研究論文

STUDY ON MICRONIZATION OF MEDICAL COMPOUND FOR NASAL SUSPENSION

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For the purpose of developing a pharmaceutical suspension for nasal spray containing fine drug substances of controlled particle size, a wet micronization method, using ultrasonic homogenization after converting the particle shape to a fragile structure by spray drying, was examined. It was found that the average particle size of spray dried powder could be reduced to the submicron level. It was also found that the particle size could be controlled by suspension temperature before ultrasonic homogenization because the temperature of the suspended solution is one of the critical parameters for particle size reduction.

In addition, the mechanism of particle size reduction was considered in terms of the change of particle shape and crystal form during the micronization process.

Key Words: Micronization, Suspension, Particle size, Spray drying, Ultrasonic homogenization

1. INTRODUCTION

In the pharmaceutical field, active drug substances rarely are administered as chemical entities but almost always in some kind of formulation. From the efficacy point of view, formulated drug products should be designed so as to maximize the potential activity of drug substances. To optimize the performance of drug products, it is necessary to have a complete understanding of the physicochemical properties of drug substances prior to formulation into drug products. Physicochemical properties of drug substances sometimes affect the product profiles, particularly particle size, which often strongly affects the dissolution rate[1], absorption rate[2] and bioavailability[3]. Therefore, various micronization methods for drug substances have been tried in order to improve the physicochemical properties of drug products[4, 5]. Since sonification has been used as a micronization method[6, 7] as well as a dispersion method of drug substances in suspension, a wet micronization method was considered. However, there is no report of reducing the particle size to submicron level by sonification.

For the purpose of developing a pharmaceutical suspension for nasal spray containing fine drug substances, we endeavored to reduce the particle size of drug substances to submicron level by a wet micronization method, using ultrasonic homogenizer after converting the particle shape to a fragile structure by spray drying.

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2. EXPERIMENTAL

2.1 MATERIALS

A new steroid substance developed at Schering-Plough U.S.A. was used as the drug substance. Specifications of the steroid are shown in Table 1. Benzalkonium chloride, polysorbate 80, propylene glycol and glycerin were used as suspending reagents. All suspending reagents used were GP grade.

Table 1 Specifications of active drug substance

Empirical formula:	$C_{27}H_{30}C_{l2}O_6 \cdot H_2O$
Molecular weight:	539.45
Appearance:	White crystalline powder
Melting point:	215°C
Solubility:	Soluble in acetone and chloroform; practically insoluble in water

2.2 EQUIPMENT

PULVIS MINISPRAY (Yamato Co. Ltd.) was used as the spray dryer and ultrasonic homogenizer, and US-600 (Nihon Seiki Co. Ltd.) was used for micronization. X-ray powder diffractometer,

RAD-RB (Rigaku Co. Ltd.), and spectrophotometer, 215 (Hitachi Co. Ltd.), were used for determination of crystallinity. Particle size distribution analyzer, CAPA-700 (Horiba Co. Ltd.) and scanning electron microscope, S-650 (Hitachi Co. Ltd.), were both used for the particle size and particle shape determination. Median particle size was measured by volume basis.

2. 3 MICRONIZATION METHOD

Drug substances dissolved in methylene chloride were spray dried (spray dried powder) under the conditions listed in Table 2.

Table 2 Conditions of spray drying

Spray solution : 3% active drug substance in methylene chloride
Spray speed : 20 ml/min.
Atomizing air pressure : 294 kPa
Drying air :
Inlet temperature : 55°C
Outlet temperature : 35°C
Flow rate : 0.4 m^3/min.

After suspending spray dried powder (suspended powder) in the solution containing suspending reagent, suspended powder was micronized (micronized powder) by the ultrasonic homogenizer. Typical conditions of micronization method are listed in Table 3.

