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Spray-dried composite particles of erythritol and porous silica for orally disintegrating tablets prepared by direct tableting

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ABSTRACT

This study investigated the preparation of orally disintegrating tablets (ODTs), which were prepared from spray-dried composite particles (CPs) of erythritol and porous silica (Sylysia 350) by direct tableting. Powder X-ray diffraction and differential scanning calorimetry indicated that erythritol was embedded in silica pores and remained in the crystalline state. CPs containing erythritol/porous silica ratios of 1:1, 2:1, and 3:1 showed excellent compactability resulting from strong binding properties. Although erythritol powder has poor compactability and caused problems during tableting, adding a small amount of CPs to erythritol improved tablet hardness. CPs containing an erythritol:porous silica ratio of 2:1 most effectively improved erythritol compactability. Erythritol powder containing CPs showed higher deformability than that of physical mixtures, and CPs inhibited elastic recovery after compression because of strong interparticulate bonding. Furthermore, CPs retained function as dry binders when stored under humid conditions. Placebo ODTs prepared with CPs (erythritol:porous silica ratios of 1:1, 2:1, and 3:1) and crospovidone (Kollidon® CL) as a disintegrant showed both excellent tablet hardness and rapid disintegration. We confirmed that the use of CPs improved manufacturing of ODTs containing active pharmaceutical ingredients using an appropriate compression pressure.

1. Introduction

Orally disintegrating tablets (ODTs) were designed as a user-friendly dosage form for persons who have difficulty taking oral medications, such as the elderly and children. Additionally, ODTs are useful not only for individuals who have difficulty swallowing but also for other usual patients because it is able be taken with a small amount of water or saliva [1]. Commercially available ODTs are generally produced by modifications to conventional tableting processes, which can be classified into molded tablet, wet-compacted tablet, and compressed tablet methods [2]. The molded tablet is prepared by drying after filling the pockets of press-through packaging with a drug solution or suspension containing excipients [3–5]. The tablet disintegrates instantly in the oral cavity; however, its structure is so brittle that it cannot be handled easily. The wet-compacted tablet is prepared by drying after low-pressure compression of wet granules containing the drug using special equipment, such as a wet-tableting machine [6]. The compressed tablet is prepared using the conventional tableting process [7–11]. Sugar alcohols such as mannitol and erythritol are often used in this method because they rapidly dissolve and have a sweet taste. However, the sugar alcohols often have poor compactability and can cause problems during tableting, including capping and sticking [12]. Although erythritol has properties that are ideal for use as a base of an ODT, such a fresh taste and no calories, its compactability is insufficient for tableting [13]. Therefore, improved compactability of sugar alcohols would enable the design of an ideal ODT.

Direct compression is a convenient method because no special manufacturing facilities or granulation processes are required [14–17]. However, the use of a direct tableting system to prepare ODTs with bases with a low compactability, such as mannitol and erythritol, can cause major problems. To overcome these problems, filler binders, which provide excellent compactability and do not prevent water absorption into the tablet, are often required for ODT preparations.

In our previous work, it was found that a small addition of spray-dried composite particles (CPs) containing porous silica with an active pharmaceutical ingredient (API) markedly improved the compactability of powders that typically have poor compactability. Resultant tablets exhibited a rapid dissolving rate in a dissolution apparatus that simulated the gastrointestinal tract [18]. However, ODTs with rapid dissolving properties in a small amount of saliva were not obtained in this research. The advantages of preparing CPs using a spray drying method that uses water as a solvent include control of particle size, production of an organic-free solvent, high reproducibility, and a continuous manufacturing process [19,20].

In this study, we attempted to improve the compactability of sugar alcohols using spray-dried CPs containing porous silica and applied this method to preparation of direct-compressed ODTs as a platform

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technology. Erythritol was used as a base ingredient with poor compactability. CPs containing different erythritol/porous silica ratios were characterized to clarify the mechanisms by which CPs improve filler compactability. Finally, the CP formulations were optimized to prepare placebo and drug-loaded ODTs that rapidly disintegrate in water.

2. Materials and methods

2.1. Materials

Erythritol was purchased from B Food Science Co., Ltd. (Chita, Japan). Porous silica (Sylysia®350) was supplied by Fuji Silysia Chemical, Ltd. (Kasugai, Japan). The specific surface area, average pore size, and pore volume of Sylysia®350 are 287.3 m^2/g, 21.2 nm, and 1.4 mL/g, respectively, according to information provided by the supplier. Ascorbic acid for use as a model drug compound was purchased from Junsei Kagaku Company, Ltd. (Tokyo, Japan). Crospovidone (Kollidon® CL) was obtained from BASF (Ludwigshafen, Germany). Magnesium stearate was obtained from Kishida Chemical Co., Ltd. (Osaka, Japan).

2.2. Preparation of spray-dried CPs and tablets

Four types of CPs with different erythritol/porous silica ratios (0.5:1, 1:1, 2:1, and 3:1) were prepared by spray drying. Porous silica (1 g) was added to a solution containing erythritol (0.5, 1.0, 2.0, or 3.0 g) dissolved in 100 mL of purified water. This suspension was fed into the chamber of a spray dryer (GS31, Yamato Scientific Co., Ltd., Tokyo, Japan) at the rate of 10 mL/min from a nozzle with a diameter of 406 μm and an atomizing pressure of 0.12–0.15 MPa. The inlet and outlet air of the drying chamber were maintained at 150 °C and 80 °C, respectively. Particles were dried in a desiccator with blue silica gel under reduced pressure for 24 h before their properties were tested and used to prepare tablets. In the present article, the terms CP-0.5, CP-1, CP-2, and CP-3 indicate CPs with erythritol:porous silica ratios of 0.5:1, 1:1, 2:1, and 3:1, respectively. Physical mixtures for tableting were prepared by mixing each component powder in a glass vial. A single punch tableting machine (Model N-30EX; TabAll, Okada Seiko, Tokyo, Japan) was used with flat-faced punches (diameter, 8 mm) to produce tablets weighing 200 mg. The formulation powder was compressed at 100–200 MPa. The pressure transmission ratio (PTR) was calculated by dividing the lower punch pressure by the maximum upper punch pressure [21]. The compression speed was 10 strokes/min. CPs were stored under stabile conditions in chambers in a temperature- and humidity-controlled room.

