Improved Inhalation Behavior of Steroid KSR-592 *in Vitro* with Jethaler® by Polymorphic Transformation to Needle-Like Crystals (β-Form)

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Purpose. The aim of the present study was to improve the dry powder inhalation behavior of steroid KSR-592 with lactose by altering the crystal shape and the particle size of the drug for use in a newly designed inhalation device, Jethaler®.

Method. The shape of the crystals was changed by polymorphic transformation of original crystal (α-form) to β-form by agitating α-form crystals in hexane containing 5% ethanol. The inhalation properties of the resultant crystals *in vitro* were evaluated with a twin impinger and cascade impactor.

Results. Needle-like crystals (β-form) with dimensions of 1.8 μm in width × 41μm in length were obtained by the polymorphic transformation, the kinetics of which was described by the Avrami equation. The β-form crystals loaded on lactose particles were easily separated and crushed into fine particles in the airstream produced in the Jethaler®, which increased dramatically the respirable fraction (RF) deposited in the twin impinger (43.8%) and the fine particle fraction (FPF) of the cascade impactor (FPF = 39.3%) compared with their values for the original crystals (RF = 5.8%, FPF = 4.7%).

Conclusion. The dry powder inhalation properties of steroid KSR-592 (platelike crystal, α-form) were improved dramatically by changing the crystal shape to a needle-like shape by the polymorphic transformation to the β-form.

KEY WORDS: dry powder inhalation; polymorphic transformation; needle-like crystal; steroid; Jethaler®; inhalation device.

INTRODUCTION

Steroids are very effective drugs for controlling the symptoms and preventing the exacerbation of asthma (1–3). Treatment using an aerosolized steroid has distinct advantages over that with oral steroids for asthmatic therapy, because lowering the dosage required for the direct delivery into the lungs results in reduced adverse effects of the steroid. Recently, dry powder inhalation (DPI) was proposed as an alternative to pressurized metered-dose inhalation aerosols, because DPI does not require a propellant such as chlorofluorocarbon; furthermore, the inhalation of the active component is easily achieved without any synchronized emission control from the device, because only inhalation is required. For DPI formulations, it is necessary that the aerodynamic diameter of the active components be 0.5–7μm (4,5) to deposit the drug on an adequate area of the lung tissue. However, the cohesive force between the drug particles or the adhesion of the drug particle to a carrier particle such as lactose often results in insufficient dispersion of the drug particles at emission, thus decreasing the amount of drug delivered to the respiratory tract. The dispersion and subsequent deposition profiles of drug particles during inhalation are governed by the physicochemical properties of both the drug and the carrier particle (6,7) and, furthermore, by the design of the inhalation device (8).

During the course of studies on particle engineering for the DPI formulation of KSR-592: (+)-methyl 9α-chloro-6α-fluoro-11β-hydroxy-16α-methyl-3-oxo-17α-prorponyloxyandrosta-1,4-diene-17α-carboxylate, it was found that aerosolization of the drug was difficult because of its strong cohesive and adhesive properties. To overcome these undesirable properties, we altered the shape of the primary crystals to provide excellent separation of the drug from the carrier particle (lactose) at inhalation. It was reported earlier that particle shape was an important factor affecting powder dispersion (9,10) and lung deposition behavior (11). Elongated, fibrous particles have been found to show improved deposition in the lung (12–14). The contact state between fibrous particles is extremely unstable, promoting excellent fluidization and deaggregation properties (15). To improve separation properties of the drug deposited on carrier lactose on inhalation, we succeed in transforming the plate-like shape of the original crystals (α-form) to new needle-like crystals (β-form) by polymorphic transformation. We mixed the needle-like crystals with carrier lactose so as to maintain their original coarse particle size. The inhalation behavior of this formulation with (β-form) crystals was investigated by using a newly designed device, the Jethaler®, equipped with a milling chamber. The β-form crystals in the lactose formulations were separated efficiently from the carrier lactose and disintegrated effectively into fine particles suitable for DPI by inhalation with Jethaler®. To evaluate the milling action of the Jethaler®, we compared the inhalation performance between the former device and the Diskhaler®, which is a clinically used device without a milling system. Furthermore, we investigated the effect of particle size on the profile of separation of the drug particle from the carrier lactose by comparing coarse needle-like particles with fine ones.

