Spray Freeze-Dried Porous Microparticles of a Poorly Water-Soluble Drug for Respiratory Delivery

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Particles of poorly water-soluble drugs were prepared to develop a dry powder inhaler (DPI). Spray freeze-drying (SFD) technique using a four-fluid nozzle (4N), which has been developed by authors, was applied in this research. Ciclosporin and mannitol were used as a poorly water-soluble model drug and a dissolution-enhanced carrier, respectively. The organic solution of ciclosporin and aqueous solution of mannitol were separately and simultaneously atomized through the 4N, and the two solutions were collided with each other at the tip of the nozzle edge. The spray mists were immediately frozen in liquid nitrogen to form a suspension. Then, the iced droplets were freeze-dried to prepare the composite particles of the drug and carrier. tert-Butyl alcohol (t-BuOH) was used as the organic spray solvent due to its relatively high freezing point. The resultant composite particles with varying drug content were characterized depending on their morphological and physicochemical properties. The particles contained amorphous ciclosporin and δ-crystalline mannitol. The characteristic porous structure of SFD particles potentially contributed to their good aerodynamic performance. A series of particles with a similar size distribution and different drug content revealed that the incorporation of mannitol successfully improved the cohesive behavior of ciclosporin, leading to enhanced aerosol dispersion. The dissolution test method using low-volume medium was newly established to simulate the release process from particles deposited on the surface of the bronchus and pulmonary mucosa. The composite with hydrophilic mannitol dramatically improved the in vitro dissolution behavior of ciclosporin in combination with the porous structure of SFD particles.

Key words spray freeze-drying; liquid nitrogen; ciclosporin; porous particle; tert-butyl alcohol

Inhalation is the most appropriate route to deliver drugs to treat respiratory disorders such as asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis.1–3 This route directly targets the site of action and reduces the occurrence of systemic adverse effects. In addition, there is increasing interest in the use of pulmonary delivery to administer systemically-acting macromolecules, such as inhaled insulin product.4 The aerodynamic size of drug particles should be 5–6 μm or less for optimal airway deposition.5–7 However, particles in this size range have potentially cohesive property and tend to disperse poorly.

One approach to achieve excellent inhalation delivery by simultaneously improving the micromeritic properties and reducing the cohesive properties of agents is to design spherical particles with relative large geometric diameters and low particle mass densities. Inter-particulate cohesion could be reduced by enlarging and spheronizing the individual particle, and aerosol performance could be improved by decreasing the weight of the particles, ultimately like soap bubbles. In particular, particle design focused on particle density has been specifically researched for inhalation delivery. Edwards et al. developed large porous particles by spray-drying a solution of carboxylate-based polystyrene nanoparticles into an extremely thin-walled macroscale structure.8,9 Furthermore, Ungaro et al. prepared gas-foamed large porous particles based on poly(lactic-co-glycolic) acid polymer (PLGA) via a double emulsion-solvent evaporation technique.10–12 These reports concluded that spherical particles with hollow or porous internal structures exhibited extremely better flow and aerosolization properties than the normal mechanically micronized crystalline.

We previously developed a spray freeze-drying (SFD) method, which is a combination of conventional spray-drying and freeze-drying techniques.13,14 In this method, a solution of the drug and release-modified excipient is co-sprayed into liquid nitrogen, causing the solution to immediately freeze and form a suspension. Then, the iced droplets are lyophilized by a freeze-dryer to prepare composite particles, which are then characterized by fine porous structure producing a large specific surface area; this method is extremely attractive for the development of particles for dry powder inhaler (DPI) because of their specific low density. Therefore, this SFD technique was applied to develop dry powders for inhalation.

