Preparation of Functional Composite Particles of Salbutamol Sulfate Using a 4-Fluid Nozzle Spray-Drying Technique

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A previous study on spray-drying demonstrated that it could promote the solubility of poorly water-soluble drugs using water-soluble polymers. Here, the preparation of composite particles of salbutamol sulfate (Sb) with water-insoluble polymers, such as Eudragit® RS (RS) or Eudragit® RL (RL) as a carrier, was examined. Despite the water insolubility of both polymers, the permeability of water was low in the former but high in the latter. We attempted to prepare controlled release composite particles by exploiting the characteristics of these carriers. The composite particles of the three components (Sb, RS, and RL) were prepared using a 4-fluid nozzle spray-dryer, and their physico-chemical and dissolution properties were compared with physical mixtures. Examination of particle morphology by scanning electron microscopy (SEM) revealed that the particles from the spray-drying process had atomized to several microns and were spherical. Analysis by X-ray diffraction and differential scanning calorimetry revealed that diffraction peaks and heat of fusion of Sb in the spray-dried samples decreased, indicating that the drug was amorphous and formed a solid dispersion. FT-IR analysis suggested that the amino group of Sb and a carbonyl group of the polymers formed a hydrogen bond. A dissolution test of Sb-RS-RL particles prepared using the 4-fluid nozzle spray-drying method showed that release rates were depressed significantly compared to the physical mixture at pH 1.2 and 6.8, and the depression was greater when RS was used instead of RL, presumably because of the permeability difference. The compression of these particles into tablets revealed that desirable controlled released dosage forms could be prepared. In addition, Sb was used to simulate an anti-asthmatic drug. For this an Andersen cascade impactor for dry powder inhalers was used to investigate delivery to the lungs.

Key words 4-fluid nozzle spray-drying; salbutamol sulfate; Eudragit®; solid dispersion; sustained release

Solid dispersion is one technique that has been used to improve the dissolution of poorly water-soluble drugs.[1,2] Water-soluble polymer carrier systems, such as polyethylene glycol (PEG),[3—6] polyvinylpyrrolidone (PVP),[7,8] and hydroxypropylcellulose (HPC)[4,5,9—11] are the most common carriers for solid dispersions, and have been used in fast-release preparations. Solubility is improved by distributing the medicine in molecular form in the carrier under high-energy conditions to form an amorphous solid.[12,13] Most studies in this field have concentrated on improving the dissolution of poorly water-soluble drugs. Emara *et al.*[14] improved the dissolution of nifedipine prepared with the fusion method. Yamashita *et al.*[15] prepared solid dispersions of tacrolimus using PEG, PVP, and HPMC. He *et al.*[16] reported the formation of a solid dispersion when cimeditine was dispersed in chitosan through spray drying.

However, only a few studies have investigated the slow release of a drug after formation of a solid dispersion using spray-drying. Shaikh *et al.*[17] conducted spray-drying using acetaminophen (Act) and ethylcellulose (EC) in an attempt to achieve sustained release of Act. Furthermore, Corrigan *et al.*[18] performed spray-drying using salbutamol sulfate and chitosan and examined absorbability of the drug released from the microparticles.

Based on the results of a previous report,[19—21] this study examined the 4-fluid nozzle spray-drying technique because the sustained-release particles obtained from the technique are finer. Composite particles also were designed to slowly release salbutamol sulfate (Sb) in the digestive tract using a solid dispersion in water insoluble Eudragit® RS (RS) or Eudragit® RL (RL) as a carrier. In addition, the possibility for administration of the particles to the lungs also was evaluated because of the extremely fine size and spherical shape of the particles prepared by 4-fluid nozzle spray-drying.

Experimental

Materials Salbutamol sulfate (Sb) was obtained from Dolder Ltd. (Switzerland). Aminoalkyl methacrylate copolymers RS and RL (Eudragit® RS and RL), used as a carrier, were supplied by Rohm Pharma GmbH (Darmstadt, Germany). Kristmundsdottir *et al.*[22] reported the water permeability of Euidragit RS and RL.

Features of 4-Fluid Nozzle Spray-Dryer The 4-fluid nozzle spray-dryer (Micro Mist Spray Dryer, MDL-050B, Fujisaki Electric Co., Ltd., Japan) includes two gas supply routes (0.2×2.0 mm) and two liquid-feed paths (0.25×2.0 mm), as described previously.[20,23,24] Gas and liquid mix instantaneously using an outside mixing mode, which gathers the collision focal points at the tip of the nozzle edge. 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 has a smaller particle size distribution than those produced by the conventional 2-fluid nozzle spray-drier.[20] Moreover, the 4-fluid nozzle spray-dryer can spray two different solutions at once. By spraying two solutions with different dissolved substances, composite particles can be obtained.

