Particle Design Using a 4-Fluid-Nozzle Spray-Drying Technique for Sustained Release of Acetaminophen

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We prepared matrix particles of acetaminophen (Act) with chitosan (Cht) as a carrier using a newly developed 4-fluid-nozzle spray dryer. Cht dissolves in acid solutions and forms a gel, but it does not dissolve in alkaline solutions. Therefore, we tested the preparation of controlled release matrix particles using the characteristics of this carrier. Act and Cht mixtures in prescribed ratios were dissolved in an acid solution. We evaluated the matrix particles by preparing a solid dispersion using a 4-fluid-nozzle spray dryer. Observation of the particle morphology by scanning electron microscopy (SEM) revealed that the particles from the spray drying process had atomized to several microns, and that they had become spherical. We investigated the physicochemical properties of the matrix particles by powder X-ray diffraction, differential scanning calorimetry, and dissolution rate analyses with a view to clarifying the effects of crystallinity on the dissolution rate. The powder X-ray diffraction peaks and the heat of the Act fusion in the spray-dried samples decreased with the increase of the carrier content, indicating that the drug was amorphous. These results indicate that the system formed a solid dispersion. Furthermore, we investigated the interaction between the drug and carrier using FT-IR analysis. The FT-IR spectroscopy for the Act solid dispersions suggested that the Act carboxyl group and the Cht amino group formed a hydrogen bond. In addition, the measurement results of the ^{13}C CP/MAS solid-state NMR, indicated that a hydrogen bond had been formed between the Act carbonyl group and the Cht amino group. In the Act-Cht system, the 4-fluid-nozzle spray-dried preparation with a mixing ratio of 1 : 5 obtained a sustained release preparation in all pH test solutions.

Key words acetaminophen; chitosan; spray drying; solid dispersion; sustained release

Research for the purpose of improving the dissolution of poorly water-soluble drugs is mainly reported in this field.[1,2] The solid dispersion technique, which was first used to enhance the dissolution rate of poorly water-soluble drugs[3,4] is now used to sustain drug release.[5—7] Historically, water-soluble carriers such as polyethylene glycol (PEG),[8,9] polyvinylpyrrolidone (PVP),[10,11] and hydroxypropylcellulose (HPC),[12—14] have been the most common carriers for solid dispersions. Solid dispersions of nifedipine and carrier polymers such as hydroxypropylmethylcellulose acetate succinate (HPMCAS) were prepared using the solvent method.[15] Emara *et al.*[16] improved the dissolution of nifedipine prepared with the fusion method. Yamashita *et al.*[17] prepared solid dispersions of tacrolimus using PEG, PVP, and HPMC. He *et al.*[18] reported that a solid dispersion was formed when cimeditine was dispersed in chitosan molecules through spray drying. Corrigan *et al.*[19] tried to make an amorphous drug by spray drying using PVP as a carrier. Matsuda *et al.*[20] reported that the amorphism and physical stability of spray-dried flusemide. Kislalioglu *et al.*[21] prepared solid dispersion of ibuprofen using Eudragit. Generally, the dissolution rate of a drug quickens when a solid dispersion is formed using a polymer as a carrier. We reported that naproxen-α-lactose monohydrate solid dispersions,[22] prepared using melting methods, supported the notion of the existence of a high-energy amorphous drug phase in systems containing more than 50% α-lactose monohydrate. The dissolution data suggested that the dissolution rate of this phase was 7—20-fold greater than the crystalline drug. However, only a few studies have investigated the slow release of a drug after the formation of a solid dispersion using spray-drying. Shaikh *et al.*[23] performed spray-drying using acetaminophen (Act) and ethylcellulose (EC) and tried to achieve a sustained release of Act. Their results demonstrated that it is possible to form a solid dispersion by dispersing Act using a spray-drying technique with EC molecules in a molecular state. Interaction mechanisms between the drug and the carrier in solid dispersions have also been studied. We investigated the interaction of ibuprofen with PVP in a solid state by IR and ^{13}C-NMR.[24] We also examined the interaction between carbamazepine or ethenzamide and lactose by IR.[25] In these cases, there appeared to be an interaction between the carriers of the drug and the hydrogen bonds. The dissolution rate of the drug quickened considerably in comparison with original drug through such an interaction.