In this research, ciclosporin, which is currently used as an immunosuppressant for treating a number of autoimmune diseases due to its wide biological activities, including antifungal, anti-inflammatory, and anti-parasitic properties,15 was used as a model drug. This drug is a macromolecular cyclic peptide and is practically insoluble in water.16 To improve its solubility at respiratory sites, which do not have a sufficient volume of dissolution medium, water-soluble mannitol was incorporated as a hydrophilic excipient due to its pulmonary precedent in pharmaceutical products. Yamasaki et al. have reported the development of inhalable nano-matrix particles with the same combination of drug and excipient,19 but the technique was different from that used in this report. Ciclosporin and mannitol were dissolved in water and an organic solvent, respectively, because they do not have a common dissolving solvent. tert-Butyl alcohol (t-BuOH) was newly used as a spray solvent for ciclosporin because it is freely miscible with water and has a relatively high freezing point (25.4°C) among organic solvents. In addition, a four-fluid nozzle (4N) with two liquid supplying lines was applied to attain simultaneous spraying of above two solutions. The composite

The authors declare no conflict of interest.

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particles obtained by the current SFD method were fully characterized based on their physicochemical and pharmaceutical properties including their in vitro aerosol and dissolution performances.

**Experimental**

**Materials** Ciclosporin A, as an active pharmaceutical drug, was purchased from Hangzhou Zhongmeihuadong Pharmaceutical Co., Ltd. (Hangzhou, China). D-Mannitol (Mannit P) was provided by Mitsubishi Shoji Foodtech Co., Ltd. (Tokyo, Japan). Ciclosporin A and d-mannitol are briefly described as ciclosporin and mannitol in this report, respectively. Mannitol, a water-soluble additive is also referred to as “carrier” in this paper. tert-Butyl alcohol and polysorbate 80, shortly described as t-BuOH and Tween 80 in this paper respectively, were purchased from Wako Pure Chemical Co., Ltd. (Tokyo, Japan) was used to lyophilize the iced composite particles.

**Manufacturing Instruments** The spray-dryer with a 4N (MDL-050B; Fujisaki Electric, Co., Ltd., Tokushima, Japan) was used in this study. The freeze-dryer (FD-550; Tokyo Rikakikai Co., Ltd., Tokyo, Japan) was used to lyophilize the iced composite particles.

**SFD Procedure** The spray freezing process using the 4N is illustrated in Fig. 1. The 4N, which has two compressed air supply lines and two liquid feed passages, was schematically magnified to allow the readers to understand its structure and function well. tert-ButOH and water were adopted as the spray solvents to dissolve ciclosporin and mannitol, respectively. Two spray solutions of drug and carrier were separately supplied to the nozzle part of the spray-dryer. Each spray solution was simultaneously atomized by compressed air, and immediately collided and mixed with each other at the tip of the nozzle edge (edge angle: 60°). The finely splattered mists in the air were trapped by liquid nitrogen under stirring and immediately frozen. After spraying of all of the solutions, most of liquid nitrogen was evaporated in an ambient condition, keeping the droplets frozen. Then, the vessel containing the frozen droplets was put into the chamber of the freeze-dryer to sublime the iced water and tert-ButOH, resulting in the production of composite SFD particles. The schematic diagram of the entire apparatus and procedure for the current SFD technique was also reported in our previous paper.13)

The formulations of the spray solutions in this study are summarized in Table 1. Six types of particles with different drug content (0%, 5%, 10%, 20%, 50%, and 100%) were prepared by changing the loading amounts of ciclosporin and mannitol, and abbreviated to Cic0%, Cic5%, Cic10%, Cic20%, Cic50%, and Cic100%, respectively. The volumes of both solutions were fixed at 10 mL in all formulations. The two spray solutions were supplied to the 4N at the same speed of 5 mL/min (total feeding speed: 10 mL/min), and each of the fine mists was atomized by the pressure of the compressed air at a flow rate of 20 L/min (total blowing speed: 40 L/min). In case of Cic0%, two parts of the aqueous solution of mannitol (10 mL each) were fed to the 4N by passing through separate liquid-supplying lines and mixed at the tip of the nozzle edge. Cic100% was prepared by spraying two parts of the organic solution in the same manner. The concentration of total solid materials in the spray solution after mixing both the drug and carrier solutions was fixed at 10% w/v (2.0 g/20 mL) in all formulations. The iced droplets were freeze-dried in a vacuum at −30°C for 24 h, and further dried at 40°C until the vacuum level decreased to ≤5 Pa. The resultant spray freeze-dried (SFD) composite particles were collected and stored in glass vials in a desiccator at room temperature before the characterization measurement.

