NOTE

Low-Density Microparticles with Petaloid Surface Structure for Pulmonary Drug Delivery

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ABSTRACT: The morphology of spray-dried particles composed of psicose and hydroxypropyl methylcellulose was modified by adding ammonium bicarbonate (ABC) to the solution. The surface structure of the particles was altered by immediate transformation of ABC to gaseous components during the spray drying. As a result, low-density microparticles with a petaloid surface structure, which was controllable by changing the evaporation rate of ABC, was obtained. This technique should be useful for modifying characteristics of solid particles for pulmonary drug delivery. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:1309–1313, 2014
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INTRODUCTION

New chemical entities developed for the pharmaceutical industry may have unfavorable physicochemical characteristics that prevent the use of common formulation technologies. The most common problematic property has been low aqueous solubility, and thus various options for overcoming the problem have been developed including physicochemical modification of the compound and use of formulation technologies that provide a supersaturated state in the gastrointestinal tract.[1] Low permeability is still a very difficult problem, and no promising technologies have been developed yet, although demand on this matter is increasing because of the increase of biopharmaceuticals. Some carriers and additives have been used effectively,[2–4] whereas other administration routes, including injection or inhalation, may be better options for the systemic administration of such drugs.

Dry powder inhalation is notably regarded as a convenient method for the delivery of pulmonary drugs because it can promote stabilization and administration of a large amount of drugs compared with other methods such as uses of metered dose inhalers and nebulizers.[5–7] Spray drying, which allows control of particle size by varying instrumental and solution conditions,[8–10] is one of the most common methods to manufacture inhalation particles. In addition to micronization, preparation of low-density particles, including hollow[11,12] or porous[13–15] particles, is a promising way for improving inhalation efficiency because this leads to a decrease in aerodynamic size. Surface characteristics, including surface roughness[16] and surface energy,[17] are also important for controlling the dispersion efficiency of the particles.

Our previous report[18] described that a compound with a low glass transition temperature (T_g) was successfully spray-dried with the aid of excipients. Psicose was difficult to spray dry because it has a very low T_g of −6.5°C. However, addition of hydrophilic polymers enabled the formation of spray-dried particles. The most effective polymer was hydroxypropyl methylcellulose (HPMC) because it had low miscibility with psicose and it spontaneously accumulated in the surface region of the particles to protect psicose from the contact with moisture. The difference in molecular weight between psicose and HPMC was another important factor that influenced their phase separation during the drying process. Further study to control particle morphology was attempted in this study using ammonium bicarbonate (ABC) as another component. The ABC was readily transformed to the gaseous components, carbon dioxide and ammonia, during spray drying, which resulted in the formation of porous particles.[14,15] The present study describes another type of particles, microparticles with petaloid surface structure, obtained using ABC for spray drying, which provides another option for improving inhalation property of the drug particles.

MATERIALS AND METHODS

Materials

Psicose was supplied from Kagawa University Rare Sugar Research Center (Miki, Kagawa, Japan). HPMC, which contains 28%–30% of methoxyl and 7%–12% of hydroxypropoxyl substituents and had the averaged molecular weight of approximately 20 kDa (grade E), was obtained from Shin-Etsu Chemical (Tokyo, Japan). ABC was purchased from Nacalai Tesque (Kyoto, Japan). All the reagents were used as supplied.

Spray Drying

Spray drying was performed using a Buchi B-290 spray dryer (Buchi Labortechnik, Flawil, Switzerland) with the following operational conditions: solution feeding rate of 2 mL/min, total solution concentration of 1.5 wt %, and atomizing

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pressure of 20 Pa. Relative humidity of the atmosphere was 40%–50%. More than two lots of samples were prepared for each composition.

Scanning Electron Microscopy

The morphology of the spray-dried particles was observed under a scanning electron microscope (S4800; Hitachi, Tokyo, Japan) at an accelerating voltage of 10 or 5 kV, after the samples being sputter coated for 30 s with platinum coater (E-1030 ion sputter; Hitachi). Particle size was determined by image analysis of the scanning electron microscopy (SEM) pictures using Mac-View version 4 (Mountech, Tokyo, Japan). Three hundred particles were selected randomly from the image to obtain the Heywood diameter. Volume-mean diameter was used for the analysis.

Density Measurements

True density was measured using 5-mL Gay-Lussac pycnometers (As-one, Osaka, Japan), with diethyl ether as the solvent. The measurements were performed five times, with 200 mg of the powder samples used for each measurement. Bulk density was evaluated by loading powder samples up to 50 mL in a 100-mL measuring cylinder, followed by the measurement of the weight.

