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EFFECTS OF MIXER AND MIXING TIME ON THE PHARMACEUTICAL PROPERTIES OF THEOPHYLLINE TABLETS CONTAINING VARIOUS KINDS OF LACTOSE AS DILUENTS

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ABSTRACT

Effect of mixing time on the flowability, compressibility, tablet hardness and dissolution of theophylline tablets was investigated using two types of mixers, i.e., twin-shell and high-speed mixers. Theophylline, three kinds of lactose (α-monohydrate, β-anhydrate and spray-dried product), disintegrator and magnesium stearate were mixed, and tablets were compressed. While the particles mixed with magnesium stearate by the high-speed mixer were coated with magnesium stearate, those mixed by the twin-shell mixer formed an ordered mixture. The dissolution differed depending on the mixing time and method.

INTRODUCTION

In pharmaceutical preparations, fluctuations in bioavailability and/or side effects are caused by nonuniformity of drug content. Thus, the role of the mixing process is

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important in manufacturing high quality pharmaceuticals. Recent studies[1-6] have indicated that some drugs and excipients interact with each other when thoroughly mixed. Specific particle-particle interactions involving drug and excipients may result in incomplete dissolution[1-5] and/or a decrease in tablet hardness.[6] The decrease in the drug dissolution rate and the tablet hardness is attributed to the addition of magnesium stearate as a lubricant in these formulations. Since magnesium stearate plays an integral part in reducing the dissolution rate with prolonged mixing, these interactions may be specific to this lubricant. These interactions and their adverse effects on drug dissolution can be avoided by carefully evaluating and selecting excipients. It is therefore important to study the effects of added magnesium stearate in drug-excipient interactions. On the other hand, recently, specific mixing states have been produced by dry mixing of fine and coarse particles, in which the fine particles adhere to the suface of coarser particles and make an "ordered" mixture.[7-8] In this study, we investigated the effect of mixing on the pharmaceutical properties of tablets containing theophylline and various kinds of lactose.

MATERIALS AND METHODS

Materials

A bulk powder (lot No. 11085) of theophylline anhydrate was obtained from Nakarai Co., Japan. α-lactose monohydrate,[10] spray-dried α-lactose (DLC 11) and β-lactose anhydrate (DLC 21)[11] were obtained from De Melkindustrie Veghel Co., Netherlands. Pregelatinized starch (PCS; Asahikasei Co., Japan) and magnesium stearate (Kishida Chem. Co.) were used as a disintegrator and a lubricant, respectively.

Measurement of specific surface area and particle diameter

The specific surface area (S_w) of the sample powder was measured 3 times by the air permeability method (Type SS-100,

Table 1. Specific surface area (S_w), average particle size ($\bar{d}$) and true density (D) of three kinds of lactose

Sample	S_w $\times 10^3$ cm^2/g	$\bar{d}$ (μm)	D (cm^2/g)
α-monohydrate	3.32	11.7	1.57
β-anhydrate	1.25	30.5	1.53
spray-dried	1.24	31.5	1.55

Shimadzu Co.). The average particle diameter was calculated from the data of the S_w by assuming a sphere. The S_w and average particle diameter of three kinds of lactose are summarized in Table 1.

Measurement of powder density

The powder density was measured 3 times by using an air pycnometer (Model 930, Beckman). The powder densities of lactose are summarized in Table 1.

Measurement of tapping rate constant

The tapping rate constants of the mixed powders were measured as follows: Sample powder (7 g) was put into a graduated cylinder (1 cm in diameter and 25 ml in volume) and the apparent volume of powder was measured during tapping (RHK-type tapping instrument, Konishi Co.). The tapping rate constants were estimated by the least-squares method based on Kuno's equation (eq. 1).

$$p_f - p_n = (p_f - p_o) \exp(-kn) \quad \text{eq. 1}$$

where p_f is the bulk density of the sample powder at infinite tapping number, p_o is the bulk density at the initial packing, p_n is the bulk density at tapping number n, k is the tapping rate constant and n is number of taps.