**Morphological Characterization** The morphology and size of the SFD composite particles were observed under a scanning electron microscope (SEM) (JSM-6060; JEOL Ltd., Tokyo, Japan). The particles were coated using platinum sputtering equipment (JFC-1600; JEOL Ltd.). The particle size...
distribution (PSD) of the original and composite particles was measured by a laser diffraction scattering method using a diffractometer with a dry dispersing unit (LMS-30; Seishin Enterprise Co., Ltd., Tokyo, Japan). The particles were dispersed into dry air at a fixed air pressure of 0.4 MPa. The diameters at 10%, 50%, and 90% of the cumulative volume distribution, shortly described as D10, D50, and D90, respectively, were represented as the size distribution. The specific surface area of the particles was measured by a surface area analyzer (Nova-1000, Quantachrome Instruments, Florida, U.S.A.) using an argon gas sorption process. The surface area per powder unit weight was calculated on the basis of the fitting of the adsorption data to the BET equation.

**Crystalline Analysis** X-Ray powder diffraction (XRPD) analysis was conducted using a Geiger-Flex diffractometer (RAD-2VC; Rigaku Co., Tokyo, Japan) with a Ni filter at 30 kV voltage and 20 mA current. Samples were scanned over 2θ range of 5° to 40° at a scan rate of 5°/min. The thermal properties of the samples were analyzed using differential scanning calorimetry (DSC) (DSC-60; Shimadzu Co., Ltd., Kyoto, Japan). Approximately 5 mg of each test sample were placed in an aluminum pan and heated with a scanning rate of 10°C/min in the range of 30–200°C under a nitrogen gas purge.

**In Vitro Aerodynamic Characterization** In vitro aerosol dispersion was evaluated using an eight-stage Andersen Cascade Impactor (AN-200; Shibata Scientific Technology Ltd., Saitama, Japan). The SFD particles corresponding to 3-mg weight (excluding CIC0%) were filled into a JP size-2 hard capsule composed of hydroxypropyl methylcellulose (HPMC) (Qualcaps Co., Ltd., Nara, Japan). The capsule was placed in a specific dry powder inhalation device (Jet Haler; Hitachi Automotive Systems Ltd., Tokyo, Japan) and punctured. The dry powder was dispersed via the device at 28.3 L/min air-flow rate for 5 s inspiration time. The upper aerodynamic cut-off diameters of stage 1 to 7 are 11.0, 7.0, 4.7, 3.3, 2.1, 1.1, and 0.65 µm, respectively. This operation was repeated five times and the collection stages of the impactor (stages 0–7) were washed with a water–acetonitrile mixture (1:1, v/v). Ciclosporin in the recovered solution was quantitated spectrophotometrically at 210 nm by an HPLC system (LC-10; Shimadzu Co., Ltd.) equipped with an ODS column (Inertsil ODS-3, 5 µm, 4.6×150 mm, GL Science, Tokyo, Japan). The ciclosporin peak was eluted at around 5 min when running the mobile phase (acetonitrile–5 mm ammonium acetate solution, 80:20, v/v) at a speed of 1.5 mL/min.

The emitted dose (ED) was defined as the total percent of ciclosporin emitted from the inhaler device and capsule. Oropharyngeal deposition (OD) was defined as the percent deposited in the “throat” part. In addition, the fine particle fraction (FPF) was defined as the total percent of the drug deposited in stage 2 and lower (≤7.0 µm; upper aerodynamic cut-off diameter of stage 2) relative to the loaded dose. The mass median aerodynamic diameter (MMAD) of the particles was also derived, and it was defined as the particles size at the 50% mark of a plot of cumulative fraction versus the effective cut-off diameter.

