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Theophylline particle design using chitosan by the spray drying

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Abstract

Solid dispersions of theophylline with chitosan as a carrier were prepared using a spray-drying method. Chitosan dissolved in an acid solution forms a gel, but it does not dissolve in an alkaline solution. Therefore, drugs which form composite particles with chitosan would gradually be released in an acid solution, and are expected to have considerably sustained release in an alkaline solution. In this study, we aimed to apply this ability to sustained release pharmaceutics.

In this study, we used theophylline as a model drug and chitosan as a carrier. Mixtures of chitosan and the drug in prescribed ratios were dissolved in an acid solution.

The physicochemical properties of the solid dispersions obtained were investigated by powder X-ray diffraction, differential scanning calorimetry, and dissolution rate analyses, with a view to clarify the effect of crystallinity on the dissolution rate. Furthermore, the interaction between the drug and the carrier was investigated by FT-IR analysis.

The powder X-ray diffraction intensity of the drug in the spray-dried samples decreased with an increase in chitosan contents, which also caused changes from crystalline to amorphous forms. These results indicated that the system formed a solid dispersion. The dissolution profiles of the drug from the physical mixtures and solid dispersions were almost the same at pH 1.2. However, at pH 6.8, the release from the solid dispersions was sustained more than that from the physical mixtures. The FT-IR spectroscopy for the theophylline solid dispersions suggested that the carbonyl group of theophylline and the amino group of chitosan formed a hydrogen bond.

Mass median aerodynamic diameter (MMAD) was measured by using a cascade impactor to evaluate the possibility of solid dispersions as dry powder inhalations. The MMAD of the spray-dried theophylline-chitosan systems were 4.5–5.0 μm. The results suggested that the spray-drying method is usefull to produce dry powders for inhalation.

Keywords: Spray drying; Particle design; Theophilline; Chitosan; Solid dispersion

1. Introduction

Numerous studies have shown that coprecipitation with polyvinylpyrrolidone (PVP) can markedly enhance the dissolution of drugs (Simonelli et al., 1969, 1976; Corrigan and Timoney, 1975). The mechanism responsible for this enhanced dissolution has been the subject of debate. Some authors have proposed that the increased drug dissolution rate is due to the formation of a high energy amorphous drug phase (Corrigan et al., 1980, 1983, 1985; Corrigan and Holohan, 1984; Corrigan, 1985). Others have attributed the effect to the molecular dispersal of the drug (Chiou and Riegelman, 1969, 1971) or an in-

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creased complexity in PVP (Shefter and Cheng, 1980), while coacervation was suggested by Sekikawa et al. (1979), and Badawi and El-Sayed (1980). Several water-soluble polymer carrier systems, such as polyethylene glycol (PEG), PVP, and hydroxypropylcellulose (Lo and Law, 1996; Law et al., 1992; Mura et al., 1996; Tantishaiyakul et al., 1996; Ozeki et al., 1993), have been used in fast-release preparations. The mechanism of the interaction between the drug and the carrier in solid dispersions has also been studied (Sekizaki et al., 1995; El-hinnawi and Najib, 1987; Doherty and York, 1969, 1987). However, there have been few studies of solid dispersions using low molecular weight substances as carriers (Allen et al., 1977; Ghanem et al., 1980; Danjo et al., 1997).

Recently, a spray-drying technique was shown to yield an amorphous form of crystalline drugs using a carrier such as PVP (Hirasawa et al., 1998) or lactose (Hirasawa et al., 1999). However, there have been few studies of solid dispersions for sustained or prolonged release type preparations.

Chitosan is a cationic natural biopolymer produced by the alkaline *N*-deacetylation of chitin, the abundant natural polymer after cellulose. It has become an interesting material in pharmaceutical application, especially as an inhalation drug (Okamoto et al., 2003), due to its biodegradability (Williams et al., 1998), biocompatibility (Lueßen et al., 1997), and low toxicity. It can easily form solid dispersions using a casting technique and a spray-drying technique. The purpose of the present study was to design a composite particle in which administration to the lungs is possible. In addition, the release of the prepared composite particle was also examined. That is to say, the release of the pharmaceutical prepared by the spray-drying technique was related to the crystallinity of the theophylline-chitosan systems. Chitosan dissolves in an acid solution, but swells in an alkaline solution and does not dissolve.