MATERIALS AND METHODS

Preparation of Needle-Like Crystals

Original KSR-592 crystals (1.5 g) (α-form) was added to hexane (80 mL) containing 5% ethanol, and the suspension was agitated at 8000 rpm for 15 min by using a homogenizer (Nissei, Japan). During the agitation process, the original platelet-like crystals were transformed to needle-like crystals (β-form). The resultant crystals were filtered, washed with hexane, and dried in an oven at 60°C for 12 h. The obtained aggregate of the needle-like crystals was deaggregated by using a blender equipped with two blades (Chemical Blender R-8; Nihon Rikagaku, Kikai, Japan).

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X-Ray Powder Diffraction Analysis of Crystals and Measurement of Polymorphic Transformation Rate

The crystalline forms of needle-like crystals (β-form) and original crystals (α-form) were analyzed by using an X-ray powder diffractometer (RINT2000, Rigaku, Japan; Cu,40kV, 40mA; scanning speed 2°/min). The polymorphic transformation rate during the agitation process was determined by comparing the diffraction peak height of α- and β-form crystals at $2\theta = 8.4°$ and 9.9°, respectively, on the diffraction patterns.

Preparation of DPI Formulations

Coarse needle-like crystals (0.6 g) (β-form) or original crystals (α-form) was mixed with 11.4 g of lactose (Pharmatose® 325M, DMV International, Veghel, Netherlands) by the blender mentioned above, which was operated at 500 rpm for 2 min. The lactose, having a mean diameter of 60 μm, was used as the carrier particle. The DPI formulation containing fine needle-like crystals (β-form) was prepared by mixing the β-form crystals and lactose particles at a higher blending speed (1500 rpm, for 2 min) than the above-mentioned speed for the coarse ones.

Evaluation of Inhalation Properties

Inhalation properties of the KSR-592 DPI formulation prepared with needle-like crystals (β-form) or original crystals (α-form) were evaluated with a twin impinger (Copley Instruments, Nottingham, UK) and a cascade impactor (Andersen sampler AN-200 type; Andersen, Smyrna, GA, USA). Jethaler® (Unisia Jecs Corporation, Isesaki, Japan) and Diskhaler® (Glaxo Smith Kline, UK) were used as inhalation devices.

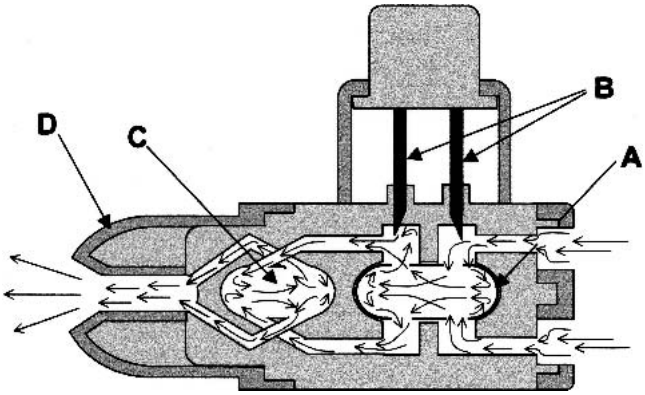

Fig. 1. Structure of Jethaler®. (A) Capsule. (B) Piercing needle. (C) Milling chamber. (D) Mouthpiece.

Jethaler® (Fig. 1) is an inhalation device equipped with a milling system that can disintegrate effectively the aggregate of the drug into primary particles by the airstream passed through the milling system on inhalation. The Diskhaler®, used clinically, is an inhalation device without a milling system such as Jethaler®. Ten milligrams of the dry powder of the drug/lactose was loaded into a No.2 hydroxypropylmethylcellulose (HPMC) hard capsule (Shionogi Qualicaps, Nara, Japan), and the capsule was placed in a Jethaler®, and in the