**Dissolution Test** Dissolution testing from the SFD particles was performed using the following two methods:

1) Soaking Method: Sample powders corresponding to 3 mg of the drug were weighed and placed into 100 mL of the dissolution medium at a holding temperature of 37±0.5°C. The medium was agitated at 300 rpm with a magnetic stirrer (HS-4SP; AsOne, Osaka, Japan). A phosphate-buffered solution containing 0.1% of Tween 80 (pH adjusted to 6.6) was used as a dissolution medium to simulate the respiratory juice. Aliquots of the solution were withdrawn through the membrane filter (pore size: 0.20 µm, DISMIC-13HP; Advan-tec Ltd., Tokyo) and diluted in methanol to the appropriate concentration. The quantity of ciclosporin was assayed using HPLC system in the same manner as described for aerosol performance. The dissolution profile of the original bulk drug was also studied as a reference. The dissolution tests for each sample were repeated in three vessels, and the average release percentage was plotted.

2) Filter Permeation Method: To simulate the release process from the particles deposited on the surface of the bronchus and pulmonary mucosa, which does not have a sufficient volume of fluid, the dissolution test with a poor medium was newly designed as shown in Fig. 2. Namely, a fiber filter (Pallflex T60A20; Nihon Pall Ltd., Tokyo) was covered on the surface of medium (100-mL volume) and entirely gotten wet. Ciclosporin with poor solubility was uniformly spread over the filter to simulate deposition of inhaled particles on the respiratory mucosa. The filter paper was fixed with a mesh and floated on the medium by using a float and a sinker to maintain the filter at the same level of the dissolution medium during the test. Aliquots of the solution passed through the filter were withdrawn at determined time points: 1, 3, 5, 10, 15, 30, 60, 120, 180 min. Other test conditions including the dissolution medium followed those of the aforementioned soaking method.

**Results and Discussion**

**Preparation of Composite Particles by SFD Process** In our previous research, the novel SFD process with the 4N was developed to prepare composite particles containing poorly water-soluble drugs, such as phenytoin and ciclosporin. These reports indicated that the resultant SFD composite particles had a porous and spherical morphology with a low particle density. The fluffy characteristics based on this unique internal structure prompted us to apply the particles to dry powder inhalation. Ciclosporin with poor solubility was
loaded as described in our previous experiments; that is, the drug was dissolved in an organic solvent and the dissolution-enhanced carrier, mannitol, was dissolved in water, which is a frequently used combination for solubilization. As an organic solvent, acetonitrile (freezing point: $-43.8^\circ$C) was replaced by t-BuOH in this study because its relatively high freezing point (25.4°C) to that of the other organic solvents was advantageous to perform the freeze-drying process in the conventional conditions (temperature and pressure). Actually 10% of water was mixed in the solvent phase to prevent the freezing of t-BuOH in the nozzle. Particles containing 100% drug content and 100% carrier content could be prepared in the current preparation system.

**Physicochemical Characteristics of the SFD Particles**

The morphological appearance of each SFD composite particle was observed under a SEM as shown in Fig. 3. All of the particles had the same spherical shape but a little bit different appearance dependent on drug content. Cic0% particle composed of only mannitol had a tight network structure, which is characteristic morphology of SFD particles as reported in previous papers [11,12], however, the surface morphology became smooth at higher drug content (Figs. 3B1, 3C1). The high-magnification photos clearly revealed that the surface closeness increased as the ciclosporin content increased, resulting in a fine honeycomb structure (Fig. 3C2). The pore diameter on the surface of the Cic50% particles was visually considered to be 100–200 nm. On the contrary, the low-magnification photos indicated that the size of the SFD particles (Fig. 3D) was obviously larger than that of the original bulk of ciclosporin (Fig. 3E), which appeared to be single-micron block-like particles. No difference in particle size was visually confirmed among particles with different drug contents. Satellite particles, which are relatively small particles ≤1 µm in diameter adherent to the main large particles, were also observed; these are assumed to be generated via splattering during droplet collision.

