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.

Keywords: Orally disintegrating tablet; microwave; famotidine; acetaminophen, ibuprofen, fluorescence

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.

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, 2003; Carnaby-Mann, 2005). Several methods have been developed for the preparation of ODTs (Seager, 1991; 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 et al., 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 and 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.

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 to 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 hours 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 were as follows: target, Cu–Kα; generator voltage, 45 kV; tube current, 40 mA; and data angle range, 2θ = 5－40°. Each tablet was gently ground using a mortar and pestle and used for measurement.

2.8. Stability study

The tablets containing 25 mg of FAM or AAP were placed on a petri dish in a desiccator alongside a saturated sodium chloride solution, and the desiccator itself was then placed in a chamber controlled at 25°C. Thus, the conditions inside the desiccator were 25°C and 75% relative humidity (RH), and the tablets were stored under these conditions for 1 or 2 weeks. The physical properties of the tablets, such as their thickness, hardness, and disintegration time, were subsequently evaluated as described above.

2.9. Dissolution study

The famotidine ODTs (FAM-ODTs), acetaminophen ODTs (AAP-ODTs), and IBU-ODTs were subjected to a dissolution study using a dissolution tester (NTR-6100A, Toyama Sangyo) with UV-VIS spectrometer (UV-1700, Shimazu), in accordance with the dissolution test method described in the Japanese Pharmacopoeia 2nd method (paddle method). The paddle rotation speed and dissolution media temperature were set at 50 rpm and 37°C, respectively. Water (900 mL) was used for FAM-ODTs and AAP-ODTs and phosphate buffer (pH 6.8, 900 mL) was used for

IBU-ODTs as the dissolution test medium. The releases of FAM, AAP, and IBU were detected by differences in the absorbance characteristics at 285 and 450 nm, 243 and 350 nm, and 264 and 450 nm, respectively. Three tablets of each sample were used for the measurements and the averaged results were reported.

2.10. Evaluation of assay and decomposition in acetaminophen tablet

An assay for the AAP-ODTs was performed according to the HPLC method described in the Japanese Pharmacopoeia. Chromatographic analysis was performed on a HPLC system (2487 Dual λ Absorbance Detector, Waters, Milford, MA, USA) using a Mightysil RP 18GP (150 × 4.6 i.d., 5 μm particle size) column. The mobile phase used for the analysis consisted of 0.05 mol/L potassium phosphate solution (pH 4.7) and methanol (4:1 v/v). The flow rate was set at 0.7 mL/min to allow for the retention time of AAP to be adjusted to approximately 5 min. AAP was detected by the absorbance at 225 nm.

A working standard of AAP was prepared by dissolving 25 mg of AAP in the mobile phase. The three tablets were crushed and 25 mg samples of the resulting powder were accurately weighed and placed into a 25 mL measuring flask. Approximately 20 mL of the mobile phase was then added to the powder, and the resulting mixture stirred magnetically for 60 min before being made up to a total volume of 25 mL. The resulting sample solution was then centrifuged at 10,000 ×g for 10 min, and the supernatant liquid was collected and used for injection.

The assay was calculated based on the peak area derived from the AAP working standard.

2.11. Evaluation of assay and decomposition in famotidine tablet

The evaluation of assay and related substance of FAM-ODTs was performed in a similar manner to the HPLC method previously reported by Helali et al. (2004). Chromatographic analysis was performed according to the HPLC system described above (Section 2.10) with an L-Column ODS (250 × 4.6 i.d., 5 μm particle size) column. The mobile phase used for the analysis consisted of 0.1 mol/L phosphate potassium solution (pH 3.0) and acetonitrile (13:87 v/v). The pH of the potassium phosphate solution was adjusted with phosphoric acid. Triethylamine (2% v/v) was added to the potassium phosphate solution. The flow rate was set at 1.0 mL min^{-1} and a wavelength of 265 nm was used for the detection.

The assay was calculated based on the peak area derived from the FAM working standard.

3. Results and discussion

3.1. Impact of Loading of APIs on the Physical Properties of the Tablets

The solubility of an API is considered to be one of the most important characteristics in terms of its impact on the disintegration ability of an ODT. Furthermore, given that the MW treatment results in the heating of the tablet, the potential impact of the API's melting point should also be considered. With this in mind, FAM, IBU, and AAP were used in the current study as model APIs because they have different aqueous solubility and melting point. AAP has the highest aqueous solubility (15.8 mg/mL) and melting point (T_m = 169°C) among the three APIs tested, whereas FAM has a high melting point (T_m = 164°C) and low aqueous solubility (1.9 mg/mL). In contrast, IBU has a low aqueous solubility (0.077 mg/mL) and low melting point (T_m = 76°C).