2. Experimental

2.1. Materials

Theophylline (Theo, model drug) was purchased commercially (Wako Pure Chemical Industries, Ltd.). Chitosan (Chit, carrier) was kindly supplied by Japan Chelate Co., Ltd., of which the degree of deacetylation was calculated to be 89.0% from the amino group content, and with a coefficient of viscosity of 70 mPa s. Other materials and solvents were of analytical reagent grade. Theo and Chit were sieved by JIS screens of 106–75 and 75–53 μm, respectively, before use.

2.2. Preparation of matrix particles

Theo and Chit were dissolved in 0.5% acetic acid aqueous solution. These solutions were spray dried under the following conditions: inlet temperature was 140 °C, the drying air flow was 0.50 m^3/min, the atomizing air pressure was 50 kPa, and the outlet temperature was 90–95 °C The matrix particles were prepared by spray drying using a SD-1000 instrument (Tokyo Rikakikai Co., Ltd., Japan).

2.3. Preparation of physical mixtures

The physical mixtures were prepared by mixing the drug and the carrier (ratios of the drug and carrier were 1:1, 1:3 and 1:5) using a test tube mixer (Scientific Industries, Vortex-Genie 2, Japan) for 10 min at a constant amplitude and rate.

2.4. Confirmation of the particle morphology

A scanning electron microscope (SEM, JOEL Type JSM-T20) was used to observe the morphology of the matrix particles.

2.5. Measurement of mass median aerodynamic diameter

The mass median aerodynamic diameter (MMAD) of the matrix particles was measured using a cascade impactor (Low Volume Air Sampler Andersen Type AN-200, Shibata Kagaku Co., Ltd., Japan) in order to evaluate the possibility for use as an inhalant. The hydroxypropylmethylcellulose (HPMC) capsule (no. 2) was filled with a sample of 10 mg and the mass of the sample, which remained after attraction in each stage of the cascade impactor for 5 s at an inhalation speed of 28.3 l/min, was measured. The MMAD was calculated using the log normality establishment distribution table.

2.6. Measurement of particle size distribution

Particle size was measured using laser diffraction scattering particle size distribution measurement equipment (Seishin Kigyo Co., Ltd., Japan, Type LSM-30). The evaluation was carried out by the particle size distribution.

2.7. Confirmation of crystallinity of the drug

2.7.1. Powder X-ray diffraction

Powder X-ray diffraction analysis was performed with a Rigaku Geiger-Flex diffractometer (Rigaku, Rad-2VC, Japan) using a Ni-filter, Cu Kα radiation, a voltage of 40 kV, and a current of 20 mA. The scanning rate was 5°/min over a 2θ range of 5–45°.

2.7.2. Thermal analysis

Differential scanning calorimetry (DSC) was carried out with a type 3100 instrument (MAC Science Co., Ltd., Japan). The operating conditions in the open pan system were: sample weight, 10 mg; heating rate, 10 °C/min.

2.8. Infrared spectroscopy

FT-IR spectra were obtained with a type FT-200 instrument (Horiba Co., Ltd., Japan) using the transformation of 100 scans by the KBr disk method.

2.9. Dissolution test

Dissolution tests were performed according to the JPXIV paddle method using sample powders, including 50 mg of the drug and 1000 ml of the dissolution medium at pH 1.2 or pH 6.8 at 37±0.1 °C. The rotation speed of the paddle was 100 rpm. The quantity of theophylline was assayed by HPLC at 275 nm. The mobile phase was 20 mM acetic acid buffer:CH_3CN:CH_3OH = 900:35:65 (v/v/v), which flowed through an ODS column (Cosmosil 5C18-AR II, 4.6 mm × 150 mm, Nacalai Tesque) at a flow rate of 1.0 ml/min.