Cascade Impactor

A nonviable eight-stage Cascade Impactor AN-200 (Tokyo Dylec, Tokyo, Japan) was used to evaluate inhalation properties of the spray-dried particles. Approximately 100 mg of powder was loaded into a diskhaler, followed by the administration for 5 s at an air flow of 28.3 L/min. A small amount of liquid paraffin was loaded onto the collector to trap the particles. The deposited amount was evaluated by weight. The particles collected during stages 2–7 were defined as fine particles. Fine particle fraction (FPF) was defined as a fraction of the fine particles with reference to the total mass of formulation loaded into the inhalation device.

Specific Surface Area

Specific surface area was determined by nitrogen adsorption method on a Belsorp mini (Bel Japan, Osaka, Japan). Approximately 100 mg of samples was dried at 50°C for 30 min under vacuum, and dead volume of the sample cell was measured at room temperature prior to measurements. Nitrogen adsorption/desorption measurements were performed using sample cells and an empty reference cell immersed in liquid nitrogen. Each measurement was repeated twice to obtain the mean surface area calculated by the BET (Brunauer-Emmett-Teller) method.

Angle of Repose

A cone-shaped pile of powder was formed on a 72-mm diameter circular steel base by dropping the powder from a funnel using an angle of repose tester manufactured by Tsutsui Scientific Instruments (Tokyo, Japan).

RESULTS AND DISCUSSION

Physical Characteristics of HPMC–Psicose (ABC-free) Particles

Although psicose cannot be spray-dried by itself because of its low T_g of −6.5°C, it can be manufactured with the addition of excipients. HPMC exhibited very high loading capacity for psicose because of its low hygroscopicity and low miscibility with psicose.[18] It should be meaningful to recall the particle formation mechanism in the spray drying process for understanding the effect of HPMC. When a formulation contains two components mixed in a noncrystalline state, the miscibility of the components is basically determined by thermodynamics. However, in practice, the formulation may not have the equilibrium structure. For spray-dried particles, a heterogeneous structure may be created by a difference in the molecular weight of the components because large molecules may be left on the surface of the particles if their diffusion during the drying process is slower than the shrinkage of the droplets. The thermodynamic miscibility seemed to be a factor that influenced the phase separation as well. When HPMC was used as an excipient, particles were obtained for HPMC–psicose ratio up to 2:8 in a reproducible manner. Particles were obtained occasionally even at a HPMC–psicose ratio of 1:9. This was possible because of the clear phase separation of the components and low hygroscopicity of HPMC that inhibited access of moisture to the psicose-rich inner phase. The mean diameter and true density of HPMC–psicose particles were about 5–6 μm and 1.55 g/cm,[3] respectively, regardless of the mixing ratio, and the particles had a wrinkled surface. Further details can be found in our previous paper.[18]

Inhalation Properties of HPMC–Psicose Particles

The spray-dried particles of HPMC–psicose were subjected to cascade impactor analysis to investigate the inhalation properties. Figure 1 shows the particle distribution for each stage. Psicose content did not greatly influence the distribution of the particles, which was expected because no significant differences existed in the physical characteristics of the particles.[18] Although the greatest amount was found for stage 0, a relatively large amount was found for stages 2, 3, and 4 as well.

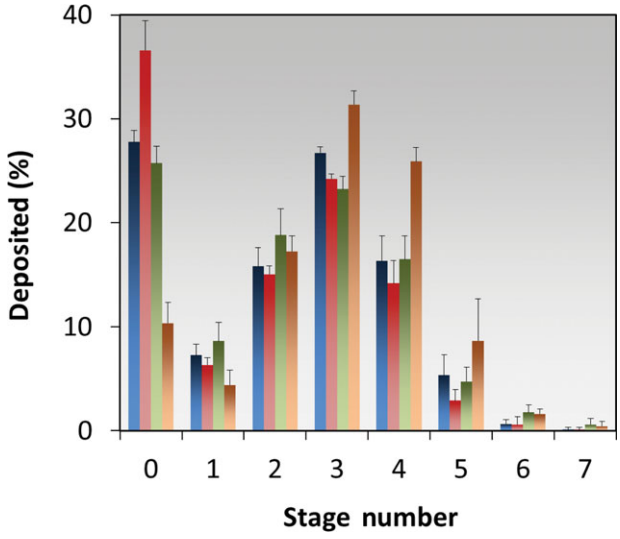

Figure 1. Evaluation of HPMC–psicose spray-dried formulations using an eight-stage cascade impactor. Psicose content was 20%, 40%, 60%, and 80% (left to right). Deposited amount (%) on each stage was presented with reference to emitted dose. Emitted fraction from the device was 36.8%, 25.2%, 25.0%, and 23.8%, respectively. Data are shown as means with SD error bars.

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