To evaluate impact of loading the APIs on the tablet properties, ODTs containing 10% of each of APIs were prepared under the same conditions (i.e., granulation fluid amount: 900 μL, compression force: 0.5 kN) with or without MW treatment, and the thickness, hardness, and disintegration time of the resulting tablets were subsequently evaluated (**Fig. 1**). The ODTs containing the APIs swelled as a consequence of the MW treatment, with the degree of swelling being similar to that observed for the placebo tablets (**Fig. 1a**). Potential changes in the internal structures of the tablets resulting from the MW treatment were evaluated using X-ray computed tomography (CT). The X-ray attenuation coefficient distributions of the MW-untreated and MW-treated ODTs were compared (**Fig. 2a, b, c**). The X-ray attenuation coefficient is largely dependent on the atomic elements making up the materials and the density (Sinka et al., 2004; Noguchi et al., 2013). Since the MW treatment does not lead to changes in the composition of tablets, except for the evaporation of water, the observed differences in the attenuation coefficients were attributed to differences in the density of solid components. The distributions of the different ODTs shifted to lower values, which indicated that the porosity of the tablets increased as a consequence of the swelling. In this figure, the results obtained from MW-untreated and MW-treated ODTs were shown as semi-solid and solid lines, respectively. The distribution of attenuation coefficients of those ODTs was slightly shifted to smaller side and this result explained that the density of solid components in the tablet decreased by increases in thickness following MW treatment. CT slice images of the IBU-ODTs are shown in **Fig. 2d and e**, where the bright and dark areas represent areas of high and low density of the components, respectively. The dark area, in particular, increased significantly at the center of the tablet following MW treatment. This result suggested that the density at the center of the tablet was being reduced by

the swelling Although the decrease in density of solid components in the tablets was observed, the tablet harnesses of FAM-ODTs, AAP-ODTs, and IBU-ODTs increased by 35 N, 20 N, and 28 N by MW treatment, respectively (**Fig. 1b**). The disintegration time of FAM-ODT and AAP-ODT slightly retarded compared with the placebo (**Fig. 1c**). However, their disintegration times did not exceed 30 seconds, suggesting that the MW treatment did not have a considerable impact on disintegration time of the ODTs containing FAM and AAP. On the other hand, the disintegration time of the IBU-ODT was significantly delayed by up to 3 min following the MW treatment. Previously, Ritesh et al. (2012) reported that the disintegrations of ODTs prepared by the direct compression method were not delayed by the addition of ibuprofen in a range between 0 to 50 mg. Based on differences in the methods of preparation, it was assumed that the IBU melted during the MW treatment and formed agglomerates, which would have prevented water from penetrating the tablets, and led to the observed delay in the disintegration of the tablets. To confirm whether this phenomenon was associated with the melting of the IBU during the MW treatment, we also prepared IBU-ODTs containing ANS via the direct compression method. The main advantage of this technique over the wet molded method is that it avoids the formation of excessive interactions between the IBU and ANS during tablet preparation. Furthermore, this technique allows for the heat treatment process to be conducted in a static heat chamber instead of a MW oven, and therefore allows for better control over the heat treatment process. ANS is known as an environmentally-responsive fluorescence probe that exhibits strong fluorescence properties as well as high quantum yields under non-protic condition (Edward et al., 1983; Lubert, 1965; Oktay and Ben, 2007). To definitively confirm the effect of the interaction between IBU and ANS, we initially attempted to evaluate any changes in the fluorescence of

the physical mixture of ANS and IBU before and after the melting treatment (90°C). As shown in **Fig 3a**, the physical mixture showed weak green fluorescence prior to the melting treatment, whereas the mixture showed strong blue fluorescence after the treatment process. Based on this result, it was confirmed that the interaction between ANS and IBU was enhanced by the melting of IBU. The fluorescence properties of the heat-treated IBU-ODTs containing ANS were then compared with those of the ODTs that had not been subjected to the heat treatment. The appearances of these samples under illumination at the excitation wavelength of ANS (365 nm) are shown in **Fig. 3b**.The heat-treated ODTs showed strong fluorescence, whereas the untreated tablet showed only weak fluorescence. This difference in the fluorescence intensities was quantitatively detected, as shown in **Fig. 3c**, and the fluorescence intensities obtained from the heat-treated ODTs were 5-fold greater than those of the untreated ODTs. These changes in fluorescence intensity indicated that the ANS was being incorporated into the agglomerated hydrophobic IBU particles as a consequence of the melting of IBU during the heat treatment. In fact, the surface temperatures of the IBU-ODTs prepared using our technology were approximately 100 to 110°C, indicating that the agglomeration of the IBU observed in the IBU-ODTs containing ANS must have occurred.