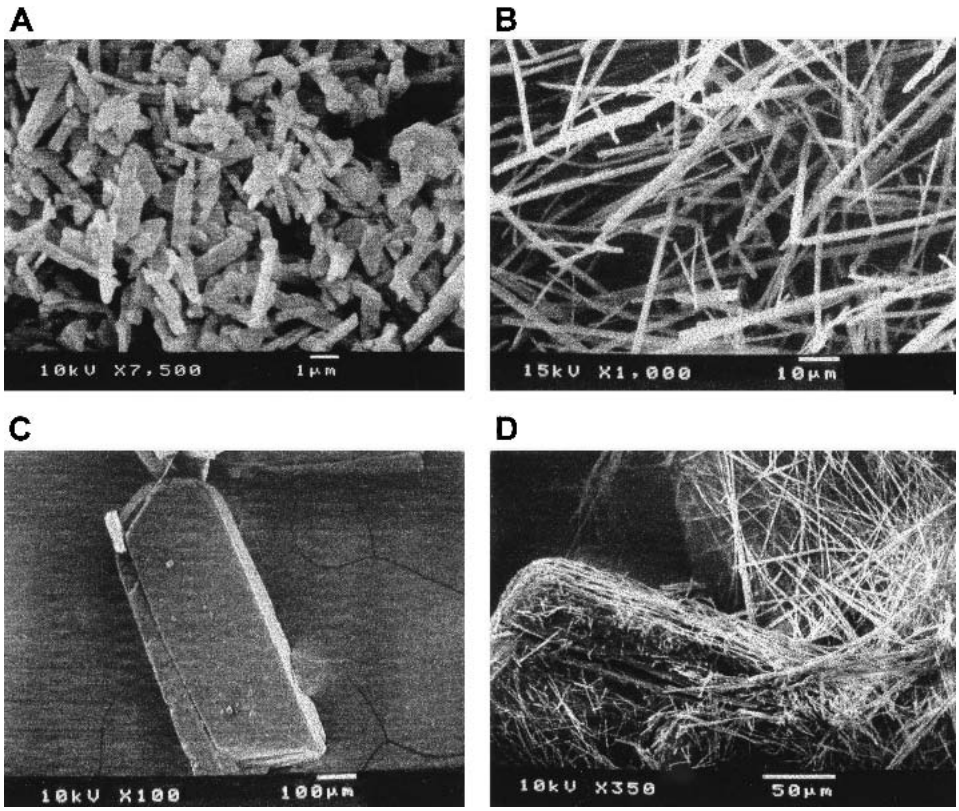

Fig. 2. SEM photograph of original crystals and needle-like crystals of KSR-592. (A) Original α-form crystals (mean diameter: 2.2 μm). (B) Needle-like crystals (β-form). (C) Coarse α-form crystal. (D) Mixture of α-form and β-form crystals (stirred for 1 h in hexane containing 5% ethanol).

case of the Diskhaler®, an equivalent amount of the DPI formulation was loaded directly into the powder filling space directly behind the mouthpiece of the device. The device, a Jethaler® or Diskhaler®, was installed on the cascade impactor or twin impinger connected to a vacuum pump. The dry powder aerosol was emitted from the device for a proper time period under a specified-airflow rate (i.e., 60 L/min and 28.3 L/min for twin impinger and cascade impactor, respectively). After emission, the inside of capsule and device and each stage of the evaluation apparatus were rinsed with methanol, and the drug content of each rinse solution was determined by high-performance liquid chromatography (HPLC). The amount of lactose deposited was determined by the increase in the weight of each part of the inhalation device and each stage of the evaluation apparatus after emission.