3. Results and discussion

3.1. Confirmation of matrix particles

SEMs of the Theo–Chit systems are shown in Fig. 1. Theo was an acicula particle. Although the spray-drying pharmaceutical preparation of this system produced spherical particles, minute acicula particles and whiskers on the particle surface occurred. Whiskers arose on the particle after a few days without observation. There are reports in which whiskers arise by the capillary condensation phenomenon in caffeine (Yuasa et al., 1981), and in tablets of ethenzamide (Yuasa et al., 1981). It was regarded that the whikers arose as a result of the theophylline, which

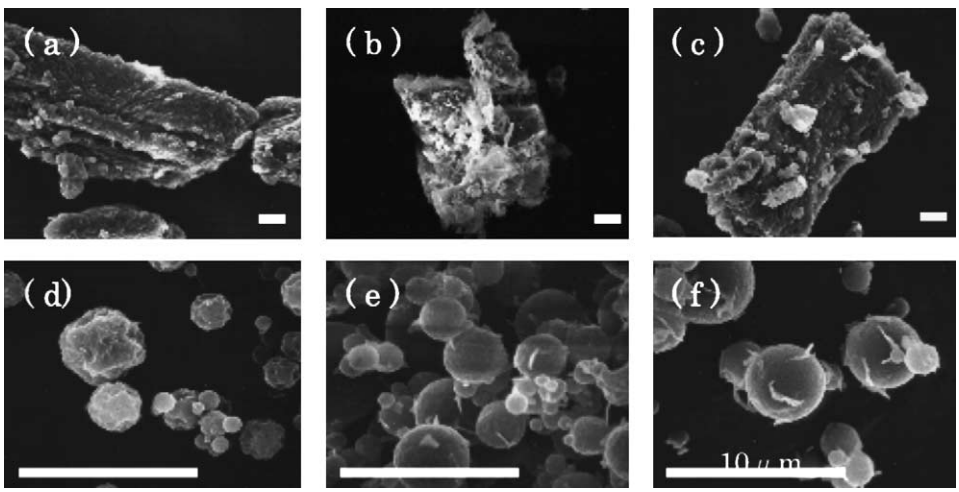

Fig. 1. Scanning electron micrographs of the Theo/Chit systems. (a) Theo; (b) Chit; (c) Theo/Chit = 1/1 PM; (d) Theo/Chit = 1/1 SD (1 day); (e) Theo/Chit = 1/3 SD; (f) Theo/Chit = 1/5 SD.

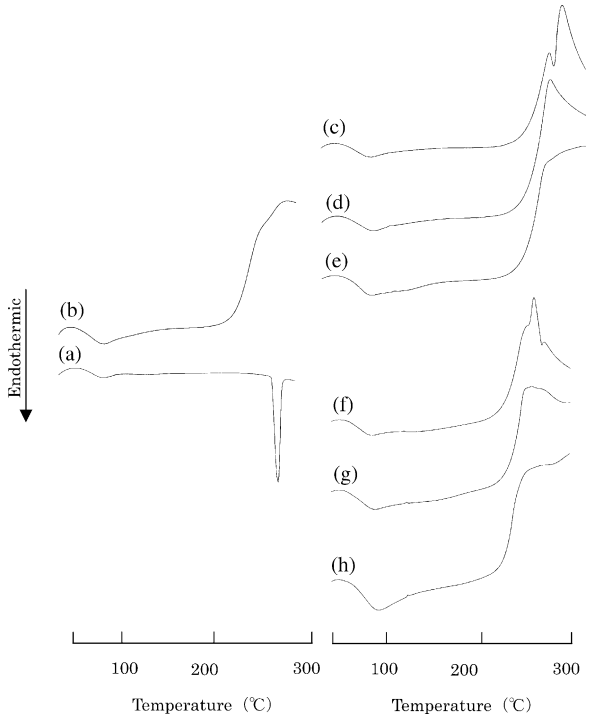

Fig. 2. DSC thermograms of the Theo/Chit systems. (a) Theo; (b) Chit; (c) Theo/Chit = 1/1 PM; (d) Theo/Chit = 1/3 PM; (e) Theo/Chit = 1/5 PM; (f) Theo/Chit = 1/1 SD; (g) Theo/Chit = 1/3 SD; (h) Theo/Chit = 1/5 SD.

resembled the structure of caffeine in the spray-dried pharmaceutical preparation that was used.