Methods mixing of the sample powders

The formulation of the tablet was as follows: Active ingredient, theophylline, 10%; diluent, lactose, 83%;

disintegrator, PCS, 5%; lubricant, magnesium stearate, 2%. All sample powders without lubricant were mixed for 60 min in a twin-shell mixer (Tokujyu Ind. Co., Model V-1, capacity: 2 l, mixing speed 28 rpm). They were then mixed with lubricant in the same twin-shell mixer or in a high-speed mixer (Fukae Powtec Co., rotor speed, 1000 rpm; agitator speed, 1500 rpm) for 0 - 60 min.

Tablet preparation

Tablets (300 mg) were compressed 1.5 cm/min using a 0.8-cm diameter punch and die at compression 0.5, 1.0 or 2.0 ton/cm^2 by a compression/tension testing machine (IS 5000, Shimadzu Co.). The surface area and volume of the tablet were calculated from the tablet thickness and diameter measured with a micrometer. The hardness of the tablet was measured 4 times using a hardness tester (Erweka Co.).

X-ray powder diffraction analysis

X-ray powder diffraction profiles were taken at room temperature with an X-ray diffractometer (XD-3A, Shimadzu Co.). The operating conditions were as follows: target, Cu; filter, Ni; voltage 20 kV, current, 5 mA; receiving slit, 0.1 mm; time constant, 1 s; counting range, 1 kcps; scanning speed 1° 2θ/min. The X-ray diffraction profiles of lactose samples were identified using diffraction patterns reported previously,[10,11], as shown in Figure 1.

Scanning electron microscopy

Scanning electron microphotographs of samples were taken with a model JSM-T20 (Jeol Co.) microscope at a magnification of x 35 - 5000.

Dissolution study using the dispersed amount method

Dissolution profiles of theophylline tablets were investigated in the 1st fluid (pH 1.2) at 37 $\pm$ 0.5°C (JP XI) using a dissolution instrument (TR 5S, Toyama Sangyo). The sample tablet was put into 600 ml of dissolution medium in a 1000-ml

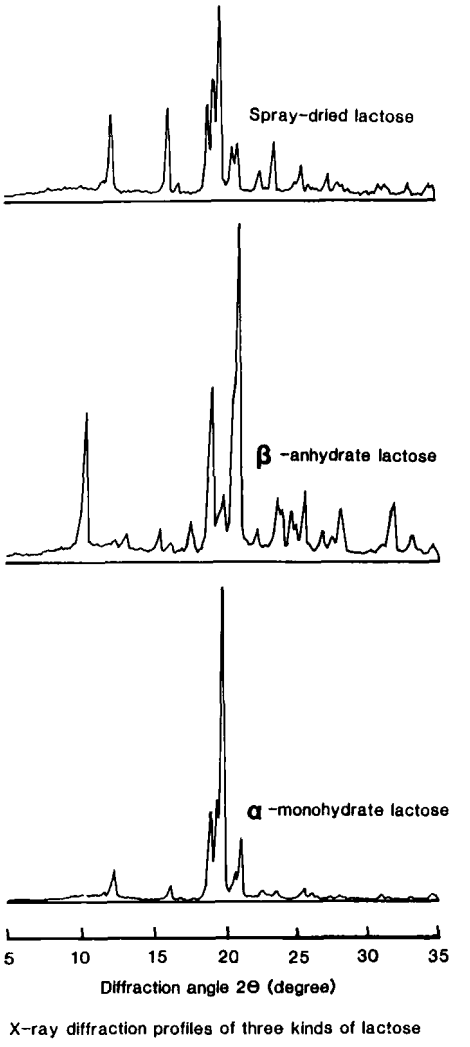

Fig. 1. X-ray powder diffraction profiles of three kinds of lactose

round bottomed flask with a plastic cover, and was rotated by the paddle at 70 ± 5 rpm. The solution was pumped into a quartz flow-through cell and the concentration was determined spectrophotometrically at 280 nm. Dissolution profiles were measured 3 times for each formulation.

