Preparation and Evaluation of Swelling induced-Orally Disintegrating Tablets by Microwave Irradiation

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Abstract

A major challenge in the development of orally disintegrating tablets (ODTs) is to achieve a good balance between tablet hardness and disintegration time. In this study, an advanced method was demonstrated to improve these opposing properties in a molded tablet using a one-step procedure that exploits the swelling induced by microwave treatment. Wet molded tablets consisting of the delta form of mannitol and silicon dioxide were prepared and microwave-heated to generate water vapor inside the tablets. This induced either swelling or shrinking of tablets, in the extent of each being dependent on tablet formulation and manufacturing conditions. A two-level full factorial design method was used to evaluate the effects of several variables in formulation and manufacturing conditions on the tablet properties, hardness, disintegration time and change in shape. The variables investigated in this study were: ratio of silicon dioxide in formulation, water volume added in granulation, ratio of water absorbed by silicon dioxide prior to granulation, and microwave irradiation time. Swelling of tablet by microwave irradiation was observed in the batches with high ratio of silicon dioxide and low levels of water volume. The disintegration time was clearly shortened by induction of the swelling, while tablet hardness increased. We demonstrated that the water vapor generated by microwave irradiation promoted a change in the crystalline form of mannitol from delta to beta, and that this may have contributed to an increase in tablet hardness. Additionally, it was found that new solid bridges were formed between the granules in the tablet via the pathway from dissolution of mannitol in water vapor to congelation, resulting in an increase in tablet hardness. Thus, both tablet hardness and disintegration properties of the molded tablets were
improved by the proposed one-step method and the appropriate ranges for variables are indicated. In addition, multiple regression modeling was used to optimize formulation and manufacturing conditions, and the tablets obtained under these optimized conditions showed both swelling and desirable tablet properties. Therefore, we concluded that this one-step method using microwave irradiation would be a useful method for preparing the ODTs.

**Keywords:** Orally disintegrating tablet; microwave; experimental design; multiple regression analysis

**Abbreviations:** ODT, orally disintegrating tablet; SEM, scanning electron microscopy; DS, degree of swelling
1. Introduction

The orally disintegrating tablet (ODT) is one of the most attractive drug delivery technologies. It is soluble in saliva after oral administration and is able to be swallowed without water, unlike traditional tablets. To date, many technologies have been developed for preparing ODTs and the products of these technologies have been commercialized. Zydis® is a well-known technology that involves freeze-drying of suspensions or solutions containing active ingredients and water soluble polymer into pockets of blister packaging sheets (Seager, 1991). While tablets prepared using the Zydis® technology dissolve rapidly on the tongue, they tend to be very brittle and require careful handling.

As an alternative technique for preparing ODTs, molded tableting technique that compresses wet granules at low compression force has been developed to achieve rapid disintegration in conjunction with high tablet hardness compared with those prepared by standard compression method (Morita et al, 2002). Molded tablets have high porosity; thereby allowing greater water penetration into the tablets and accelerating tablet disintegration. However, their porous structure still tends to make tablets fragile in case they suffer any physical impacts. To overcome this problem, various techniques that promote the transition of tablet components from an amorphous to crystalline form have been developed to increase tablet hardness. For instance, Sugimoto et al. reported that when tablets containing amorphous form of sucrose were placed under temperature- and humidity-controlled conditions in order to promote crystallization of sucrose, the change to a
crystalline form resulted in an increase in the number of contact points between granules in tablet, and consequently an increase in hardness (Sugimoto et al, 2005 and 2006). In addition, another method utilized different types of sugar alcohols with different melting points; namely, since one of the sugar alcohols was melted by heating in tablets, it acted as a type of glue to form solid surface bridges (Kuno et al, 2005). However, while tablet hardness was elevated by the formation of new bonds, a shift toward a larger sugar particle pore also occurred. That phenomenon causes a delay in disintegration time of the tablets. According to these reports, the preparation of ODTs that fulfill physicochemical demands, such as high tablet hardness and rapid disintegration, remains difficult, but it has been highly desirable in the pharmaceutical research field.