Table 3 Conditions of ultrasonic homogenization

Sample solution : 30 ml of benzalkonium chloride solution
suspended spray dried powder
Conditions of ultrasonic homogenizer :
Power : 600 W
Frequency : 20 ± 2 kHz
Tip diameter : 36 mm

The effects of suspending reagents, concentration of spray dried powder, concentration of suspending reagent and suspending temperature of spray dried powder on the reduction of particle size of drug substances were evaluated as follows :

2.3.1 SUSPENDING REAGENTS Spray dried powder (50 mg/ml) was suspended in a solution of benzalkonium chloride, polysorbate 80, propylene glycol and glycerin (1.2 mg/ml) at 20°C.

2.3.2 CONCENTRATION OF SPRAY DRIED POWDER Four, 50, and 100 mg/ml of spray dried powder were suspended in 1.2 mg/ml of benzalkonium chloride solution at 20°C.

2.3.3 CONCENTRATION OF SUSPENDING REAGENT Spray dried powder (50 mg/ml) was suspended in 1.2, 2.4, and 5 mg/ml of benzalkonium chloride solution at 20°C.

2.3.4 SUSPENSION TEMPERATURE Spray dried powder (50 mg/ml) was suspended in 1.2 mg/ml of benzalkonium chloride solution at 2, 5, 20, 40, and 60°C.

3. RESULTS

3. 1 SUSPENDING REAGENTS

Since agglomeration of drug substances was observed during ultrasonic homogenization when polysorbate 80, propylene glycol and glycerin were used and was not observed when benzalkonium chloride was used, benzalkonium chloride was selected as the suspending reagent.

3. 2 CONCENTRATION OF SPRAY DRIED POWDER

As shown in Fig.1, the concentration of drug substances had no effect on the reduction of particle size of drug substances. Substantial reduction in particle size was noted after 5 min. exposure time; a plateau was reached at that time, and longer exposure caused little or no further reduction in the mean particle diameter. Fine particles, averaging less than 1.0 μm, were obtained in each trial.

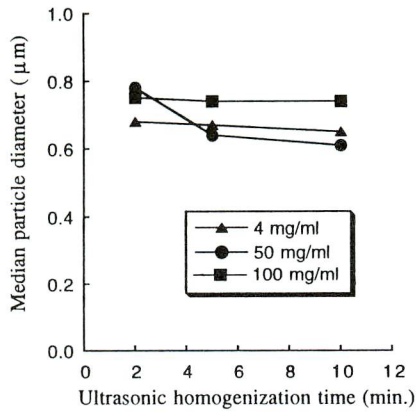

Fig.1 The effect of concentration of spray dried powder on reduction

3. 3 CONCENTRATION OF SUSPENDING REAGENT

As shown in Fig.2, the concentration of benzalkonium chloride had a negligible effect on the reduction of particle size of

drug substances, but smaller particle size of drug substances was observed with higher concentration of benzalkonium chloride. Micronization was completed within 5 min. and fine particles, averaging less than 1.0 μm, were obtained in each trial.

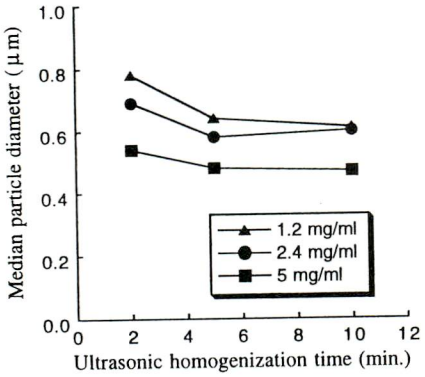

Fig.2 The effect of concentration of suspending reagent on reduction

3.4 SUSPENSION TEMPERATURE

As shown in Fig.3, suspension temperature influenced the reduction of particle size of drug substances, with lower suspension temperatures resulting in smaller particle sizes. Fine particles, averaging less than 1.0 μm, were obtained in each trial. Particularly very fine particles, the average particle size of which was 0.26 μm and 0.30 μm respectively, were obtained when the suspension temperature was 2°C and 5°C.

The particle size distribution of micronized powder after suspension at 2°C is listed in Fig.4. This result indicated that the particle size distribution of micronized powder was sharp and 90% of particles were distributed between 0.1 μm and 0.6 μm.