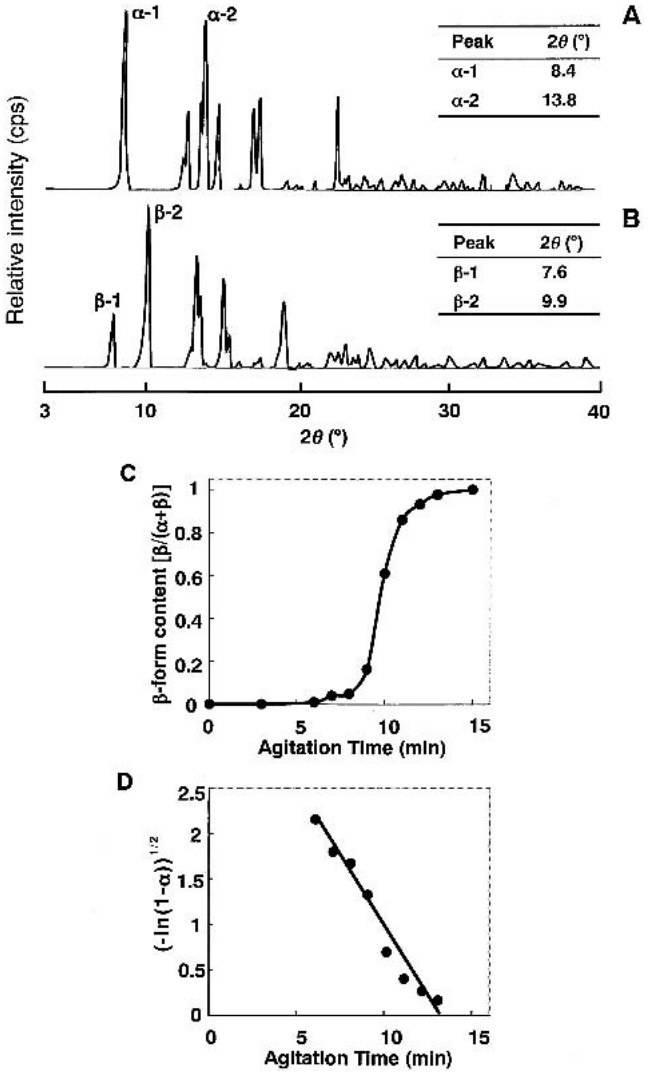

Fig. 3. Powder X-ray diffraction pattern of polymorphs of KSR-592 and the kinetics of the crystal transformation from original crystal (α-form) to needle-like crystal (β-form) by the agitation method. (A) Powder X-ray diffraction pattern of original crystal (α-form). (B) Powder X-ray diffraction pattern of needle-like crystals (β-form). (C) Transformation process of crystals from α-form to β-form. Agitation speed: 8000 rpm. (D) Plots of $[-\ln(1-\alpha)]^{1/2}$ vs. agitation time for the KSR-592 polymorphic transformation.

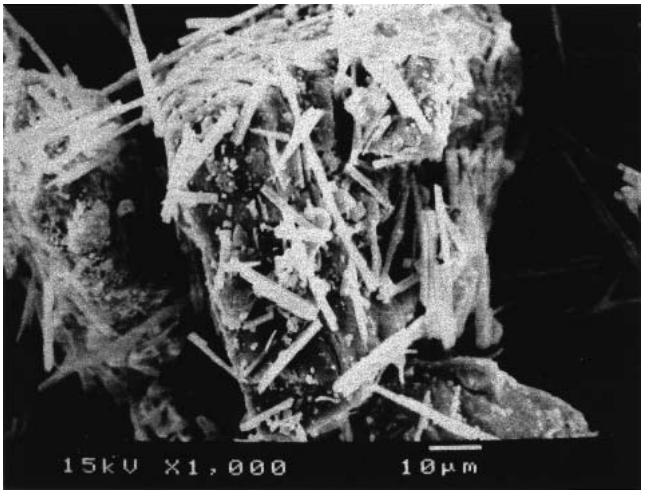

Fig. 4. SEM photograph of KSR-592 DPI formulation prepared from needle-like crystals (β-form).

Characterization of Physicochemical Properties of Drug Crystals and Drug-Lactose Mixtures

The drug crystals and the drug-lactose mixture were coated with gold to a thickness of 100–200 Å and observed under a scanning electron microscope (SEM)(LMV-5200LV; Nihon Denshi, Japan). The particle size of the needle-like crystals prepared by the agitation process was determined by calculating the average of the length and the width of 200 crystals measured with a caliper on the SEM photographs. The particle size of the crystals was also measured by using a Coulter Counter (Multi-sizer II Type; Beckman Coulter, Inc., Fullerton, CA) equipped with a 50- or 100-μm orifice tube. After dispersing the crystals in an isotonic-buffer solution containing a small amount of Tween 80, the mean particle size of 50,000 particles measured was determined. It was confirmed that the dissolution of the drug in the dispersing medium was negligible for the measurement of particle size because of its extremely low solubility (<0.15 μg/mL). Furthermore, no change in morphology of crystals was detected by SEM observation during the test. The particle size of the drug in the dry powder for inhalation was measured by using the Coulter Counter method after the lactose particles had been selectively dissolved in the dispersing medium. The particle size (volume mean diameter) of the drug deposited in the cascade impactor (from throat to stage 7) after emission was measured by the Coulter Counter method. The deposited particles were rinsed with isotonic-buffer containing a small amount of Tween 80, and the collected suspensions were used for the measurement of particle size.

RESULTS AND DISCUSSION

Polymorphic Transformation to the Needle Crystal of KSR-592 (β-Form)

SEM photographs of original crystals of KSR-592 and polymorphic transformed crystals prepared by the agitation process are shown in Fig. 2.

The original crystals of KSR-592 (plate-like crystal: Fig. 2A) were transformed to needle-like ones (Fig. 2B) by the agitation (8000 rpm for 15 min) of the original crystals dis-