In this paper, we propose an advanced and novel one-step ODT preparation method using a molded tablet containing a water carrier such as silicon dioxide, and a sugar alcohol such as mannitol, in combination with microwave irradiation treatment. Microwave technology has been widely used in food processing for the purpose of heating, thawing, sterilizing and bulking. Some applications for pharmaceutical processing have also been reported. For example, a solid dispersion was prepared from physical mixture containing ibuprofen, PVP/VA 60/40 and beta-cyclodextrin by microwave irradiation treatment (Moneghini et al, 2008). In addition, microwave irradiation has been utilized to process drug dosage forms as microspheres (Vandelli et al, 2004) and polymeric gel beads (Wong et al, 2002). The concept proposed here utilizes microwave irradiation (Fig. 1); we hypothesized that it could produce water vapor from the water carrier in a wet molded tablet and could also dissolve the
surface of sugar alcohol granules to form new solid bridges between particles. Water vapor can also expand the pores inside molded tablets creating new channels for water uptake without the need for sublimation and/or chemical reaction that generates gas like carbon dioxide, as previously reported (Koizumi et al, 1997; Tamura et al, 1999). Therefore, we predicted that the new solid bridges between particles would increase tablet hardness and the new channel for water uptake would contribute to shorten the disintegration time.

Accordingly, the aim of this study is to evaluate the effects of various manufacturing parameters on tablet properties using a two-level full factorial experimental design in order to test our hypothesis and find the appropriate conditions to prepare the desirable ODT.

2. Material and Methods

2.1. Materials

Silicon dioxide, marketed as Adsolider-102®, was provided from Freund (Tokyo, Japan).

Mannitol which has delta crystalline form, marketed as Parteck® delta M, was provided from Merck (Tokyo, Japan). All of the reagents used were of analytical grade available from commercial sources and all solutions were prepared with deionized water.

2.2. Preparation of ODTs
Silicon dioxide was weighed and placed in a mortar. Deionized water (medium A) was dropped into the mortar using a pipette and stirred using a pestle until all of the water was completely absorbed by the silicon dioxide. Mannitol was then added into the mortar to be a total of six grams as solid content and mixed well. An additional volume of water (medium B) was then added and the mixture was granulated for approximately 5 minutes. The wet granules were sieved using a sieve specified as No. 16 (1 mm) in the Japanese Pharmacopoeia. The sieved wet granules were weighed for each tablet (approximately 250 mg as dried tablet) and compressed using a compaction test apparatus (Autograph AG1 5 kN, Shimadzu, Kyoto, Japan), fitted with a 9.5 mm diameter flat face punches. Weighed wet granules were hand-filled into a die. Compression was performed at a speed of 10 mm/min until the compression force reached 0.5 kN. Wet molded tablets were microwave-heated using a microwave oven (EMO-FZ40, SANYO, Japan) at 500 W for 0 – 2 minutes. After microwave treatment, the tablets were then dried in a thermostatic chamber set at 80°C for 24 hours. The obtained tablets were then placed in a desiccator with silica gel to avoid water uptake from the air until used for measurements of tablet characteristics.

2.3. Experimental Design

A two-level full factorial design was used to analyze the relationship between investigated variables and tablet properties, as summarized in Table 1. The ratio of silicon dioxide ($X_1$), total water amount ($X_2$; (medium A + medium B) / solid content × 100), ratio of absorbed water ($X_3$;
medium A / (medium A + medium B) × 100) and microwave irradiation time ($X_4$) were selected as variables. A high ratio of absorbed water means that more water was absorbed by silicon dioxide particles prior to mixing with mannitol. The center composite orthogonal experimental design for four factors was applied to prepare the model formulations. Central experimental points were repeated 3 times for evaluating any potential experimental errors.

2.4. Characterization of tablets

2.4.1. Tablet hardness

Tablet fracture strength was defined as the force required in breaking the tablet by radial compression. The tablet hardness was determined using a tablet hardness tester (KHT-20N, Fujiwara Scientific, Japan). Measurements were repeated three times and the average was reported.

2.4.2. Disintegration time

Disintegration time was measured using a rapid disintegration tablet tester (ODT-101, Toyama Sangyo) (Narazaki et al, 2004; Harada et al, 2006). Purified water was used as medium. The medium temperature was kept at 37 °C. Each tablet was placed on the wire gauze, slightly immersed in the medium, and then compressed by the shaft. The compression force was easily adjusted using the weight. The tablet was crushed by the rotary shaft and the tablet disintegrated into the medium. The time was counted between the times that the weight touched the tablet and the wire gauze and
reported as disintegration time. The rotation speed and weight were set at 25 rpm and 15 g, respectively. Measurements were repeated three times and the average was reported.

2.4.3. Swelling degree

Degree of swelling (DS) was defined as described below:

\[ DS = \text{Thickness}_{\text{Center}} - \text{Thickness}_{\text{Edge}} \]

\( \text{Thickness}_{\text{Center}} \) and \( \text{Thickness}_{\text{Edge}} \) are the thickness of the center and edge of the tablet. The thickness of the tablets was measured with a micrometer with a precision of 0.01 mm (IDF-1030, Mitsutoyo Corporation, Kanagawa, Japan). For the thickness measurement, three tablets were randomly selected and average values were used for calculation.