Preparation of Physical Mixtures The physical mixtures (PM) were prepared using a vortex mixer (Scientific Industries, Type Vortex-Genie 2, Japan) for 10 min at a constant amplitude and rate at a 1 : 1 mixing ratio of drug and carrier.

Preparation of Composite Particles Ten grams of Sb were dissolved in 1000 ml of purified water, and 10.0 g of carrier were dissolved in 1000 ml of 50% w/v aqueous methanol solution. The two solutions were supplied from separate lines and spray-dried using a 4-fluid nozzle system under the following conditions: inlet temperature, 150 °C; outlet temperature, 70—80 °C; spray rate, 10 ml/min; blower, 60 Hz; spray air volume, 35 l/min; drying air volume, 0.8 m^3/min.

Determination of Particle Morphology The particles were analyzed using scanning electron microscopy (SEM, JEOL Ltd., Type JSM-6060, Japan). Prior to examination, samples were mounted on a stand using double-sided adhesive and coated with a thin layer of platinum (approximately

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20 nm) under vacuum. The scanning electron microscope was operated at an acceleration voltage of 15 kV.

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

Powder X-Ray Diffraction Powder X-ray diffraction analysis was performed with a Rigaku Geiger-Flex diffractometer (Rad-2CV) using Ni-filtered Cu$K\alpha$ radiation, a voltage of 30 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 performed with a DSC-60 instrument (Shimadzu Co., Ltd., Japan). The operating conditions in the open pan system included a sample weight of 10 mg and a heating rate of 5°/min.

Infrared Spectroscopy FT-IR spectra were obtained with an FT/IR 4000 spectrometer (JASCO Corporation, Japan), using the transformation of 100 scans obtained by the KBr disk method.

Preparation of Model Tablets A flat-face model tablet, containing 50.0 mg Sb and having a diameter of 10.0 mm, was prepared using a universal tension and compression tester (Shimadzu Autograph AG5000D, Japan) at a compression pressure of 62.4 MPa.

Dissolution Tests Since Sb is used for dry powder inhalation and an oral administration drug, dissolution tests were performed with powder and tablets. Initially, because the powder particles float on a surface, dissolution tests were performed on the sample powder using the Japanese Pharmacopoeia XV (JPXV) rotating basket method, involving 50 mg of the drug and 1000 ml of the dissolution medium at pH 1.2 or 6.8 at 37.0±0.5 °C. Rotation speed of the paddle was 50 rpm. In addition, dissolution tests were conducted on the model tablet (containing 50 mg of the drug) using the JP XV paddle method. Test conditions were the same as for the powder.

The quantity of Sb was assayed by HPLC (SPD-10A, Shimadzu Co., Ltd., Japan) at 224 nm. The mobile phase was 0.025 mol/l sodium dihydrogen phosphate solution (pH 2.8) : acetonitrile : methanol=90 : 9 : 1, which flowed through an ODS column (Inertsil ODS-3, 4.6×150 mm, GL Sciences Inc. Japan) at a rate of 1.0 ml/min.

Evaluation of *in Vitro* Inhalation Properties A hydroxypropyl methylcellulose (HPMC) capsule (size 2, Shionogi Qualicaps Company, Nara, Japan) with 10 mg of a 4-fluid nozzle spray-dried sample was loaded into a Jethaler inhaler (Hitachi Unisia Automotive, Ltd., Type AN-200, Japan). The samples were dispersed into an Andersen Cascade Impactor (Shibata Scientific Technology Ltd., Japan) from the Jethaler for 10 s at an air flow rate of 40.0 l/min. The sample deposited at each stage of the impactor was dissolved in purified water and assayed by HPLC. Output efficiency (OE) was determined as percent of total powder mass exiting from the capsule and device. The respirable fraction (RF) of Sb powder was determined by dividing the powder mass recovered from stage 2—7 (<7.0 μm) of the impactor by the OE value. A plot of the cumulative amount of powder deposited at each stage of the impactor on the probability scale axis *versus* the logarithm of effective cut-off diameter for that stage allowed calculation of the mass median aerodynamic diameter (MMAD) of the particles.