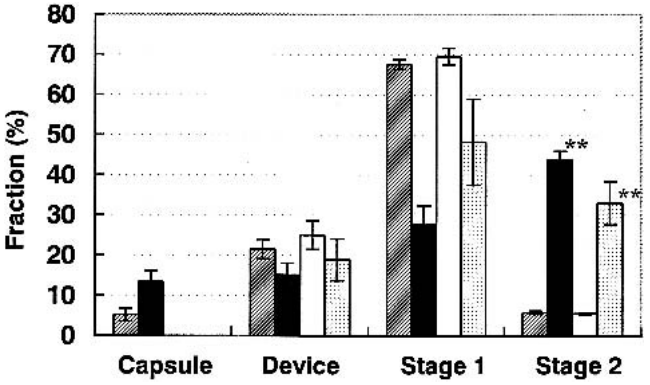

Fig. 5. Inhalation properties of needle-like crystals and original crystals evaluated with the twin impinger. Flow rate: 60 L/min; ▨: original crystals (α-form)/Jethaler®; ■: needle-like (β-form) crystals/Jethaler®; □: original (α-form) crystals/Diskhaler®; ⬚: needle-like (β-form) crystals/Diskhaler®. The value represents means ± SD (n = 5). Statistical significance: **$p < 0.01$ compared with the original crystals/Jethaler® or Diskhaler®.

persed in hexane containing 5% ethanol. The crystal transformation was also confirmed by using several pieces of coarse original crystals (Fig. 2C) dispersed in 2 mL of hexane containing 5% ethanol at a lower agitation speed (50 rpm). After 30 min of agitation of these coarse crystals, a few needle-like crystals appeared in the medium. The amount of needle-like crystals increased continuously with further stirring, and the needle-like crystals adhered to the surface of the original crystals during the agitation (Fig.2D). Finally (after 14 h), the original crystals disappeared completely from the medium, having been transformed to needle-like crystals like those seen in Fig. 2B. This finding suggests that this crystal transformation occurred even without seeding needle crystals. Powder X-ray diffraction patterns of the original crystals and crystals obtained in the above transformation tests are shown in Fig. 3 A and B.

The characteristic X-ray diffraction peaks of the original crystals and transformed needle-like crystals appeared at $2\theta = 8.4°$and 13.8°and at $2\theta = 7.6°$ and 9.9°, respectively. It was found that the original and transformed needle-like crystals melted at 267 and 276°C, respectively, as detected by inspection of the thermograms obtained by diffraction scanning calorimetry (DSC). The powder X-ray diffraction and the thermal analyses clearly showed that polymorphic transformation of the original crystals had occurred during the agitation process. The crystal forms of the original crystal and needle-like crystal were termed α-form and β-form, respectively. The kinetics of the crystal transformation from α-form to β-form by this agitation method is shown in Fig. 3C. The crystal transformation occurred rapidly after an induction period, exhibiting a sigmoid curve for β-form content (%). The polymorphic transformation was complete within 15 min of agitation at 8000 rpm. The solubility of α and β-form crystals in the medium used for crystal transformation was 215 and 120 μg/mL, respectively, at 25°C. At the initial stage, it was assumed that the α-form crystals and the oversaturated solution of dissolved β-form were coexistent. During the induction period shown in Fig. 3C, the nuclei of β-form crystals were produced, leading to the crystallization of the β-form. This crystallization induced the dissolution of α-form crystals to maintain their equilibrium (saturated) solution. This procedure continued until completion of the polymorphic transformation of the α-form crystals to the β-form crystals. The kinetics of polymorphic transformation was described by a two-dimensional nuclear growth equation, $[-\ln(1-\alpha)]^{1/2} = kt$ (Avrami equation),where α is the amount of α-form crystals, t is the agitation time, and k is the rate constant of polymorphic transformation, as shown in Fig. 3D. This finding indicates that the transformation of the α-form to the β-form progressed by the creation of nuclei of β-form from many points on the crystal surface of the α-form crystal and subsequent growth of these nuclei to needle-like crystals. This result is consistent with the SEM data (Fig. 2D), which showed that the needle-like crystals adhered to the surface of the original crystals. The mean particle size of the β-form crystal was 1.8 μm wide and 41 μm long by the measurement of 200 crystals on SEM photographs. The mean volume of crystals (133×10^{-5} cm^3), calculated by multiplying the three dimensions ($1.8 \times 1.8 \times 41$ μm), coincided reasonably with that (125×10^{-5} cm^3) determined by the Coulter Counter method (volume mean diameter = 6.2 μm).

DPI Formulations of Needle-Like Crystals (β-Form)

A SEM photograph of the dry powder formulation prepared by mixing the needle-like drug crystals (β-form) with carrier lactose is shown in Fig. 4.