In this paper, we present a new particle engineering technology with the aim of designing the slow release of matrix particles for oral administration. In this formation, we attempt to achieve slow release in the digestive tract using chitosan (Cht) as the carrier and solid dispersions in carriers and between drugs. Chitosan has been shown to possess mucoadhesive properties[26—28] due to attractive molecular forces formed by electrostatic interaction between positively charged chitosan and negatively charged mucosal surfaces.

We then, attempted particle design for the slow release of the drug by forming a solid dispersion using a 4-fluid-nozzle spray-drying technique that used Cht as a carrier.

Experimental

Materials Japan Chelate Co., Ltd. supplied a chitosan (Cht) carrier with a calculated deacetylation degree of 89.0% from the amino group content, and with a coefficient of viscosity of 70 mPa·s. Fujisawa Astor Co., Ltd. supplied acetaminophen (Act) as a model drug. Other materials and solvents were of analytical reagent grade.

Features of the 4-Fluid-Nozzle Spray Dryer The 4-fluid-nozzle spray

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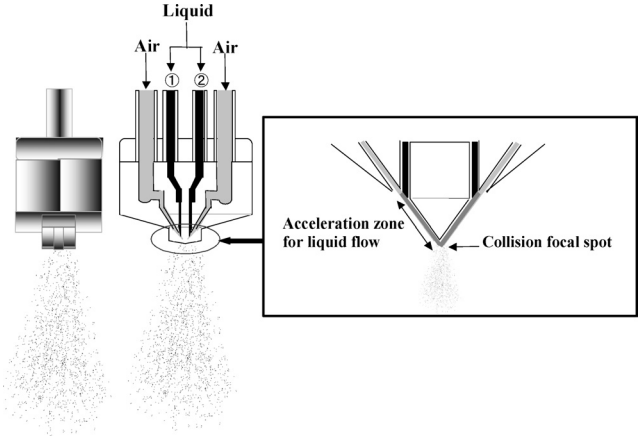

Fig. 1. 4-Fluid Nozzle Mechanism

Table 1. Operating Conditions for Spray Drying

Inlet temperature (°C)	150
Outlet temperature (°C)	75—85
Spray rate (ml/min)	10
Blower (Hz)	60
Spray air volume (l/min)	40—40
Drying air volume (m^3/min)	0.8

dryer (Micro Mist Dryer, MDL-050B, Fujisaki Electroric Co., Ltd., Japan) installed two gas supply route (0.2×2.0 mm) and two liquid-feed roads (0.25×2.0 mm), as shown in Fig. 1. The nozzle edge is composed of a slope that acts as a fluid flow plane, and the edge tip has a 2.0 mm straight section. Gas and liquid instantaneously mix by the outside mixed mode, which is made to gather the collision focus points at the tip of the nozzle edge. That is, the liquid extended by the gas is atomized in the shock wave that arises from the collision focus of the edge tip. Therefore, in this method the mean particle size is also a smaller than in the conventional 2 fluid nozzle spray drier for particle size distribution.

Preparation of Physical Mixtures The physical mixtures were prepared by mixing the drug and the carrier (the tested weight ratios of the drug and the carrier were 1 : 1 and 1 : 5, 10 g : 10 g, and 2 g : 10 g) using a test tube mixer (Scientific Industries, Vortex-Genie 2, Japan) for 10 min at a constant amplitude and rate. However, Act used the spray drying particles under the condition outlined in Table 1.

Preparation of Composite Particles The physical Act and Cht mixtures (which had weight ratios of 1 : 1 and 1 : 5, respectively) were dissolved in 1000 ml water. These solutions were spray-dried under the following conditions: the inlet temperature was 150 °C, the drying air flow rate was 0.80 m^3/min, the atomizing air pressure was 100 kPa, and the outlet temperature was 75—85 °C. The matrix particles were prepared by spray drying using the 4-fluid-nozzle spray dryer.

Confirmation of the Particle Morphology A scanning electron microscope (SEM, JEOL Type JSM-T20, Japan) was used to observe the morphology of the original drug, the physical mixture, and the matrix particles.