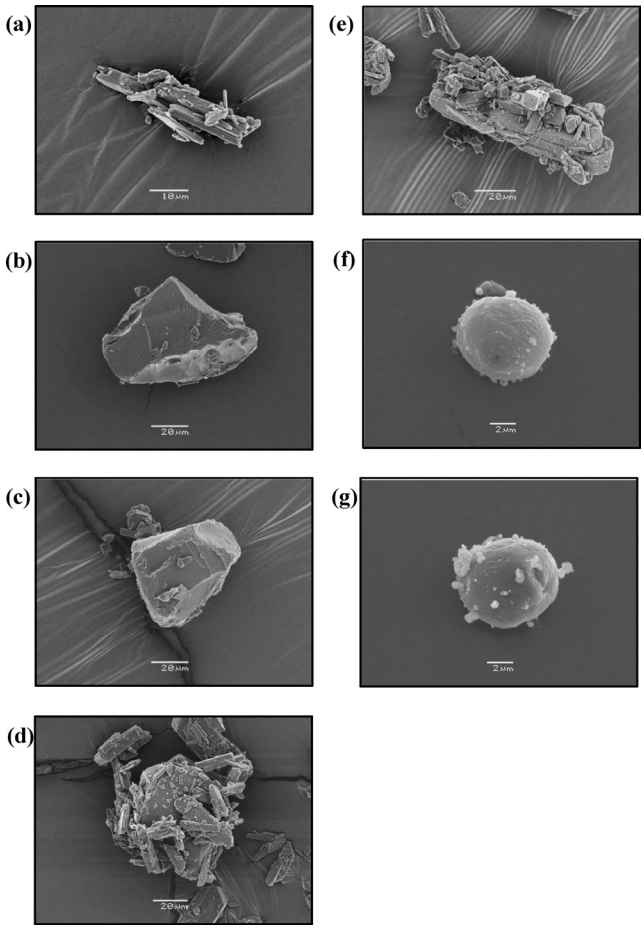

Fig. 1. Scanning Electron Micrographs of Samples

(a) Salbutamol sulfate, (b) Eudragit® RS, (c) Eudragit® RL, (d) Sb : RS=1 : 1 PM, (e) Sb : RL=1 : 1 PM, (f) Sb : RS=1 : 1 SD, (g) Sb : RL=1 : 1 SD.

Table 1. Mean Particle Size (Heywood Diameter) of Samples by Laster-Diffraction and Scattering Method

Sample	Mean particle size (μm)
Sb	10.54
Sb : RS=1 : 1 SD	2.65
Sb : RL=1 : 1 SD	2.37

n=3.

Results and Discussion

Confirmation of Composite Particles Scanning electron micrographs of the samples are shown in Fig. 1. The Sb consisted of slender rod-shaped and agglomerated particles, while RS and RL consisted of angular particles with a smooth surface. Examination of these physical mixtures confirmed that Sb particles adhere to the surface of RS and RL particles. The spray-dried composite particles were spherical. The mean particle diameters (Heywood diameter) obtained from the particle size distribution curves are shown in Table 1. The mean particle diameter of the 4-fluid nozzle spray-dried samples (mean particle diameter was about 2 μm) was less than the mean particle diameter of the original Sb (mean particle diameter of 10.5 μm).

Confirmation of Crystallinity of Sb in Composite Particles Figure 2 shows powder X-ray diffraction patterns for Sb, RS, RL, their physical mixtures, and the samples prepared using 4-fluid nozzle spray-drying techniques. Sb produced many characteristic peaks, indicating a highly crystalline structure, whereas RS and RL exhibited signs of being amorphous due to the lack of diffraction peaks. In the physical mixture, the distinctive diffraction peaks of Sb persisted with a marked decrease in their intensity compared with original Sb crystals. In contrast, the 4-fluid nozzle spray-dried samples exhibited signs of amorphism, suggesting that the drug could be dispersed homogenously in an amorphous state through the formation of a solid dispersion. Figure 3 shows the DSC thermograms for Sb, RS, RL, their physical mixtures, and the samples prepared using 4-fluid nozzle spray-drying techniques. The figure shows an endothermic peak with a melting point for Sb near 186.9 °C. In the physical mixture, only the endothermic peak decreased compared with Sb because of the dilution effect caused by the carrier. The endothermic peak upon fusion of the Sb was not observed in samples prepared using the 4-fluid nozzle spray-

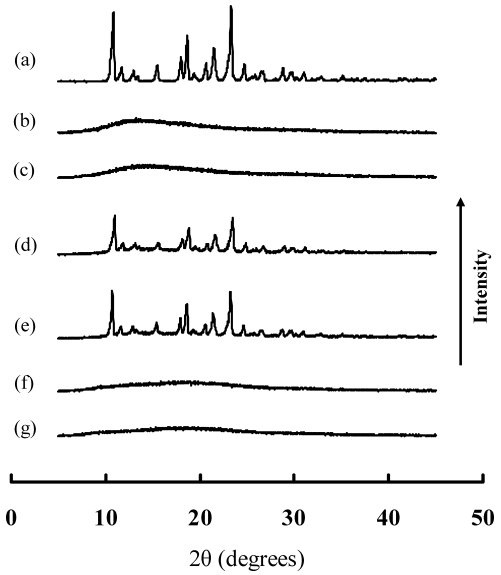

Fig. 2. Powder X-Ray Diffraction Patterns of Samples

(a) Salbutamol sulfate, (b) Eudragit® RS, (c) Eudragit® RL, (d) Sb : RS=1 : 1 PM, (e) Sb : RL=1 : 1 PM, (f) Sb : RS=1 : 1 SD, (g) Sb : RL=1 : 1 SD.

