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Impact of active ingredients on the swelling properties of orally disintegrating tablets prepared by microwave treatment

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ABSTRACT

The impact of different active pharmaceutical ingredients (APIs) loading on the properties of orally disintegrating tablets (ODTs) prepared according to our previously reported microwave (MW) treatment process was evaluated using famotidine (FAM), acetaminophen (AAP), and ibuprofen (IBU). None of the APIs interrupted the tablet swelling during the MW treatment and the tablet hardness were improved by more than 20 N. MW treatment, however, led to a significant increase in the disintegration time of the ODTs containing IBU, but it had no impact on that of the ODTs containing FAM or AAP. This increased disintegration time of the ODTs containing IBU was attributed to the relatively low melting point of IBU (T_m = 76 °C), with the IBU particles melting during the MW treatment to form agglomerates, which interrupted the penetration of water into the tablets and delayed their disintegration. The effects of the MW treatment on the chemical stability and dissolution properties of ODTs were also evaluated. The results revealed that MW treatment did not promote the degradations of FAM and AAP or delay their release from the ODTs, while dissolution of the ODTs containing IBU delayed by MW treatment. Based on these results, the MW method would be applicable to the preparation of ODTs containing APIs with melting points higher than 110 °C.

1. Introduction

Orally disintegrating tablets (ODTs) are designed to dissolve or disperse in a small amount of water in the oral cavity to enable patients with dysphagia or restricted water intake to swallow tablets, and therefore represent one of the most patient friendly dosage forms available for the ingestion of medicines (Shoriken et al., 2003; Carnaby-Mann and Crary, 2005). Several methods have been developed for the preparation of ODTs (Seager, 1998; Mizumoto et al., 2005; Sugimoto et al., 2005; Kuno et al., 2005), and these methods have ultimately resulted in the commercialization of ODTs. The wet molding method is one of those techniques and the method produces ODTs having porous tablets resulting rapid disintegration in oral cavity (Tsushima, 2001). Although the tablet hardness of wet molded tablet is greater than lyophilized tablets, some products prepared by wet molding method have issue of fragile. To overcome this issue, we have recently developed and reported a novel method for the preparation of ODTs using microwave (MW) technology (Sano et al., 2011, 2013). In our previously reported method, the ODTs were prepared according to a wet molding method and the resulting wet tablets, which contained sugar alcohol and water-absorbable materials, were then heated by MW irradiation. During the MW treatment, the ODTs effectively swelled, which led to a reduction in the density of the solid component of the resulting tablets and a decrease in the disintegration time. In contrast, the water vapor generated in the tablet during the MW treatment promoted the formation of solid bridges between the granules that contributed to an increase in the hardness of the tablets. Using this methodology, we demonstrated that it was possible to improve the hardness and disintegration properties of the ODTs, and expanded the design space available for formulation and preparation of tablets using the wet molding method. However, we never evaluated the impact of loading of drug substances into these tablets.

In this study, we have evaluated the impact of loading of specific active pharmaceutical ingredients (APIs) on the properties of ODTs manufactured using our previously reported methodology. Famotidine, acetaminophen and ibuprofen were selected as model APIs for this study because they have different melting points as well as different solubilities in water.

Abbreviations: APIs, Active pharmaceutical ingredients; AAP, Acetaminophen; FAM, Famotidine; IBU, Ibuprofen; L-HPC, Low-substituted hydroxypropyl cellulose; ODT, Orally disintegrating tablet; XCT, X-ray computed tomography.

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2. Materials and methods

2.1. Materials

D-Mannitol, in its δ crystalline form, which were marketed as Parteck® delta M and L-HPC (mean particle size and hydroxypropoxy group: NBD-020, 45 μm), were supplied by Merck Ltd. (Tokyo, Japan) and Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan), respectively. D-Mannitol, in its β crystalline form, was purchased from Merck Ltd. Famotidine (FAM) was supplied from Yoshindo Inc. (Toyama, Japan), acetaminophen (AAP) from Iwaki Seiyaku Co., Ltd. (Tokyo, Japan) and ibuprofen (IBU) from BASF Japan (Tokyo, Japan). The fluorescence probe, 8-anilino-1-naphtalenesulfonic acid (ANS), was purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan).

