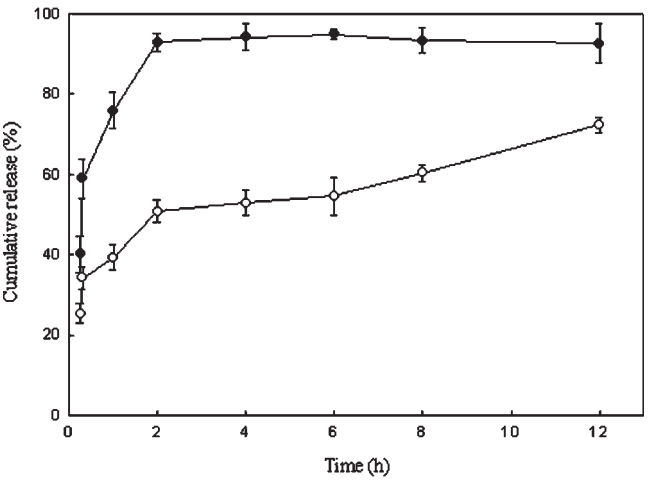

Figure 6 Release profile of TH from the spray-dried microspheres at pH 6.8 (Mean ± SD, $n = 5$): (●) TH/CTS and (○) TH/CTS/β-CD microspheres.

CONCLUSIONS

TH/CTS and TH/CTS/β-CD microspheres were successfully produced by a spray-drying method and were produced with sufficient production yield, high drug load, and encapsulation efficiency. SEM showed that the microspheres possessed a spherical shape with smooth or wrinkled surfaces. The volume distribution of 50% of the TH/CTS/β-CD microspheres was below 4.90 μm, which showed the possibility for inhalation. FTIR spectroscopy demonstrated that the carbonyl group of TH formed hydrogen bonds with the amide group of CTS and the hydroxyl group of β-CD. Furthermore, the TH/CTS and TH/CTS/β-CD microspheres possessed better adaptability. The TH/CTS/β-CD microspheres achieved a sustained release at pH 6.8 and provided a release of 72.0% within 12 h. These results suggest that the TH/CTS/β-CD microspheres would be effective as sustained pulmonary drug carriers.

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