The cumulative particle size distribution (PSD) curves and representative diameters of various SFD particles and bulk particles are shown in Fig. 4 and Table 2, respectively. It was found that all PSD curves of the SFD particles, excluding Cic100%, nearly overlapped, indicating that particles with the same size distribution were obtained. The distribution was ranged from 2 to 20 µm, and the mean diameter (D50) was approximately 6–7 µm, which appeared to be slightly larger than the optimum inhalable size. The fixed spray conditions such as the liquid-feeding speed (10 mL/min), air-blowing speed (40 L/min), and solid concentration of the spray solution (10% w/v) may successfully produce spray mists with similar size, resulting in SFD particles with similar size because the mists were freeze-dried while keeping their sizes and shapes. With respect to Cic100%, its distribution curve indicated a shift to the larger particle side when the cumulative frequency exceeded 50%, which is attributed to some aggregation between particles, as suggested by the SEM images. Conversely, the ciclosporin bulk particles, which are jet-milled products, had a single-micron distribution that is apparently suitable for inhaled delivery. The data of the specific surface area of the particles measured by a gas adsorption method are also shown in Table 2. The surface area of the SFD particles was much larger than that of the bulk particles. The surface area increased as the drug content increased. In particular, Cic100% particles were 45-fold larger than ciclosporin bulk material. These results were highly consistent with the fine mosaic appearance shown in the SEM photographs (Fig. 3). These physicochemical properties demonstrated that the resultant composite particles had spherical external and micro-porous internal structures, which are the characteristic of SFD products.

**Crystalline Properties of the SFD Particles**

The crystalline properties of the composite particles prepared by the present SFD method were examined by XRPD and DSC. The

![Fig. 3. Scanning Electron Microphotographs of the SFD Composite Particles with Varying Ciclosporin Content and Ciclosporin Bulk](image-url)
XRPD patterns and DSC curves of all of the particles are shown side-by-side in Fig. 5 together with the data for each original bulk sample. The bulk material of ciclosporin as received was found to be amorphous based on its hollow XRPD pattern and no endothermic event in the DSC thermogram (Fig. 5H), which has been occasionally reported in other studies. The starting material of mannitol was identified as a stable β form detected by the characteristic diffraction peaks at 14.5°, 18.7°, and 23.3° of 2θ and the onset melting temperature at 166°C. By contrast, all of the SFD particles had different diffraction profiles with peaks at 9.4° and 21.7° of 2θ, which are specific peaks of the metastable δ form, and a lower endothermic peak (onset: 164°C), indicating that the crystalline form of mannitol was transformed during the SFD process. This polymorphic transition of mannitol during crystallization below 0°C was well consistent with the previous findings of Yoshinari et al. In addition, the hollow XRPD pattern and lack of DSC events for the Cic100% particles (Fig. 5G) revealed that ciclosporin remained amorphous even after the freeze-drying process. The fine texture of the SFD particles shown in Fig. 3C2 was likely attributable to amorphous ciclosporin.