3.2. Degree of crystallinity of theophylline in matrix particles

DSC thermograms for Theo, Chit, their physical mixtures and samples which were prepared by spray drying, are shown in Fig. 2. There was an endothermic peak with a melting point for Theo near 274° C, as shown in Fig. 2. The endothermic peak that accompanied the crystal melting in Theo:Chit 1:3 and 1:5, which were prepared with an acetic acid solution, had disappeared on the spray-dried matrix particles. Chit exhibited a peak from the exothermic reaction with the decomposition near 200 °C. These results indicated that Theo had been amorphized. However, the endothermic peak disappeared in the physical mixture due to the endothermic peak of Theo and the exothermic peak of Chit overlapping.

Table 1
Melting point and heat of fusion (ΔH) of the theophylline systems

Sample	Melting point (°C)	ΔH (J/g)
Theo	273.6	105.3
Theo/Chit = 1/1 PM	–	16.7
Theo/Chit = 1/3 PM	–	–
Theo/Chit = 1/5 PM	–	–
Theo/Chit = 1/1 SD	–	6.6
Theo/Chit = 1/3 SD	–	–
Theo/Chit = 1/5 SD	–	–

PM, physical mixture; SD, solid dispersions; –, peaks were not detected.

The melting point and the heat of fusion of the samples are shown in Table 1. However, for samples prepared using the spray-drying technique the ΔH values were very small, as shown in Table 1, suggesting a decrease in the crystallinity of the original crystalline.

Powder X-ray diffraction patterns for Theo and Chit, their physical mixtures, and the samples, prepared using the spray-drying technique, are shown in Fig. 3. Many sharp peaks were observed in the diffraction patterns of Theo. Chit exhibited signs of being amorphous, as a diffraction peak was not observed. In the physical mixture, the diffraction peaks decreased with an increase in the mixing ratio of chitosan, however, crystallinity was confirmed. In the spray-drying samples of the 0.5% acetic acid solution system, the diffraction peaks decreased with an in-

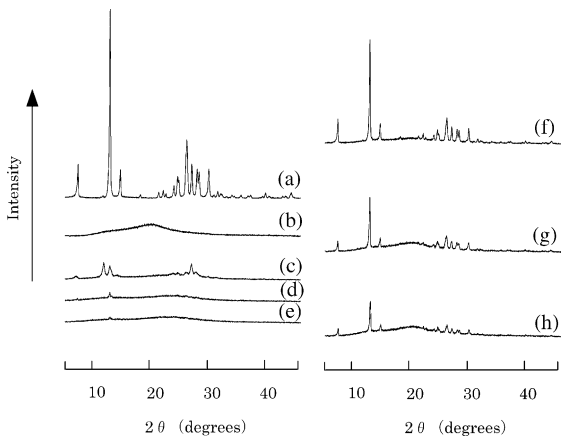

Fig. 3. Powder X-ray diffraction patterns of the Theo/Chit systems. (a) Theo; (b) Chit; (c) Theo/Chit = 1/1 SD; (d) Theo/Chit = 1/3 SD; (e) Theo/Chit = 1/5 SD; (f) Theo/Chit = 1/1 PM; (g) Theo/Chit = 1/3 PM; (h) Theo/Chit = 1/5 PM.

crease in the chitosan content, and a diffraction peak was only slightly observed when the mixing ratio of Theo and Chit was 1:5. Further, we tried to confirm the crystallinity of pharmaceutical preparation which we got this time by DSC. The measurement results were shown in Fig. 2. The endothermic peak with the melting of Theo overlapped with the exothermic peak of Chit by the decomposition and it was difficult to calculate ΔH of Theo except for the 1:1 physical mixture and 1:1 spray-dried sample. The calculated heat of fusion quantity from these peak areas were shown in Table 1. These results suggested that the 1:5 spray-dried samples (Theo/Chit = 1/5) had formed solid dispersions. These X-ray diffraction studies and DSC measurements suggested that although the drug and the carrier could not form solid dispersions by physical mixing, solid dispersions could be obtained when the mixtures were spray dried. The degree of crystallinity of the drug in the solid dispersions was dependent on the ratio of the drug to carrier.