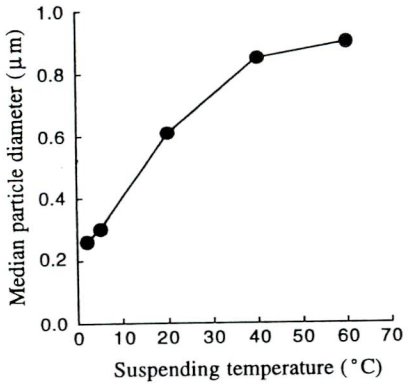

Fig.3 The effect of suspension temperature on reduction

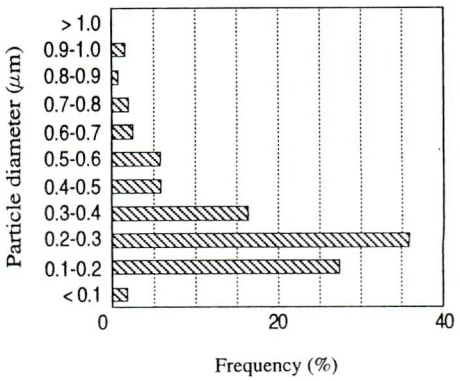

Fig.4 The particle size distribution of micronized powder after suspension at 2°C

3.5 CRYSTALLINITY AND PARTICLE SHAPE

3.5.1 CRYSTALLINITY The X-ray powder diffraction patterns of original drug substances, spray dried powder and micronized powder are shown in Fig.5. The results of X-ray powder diffractometry indicated that spray dried powder was amorphous because a diffraction peak was not observed and the micronized powder was the same monohydrate crystal as the original drug substances. The IR spectra of original drug substances, spray dried powder and micronized powder are shown in Fig.6. The characteristic absorption band of monohydrate powder (3,565 cm^{-1}), arising from O-H stretching vibration of crystal water, disappeared in the spectrum of spray dried powder and appeared in the spectrum of micronized powder. The results indicated that spray dried powder was anhydrous and micronized powder was the same monohydrate as the original drug substances. X-ray powder diffractometry and IR spectrometry findings suggested that the original drug substances were monohydrate crystals, spray dried powder was anhydrous amorphous and micronized powder was monohydrate crystal. It was also confirmed that when the suspension temperature was above 20°C, spray dried powder (anhydrous amorphous) was rapidly converted to monohydrate crystal before ultrasonic homogenization was below 5°C, spray dried powder was not converted to monohydrate crystal before ultrasonic homogenization but was converted after ultrasonic homogenization.

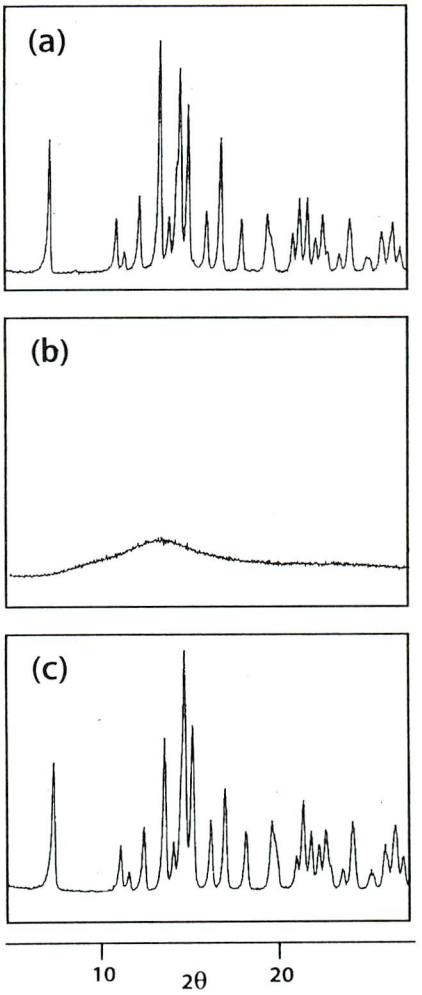

Fig.5 X-ray diffraction patterns of powder
(a) Original drug substance
(b) Spray dried powder
(c) Micronized powder