Measurement of Particle Size Distribution Particle size distribution was measured using laser diffraction scattering particle size distribution measurement equipment (LSM-30, Seishin Kigyo Co., Ltd., Japan).

Powder X-Ray Diffraction Powder X-ray diffraction analysis was performed with a Rigaku Geiger-Flex diffractometer (Rad-2VC, Japan) using a Ni-filter, Cu$K\alpha$ 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°.

Thermal Analysis Differential scanning calorimetry (DSC) was carried out with a type of DSC-60 instrument (Shimadzu Co., Ltd., Japan). The operating conditions in the open pan system were: sample weight, 10 mg; heating rate, 10 °C/min.

Infrared Spectroscopy FT-IR spectra were obtained with a type FT/IR4000 spectrometer (JASCO Corporation, Japan) using a transformation of 100 scans obtained using the KBr disk method.

^{13}C CP/MAS Solid-State NMR Spectrum The interaction between Cht and Act was confirmed using a ^{13}C CP/MAS solid-state NMR (JNM-ECA-500, JEOL, Japan) with a 4 mm CPMAS.

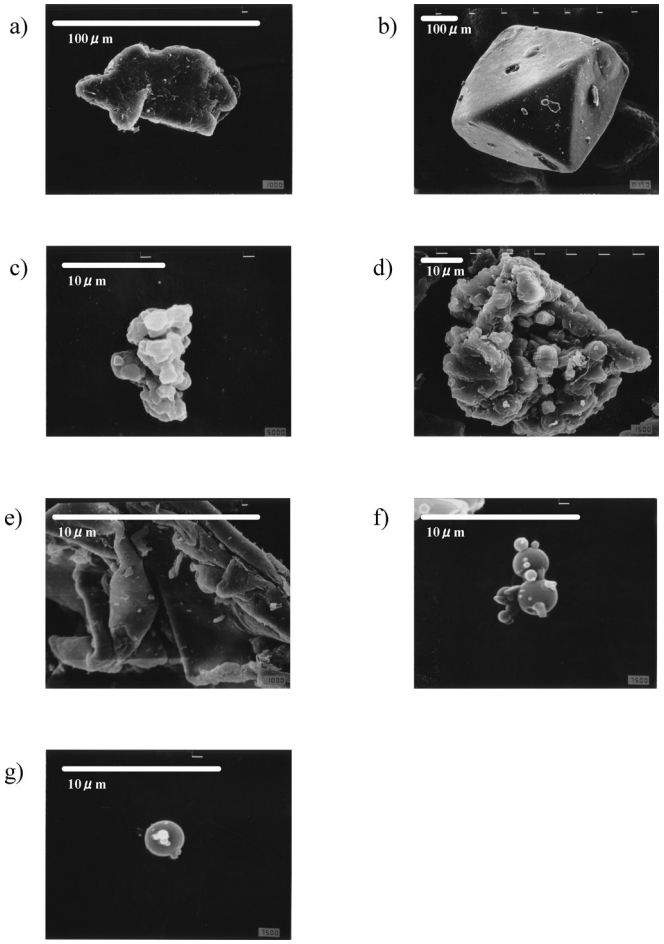

Fig. 2. SEM Sample Photographs

(a) Chitosan; (b) acetaminophen; (c) acetaminophen S.D.; (d) Act : Cht = 1 : 1 P.M.; (e) Act : Cht = 1 : 5 P.M.; (f) Act : Cht = 1 : 1 S.D.; (g) Act : Cht = 1 : 5 S.D.; P.M.: physical mixture, S.D.: spray dried.

Preparation of Model Tablet A flat-face model tablet, 50 mg in Act weight and 10-mm in diameter, was prepared using a universal tension and compression tester (Shimadzu Autograph AG5000D, Japan) at compression pressure of 62.4 MPa.