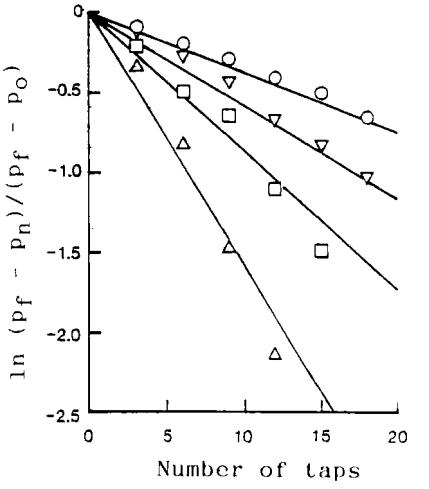

Fig. 2. Effect of mixing time by high-speed mixer on Kuno's plots for α-monohydrate
○, unmixed; □, mixed for 5 min; △, mixed for 15 min; ▽, mixed for 30 min.

RESULTS

Effects of mixer and mixing time on the powder flowability

Figure 2 shows the effect of mixing time by the high-speed mixer on Kuno's plot for α-monohydrate. The plots of all samples showed straight lines, and the tapping rate constants were estimated from the plots by the least-squares method.

Figure 3 shows the effect of mixing time on the tapping rate constants. In the case of mixing by the twin-shell mixer, the tapping rate constant of all samples increased with increased mixing time, indicating that the powder flowability depended on the degree of mixing. However, the tapping rate constants of all samples mixed for 30 min by the high-speed mixer decreased.

Effects of mixer and mixing time on compactivity

Duberg and Nyotrom[12] reported that the slope of the linear portion of the compression curve in a Heckel plot reflects the deformability of the tablet, and derived the yield pressue (Py)

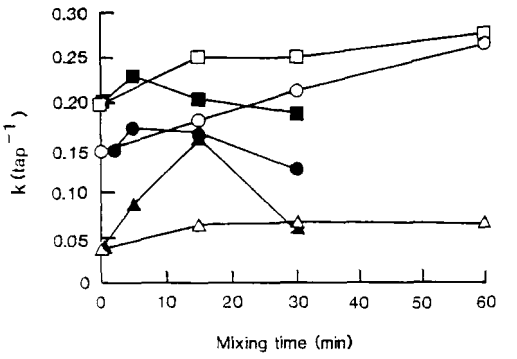

Fig. 3. Effects of mixer and mixing time on tapping rate constant ○ ●, spray-dried; □ ■, β-anhydrate; △ ▲, α-monohydrate. The open and closed symbols indicate twin-shell and high-speed mixers, respectively.

from Heckels equation (eq. 2).

$$\ln(1/(1-D)) = K P + A \qquad \text{eq. 2}$$

$$Py = 1/K \qquad \text{eq. 3}$$

Figure 4 shows the effects of mixer and mixing time on Heckel plots for α-monohydrate. All Heckel plots of samples mixed by the twin-shell mixer showed a similar pattern, but those mixed by the high-speed mixer depended on the mixing time. These results indicate that the twin-shell mixer was less effective than the high-speed mixer.

Figure 5 shows the effect of mixer and mixing time on tablet deformability. The Py of lactose powders mixed with the twin-shell mixer did not change with mixing time. In contrast, in the case of the high-speed mixer the Py depended on the type of lactose. The Py for β-anhydrate was lowest when mixed for 15 min, and was increased by further mixing. The Py of the spray-dried product after 30 min of mixing was about double that of the initial smple. The Py's of α-monohydrate were unchanged.

Figure 6 shows the effects of mixer and mixing time on tablet hardness. The order of the hardness of tablets using