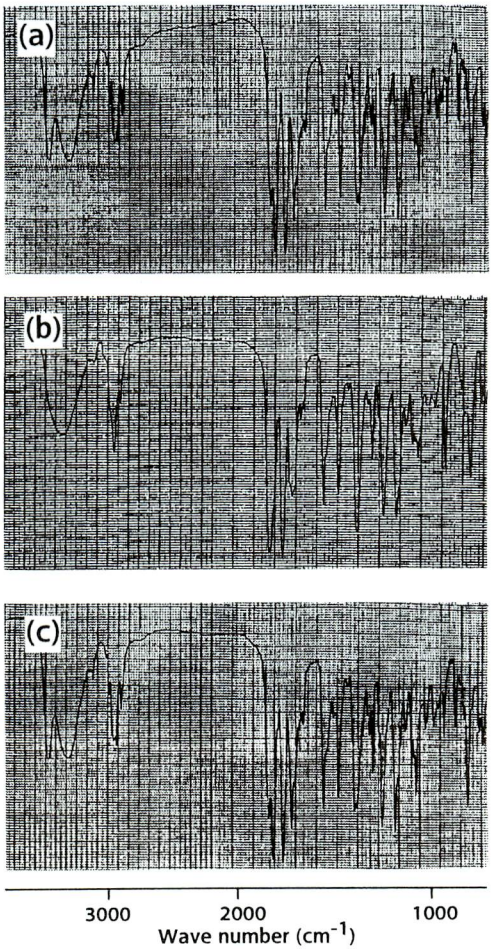

Fig.6 Infrared spectra of powder
(a) Original drug substance
(b) Spray dried powder
(c) Micronized powder

3.5.2 PARTICLE SHAPE Electron microphotographs of each powder are shown in Fig.7. Original drug substances were non-specific; spray dried powder was observed as spherical and as having a hollow thin shell; and micronized powder was observed as short and tubular. The powder suspended below 5°C had the same spherical shape and hollow thin shell as the spray dried powder, and the powder suspended above 20°C had needle-like structure.

4. DISCUSSION

4.1 ESTIMATED MECHANISM OF MICRONIZATION

Before conducting this study it was expected that micronization would be caused effectively by making the shape of original drug substances more fragile by creating a hollow thin shell by spray drying. As was expected, spray dried powder suspended at 20°C was reduced in size to submicron level (average particle size : 0.6 μm) by ultrasonic homogenization. However, the results of

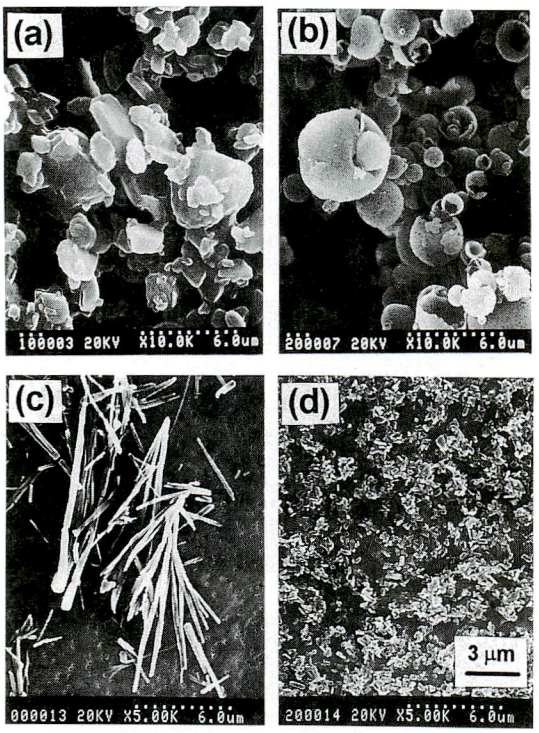

Fig.7 Electron micrographs of powder
(a) Original drug substance
(b) Spray dried powder
(c) Suspended powder
(d) Micronized powder