**Aerodynamic Performance of the SFD Particles** Each SFD sample filled into a hard capsule was placed in a specific inhaler and puffed into the Cascade Impactor via a “throat” part under a fixed air-flow rate (28.3 L/min). The deposition patterns and inhalation characteristics of the SFD particles with various ciclosporin contents are displayed in Fig. 6 and Table 3, respectively. The ciclosporin bulk particles had poor output characteristics with a relatively low ED value (73.1%) despite their favorable size distribution for inhaled delivery, which was demonstrated by SEM observation (Fig. 3) and laser diffraction analysis (Fig. 4). In accordance with commonly recognized, the jet-milled ciclosporin particles (described as “Cic bulk”) were highly adhesive, resulting in the highest residual amount in capsule and the highest deposition on the device and throat components. It was assumed that the bulk particles tend to be trapped in the oropharyngeal region when inhaled. As a result, the FPF value, a parameter of the respirable fraction, was not sufficient (28.9%). In contrast, the ED values of all of the SFD particles exceeded 95%, which is attributable to improved adhesion due to the enlargement and spheronization of each primary particle. Differences in aerodynamic performance were observed among various SFD particles although their PSDs were nearly equivalent, excluding that of Cic100% sample. The deposition on stage 0 and that on stage 1–7 increased and decreased as the ciclosporin content increased, respectively. Especially aerodynamic delivery to stages 1–3 was increased compared to that of the bulk sample, although the geometric sizes of the SFD particles were larger than that of the bulk. Consequently, the FPF value increased with an increase of the mannitol content in the

![Image](https://example.com/image.png)

**Fig. 4. Cumulative Particle Size Distribution Profiles of the SFD Composite Particles with Varying Ciclosporin Content**

**Fig. 5. X-Ray Powder Diffraction Patterns (Left) and Differential Scanning Calorimetry Profiles (Right) of the SFD Composite Particles with Varying Ciclosporin Content**

**Table 2. Representative Particle Size and Specific Surface Area of the SFD Composite Particles with Varying Ciclosporin Content**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cic bulk</th>
<th>Cic0%</th>
<th>Cic5%</th>
<th>Cic10%</th>
<th>Cic20%</th>
<th>Cic50%</th>
<th>Cic100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>D10 (µm)</td>
<td>0.86</td>
<td>2.59</td>
<td>2.42</td>
<td>2.39</td>
<td>2.53</td>
<td>2.49</td>
<td>2.25</td>
</tr>
<tr>
<td>D50 (µm)</td>
<td>2.20</td>
<td>6.54</td>
<td>6.77</td>
<td>5.87</td>
<td>6.24</td>
<td>6.97</td>
<td>7.89</td>
</tr>
<tr>
<td>D90 (µm)</td>
<td>7.40</td>
<td>14.25</td>
<td>15.69</td>
<td>12.42</td>
<td>13.56</td>
<td>17.80</td>
<td>26.47</td>
</tr>
<tr>
<td>Specific surface area (m²/g)</td>
<td>2.48</td>
<td>15.4</td>
<td>26.6</td>
<td>29.6</td>
<td>37.8</td>
<td>73.7</td>
<td>111.1</td>
</tr>
</tbody>
</table>
particles. CM5% particles exhibited the highest value (36.4%) among the samples. It was considered that co-formulation with mannitol could improve the adhesive and cohesive behaviors of ciclosporin and confer the inherent fluffy characteristics of lightweight particles. However, it was found that further improvement is necessary to decrease the deposition on stage 0. Replacement of the current inhaler device by that with higher dispersion energy such as Aerolizer could be effective for increasing the respiratory fraction, as reported by Yamasaki et al.19)

Dissolution Behavior of the SFD Particles The release properties from the SFD composite particles were examined in a simulated respiratory fluid adjusted at pH 6.6. The tests were performed using the following two methods: A) a normal soaking method in a large volume of medium and, B) a filter permeation method in a small volume of medium as shown in Fig. 2. The latter was newly designed to simulate the release process from the particles adhered to the surface of the bronchus and pulmonary mucosa. The release profiles of the particles including ciclosporin bulk are shown in Figs. 7A and B. The measurement was highly reproducible in triplicate trials for each sample. As expected, ciclosporin bulk showed a slow release profile in both methods due to its poor solubility. Cic100% without including mannitol also displayed a similar pattern. In particular, the release curves of Cic100% leveled off to a plateau at nearly 15% in method (B). These results suggest that even successfully aerosolized drug particles that reached to the respiratory region might not be sufficiently available to facilitate treatment efficacy. In the meanwhile, the dissolution from the SFD particles, excluding Cic100%, was significantly improved. The rate of dissolution increased as the mannitol content in the particles increased. It was expected that mannitol accelerated the introduction of medium into the particles, resulting in a significant increase in the effective surface area for dissolution. Even in the permeation method with an insufficient volume of medium, the incorporation of this hydrophilic sugar alcohol was considerably effective for improving the slow dissolution of ciclosporin. These results indicated that the water-introducing effect of mannitol is important to promote the drug release in such low-volume medium. In addition, the newly designed filter permeation method would be a sensitive tool to evaluate the dissolution of poorly soluble drugs in regions with low fluid volume such as the lungs and bronchus.