Dissolution Test Dissolution tests were performed on the model tablet using the JPXIV paddle method, including 50 mg of the drug and 1000 ml of the dissolution medium at pH 1.2 or pH 6.8 at 37±0.5 °C. The rotation speed of the paddle was 75 rpm. The quantity of acetaminophen was assayed by HPLC at 225 nm. The mobile phase was a 0.05 M KH_2PO_4 solution : CH_3OH = 4 : 1 (v/v), which flowed through an ODS column (Cosmosil 5C18-AR, 4.6×150 mm, Nacalai Tesque, Japan) at a rate of 0.5 ml/min.

Results and Discussion

Confirmation of Matrix Particles Formation Scanning electron micrographs of the samples are shown in Fig. 2. Act and Cht consisted of irregular-shaped particles. Examination of the electron micrographs confirmed that the drug and the carrier were mixed almost uniformly in the physical mixture. The matrix particles prepared by 4-fluid-nozzle spray-drying were spherical with a smooth surface.

Figure 3 shows the particle size distribution obtained under the conditions used here for spray drying. The mean particle diameter of the 4-fluid-nozzle spray-dried sample of Act : Cht = 1 : 1 S.D. (the mean particle diameter was about

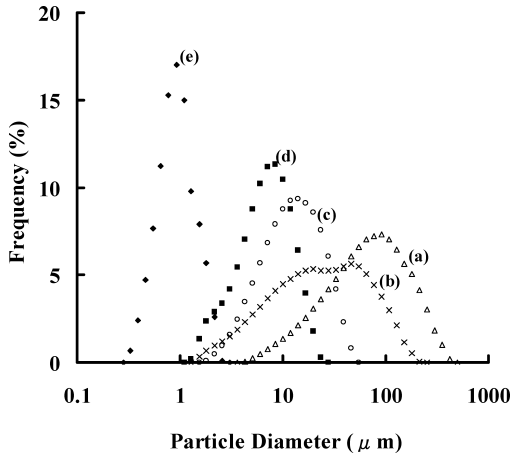

Fig. 3. Particle Size Distribution of Samples

(a) Chitosan; (b) acetaminophen; (c) acetaminophen S.D.; (d) Act : Cht=1 : 1 S.D.; (e) Act : Cht=1 : 5 S.D.

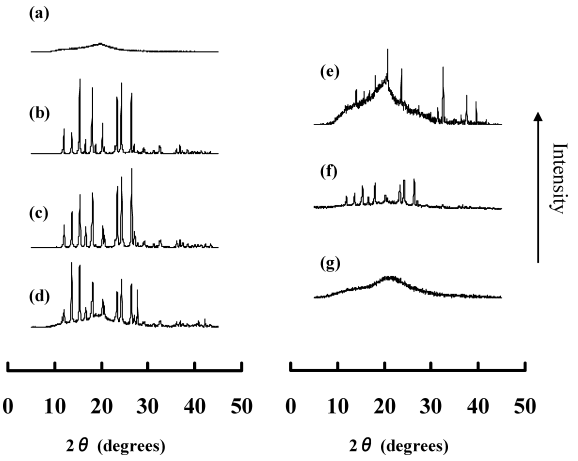

Fig. 4. Powder X-Ray Diffraction Patterns of Samples

(a) Chitosan; (b) acetaminophen; (c) acetaminophen S.D.; (d) Act : Cht=1 : 1 P.M.; (e) Act : Cht=1 : 5 P.M.; (f) Act : Cht=1 : 1 S.D.; (g) Act : Cht=1 : 5 S.D.

10 μm) decreased further than the mean particle diameter of the sample (the mean particle diameter was 15 μm) when only Act was spray dried. However, the mean particle diameters of the 4-fluid-nozzle spray-dried Act : Cht=1 : 5 S.D. samples (the mean particle diameter was 1.0 μm) decreased considerably more than the mean particle diameters of other samples, as shown in Fig. 3.