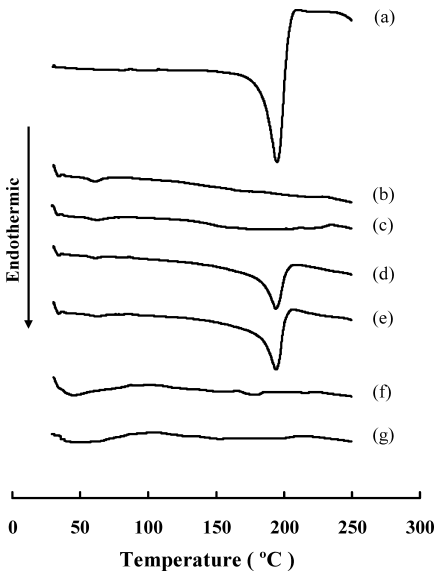

Fig. 3. DSC Thermograms of Samples

(a) Salbutamol sulfate, (b) Eudragit® RS, (c) Eudragit® RL, (d) Sb : RS=1 : 1 PM, (e) Sb : RL=1 : 1 PM, (f) Sb : RS=1 : 1 SD, (g) Sb : RL=1 : 1 SD.

drying technique. These DSC thermograms also indicated the amorphizability of the Sb, as did the results from powder X-ray analysis. Melting points (mp) and heat of fusion (ΔH) results for the samples are listed in Table 2, together with the index of crystallinity, X_c. The X_c values are calculated according to the following equation:

$$X_c(\%)=(\Delta H/\Delta H_0)\times 100 \quad (1)$$

where ΔH_0 is the heat of fusion of the crystalline form of Sb, and ΔH is the heat of fusion of the samples. From the results shown in Table 2, the ΔH value of the physical mixture decreased more than originally predicted due to the dilution effect of mixing by RS and RL. ΔH values could not be calculated due to the lack of an endothermic peak for samples produced by the spray-drying technique.

Table 2. Melting Point (mp), Heat of Fusion (ΔH) and Crystallinity (X_c)

Sample	mp (°C)	ΔH (kJ/mol)	X_c (%)
Sb	186.91	160.21	100.0
Eudragit® RS	ND	ND	ND
Eudragit® RL	ND	ND	ND
Sb : RS=1 : 1 PM	184.16	53.96	67.4
Sb : RL=1 : 1 PM	184.91	59.48	74.3
Sb : RS=1 : 1 SD	ND	ND	ND
Sb : RL=1 : 1 SD	ND	ND	ND

ND: peaks were not detected.

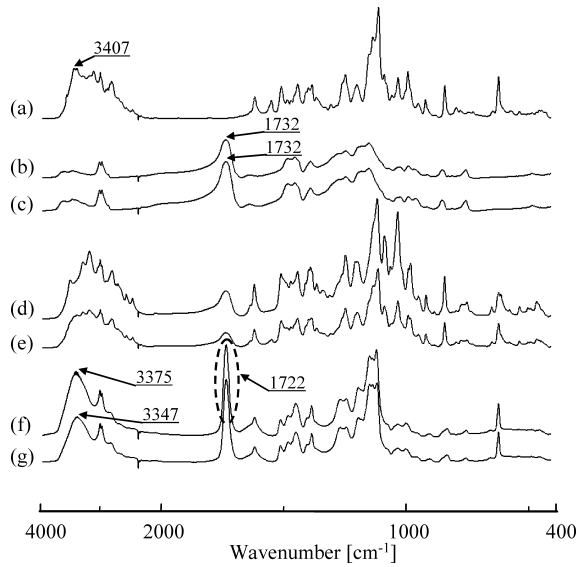

Fig. 4. FT-IR Spectra of Samples

(a) Salbutamol sulfate, (b) Eudragit® RS, (c) Eudragit® RL, (d) Sb : RS=1 : 1 PM, (e) Sb : RL=1 : 1 PM, (f) Sb : RS=1 : 1 SD, (g) Sb : RL=1 : 1 SD.