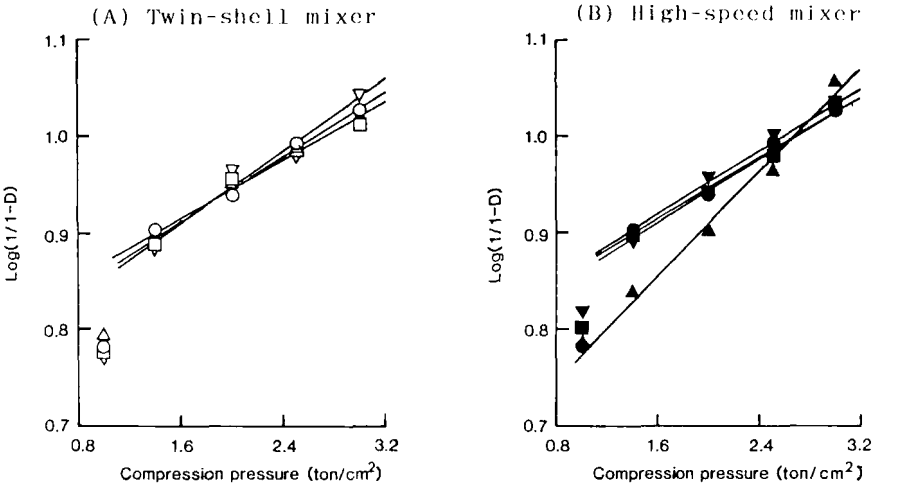

Fig. 4. Effects of mixer and mixing time on Heckel plots for α-monohydrate
○ ●, unmixed; □, mixed for 15 min by twin-shell mixer; △, mixed for 30 min; ▽, mixed for 60 min; ■, mixed for 5 min by high-speed mixer; ▲, mixed for 15 min; ▼, mixed for 30 min.

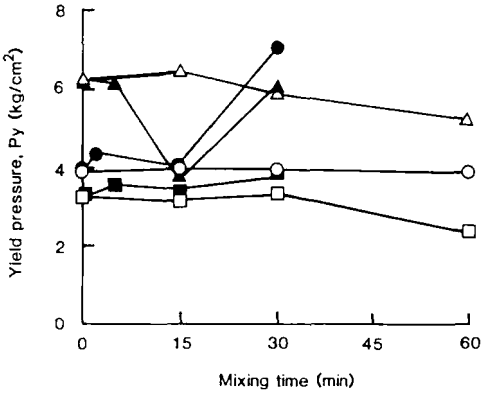

Fig. 5. Effects of mixer and mixing time on the yield pressure
○ ●, spray-dried; □ ■, β-anhydrate; △ ▲, α-monohydrate. The open and closed symbols indicate twin-shell and high-speed mixers, respectively.

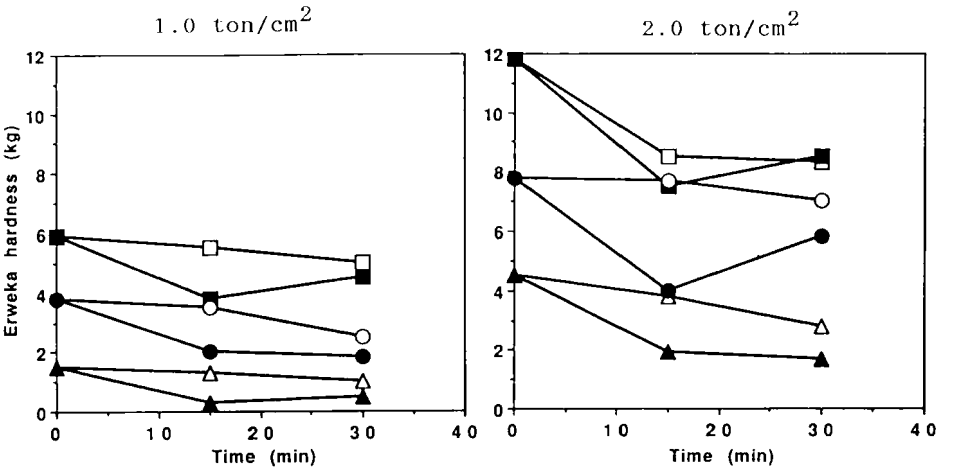

Fig. 6. Effects of mixer and mixing time on tablet hardness
○ ●, spray-dried; □ ■, β-anhydrate;
△ ▲, α-monohydrate. The open and closed symbols indicate twin-shell and high-speed mixers, respectively.

lactose was β-anhydrate > spray-dried > α-monohydrate. The hardness of all lactose tablets mixed by the twin-shell mixer slightly decreased with increased mixing time. However, the hardness of all lactose tablets mixed by the high-speed mixer for 15 min was lower than that of the unmixed tablets, and the hardnesses of α-monohydrate and β-anhydrate mixed for 30 min were greater than those mixed for 15 min.