Confirmation of the Crystallinity of Act in Matrix Particles Figure 4 shows the powder X-ray diffraction patterns for Act, the carrier, their physical mixtures, and the samples prepared using the 4-fluid-nozzle spray-drying technique. Many sharp peaks were observed in the Act diffraction patterns. Cht exhibited signs of being amorphous, because diffraction peaks were not observed. However, in the physical mixtures, although the amplitude of the diffraction peaks decreased with an increase in the mixing ratio of Cht, we could still confirm crystallinity. On the other hand, the diffraction peaks decreased, and Act's crystallinity remained on the spray dried sample of Act : Cht=1 : 1. However, the 4-fluid-nozzle spray-dried sample with Act and Cht (with a mixing ratio of 1 : 5) exhibited signs of being amorphous, because diffraction peaks were not observed. These results indicate that the 4-fluid-nozzle spray-dried samples with 1 : 5 mixing

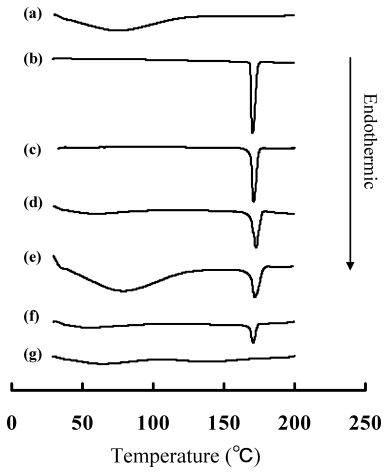

Fig. 5. DSC Thermograms of Samples

(a) Chitosan; (b) acetaminophen; (c) acetaminophen S.D.; (d) Act : Cht=1 : 1 P.M.; (e) Act : Cht=1 : 5 P.M.; (f) Act : Cht=1 : 1 S.D.; (g) Act : Cht=1 : 5 S.D.

Table 2. 70% Dissolution Time (T_{70}) of Acetaminophen

	pH 1.2 T_{70} (h)	pH 6.8 T_{70} (h)
Act S.D.	0.24	0.22
Act : Cht=1 : 1 P.M.	1.14	0.75
1 : 5 P.M.	4.36	1.32
Act : Cht=1 : 1 S.D.	1.72	0.71
1 : 5 S.D.	8.66	9.12

ratios formed solid dispersions, which implies that the drug could be dispersed homogeneously in an amorphous state.

DSC measurements were carried out in order to confirm the matrix particles that were suggested by the X-ray diffraction results. Figure 5 shows the DSC Act thermograms, the carriers, their physical mixtures, and the samples prepared using the 4-fluid-nozzle spray-drying technique. The melting points of the samples are listed in Table 1 together with the heat fusion results for the samples (ΔH), which were used as an index of crystallinity, Xc. Xc was calculated according to the following equation.

$$\text{Xc}\ (\%)=(\Delta H/\Delta H_0)\times 100 \quad (1)$$

where ΔH_0 is the heat of fusion of the crystalline form and ΔH is the heat of fusion of the samples.

The ΔH values of the physical mixture showed that they were almost equal. However, for the samples prepared using 4-fluid-nozzle spray drying with a ratio of Act : Cht=1 : 1, the ΔH values were very small, as Table 2 shows, suggesting a decrease in the Act crystallinity. However, the ΔH of Act : Cht=1 : 5 in the 4-fluid-nozzle spray-drying technique was not calculated, because their samples had no endothermic peaks.

The X-ray diffraction results and the DSC measurements suggested that, although Act and the carrier could not form solid dispersions with simple physical mixing, solid dispersions could be obtained when the mixtures of the Act : carrier=1 : 5 were 4-fluid-nozzle spray-dried. The degree of Act crystallinity in the solid dispersions was dependent on the ratio of the drug to carrier.