2.3. Physicochemical properties of CPs and tablets

Particle sizes of CPs were measured using a laser diffraction size analyzer (LDSA-2400A; Nikkiso Co., Ltd., Tokyo, Japan), which used a dispersion-in-air method at 3.0 kg/cm^2. The CP shapes were determined by scanning electron microscopy (SEM; VE-8800; Keyence Corp., Osaka, Japan). After degassing the sample powder at 60 °C for at least 8 h (Flow Prep060; Shimadzu Corporation, Kyoto, Japan), the specific surface areas of CPs were determined using the conventional Brunauer–Emmett–Teller method for adsorption of nitrogen gas (Gemini 2375; Shimadzu Corporation).

Thermal analysis of erythritol in CPs was performed using a differential scanning calorimeter (DSC; DSC6200; Seiko Instruments Inc., Chiba, Japan). The sample powder (2–5 mg) was placed in an aluminum sample pan and measured as the temperature was increased at a rate of 10 °C/min.

The powder X-ray diffraction (PXRD) patterns of erythritol in CPs were recorded using a PANalytical X'Pert PRO diffractometer (PANalytical BV, Almelo, Netherlands). The measurement conditions for PXRD were as follows: target, Cu-Kα; generator voltage, 45 kV; tube current, 40 mA; and data angle range, $2\theta = 5°–40°$.

The tablet crushing load, which represents the force required to break a tablet by compression in the radial direction, was measured using a particle hardness tester (GRANO; Okada Seiko Co., Ltd., Toyo, Japan) at a crushing velocity of 50 μm/min. The tensile strength required for crushing was calculated using the following equation: tensile strength $= 2F / (\pi DT)$, where F is the crushing load and D and T are the diameter and thickness of the tablet, respectively.

2.4. Analysis of compression behavior

Heckel analysis was performed to determine the deformability of the powder bed during compression. The formulation (200 mg) was compressed using an instron-type hydraulic press (Autograph AG-5000, Shimadzu Corporation) with flat-faced punches and a die with a diameter of 8 mm, compression pressure of 100 MPa, and compression speed of 10 mm/s. The parameter reflecting the deformability of a powder bed during compression was calculated using the Heckel equation [22]: $\ln(1/\varepsilon) = P/Py + A$, where ε is the porosity of the compressed powder at pressure P and Py is the yield pressure, which is determined by linear regression for pressures between 30 and 70 MPa. The porosity was calculated from the true density measured using a helium pycnometer (Ultrapycnometer 1000 Version 2.2; Quantachrome Instruments, Boynton Beach, FL, USA).

The percent of expansion energy (EE) to input energy (IE), which represents the elastic recovery of the powder during the compression process, was calculated using the following equation [23]: Elastic recovery (%) $= [\mathrm{EE\ (J)}] / [\mathrm{IE\ (J)}] \times 100$, where IE is the gross compression energy, and EE is the energy lost by instantaneous elastic recovery of the compact during the pressure release, which is calculated with force–displacement profiles.

2.5. Disintegration test

Disintegration time was determined using an disintegration tester specific for ODTs (ODT-101; Toyama Sangyo Co., Ltd., Osaka, Japan) with a load of 20 g rotating at a velocity of 75 min^{-1} and purified water heated to 37 °C ± 2 °C [24,25].

3. Results and discussion

3.1. Physicochemical properties of CPs with different erythritol/porous silica ratios

It was expected that the erythritol/porous silica ratio in CPs and the powder properties of CPs affect the characteristic of tablets after compression.

The yield of the spray drying process was 65%–75% for all CPs. The particle distributions of CPs containing different erythritol and porous silica ratios were measured using a LDSA under dry dispersion conditions (Table 1). The median particle size (D50) for all CPs was 3–5 μm, which is much smaller than that of untreated erythritol (UNT-E; 24.1 μm). The D50 of CP-0.5, CP-1, and CP-2 was comparable with that

Table 1
Particle size of CPs containing different erythritol/porous silica ratios under dry dispersing conditions.

Sample	Erythritol/porous silica	Particle size		
		D_{16}	D_{50}	D_{84}
Untreated erythritol	1/0	9.1 ± 0.5	24.1 ± 2.7	61.0 ± 9.3
Porous silica	0/1	2.0 ± 0.0	3.6 ± 0.0	5.5 ± 0.0
CP-0.5	1/2	2.0 ± 0.1	3.6 ± 0.1	5.5 ± 0.2
CP-1	1/1	2.0 ± 0.0	3.7 ± 0.1	5.4 ± 0.1
CP-2	2/1	2.3 ± 0.2	3.9 ± 0.2	5.7 ± 0.1
CP-3	3/1	3.2 ± 0.1	5.2 ± 0.2	8.0 ± 0.3

Data are expressed as mean ± SD ($n = 3$).
CP, composite particle.