3.3. Release rate of theophylline from matrix particles

Fig. 4 shows the result of the release of theophylline. In the acidic medium (pH 1.2), the release rate of the spray-dried pharmaceutical was delayed more than the original, with exception to the physical mixture and Theo/Chit = 1/1. This was caused by dissolving after chitosan formed a gel in the acid solution. On the other hand, in the alkaline medium (pH 6.8), the release rate of the spray-dried pharmaceutical was sustained more than original and the physical mixture, with exception to Theo/Chit = 1/1. It seemed to gradually generate the diffusion of the drug in this case, since chitosan is insoluble in an alkaline solution.

The release mechanism of the pharmaceutical preparation prepared by this time was different in the acid solution and in the alkaline solution, because chitosan was used as the carrier. A dissolution-type mechanism would explain the drug release in the acid solution, while a matrix-type mechanism would be applied to the drug release in the alkaline solution. In case of dissolution type, it is analyzed by Noyes–Whitney equation and Hixson–Crowell equation. On the other hand, it is analyzed by Higuchi equation, when it is matrix type. With the present pharmaceutical preparations, the fitness to a dissolution equation was good in the initial release stage. However, there is a problem on analyzing the phenomenon because the release mechanism seems to differ by the solution pH. Therefore, the release results obtained in this study should be compared using the 70% release time T_{70}. T_{70} is shown in Table 2.

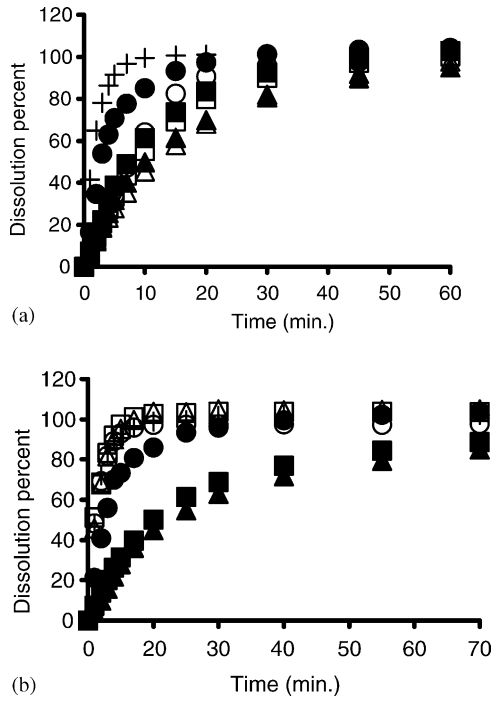

Fig. 4. Release profiles of the Theo/Chit systems. (a) pH 1.2; (b) pH 6.8. (+) Theo; (○) Theo/Chit = 1/1 PM; (□) Theo/Chit = 1/3 PM; (△) Theo/Chit = 1/5 PM; (●) Theo/Chit = 1/1 SD; (■) Theo/Chit = 1/3 SD; (▲) Theo/Chit = 1/5 SD. Each point represents the average ($n = 3$).

The physical mixture was regarded as showing a release rate equal to the composite particles, because the

Table 2
70% dissolution time T_{70} of theophylline

Sample	pH 1.2 fluid, T_{70} (mm)	pH 6.8 fluid, T_{70} (mm)
Theo	2.39	1.90
Theo/Chit = 1/1 PM	11.64	2.06
Theo/Chit = 1/3 PM	15.38	2.09
Theo/Chit = 1/5 PM	21.39	2.17
Theo/Chit = 1/1 SD	4.62	4.00
Theo/Chit = 1/3 SD	13.58	21.45
Theo/Chit = 1/5 SD	20.09	28.09

PM, physical mixture; SD, solid dispersions.

dissolution of theophylline was controlled so that the chitosan could form a gel in the acid solution. However, though chitosan had no effect on the dissolution of theophylline in the physical mixture, because chitosan swells in a pH 6.8 solution, the release from the matrix particles was controlled.

For Theo/Chit = 1/1, the lowering effect of the crystallinity was greater than the swelling effect of the chitosan, since the solid dispersion was not perfect, and the dissolution of theophylline was accelerated.