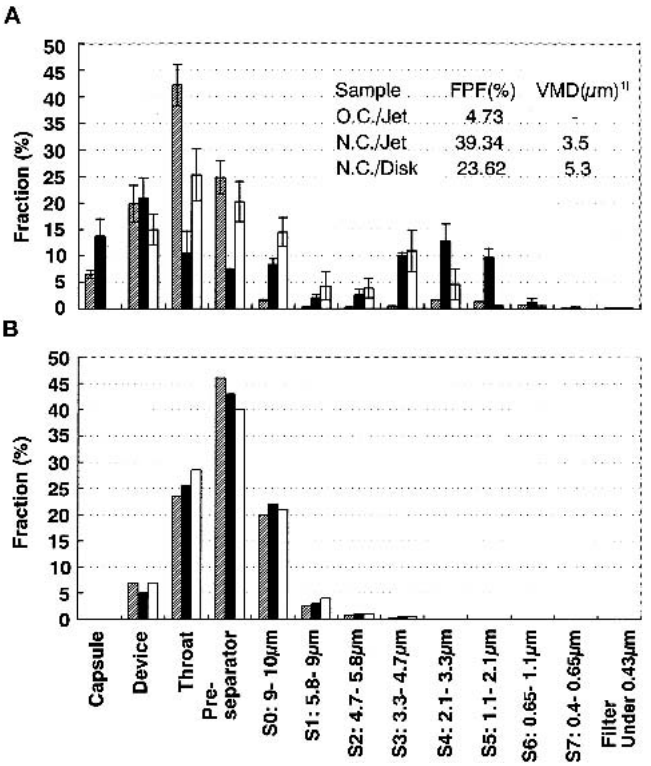

Fig. 6. Inhalation properties of needle-like crystals and original crystals evaluated with the cascade impactor. (A) Deposition pattern of KSR-592. (B) Deposition pattern of lactose. Flow rate: 28.3 L/min; ▨: original (α-form) crystals/Jethaler® (O.C./Jet.); ■: needle-like (β-form) crystals/Jethaler® (N.C./Jet); □: needle-like (β-form) crystals/Diskhaler® (N.C./Disk). The value are presented as the means ± SD (n = 3).

[1] Volume mean diameter (VMD) of the drug particles deposited from the throat to stage 7 of the cascade impactor after emission.

The drug crystals adhered to the surface of the lactose particles, as shown in this figure. The median diameter of the drug crystals in the drug-lactose mixture was 5.8 μm as determined by the Coulter Counter, which indicated that the drug crystals had disintegrated little during the process of being mixed with the lactose particles.

Inhalation Properties of the Drug Crystal Loaded onto Carrier Lactose

The inhalation properties of α- and β-form drug crystals loaded onto the carrier lactose and emitted from the Jethaler® were first evaluated by means of the twin impinger (Fig. 5).

The respirable fraction (RF) value (percent of the drug particles reaching stage 2 of the twin impinger) of the β-form crystals (43.8%) was much higher than that of the α-form crystals having a median diameter of 2.2 μm (5.8%). Even with the Diskhaler®, a significantly higher RF value (32.9%) was obtained for β-form crystals than for α-form crystals (5.4%), although the value for β-form crystals was lower than that for the Jethaler®. These data suggested that the milling function of the Jethaler® could improve the RF value of β-form crystals. The differences in inhalation behavior between the two crystalline forms were also proved by means of the cascade impactor (Fig. 6).

The cascade impactor deposition pattern of the β-form crystals loaded onto lactose particles emitted from the Jethaler® exhibited the maximal deposition at stage 4 (2.1–3.3 μm) in the fine particle fraction (FPF: stages 2–7), which corresponded to the RF of the twin impinger. The β-form crystals emitted from the Jethaler® reached a lower stage than those from the Diskhaler®. Furthermore, the volume mean diameter of the drugs deposited from the throat to stage 7 (3.5 μm) was smaller than that of the DPI formulation (5.8 μm). This finding indicates that the β-form crystals were crushed into fine crystals by the airstream produced by the milling function of the Jethaler® at emission. On the other hand, the deposition pattern of the mixture prepared with needle-like crystals obtained by using the Diskhaler® showed that most of the drugs deposited in FPF were distributed on the stage 3 (3.3–4.7 μm). The volume mean diameter (5.3 μm) of the drugs deposited in the impactor (from throat to stage 7) was slightly smaller than that of the DPI formulation (5.8 μm), suggesting that the drug particle was emitted without being crushed to fine particles by the dispersion force of the airstream in the Diskhaler®. In contrast, the deposition pattern of lactose particles was not affected by the difference in the crystalline form of the drug or by the inhalation device. Almost all of the lactose particles were deposited preferentially on the throat, preseparator, and stage 0–1. This finding indicates that β-form drug crystals that adhered to the surface of carrier lactose particles were detached more efficiently compared with the α-form crystals. The liberated β-form crystals might have been preferentially crushed by the shear force in the airstream in the milling system of the Jethaler®. SEM photographs of β-form crystals and lactose particles collected in the separator, stages 3, 4, and 5 of the cascade impactor when emitted from the Jethaler® are shown in Fig. 7.