Dissolution profiles of theophylline tablets

Figure 7 shows the dissolution profiles of α-monohydrate tablets mixed by the twin-shell and high-speed mixers. All dissolution rates for tablets mixed by the high-speed mixer were much higher than those of tablets mixed by the twin-shell mixer. Figure 8 shows the effects of mixer and mixing time on the time required for 50% dissolution ($T_{50\%}$). With the twin-shell mixer there was no effect of mixing time on the dissolution rate. On the other hand, $T_{50\%}$ for tablets mixed by the high-speed mixer

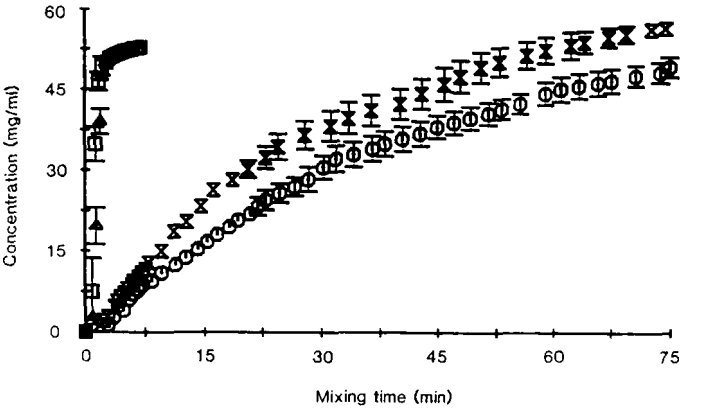

Fig. 7. Effects of mixer and mixing time on the dissolution profiles for α-monohydrate □, unmixed; △, mixed for 30 min by twin-shell mixer; ○, mixed for 15 min by high-speed mixer; ⧖, mixed for 30 min.

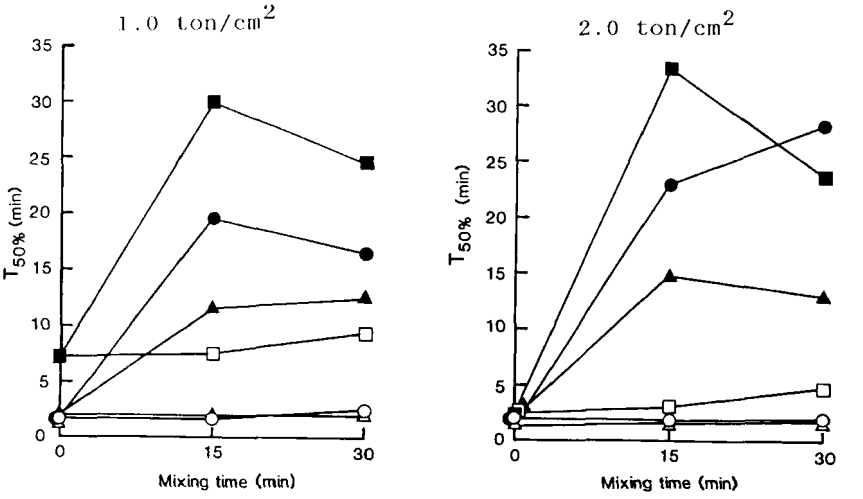

Fig. 8. Effects of mixer and mixing time on the time required for 50% dissolution
○●, Spray-dried; □■, β-anhydrate; △▲, α-monohydrate. The open and closed symbols indicate twin-shell and high-speed mixers, respectively.