Conclusion Porous and lightweight ciclosporin particles were successfully prepared by the SFD technique using 4N. The use of t-BuOH as a spray solvent enabled the preparation of composite particles with any content of the poorly water-soluble drug and dissolution enhanced excipient without changing the conventional freeze-drying conditions of the aqueous system.

Table 3. Inhalation Characteristics of SFD Composite Particles with Varying Ciclosporin Content

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cic bulk</th>
<th>Cic5%</th>
<th>Cic10%</th>
<th>Cic20%</th>
<th>Cic50%</th>
<th>Cic100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emitted dose (%)</td>
<td>73.1±4.3</td>
<td>96.8±1.8</td>
<td>94.0±1.2</td>
<td>96.4±0.9</td>
<td>95.7±1.3</td>
<td>96.6±0.8</td>
</tr>
<tr>
<td>Oropharyngeal deposition (%)</td>
<td>14.2±1.7</td>
<td>3.60±0.2</td>
<td>4.91±0.2</td>
<td>10.1±0.6</td>
<td>7.46±0.4</td>
<td>6.76±0.4</td>
</tr>
<tr>
<td>Fine particle fraction (%)</td>
<td>28.9±1.6</td>
<td>36.4±1.4</td>
<td>35.3±0.9</td>
<td>31.0±0.8</td>
<td>22.5±0.6</td>
<td>13.6±0.5</td>
</tr>
<tr>
<td>MMAD (µm)</td>
<td>8.42±0.8</td>
<td>7.67±0.7</td>
<td>8.71±0.3</td>
<td>9.48±0.3</td>
<td>12.2±0.4</td>
<td>16.4±0.5</td>
</tr>
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Each parameter expressed as mean±standard deviation (n=3).

Fig. 7. Release Profiles of Ciclosporin from the SFD Composite Particles with Varying Ciclosporin Content in Simulated Bronchial Medium (pH 6.6)

(A) Dissolution test with a large volume of medium: dissolution from the immersed samples in the medium. (B) Dissolution test with a small volume of medium: permeation of drug from wet samples through a wet filter. Key: ○ Cic5%, ▲ Cic10%, △ Cic20%, □ Cic50%, ● Cic100%, × ciclosporin bulk.

Fig. 6. Cascade Impactor Deposition Profiles of the SFD Composite Particles with Varying Ciclosporin Content, Expressed as a Percentage of the Total Loaded Amount of Ciclosporin

Data presented as mean±standard deviation (n=3). From left bar to right bar: ciclosporin bulk, Cic5%, Cic10%, Cic20%, Cic50%, Cic100%.
By applying fixed spraying conditions, particles with a comparable size distribution (D50: 6–7 µm) were obtained. The characteristic properties of the SFD particles such as high porosity, low density, and large specific surface area were clarified. It was found that the co-formulation of mannitol in the particle improved the adhesion properties of ciclosporin, resulting in enhanced aerosol performance. In addition, mannitol acted as a dissolution promoter of ciclosporin by introducing hydrophilicity into the porous SFD particles even in poor dissolution medium regions such as respiratory organs. The current formulation technique can be potentially used to develop particles for DPIs of ciclosporin or other poorly water-soluble drugs exhibiting improved aerodynamic and dissolution properties.

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