The needle-like β-form crystals as they appeared in the DPI formulation (Fig. 4) were not found on the surface of the carrier lactose particles collected in the preseparator. This

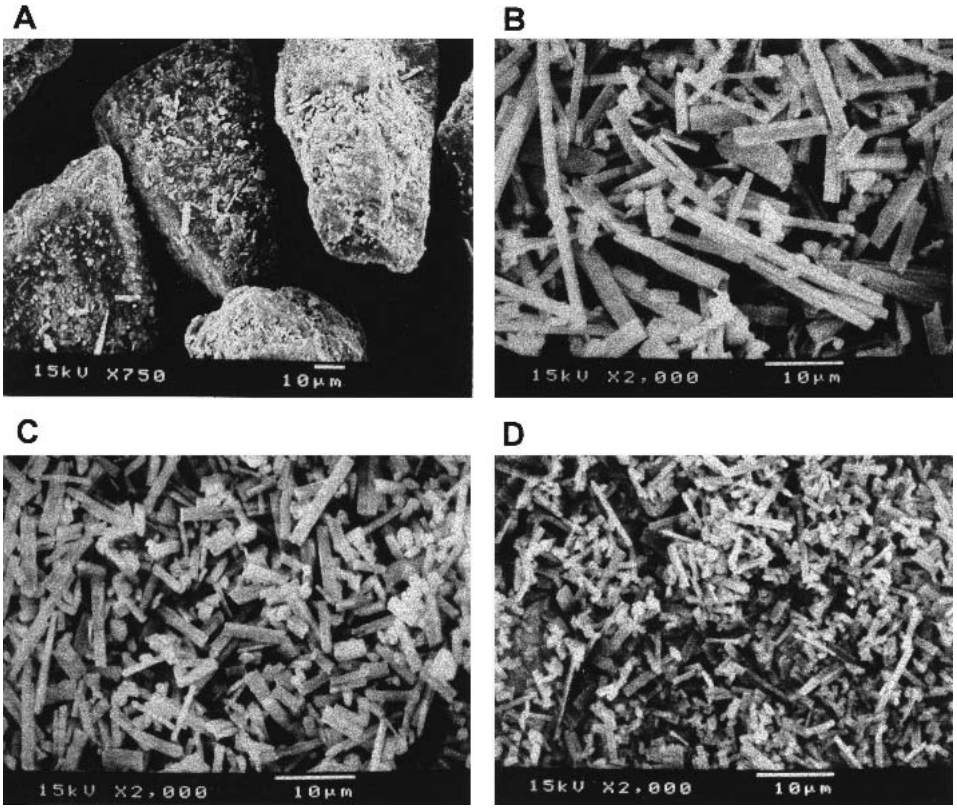

Fig. 7. SEM photograph of drug particles and lactose deposited on the preseparator and the respirable stage of the cascade impactor. (A) Preseparator. (B) Stage 3. (C) Stage 4. (D) Stage 5.