Confirment of Interaction between Act and Cht We

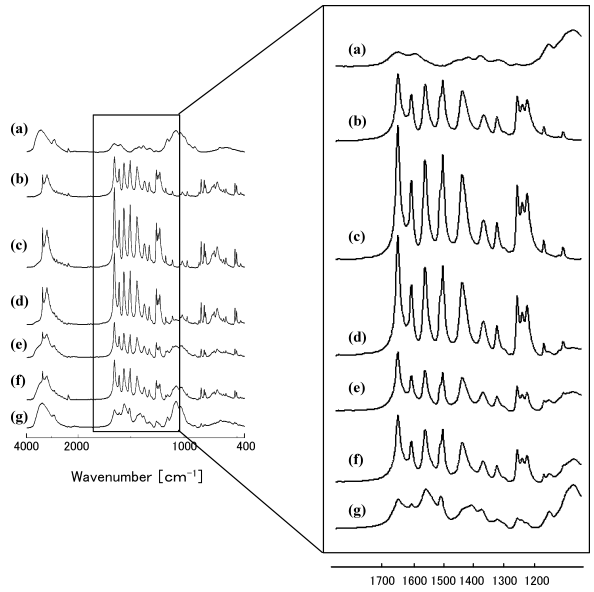

Fig. 6. FT-IR Spectra of Samples

(a) Chitosan; (b) acetaminophen; (c) acetaminophen S.D.; (d) Act : Cht = 1 : 1 P.M.; (e) Act : Cht = 1 : 5 P.M.; (f) Act : Cht = 1 : 1 S.D.; (g) Act : Cht = 1 : 5 S.D.

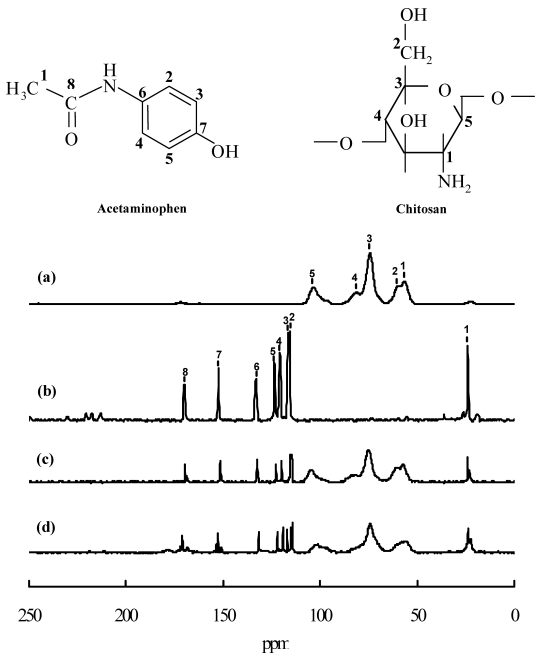

Fig. 7. Possible Structure of Solid Dispersion and Solid-State ^{13}C-CP/MAS NMR Spectra

(a) Chitosan; (b) acetaminophen; (c) Act : Cht = 1 : 5 P.M.; (d) Act : Cht = 1 : 5 S.D.

reported on the interaction of the composite particles where the Act/Cht systems were prepared in advance by spray drying. It was reported that in that time, the NH bending vibration close to 1600 cm^{-1} of Cht shifted to about a 50 cm^{-1} lower wavenumber. On the other hand, the band due to the Act carbonyl group at 1656 cm^{-1} disappeasred. These results suggest that the interaction occurred between the Act carbonyl group and the Cht NH group. Therefore, analysis was carried out focusing on the NH bending vibration close to 1600 cm^{-1} of Cht and the C=O stretching vibration close to 1656 cm^{-1} of Act.

Figure 6 shows the results of the FT-IR spectroscopy of Act, Cht, and their 4-fluid-nozzle spray-dried samples. Act showed bands at 3324.7 cm^{-1} due to a stretching vibration in the amide group, at 1564.0 cm^{-1} due to an NH bending vibration, and at 1654.6 cm^{-1} due to a stretching vibration in the carbonyl group.

On the other hand, Cht showed a broad band at 3414.0 cm^{-1} due to a stretching vibration in the hydroxyl group and a band at 1600.6 cm^{-1} due to an NH bending vibration. These bands were similarly observed for the physical Act and Cht mixtures, which suggests that there was no interaction between Act and Cht in the physical mixture. The band caused by the carbonyl group stretching vibration of Act in the 1 : 5 solid dispersion shifted slightly to a lower wavenumber, while the band caused by the Cht amino group at 1600.6 cm^{-1} disappeared. These observations suggest that the interaction was caused by the Act carbonyl group and the Cht amino group with hydrogen bonds.