3.4. Mechanism of interaction between the theophylline and chitosan systems

The mechanisms which formed each solid dispersion were examined using the measurement of a FT-IR spectra.

FT-IR spectra measurement results of the pharmaceutical preparation of the spray drying of theophylline were shown by the dissolution of the chitosan in the acetic acid, as seen in Fig. 5. In the physical mixture and Theo/Chit = 1/1, there was no change in the C=O stretching vibration near 1716 cm^{-1} for theophylline, and in Theo/Chit = 1/5, it shifted to about the 10 cm^{-1} low frequency side. On the other hand, chitosan showed bands at 1600 cm^{-1} due to an NH_2 bending vibration, existed in the physical mixture, and the oscillation strength decreased from Theo/Chit = 1/3 to 1/5 with an increase in the mixing ratio of chitosan, and it finally disappeared. From these results, it was considered that a hydrogen bond had formed between the carbonyl group of theophylline and the amino group of chitosan.

3.5. As a possible pharmaceutical preparation for inhalation

A cascade impactor usually measures the particle size distribution of an aerosol in the air. However, it has been published as an artificial respiratory tract model which evaluates pressurized metered-dose inhalers (MDIs) in BP and USP. The particle size must be 0.5–6.0 μm so that the drug may deeply penetrate the lungs. The MMAD of the present samples were 4.6 μm (Theo/Chit = 1/5) and 5.0 μm (Theo/Chit = 1/3), as shown in Fig. 6. On the other hand, the mean particle sizes measured by LMS-30 were D_{50} = 4.8 μm (Theo/Chit = 1/5) and D_{50} = 5.5 μm (Theo/Chit = 1/3), respectively, as shown in Fig. 7.

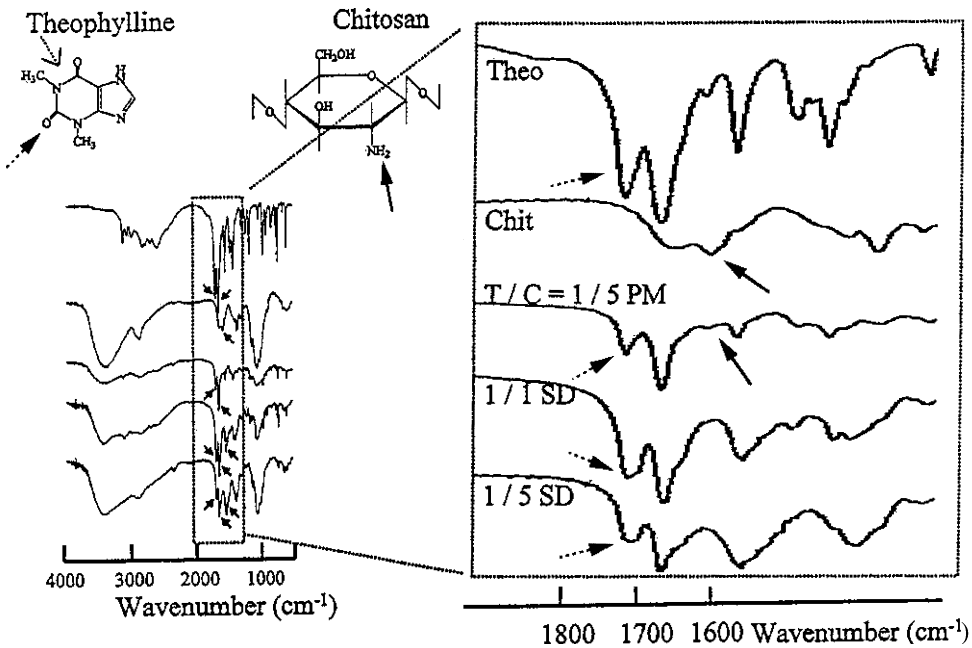

Fig. 5. FT-IR spectra of the Theo/Chit systems. (a) Theo; (b) Chit; (c) Theo/Chit = 1/5 PM; (d) Theo/Chit = 1/1 SD; (e) Theo/Chit = 1/5 SD.