Based on these results, it was concluded that this technology would be successfully applied to APIs with melting points greater than the temperatures achieved during the MW treatment, regardless of their solubility.

3.2. Impact of the Loading Amount of FAM and AAP on the Tablet Properties

We proceeded to investigate the impact of the loading amounts of FAM and AAP on the tablet properties. The loading amounts of these APIs were varied from

10% (25 mg/250 mg) to 50% (125 mg/250 mg), and the thickness, hardness, and disintegration time of the resulting tablets were evaluated. As shown in **Fig. 4a**, significant increases were observed in the thickness of the FAM-ODTs containing 10 and 20% FAM following the MW treatment. However, the degree of swelling decreased as the FAM amount ratio increased. Significant increases were also observed in the hardness of the FAM-ODTs up to 20% FAM amount ratio following the MW treatment (**Fig. 4c**). Increases in the FAM amount ratio to over 30%, however, resulted in a slight decrease in the hardness of FAM-ODTs. Increase in the FAM amount ratio led to a slight increase in the disintegration time, although the disintegration time never exceeded 30 s, even when the FAM amount ratio was 50% (**Fig. 4e**). The AAP-ODTs also showed significant swelling at an AAP amount ratio of up to 30% (**Fig. 4b**). Significant increases were also observed in the hardness of all of the AAP-ODTs following the MW treatment (**Fig. 4d**). In contrast, there were no significant changes in the disintegration time of the tablets following the MW treatment, even though the tablet hardness increased (**Fig. 4f**). Taken together, these results demonstrated that our new method could be successfully applied to the preparation of a wide range of ODTs with relatively high API amount ratio.

3.3. Impact of Moisture Absorption during Storage on Tablet Properties

The impact of moisture absorption during storage on the tablet properties was evaluated using FAM-ODT (10%) by monitoring changes in the tablet properties. The FAM-ODTs were stored at 25°C under 75% RH for 2 weeks, and the thickness, hardness, and disintegration time of the tablets were measured using samples taken both before and after 1 and 2 weeks storage under these conditions. The results are shown in **Fig. 5**. No discernible differences were observed in the thickness and

351 disintegration time of the FAM-ODTs throughout the storage period (**Fig. 5a and c**).
352 In contrast, the tablet hardness values of the MW-treated and MW-untreated tablets
353 were reduced significantly after 1 week storage, although no further reductions were
354 observed after 2 weeks for both types of tablet (**Fig. 5b**). Following 2 weeks under the
355 experimental conditions, however, the hardness value of the MW-treated tablet was
356 less than 50 N. This low hardness value could be attributed to the high water
357 absorption ability of L-HPC or a change in the crystalline form of δ-crystal mannitol.
358 L-HPC has the ability to increase its volume by absorbing water and this would
359 promote the disintegration of granules (Kawashima et al., 1993; Late et al., 2009). In
360 addition, it has been reported that the δ-crystalline form of mannitol can be converted
361 to the corresponding β-crystalline form with a reduction in particle size under high
362 humidity conditions (Yoshinari et al., 2002 and 2003). Samples of the material both
363 before and after 2 weeks of storage were collected and analyzed by X-ray powder
364 diffractometry to determine whether the δ-crystal form of mannitol had changed
365 during the simulated storage experiment (**Fig. 6**). The results of this analysis revealed
366 that no significant changes had occurred in the crystalline form of mannitol or FAM,
367 and demonstrated that there was no relationship between the observed changes in the
368 tablet hardness and the crystalline form of the materials. The observed reduction in
369 the tablet hardness of the FAM-ODTs with or without the MW treatment was
370 therefore attributed to the composition of the L-HPC. In this study, the ratio of L-HPC
371 was set at relatively high level due to easy detection for degree of swelling during
372 MW treatment. Therefore, the amount of L-HPC used when applying this technology
373 to the construction of API-ODTs should be kept to a minimum to maintain the tablet
374 characteristics in the ranges of optimized formulation.
375

3.2. Impact of Microwave Treatment on Dissolution and Impurity Profiles

The dissolution profiles of MW-treated and MW-untreated FAM-ODTs (10%), AAP-ODTs (10%), and IBU-ODTs (10%) are shown in **Fig. 7**. FAM and AAP had been completely released within 5 min and the MW treatment did not affect the dissolution behaviors of the tablets, while release of IBU was drastically delayed by MW treatment. The results obtained from IBU-ODTs were consistent with that of disintegration time. To investigate the effect of the MW treatment on the decomposition of FAM and AAP in more detail, the APIs were assayed using a HPLC method to determine the extent of any degradation. The results revealed that no new peaks or increases in the intensities of peaks derived from decomposition of APIs were observed in the HPLC chromatograms of the FAM-ODTs and AAP-ODTs following the MW treatment (data are not shown). The materials were assayed based on the peak areas of the APIs relative to those of the standard solutions. The results revealed that the assays of the MW-untreated and MW-treated FAM-ODTs (10%) were 98.4 and 99.3%, and those of the MW-untreated and MW-treated AAP-ODTs were 99.5 and 100.3%. Based on these results, it was concluded that the MW treatment did not cause the decomposition of the APIs, although the risk of decomposition should be judged on a case-by-case basis, because it could be dependent on the chemical properties of the loaded API.