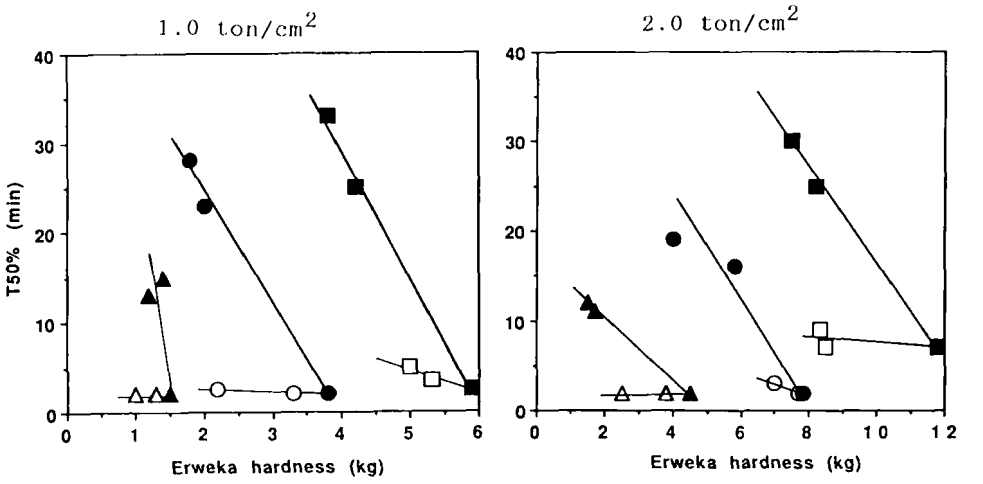

Fig. 9. Relation between tablet hardness and the time required for 50% dissolution ○ ●, spray-dried; □ ■, β-anhydrate; △ ▲, α-monohydrate. The open and closed symbols indicated twin-shell and high-speed mixers, respectively.

for 15 min were longer than those of the unmixed tablets, and the values after mixing for 30 min were lower than those after 15-min mixing.

Relation between tablet hardness and dissolution

Figure 9 shows the relation between tablet hardness and $T_{50\%}$ for twin-shell and high-speed mixers. While the tablet hardness was affected by mixing time for all mixers, tablet dissolution was affected by mixing mode, and depended on the type of mixer.

Particle size and surface morphology

Figures 10 and 11 show scanning electron microphotographs of powders mixed in the twin-shell and high-speed mixers. The surfaces of particles mixed in the twin-shell mixer were covered by numerous fine particles of magnesium stearate (Fig. 10), but in the ease of the high-speed mixer the surfaces were