2.2. Preparation of ODTs

According to the procedure described in our previous paper (Sano et al., 2013), δ crystal mannitol (35.7 g), β crystal mannitol (15.3 g), and L-HPC (9.0 g) were mixed to give the premixed excipient powder. The ratio of mannitols and L-HPC was fixed based on the result of previous study as the impact of API loading on swelling property can be easily detected. The premixed powder blend (3.0–5.4 g) and the APIs (0.6–3.0 g), including FAM, IBU, and AAP, were weighed and placed in a mortar and mixed using a pestle to obtain a homogeneous mixture. Deionized water (15–25% in weight with respect to the solid component of 6 g) was then added to the mortar and the mixture was granulated for approximately 5 min. The wet granules were then sieved using a sieve specified as the Japanese Pharmacopoeia XVI. A portion of the sieved wet granules was weighed for each tablet (approximately 250 mg as a dried tablet) and compressed using a compaction test apparatus (Autograph AG1 5 kN, Shimadzu, Kyoto, Japan), fitted with 9.5 mm diameter flat face punches. Compression was performed at a speed of 10 mm/min until the compression force reached a set value of 0.5–0.6 kN. The resulting wet molded tablets were then MW-heated in a MW oven (EMO-FZ40, SANYO, Osaka, Japan) at 500 W. The required MW irradiation time was determined as the weight loss by MW treatment reaches more than 90% of the equilibrium point. The duration of MW treatment ranged from 4 to 7 min. Five wet molded tablets were simultaneously MW-heated and then dried in a thermostatic chamber set at 40 °C for more than 16 h. Wet molded tablets, that had not been subjected to the MW treatment, were also dried in the chamber under the same conditions, and used as a reference. The resulting tablets were then placed in a desiccator with silica gel to avoid water uptake from the air prior to the measurement of their characteristics.

2.3. Surface temperature of tablets

The surface temperature of the tablets was measured using an infrared radiation thermometer (IR-TA, Chino, Tokyo, Japan).

2.4. Characterization of tablets

2.4.1. Tablet hardness

The fracture strength of the tablets was defined as the force required for breaking the tablet by radial compression. The tablet hardness was measured using a tablet hardness tester (KHT-20N, Fujiwara Scientific, Tokyo, Japan). All of the measurements were performed in triplicate.

2.4.2. Disintegration time

The disintegration time was measured using a rapid disintegration tablet tester (ODT-101, Toyama Sangyo, Osaka, Japan) (Narazaki et al., 2004; Harada et al., 2006). Purified water was used as the medium, and the medium temperature was kept at 37 ± 0.5 °C. The rotation speed and weight were set at 25 rpm and 15 g, respectively. All of the measurements were performed in triplicate.

2.4.3. Tablet thickness

The thickness was measured at the center of the tablet using a micrometer with a precision of 0.01 mm (IDF-1030, Mitsutoyo Corporation, Kanagawa, Japan). Three tablets were randomly selected for the thickness measurements, and the average values being used for the calculation.

2.5. X-ray computed tomography (CT)

X-ray CT images of the tablets were obtained using a peripheral quantitative computed tomography system (XCT ResearchSA+, Startech Medizintechnik GmbH., Pforzheim, Germany). The density distribution was obtained from a tablet, that had been sliced through its center. The voltage, current, and resolution values were 50 kV, 0.5 mA, and 0.03 mm, respectively. The distribution of X-ray attenuation coefficient was calculated using the slice.

2.6. Evaluation of internal environment of IBU-ODTs using a fluorescence probe

2.6.1. Preparation of IBU-ODTs containing fluorescence probe

Ibuprofen ODTs (IBU-ODTs) containing a fluorescence probe were prepared using ANS as an environmentally-responsive fluorescence probe. The premixed powder blend (5.3 g), ibuprofen (0.5 g), and ANS (0.1 g) were mixed, and the resulting dry blend was compressed into tablets at 5 kN using a compaction test apparatus (Autograph AG1 5 kN, Shimadzu), fitted with flat face punches made of stainless of 8.0 mm in diameter. The tablets were placed in a heat static chamber to melt the IBU and subsequently cooled in a desiccator with a desiccant (silica gel) under ambient conditions. Heating temperature was set at 100 °C, because temperature of the tablet surface just after microwaved was approximately 100 °C. A physical mixture of IBU and ANS was prepared to be used as a reference material, and half of this physical mixture was placed in a glass vial. Since IBU in the physical mixture was found to be completely melted at 90 °C by visual observation, physical mixture was heated at 90 °C for 3 h using a heat static chamber.

2.6.2. Evaluation of fluorescence property of IBU-ODTs containing ANS

The effective hydrophobicity of the tablets was estimated using the fluorescent characteristics of the ANS. The IBU-ODTs containing ANS that were prepared using the direct compression method were crushed using a pestle and a mortar, and the resulting powders were used for the evaluation process. Fluorescence spectra were recorded with an excitation wavelength of 365 nm on an F-4500 fluorescence spectrophotometer (Hitachi, Tokyo, Japan). Evaluations were conducted using a plastic cell (10 × 10 mm). The slit widths for the excitation and emission were set at 10.0 and 20.0 nm, respectively.

The appearances of the tablets and the reference material, as well as the physical mixture of IBU and ANS, were observed under UV illumination using a UV lamp (UVLMS-38 EL Series 3UV lamp, UVP, Upland, CA, USA) with a wavelength of 365 nm.

2.7. Powder X-ray diffraction

Crystal form of the mannitol in each formulation was characterized by a powder X-ray diffraction system (RINT VHF2500, Rigaku, Tokyo, Japan). The measurement conditions