Confirmation of Interaction by IR Analysis Figure 4 shows the results of FT-IR spectroscopy of Sb, the carriers, their physical mixture, and samples prepared using 4-fluid nozzle spray-drying techniques. Sb displayed a broad band at 3407 cm^{-1} due to a stretching vibration (ν_{NH}) of the amino group. RS, RL showed a band at 1732 cm^{-1} due to a stretching vibration ($\nu_{C=O}$) of a carbonyl group. Similar bands were observed for the physical mixture of Sb and RS, RL, suggesting no interaction between Sb and RS, RL in the physical mixture. The band at 3407 cm^{-1} shifted approximately 32—60 cm^{-1} downfield, and the stretching vibration bands at 1732 cm^{-1} of RS, RL shifted to a wavenumber approximately 10 cm^{-1} lower. Therefore, the 3407 cm^{-1} amino group of Sb appears to form hydrogen bonds with the 1732 cm^{-1} carbonyl group of RS, RL.

Release Rate of Sb from Composite Particles Dissolution profiles of Sb powder from the 4-fluid nozzle spray-dried samples were obtained at pH 1.2 and pH 6.8, as shown in Figs. 5(A) and (B). Release of the original Sb was 100% within 1 min, an extremely rapid release rate, indicating that Sb is highly soluble in pH 1.2 and pH 6.8 solutions. The same appears to be true for the physical mixture sample of 1 : 1 at pH 1.2 and pH 6.8. In contrast, for the 4-fluid nozzle spray-dried sample, the Sb : RS=1 : 1 SD sample was eluted most slowly. Even though the 4-fluid nozzle spray-dried sample (mean particle diameter of 2 μm) was smaller than the

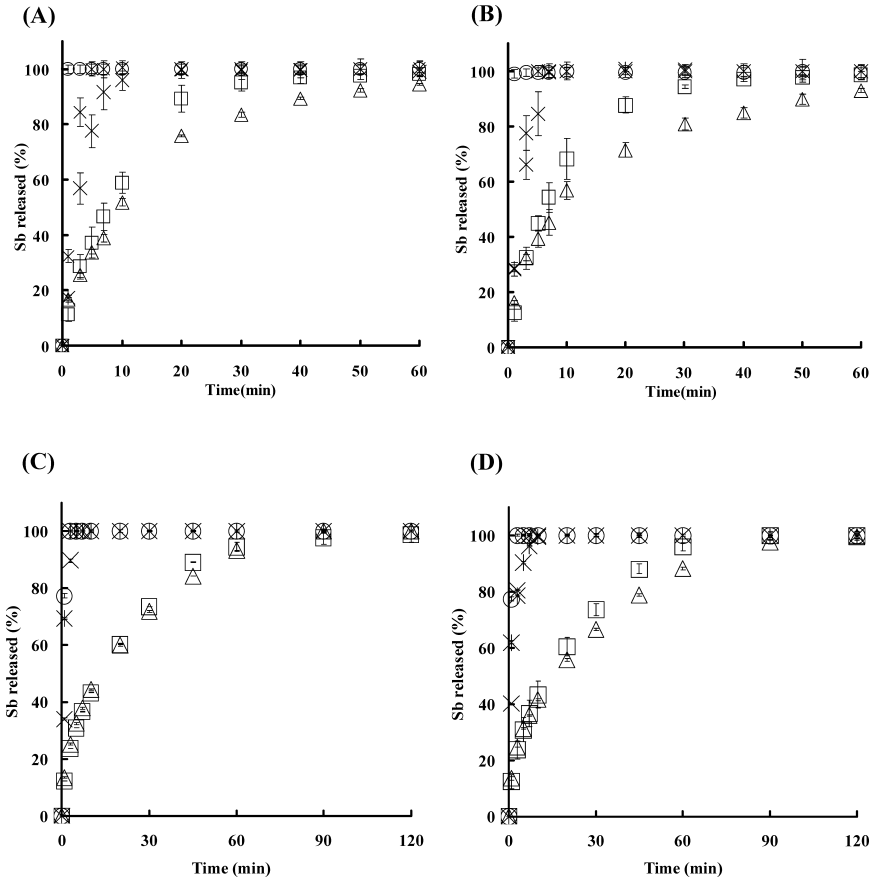

Fig. 5. Dissolution Profiles of Samples

(A) Powder pH 1.2; (B) powder pH 6.8; (C) tablet pH 1.2; (D) tablet pH 6.8. ○, salbutamol sulfate; ∗, Sb : RS=1 : 1 PM; ×, Sb : RL=1 : 1 PM; △, Sb : RS=1 : 1 SD; □, Sb : RL=1 : 1 SD. Each point represents the mean±S.D. (n=3).

original Sb (mean particle diameter of 10.5 μm), dissolution of the 4-fluid nozzle spray-dried sample was delayed, due to the insolubility of the carrier, which swells in aqueous solution. Because of this effect, the 4-fluid nozzle spray-dried sample showed sustained release.