particle shape observation indicated that the spray dried powder changed to needle-like shape during benzalkonium chloride suspension. It suggested that the needle-like crystal converted from spray dried powder was also fragile enough to be reduced by ultrasonic homogenization. In fact, spray dried powder suspended below 5°C was reduced more effectively (average particle size : 0.26 - 0.30 μm) than when suspended at 20°C, and suspended spray dried powder did not change shape and crystallinity before micronization according to the results of particle shape observation and crystallinity determination. Therefore, we summarize the mechanism of micronization as follows :

Micronization after suspension at lower temperature

Spray dried powder was not converted to monohydrate crystal when the suspended temperature was below 5°C so that the spherical particle having a fragile thin shell was not changed before ultrasonic homogenization. Therefore, a spherical particle having a fragile thin shell was reduced by ultrasonic homogenization effectively. At almost the same time as the reduction, conversion of crystallinity from anhydrous amorphous to monohydrate crystal occurred as a result of the energy of ultrasonication and the particle shape was changed to a very fine needle-like shape simultaneously. The fine needle-like shape was reduced again by ultrasonic homogenization. Therefore, it suggested that micronization occurred twice during ultrasonic homogenization as shown in Fig.8, and very fine particles were obtained effectively.

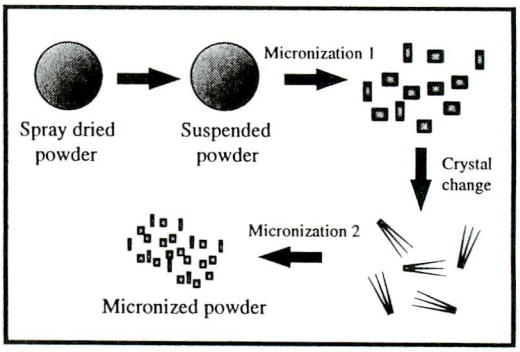

Fig.8 Mechanism of micronization at lower temperature

Micronization after suspension at higher temperature

Spray dried powder was converted to monohydrate crystal, and the shape was changed to a needle-like structure when the suspension temperature was above 20°C so that the needle-like particles were micronized by ultrasonic homogenization. Therefore, micronization occurred once during ultrasonic homogenization as shown in Fig.9.

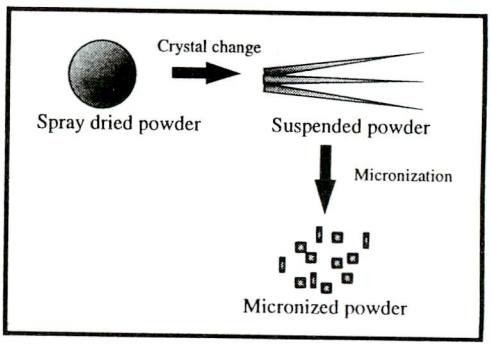

Fig.9 Mechanism of micronization at higher temperature

4.2 CONTROL OF MICRONIZATION

The reason for the particle size micronized after temperature suspension being small in proportion to the fall in suspension temperature was that the thickness of the needle-like particles converted from spherical particles with a fragile thin shell were strongly influenced by suspension temperature so that the lower the suspension temperature, the finer the needle-like shape was.

Therefore, micronization of the steroid used in this study could be simply controlled between 0.3 and 0.9 μm in mean particle diameter by the suspension temperature.

5. CONCLUSION

In this study, we established a new wet micronization method by using ultrasonic homogenization after converting the particle shape to a more fragile structure by spray drying. We confirmed that the particle size of drug substances could be reduced to 0.26 μm in mean particle diameter in a short time, and the reduction of particle size by this method could be easily controlled by the suspension temperature before ultrasonic homogenization.

Effective particle size reduction was considered to be caused by making the particle shape more fragile by not only obtaining a spherical particle having a hollow thin shell by spray drying but also by obtaining a needle-like particle by the particle shape changing by crystal conversion during the micronization process.

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