In addition, we confirmed these interactions using a ^{13}C CP/MAS solid-state NMR. Figure 7 shows the spectrum of ^{13}C CP/MAS solid-state NMR samples. There was no change in the 169.69 ppm chemical shift of the Act amino group in the physical mixture, when the Act carbonyl group and Cht amino group were observed along with FT-IR in the tip. However, the chemical shift of the carbonyl group when spray drying the mixture ratio of 1 : 5 slightly shifted to 170.09 ppm. On the other hand, in the physical mixture, the 56.45 ppm chemical shift shifted to 58.17 ppm, when the Cht animo group was observed, and when spray drying the pharmaceutical preparation, it shifted to 58.33 ppm. From the results of these ^{13}C CP/MAS solid-state NMRs and FT-IR in the tip, it appears that the pharmaceutical preparation prepared with the 4-fluid-nozzle spray-drying technique had formed an Act carbonyl group and a solid dispersion between the Cht amino group clarified by hydrogen bonds.

Release Rate of Acetaminophen from the Matrix Particles In the present study, we prepared matrix particles using the 4-fluid-nozzle spray-drying technique and focused on the sustained release of Act. The relationship between the Act release rate from the matrix particles and the interaction between the drug and the carrier was examined in the following way.

The release profiles of acetaminophen from the physical mixtures and matrix particles were obtained at pH 1.2, as shown in Fig. 8. The dissolution in which Act S.D. was the quickest is shown. The dissolution was dependently delayed at the Cht content in the case of the physical mixture, as shown in Fig. 8. This originates from the property that dissolves after Cht forms a gel in the acid solution. A spray dried sample of 1 : 1 S.D. was returned for prediction, and it showed the quick dissolution rate. In the case of this sample, the equal tendency with the physical mixture of the effect of the Cht dissolution improvement by the dissolution retard effect of the gel-formation and lowering of the crystallinity by the spray drying method canceled was shown. On the other hand, the mixture ratio showed most the dissolution delay in the 1 : 5 spray drying sample. We regard this as a major appearance of the Cht gel-forming effect, since the mixture ratio formed a solid dispersion on the 1 : 5 spray drying sample. The phenomenon in which the chitosan forms gel layer like this in the acid solution is reported by Hou *et al.*[29] and

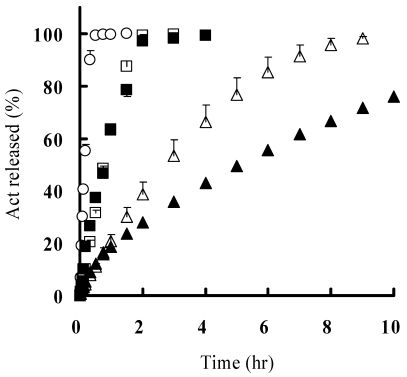

Fig. 8. Dissolution Profiles of Act–Cht Systems (Mean±S.D. (n=3)) in pH 1.2

○, acetaminophen S.D.; □, Act : Cht=1 : 1 P.M.; △, Act : Cht=1 : 5 P.M.; ■, Act : Cht=1 : 1 S.D.; ▲, Act : Cht=1 : 5 S.D.; P.M.=physical mixture, S.D.=solid dispersion.

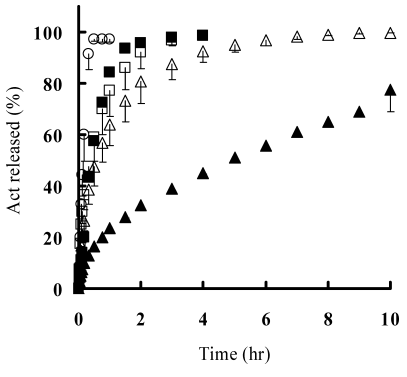

Fig. 9. Dissolution Profiles of Act–Cht Systems (Mean±S.D. (n=3)) in pH 6.8

○, acetaminophen S.D.; □, Act : Cht=1 : 1 P.M.; △, Act : Cht=1 : 5 P.M.; ■, Act : Cht=1 : 1 S.D.; ▲, Act : Cht=1 : 5 S.D.; P.M.=physical mixture, S.D.=solid dispersion.