Dissolution profiles of Sb tablets prepared from the 4-fluid nozzle spray-dried samples were obtained at pH 1.2 and pH 6.8, as shown in Figs. 5(C) and (D). The release rate in tablets for the original Sb and 1 : 1 physical mixture sample showed that they are highly soluble in pH 1.2 solutions. The 4-fluid nozzle spray-dried sample had 100% release after 2 h. Since tablets resist water penetration due to compressibility, they dissolved more slowly. The results of dissolution tests at pH 6.8 showed the same tendency as those at pH 1.2. Next, the release mechanism from composite particles was investigated using the above experimental results. Each composite particle was considered a matrix, with an assumption of release of the drug from the matrix. With these assumptions, the release rate was obtained by plotting the Higuchi equation:

$$Q = k \cdot t^{1/2} \quad (2)$$

where Q is concentration of the drug in the dissolution medium, t is release time, and k is apparent release rate constant. In addition, the 70% release time (T_{70}) was compared to the latter half of the release. Results from the Higuchi equation are shown in Fig. 6 and the calculated data are given in Table 3. However, since neither Sb powder nor the physical mixture could be considered a matrix and the Higuchi equation was not completely appropriate, it was plotted for comparison. Results from the Higuchi equation in the initial stage possessed good linearity with 4-fluid nozzle spray-dried samples.

The T_{70} value from Sb : RS=1 : 1 SD in pH 1.2 liquid increased 25-fold compared to that of the Sb powder. In addition, the T_{70} value from Sb : RL=1 : 1 SD in pH 1.2 liquid increased 20-fold compared to that of the Sb powder. In contrast, T_{70} of Sb : RS=1 : 1 SD in pH 6.8 liquid increased 27-fold compared to the Sb powder. The T_{70} value for Sb : RL=1 : 1 SD in pH 6.8 liquid increased 16-fold compared to that of the Sb powder. These results show the same tendency as those for the dissolution profiles of Sb tablets. The Sb : RS=1 : 1 SD exhibited sustained-release instead of the Sb : RL=1 : 1 SD, which suggests that the RS in a carrier conferred low permeability. In the early-stage apparent release rate constant, 4-fluid nozzle spray-dried samples decreased by about 6 times compared to the Sb powder in pH 1.2 and pH 6.8. Also, for the early-stage dissolution pattern, 4-fluid nozzle spray-dried samples exhibited slow dissolution. These results suggest that 4-fluid nozzle spray-dried samples produced ideal sustained release at all pH values tested, because RS and RL are not influenced by pH.

Mass Median Aerodynamic Diameter (MMAD) The usefulness of Sb powder in a dry powder inhaler was examined. As shown in Table 1, the 4-fluid nozzle spray-dried samples were composed of very fine particles that had potential for administration by inhalation. Thus, *in vitro* inhalation