4. Conclusion

In the current study, the effects of loading three different APIs on the properties of ODTs prepared using our previously reported novel MW technology were evaluated to develop a greater understanding of this method and its overall utility for the preparation of ODTs. FAM, AAP, and IBU were used as model drugs for

401 the current study because they have different melting points and aqueous solubility.
402 Among the APIs tested, a delay was observed in the disintegration time and
403 dissolution of the IBU-ODTs that was caused by the MW treatment. Data obtained
404 using an environment-responsive fluorescence probe demonstrated that the IBU
405 melted during MW heating process and formed agglomerates, which interrupted the
406 disintegration of the tablet. In contrast, the ODTs containing AAP and FAM, which
407 both have melting points in excess of 150°C and greatly-differing aqueous solubilities,
408 did not form agglomerates in the same way as the IBU-ODTs and had better
409 disintegration time. The hardness of the AAP-ODTs and FAM-ODTs increased
410 following the MW treatment whilst their disintegration times remained less than 30
411 seconds. In addition, the results of HPLC assays of the APIs in these ODTs revealed
412 that the MW treatment did not lead to the decomposition of the APIs. When the
413 loading amount of AAP and FAM was increased up to 50% (125 mg/250 mg), the
414 hardness of the tablets were greater than 50 N and the disintegration times were less
415 than 30 seconds, representing properties well within the general requirements for
416 ODTs. Based on these results, this novel technology has the potential to be used as an
417 effective tool for preparing ODTs with APIs with higher melting point (at least with
418 melting points greater than 110°C).

419 The wet molding tableting machine (Tsushima et al., (2001) consists of two
420 sections for compression and conveyor drying. In this machine, the wet tablets after
421 compression are continuously supplied to conveyor dryer to dry and improve tablet
422 hardness. After that, the tablets are completely dried in a static chamber. Up to now,
423 the conveyor type microwave oven has been already commercialized. If this conveyor
424 type microwave oven was attached with a wet molding tableting machine, ODT could
425 be continuously and stably prepared and second drying process using the static

chamber is not required. Therefore, our technology could be adapted to commercialization and further study would be therefore needed.

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Figure captions

Figure 1. Effect of the MW treatment on the physicochemical properties of the ODTs containing FAM, IBU, and AAP. The thickness a), hardness b), and disintegration time c) of the tablets. The grey and black bars show data obtained from the MW-untreated and MW-treated tablets, respectively. ** $P < 0.01$ and * $P < 0.05$ versus the microwave-untreated tablet.

Figure 2. Effect of the MW treatment on the density distributions of the ODTs containing FAM a), IBU b), and AAP c). Dashed line and solid line shows data obtained from MW-untreated and MW-treated ODTs, respectively. X-ray slice images of IBU-ODT before d) and after e) the MW treatment.

Figure 3. Appearance of the mixture of ANS and ibuprofen a) and IBU-ODTs containing ANS b) under illumination at a wavelength of 365 nm, as well as the fluorescence spectrum of IBU-ODTs c).

Figure 4. Effect of the drug loading on the properties of the ODTs containing FAM and AAP. The thickness a) and b), hardness c) and d), and disintegration time e) and f) of the tablets are shown in the figure. The grey and black bars shows data obtained from the MW-untreated and MW-treated tablets, respectively. ** $P < 0.01$ and * $P < 0.05$ versus microwave-untreated tablet.

Figure 5. Effect of moisture absorption on the properties of the FAM-ODTs. The MW-treated and MW-untreated FAM-ODTs were held at 25°C under 75% RH for 2 weeks. The thickness a), hardness b), and disintegration time c) of the tablets are

526 plotted in the figure.

527

528 **Figure 6.** Effect of moisture absorption on the crystalline form of the mannitol in the

529 FAM-ODTs. The X-ray diffraction spectra of the MW-untreated a) and MW–treated

530 b) tablets immediately before and 2 weeks after storage at 25°C under 75% RH.

531

532 **Figure 7.** Dissolution profiles of the FAM-ODTs, AAP-ODTs and IBU-ODTs.