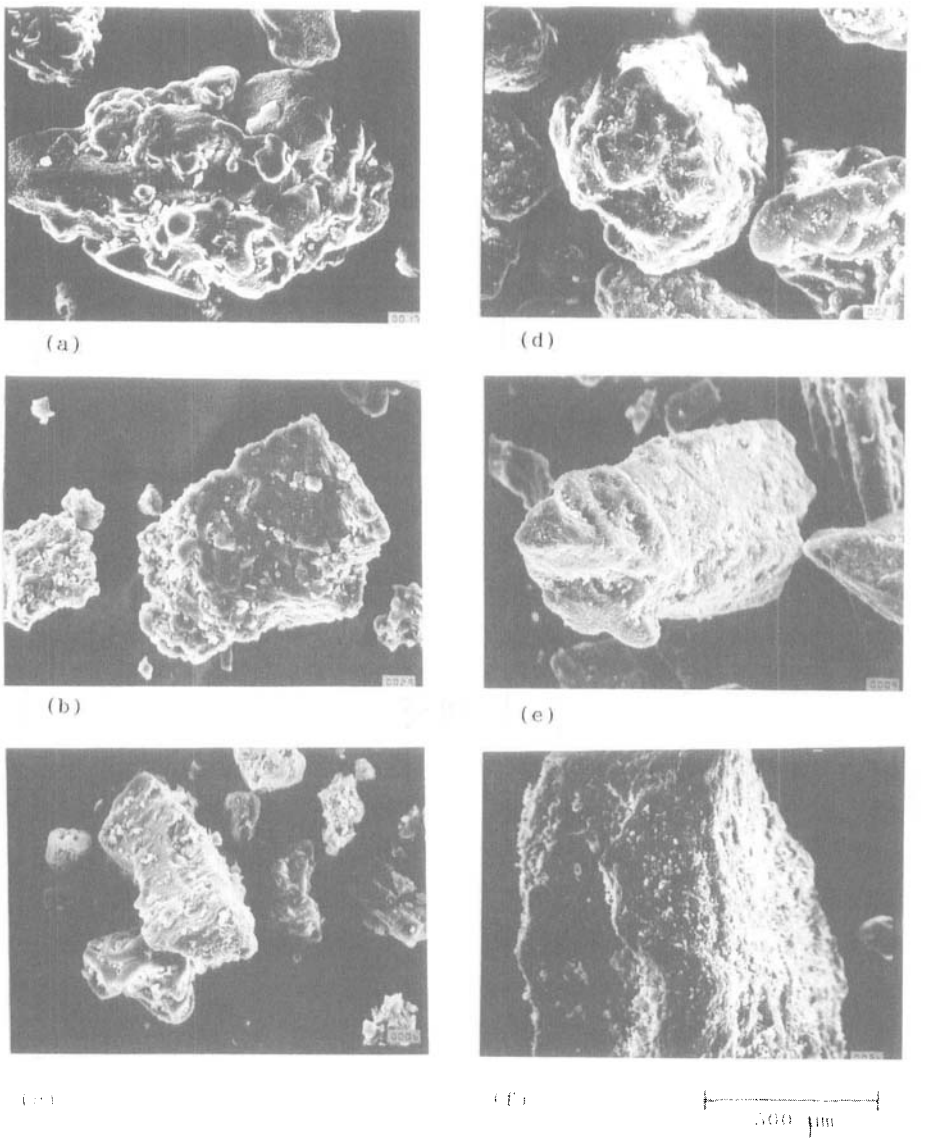

Fig. 10. Effects of mixer and mixing time on the surface morphology of the resultant secondary powders (x 1000)
(a, d), spray-dried; (b, e), β-anhydrate; (c, f), α-monohydrate;
(a, b, c), mixing for 60 min by twin-shell mixer;
(d, e, f), mixing for 15 min by high-speed mixer.