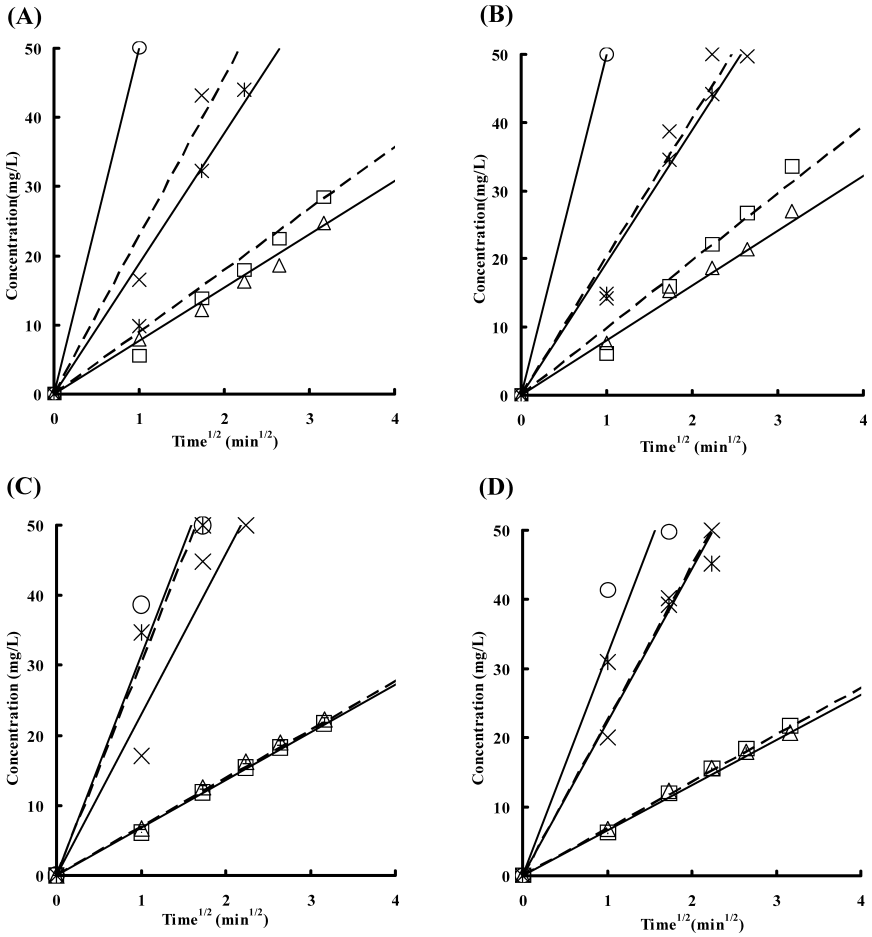

Fig. 6. Higuchi Plots for Dissolution of Samples

(A) Powder pH 1.2; (B) powder pH 6.8; (C) tablet pH 1.2; (D) tablet pH 6.8. ○, salbutamol sulfate; ∗, Sb : RS=1 : 1 PM; ×, Sb : RL=1 : 1 PM; △, Sb : RS=1 : 1 SD; □, Sb : RL=1 : 1 SD. Each point represents the mean±S.D. (n=3).

Table 3. Apparent Release Rate Constant k and 70% Release Time (T_{70})

Sample		pH 1.2		pH 6.8	
		k (mg/l/min$^{1/2}$)	T_{70} (min)	k (mg/l/min$^{1/2}$)	T_{70} (min)
Powder	Sb	50.0	0.7	50.0	0.7
	Sb : RS=1 : 1 PM	18.8	4.0	19.4	3.7
	Sb : RL=1 : 1 PM	22.9	2.4	20.3	2.7
	Sb : RS=1 : 1 SD	7.7	17.5	8.0	19.0
	Sb : RL=1 : 1 SD	8.9	13.7	9.8	10.9
Tablets	Sb	31.2	1.1	31.7	0.9
	Sb : RS=1 : 1 PM	30.3	1.0	22.0	1.9
	Sb : RL=1 : 1 PM	22.9	2.2	22.5	2.4
	Sb : RS=1 : 1 SD	7.0	28.5	6.5	31.4
	Sb : RL=1 : 1 SD	6.8	26.5	6.8	25.7

performance of the particles was evaluated using an Andersen cascade impactor and results are shown in Fig. 7. The MMADs (50% frequency oversize) were estimated from the log-probability plots of data from Fig. 7 and are shown in Table 4. In this case, air flow rate was 40.0 l/min because of a strong tendency for particles to agglomerate. Beppu *et al.*[25] prepared globular particles with a diameter range of 0.5—7.0 μm by spray-drying. In this study, the MMADs of 4-fluid nozzle spray-dried samples were less than 6.0 μm, suggesting that the 4-fluid nozzle spray-drying technique was successful in preparing powders suitable for reaching respiratory regions. In 4-fluid nozzle spray-dried samples, OE and RF were about 90% and 45%, respectively, and possessed superior inhalation performance. RS and RL do not dissolve in water and may not be suitable as a inhaler carrier. However, investigation of lung delivery of these particles provides meaningful information that can be applied to the development of better carriers.

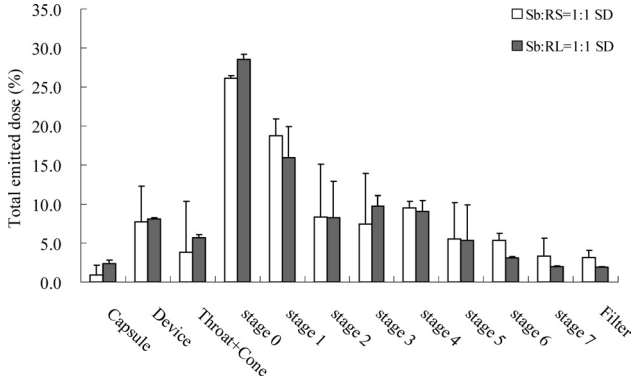

Fig. 7. *In Vitro* Inhalation Properties of Samples Evaluated with a Cascade Impactor

Table 4. *In Vitro* Powder Charateristics of Samples for Inhalation Administration

Sample	$MMAD_{d50}$ (μm)	OE (%)	RF (%)
Sb : RS = 1 : 1 SD	4.55±0.21	91.5±1.27	46.9±2.26
Sb : RL = 1 : 1 SD	5.45±0.21	89.6±0.01	43.3±0.01

OE: output efficacy (percent of total powder mass exiting from the capsule and device). RF: respirable fraction (percent of the drug mass on the respirable fraction (not more than 7.0 μm) of the impactor divided by emitted dose).