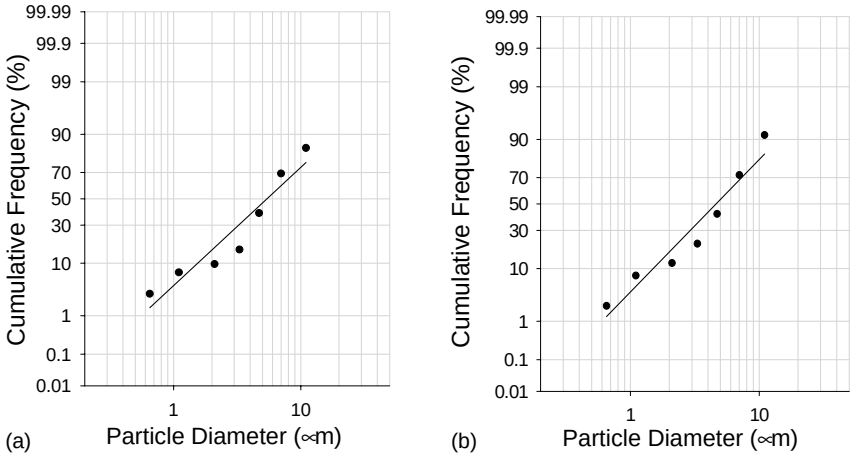

Fig. 6. Particle size distribution curves with MMAD. (a) Theo/Chit = 1/3 SD; (b) Theo/Chit = 1/5 SD.

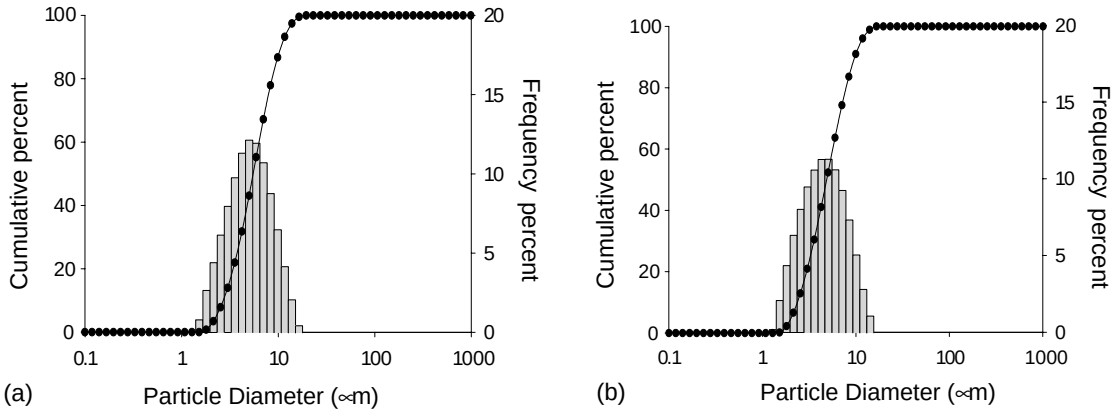

Fig. 7. Particle size distribution with LSM-30. (a) Theo/Chit = 1/3 SD; (b) Theo/Chit = 1/5 SD. (●) cumulative percent; (▩) frequency percent.

Particle size distribution of the matrix particles (Theo/Chit = 1/3 and 1/5) prepared by spray-drying technique was 0.6–10 μm as shown in Fig. 6. The particle size distribution is almost equal to that reported by Hallworth and Westmorland (1987) and Braun et al. (1996). From these results, it was suggested that the matrix particles prepared by the spray-drying technique were useful as a pharmaceutical preparation for inhalation.

4. Conclusions

(1) The matrix particles of theophylline prepared by spray drying using chitosan, which was dissolved in acetic acid, remained a little crystalline. The matrix particles of this system were spherical.

(2) The slow release of the dissolution rate of the matrix particles obtained by spray drying was made in a pH 6.8 medium, as opposed to the physical mixture.

(3) From the FT-IR measurement, a hydrogen bond seemed to have formed between the carbonyl group of Theo and the amino group of Chit.

(4) The matrix particles of the Theo–Chit systems showed a possibility for pharmaceutical administration in the lungs, because particle size was 4.6–5.6 μm.

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