Sawayanagi *et al.*[30]

Next, we examined the release of acetaminophen from the physical mixture and matrix particles in the pH 6.8 solution. The release results of are shown in Fig. 9. The effect of the atomization greatly appeared than the insolubility in the alkaline solution of the chitosan on 1 : 1 S.D. dissolution rate at pH 6.8 quickening. Equal dissolution was shown for the same reason as that in the case of 1 : 1 S.D. at pH 1.2. Dissolution of the mixture with a ratio of 1 : 5 S.D was considerably delayed in comparison with other the samples. We believe this is a result of the insoluble effect of the chitosan by the solid dispersion formation greatly appeared on the delay of the dissolution rate of 1 : 5 S.D. at pH 6.8.

We consider the dissolution mechanism of the drug in this system as being different from the Act original, the physical mixture, and the spray dried sample. Also, it seems to be different to the pH of the dissolution solution. For example, though the single drug and the physical mixtures at pH 1.2 are zero-order dissolutions, in the fact, there is no dissolution of the physical mixture at the pH 6.8 zero-order. At present, this case seems to suit the Higuchi equation, particularly when we consider the dissolution of the drug from the matrix particle prepared by spray drying. Figures 11 and 12 show the results, when these experimental dissolution results were plotted using the Higuchi equation. These samples showed

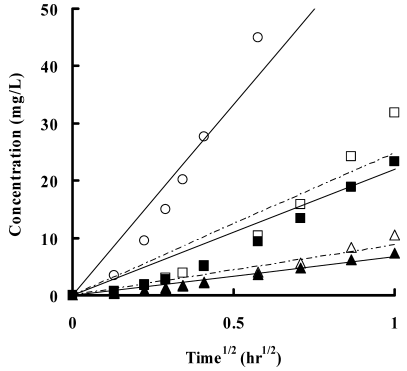

Fig. 10. Higuchi Equation Plots of Act–Cht Systems in pH 1.2

○, acetaminophen S.D.; □, Act : Cht=1 : 1 P.M.; △, Act : Cht=1 : 5 P.M.; ■, Act : Cht=1 : 1 S.D.; ▲, Act : Cht=1 : 5 S.D.

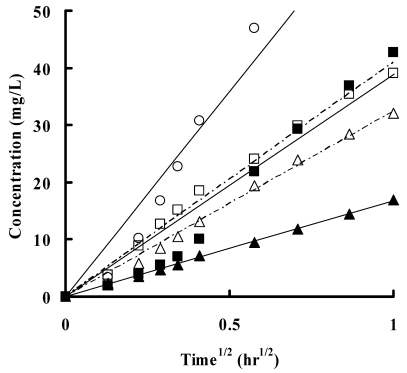

Fig. 11. Higuchi Equation Plots of Act–Cht Systems in pH 6.8

○, acetaminophen S.D.; □, Act : Cht=1 : 1 P.M.; △, Act : Cht=1 : 5 P.M.; ■, Act : Cht=1 : 1 S.D.; ▲, Act : Cht=1 : 5 S.D.

the good linearity in the initial stages of dissolution. However, analysis using the Higuchi equation is regarded as being inappropriate, because the single drug and the physical mixture have not formed a matrix. Therefore, the release results obtained in this study should be compared using a release time of 70% (T_{70}). The T_{70} values are shown in Table 2. The T_{70} of Act/Cht=1/5SD in the pH 1.2 fluid was about 36-fold higher than that of Act, and at pH 6.8 it was about 41-fold higher than that of Act.

The rate of release from the physical mixture in the pH 1.2 fluid was reduced in comparison with that of acetaminophen. This stems from the dissolving property after the chitosan forms a gel in the acid solution at the initial stage of release. Furthermore, the rate of release from physical mixture in the pH 6.8 fluid was reduced due to the insolubility in the alkaline solution of the chitosan.

Conclusions

Acetaminophen formed solid dispersions with chitosan when the mixtures of the drug and the carrier were spray-dried. As a result of the formation of solid dispersions, acetaminophen became amorphous.

Acetaminophen, which is poorly soluble in water, showed a markedly sustained release from the solid dispersions with the drug and the carrier at a ratio of 1 : 5.

The dissolution of the physical mixture and the imperfect solid dispersions in pH 1.2 and 6.8 fluids did not show a sustained release.

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