Conclusions

We investigated particle design using Sb in solid dispersions with RS, RL when mixtures of the drug and carrier were spray-dried using a 4-fluid nozzle spray-dryer. The composite particles prepared were spherical with a smooth surface, and had a mean particle diameter of about 2 μm. As a result of solid dispersion formation, Sb became amorphous and the rate of release decreased remarkably when compared with the drug alone or with the physical mixture at both pH 1.2 and 6.8. The dissolution rate decreased in the order RS>RL and corresponded to permeability. A good sustained release dosage form was obtained by compressing the particles into tablets. A plot of dissolution rate according to the Higuchi equation provided a linear relation, suggesting that the composite powders and tablets were a matrix of uniform dispersion and Sb diffused through the matrix of the particles obtained with a 4-fluid nozzle spray dryer. The increase in specific surface area suggests the possibility of effective distribution to the lung depths and an improvement in inhalation characteristics.

References

1) Simonelli A. P., Mehta S. C., Higuchi W. I., *J. Pharm. Sci.*, **58**, 538—549 (1969).
2) Simonelli A. P., Mehta S. C., Higuchi W. I., *J. Pharm. Sci.*, **65**, 355—361 (1976).
3) Mcginity J. W., Maincent P., Steinfink H., *J. Pharm. Sci.*, **73**, 1441—1444 (1984).
4) Law S. L., Lo W. Y., Lin F. M., Chaing C. H., *Int. J. Pharm.*, **84**, 161—166 (1992).
5) Mura P., Manderioli A., Bramanti G., Ceccarelli L., *Drug Develop. Ind. Pharm.*, **22**, 909—916 (1996).
6) Kumar S. G. V., Mishra D. N., *Yakugaku Zasshi*, **126**, 657—664 (2006).
7) Sekikawa H., Naganuma T., Fujiwara J., Nakano M., Arita T., *Chem. Pharm. Bull.*, **27**, 31—37 (1979).
8) Itoh S., Tagaki A., Tanabe K., Yamazaki M., *Yakuzaigaku*, **54**, 180—184 (1994).
9) Lo W. Y., Law S. L., *Drug Develop. Ind. Pharm.*, **22**, 231—236 (1996).
10) Tantishaiyakul V., Kaewnopparat N., Ingkatawornwong S., *Int. J. Pharm.*, **143**, 59—66 (1996).
11) Ozeki T., Yuasa H., Kanaya Y., Oishi K., *Chem. Pharm. Bull.*, **43**, 660—665 (1995).
12) Corrigan O. I., Holohan E. M., *J. Pharm. Pharmacol.*, **36**, 217—221 (1984).
13) Corrigan O. I., Holohan E. M., Reilly M. R., *Drug Develop. Ind. Pharm.*, **11**, 677—695 (1985).
14) Emara L. H., Badr R. M., Elbary A. A., *Drug Develop. Ind. Pharm.*, **28**, 795—807 (2002).
15) Yamashita K., Nakate T., Okimoto K., Ohike A., Tokunaga Y., Ibuki R., Higaki K., Kimura T., *Int. J. Pharm.*, **267**, 79—91 (2003).
16) He P., Davis S. S., Illum. L., *Int. J. Pharm.*, **187**, 53—65 (1999).
17) Shaikh N. A., Abidi S. E., Block L. H., *Drug Develop. Ind. Pharm.*, **13**, 1345—1369 (1987).
18) Corrigan D. O., Healy A. M., Corrigan O. I., *Eur. J. Pharm.*, **62**, 295—305 (2006).
19) Chen R., Okamoto H., Danjo K., *Chem. Pharm. Bull.*, **54,** 948—953 (2006).
20) Chen R., Okamoto H., Danjo K., *J. Drug Del. Sci. Tech.*, **17**, 129—135 (2007).
21) Takahashi H., Chen R., Okamoto H., Danjo K., *Chem. Pharm. Bull.*, **53**, 37—41 (2005).
22) Kristmundsdottir T., Gudmundsson O. S., Ingvarsdottir K., *Int. J. Pharm.*, **137**, 159—165 (1996).
23) Ozeki T., Beppu S., Mizoe T., Takashima Y., Yuasa H., Okada H., *J. Controlled Release*, **107**, 387—394 (2005).
24) Ozeki T., Beppu S., Mizoe T., Takashima Y., Yuasa H., Okada H., *Pharm. Res.*, **23**, 177—183 (2006).
25) Beppu S., Ozeki T., Sasaki Y., Mizoe T., Takashima Y., Yuasa H., Okada H., *Yakuzaigaku*, **63**, 228—237 (2003).