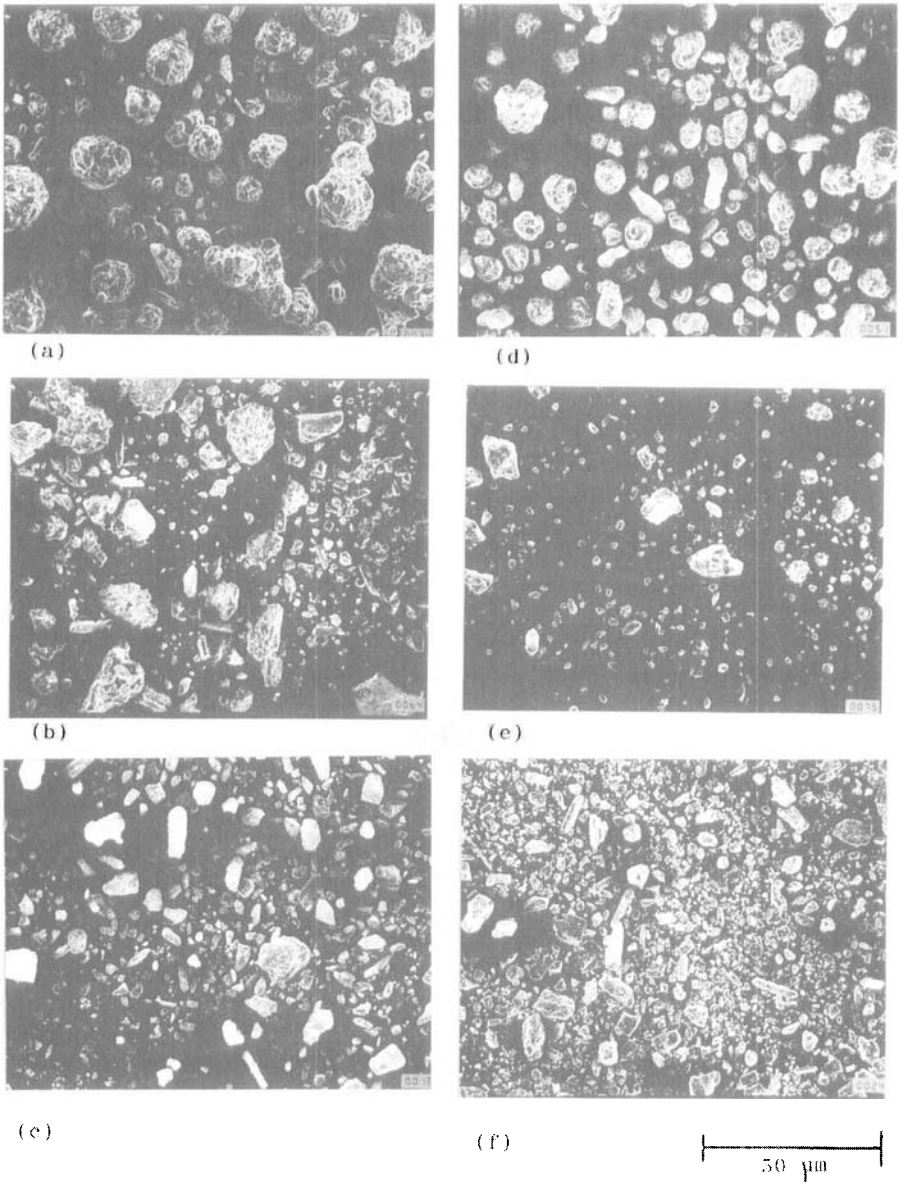

Fig. 11 Effects of mixer and mixing time on the particle size of secondary powders (x100) (a, d), spray-dried; (b, e), β-anhydrate; (c, f), α-monohydrate; (a, b, c), mixing for 60 min by twin-shell mixer;(d, e, f), mixing for 30 min by high-speed mixer.

were smaller than those obtained from the twin-shell mixer (Fig. 11).

DISCUSSION

Mixing by the high-speed mixer affected the powder flowability (Fig. 3), tablet compactivity (Fig. 5), hardness (Fig. 6) and dissolution (Fig. 7) of theophylline tablets. On the contrary, mixing by the twin-shell mixer did not significantly affect dissolution. Ishizaka et al.[7,8] reported an ordered mixture with specific mixed states produced by dry mixing of fine and coarse particles. The fine particles adhered to the coarse particles' surfaces, and then the ordered mixture was formed. The scanning electron microphotographs (Fig. 10) indicated that the powders mixed by the twin-shell mixer were the ordered mixture in which fine magnesium stearate particles adhered uniformly to the larger lactose and/or theophylline particles. On the other hand, the large particles were tightly coated with magnesium stearate by mechanochemical effect after they adhered to the surface, because the high-speed mixer imparts more mechanical energy than the twin-shell mixer. Since the powder coated with magnesium stearate was less wetable than the ordered mixtures, dissolution of the powder mixed by the high-speed mixer might take longer than that mixed by the twin-shell mixer. The tablet with mechanochemically coated particles and the ordered mixtures did not have enough mechanical strength, because magnesium stearate particles which are present between the lactose and theophylline particles disturb the bonding of particles during compression.

However, the powder flowability, tablet hardness and $T_{50\%}$ of the powder mixed by high-speed mixer for 30 min was lower than that mixed for 15 min. This finding may be explained as follows: Since the particle sizes in the powder mixed by the

high-speed mixer for 30 min were smaller than those mixed by the twin-shell mixer (Fig. 11), they may have been ground by the propeller of the high-speed mixer, which could change the powder characteristics.

β-anhydrate and the spray-dried product had better powder flowability (Fig. 2) and compactivity than α-monohydrate (Figs. 5 and 6), but the mixing effect on the dissolution of α-monohydrate was siginificantly weaker than the others (Fig. 8). The effects of mixer and mixing time on the pharmaceutical properties of lactose depended on the kind of lactose. Therefore, when a pharmaceutical preparation is designed, it is necessary to consider the type of lactose and the effect of its addition. Further, it is possible to use magnesium stearate to control the dissolution rate by mechanochemical coating.

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