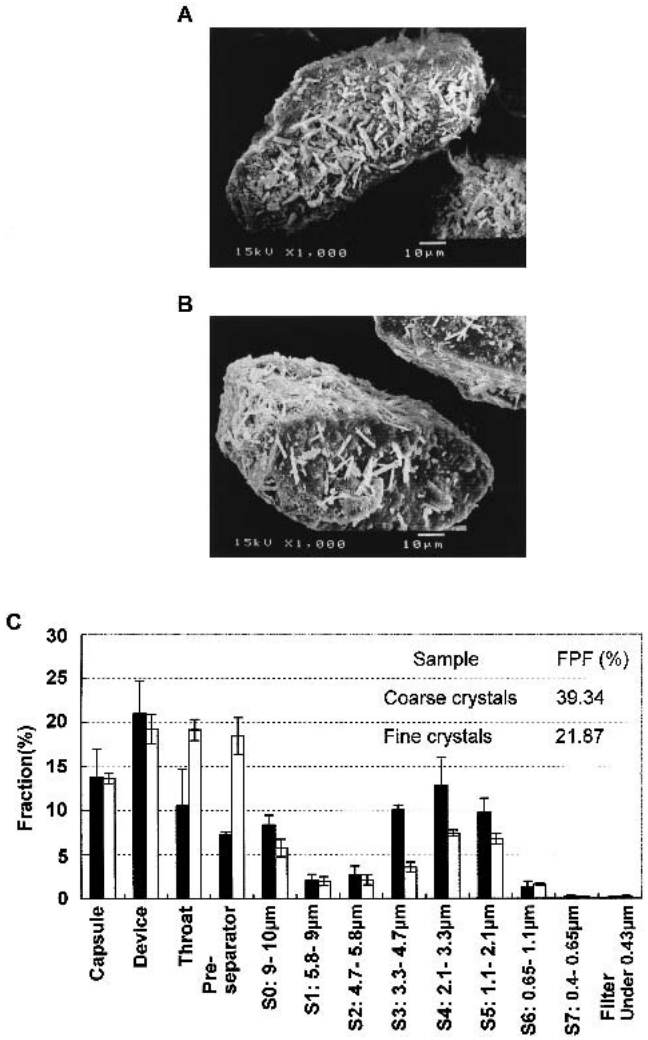

Fig. 8. Influence of crystal size on separation properties of the drug from the carrier lactose. (A) SEM photograph of KSR-592 DPI formulation prepared with fine needle-like crystals. (B) SEM photograph of lactose mixture on the preseparator. (C) Inhalation properties of coarse crystals and fine crystals evaluated with the cascade impactor. Flow rate: 28.3 L/min. Inhalation device: Jethaler® ■: coarse crystals; □: fine crystals. Each value presents the means ± SD (n = 3).

finding proved that almost all of the drug particles were liberated from the lactose particles during emission. It is surprising that smaller-sized drug particles that were not found in the DPI formulation before emission were collected on stages 3, 4, and 5 of the cascade impactor. This finding supports strongly our contention that the liberated β-form drug crystals were milled into fine particles on emission from the Jethaler®. The discrepancy between RF value and FPF value (total percent deposition at stages 2–7 of the cascade impactor) for β-form crystals obtained by using the Jethaler® (4.5%) under different airflow rate [i.e., 60 L/min (for RF) and 28.3 L/min (for FPF)], was smaller than that obtained by using the Diskhaler® (9.3%), as was shown in Figs. 5 and 6. This results suggests that the deposition profile of β-form crystals was less affected by the airflow rate inhaled with the Jethaler®, which allows us to predict a reliable inhalation behavior *in vitro* even under varied respiratory conditions.

Influence of Crystal Size on Separation Properties of the Drug from the Carrier Lactose

The effect of particle size of the β-form crystals on their separation from the carrier lactose emitted from the Jethaler® was tested with the cascade impactor. The fine β-form crystals for the DPI formulation were prepared by mixing the original coarse β-form crystals with a volume mean diameter of 6.2 μm and carrier lactose at 1500 rpm. The coarse β-form crystals were preferentially crushed into fine needle-like crystals under the high-shear force of agitation in mixing process. The resultant fine crystals were adsorbed selectively onto the surface of the lactose particles, as shown in Fig. 8A.

The volume mean particle diameter of the fine β-form crystals in the DPI formulation measured by the Coulter Counter was 2.5 μm. The inhalation properties of DPI with coarse and fine β-form crystals evaluated with a cascade impactor are shown in Fig. 8C. Compared with the coarse-crystal DPI, the fine-crystal DPI showed decreased FPF value and increased drug particle deposition in the throat and the preseparator of the cascade impactor. The SEM photographs of the lactose particles deposited in the preseparator are shown in Fig. 8B. In fine crystal DPI, many fine needle-like crystals adhered to the surface of the lactose particles as before emission (Fig. 8A), in contrast to the fewer coarse-crystals as was shown in Fig. 7A. This result indicates that fine drug crystals were not liberated from the surface of the lactose particles because of increased adhesive force between the drug particle and the lactose.

CONCLUSIONS

It was possible to transform the original plate-like crystals (α-form) of KSR-592 to needle-like crystal (β-form) having an average width and length of 1.8 and 41 μm, respectively, by agitating them in hexane containing 5% ethanol. The β-form crystals in the DPI formulation were separated from carrier lactose effectively on inhalation, because of their decreased force of adhesion to the carrier particles, leading to significantly improved RF and FPF values compared with those of the original crystals. The β-form crystals liberated from the carrier lactose particles were preferentially crushed into fine crystals through the milling function of the Jethaler®, which could be deposited on deeper (lower) stage of the cascade impactor on inhalation. The above inhalation performance of β-form crystals depended on their particle size in DPI formulation (i.e., finer crystals decreased the FPF value owing to their increased adhesion to carrier lactose particles).

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