2.4.4. Powder X-ray diffraction (PXRD)

Crystal form of the mannitol in each formulation was characterized by a powder X-ray diffraction system (RINT VHF2500, Rigaku). The measurement conditions were as follows: target, Cu–K\(\alpha\); generator voltage, 45 kV; tube current, 40 mA; and data angle range, 2\(\theta\) = 5°–40°. Each tablet was gently ground using a mortar and pestle and used for measurement.

2.4.5. Scanning electron microscopy (SEM)

SEM images of the tablet surface were obtained using the scanning electron microscope.
(VE-7300, Keyence). A whole tablet was mounted on a metal stub with double-sided adhesive tapes.

2.4.6. Specific surface area

Specific surface area was measured with a gas absorption apparatus (multi-point; model SA3100, Beckman Coulter, USA) using BET gas absorption. The absorption gas used for measurement contained N₂ and He. Measurement was conducted in duplicate and the averaged value was reported.

2.5. Statistical analysis

To determine the significance of each main factor as well as their interactions on the tablet properties, the statistical analysis was performed using the computer program ALCORA (Takayama et al, 1990). The relationships linking to the main factors and interactions with the response were determined and presented as quadratic equations of the general form in the following equation:

\[ Y = \text{intercept} + \sum \text{main effect} + \sum \text{interactions} \]

The equation coefficients were calculated using the coded values, thus the various terms can be compared directly regardless of their magnitude. Additionally, optimization was performed using the software OPTIM packaged with ALCORA. For the simultaneous optimization, the “maximum” or “minimum” response to be optimized for was selected for each response.

3. Results and Discussion
In this study, silicon dioxide and mannitol were chosen as useful constituents. Silicon dioxide is well known as an absorbent material due to its porous structure and was selected for this study as a carrier for water. The amount of water vapor generated by microwave irradiation depends on the microwave output, irradiation time, and amount of water retained inside the tablet. It is believed that silicon dioxide can efficiently retain water inside its particles until heating. In addition, the delta crystalline form of mannitol was selected as a diluent, owing to its high melting point ($T_m = 168^\circ C$), high solubility, and other unique properties. It has been reported that the delta crystalline form of mannitol can be transformed into small crystals of the beta form when kneaded with purified water or placed under high humidity conditions (Yoshinari et al, 2002 and 2003). This morphological change can contribute to an increase in hardness of mannitol-containing tablets manufactured by the conventional wet massing method.

Characterizations of tablet properties (tablet hardness, disintegration time and swelling degree) of all 19 batches prepared in this study are shown in Table 2. Multiple linear regression analysis was then performed on these data. The significance of each operational factor and its effect on the tablet properties was determined and the results are shown in Table 3. Since the coefficients were calculated using the coded values (Table 1), the various terms were able to be compared directly. Therefore, coefficients represent the positive or negative effects of four parameters and their interactions against each tablet property. Table 3 summarizes the coefficients, the $p$-value obtained by $t$-test to assess the significance of each term, and the $R^2$ value (the coefficient of determination...
which was doubly adjusted with degrees of freedom), which is an indicator of the fit of each linear regression equation.

3.1.1. Degree of swelling (DS)

As shown in Table 3, swelling of tablets was observed as expected in certain batches, which had positive value of the degree of swelling (DS); however tablets of some other batches showed a contrasting phenomenon, denting. The DS increased when the ratio of silicon dioxide (X₁; P = 0.0007) increased, and a positive interaction between the ratio of silicon dioxide and microwave irradiation time (X₁X₄; P = 0.0039) was observed. On the other hand, the DS decreased when the amount of water (X₂; P = 0.0003) increased, and a negative interaction between water volume and microwave irradiation time (X₂X₄; P = 0.0057) was also observed. In addition, the effect of variables on DS was evaluated using response surface plots (Fig. 2). The contour plots show the DS as a function of the water volume (X₂) and microwave irradiation time (X₄) at different ratios of silicon dioxide ratio (X₁) and absorbed water (X₃). As a result, the X₁ was found to determine the tendency of whether tablets expanded or shrank. Swelling was mainly observed in the tablets with a high ratio of silicon dioxide (Fig. 2c and d), whereas the tablets with a low ratio of silicon dioxide tended to shrink (Fig. 2a and b). In case of the tablets with a high ratio of silicon dioxide (X₁ = 22%), the microwave irradiation time (X₄) strongly contributed to an increase in DS. This might be due to the water vapor generated by microwave irradiation. The effect of X₄ was enhanced as the X₂ decreased,
while $X_3$ negatively affected the swelling phenomenon, suggesting that an excess amount of water might increase the adhesion of granule surface, followed by an increase in resistance against expansion; whereas an increase in $X_3$ might suppress adhesion and agglomeration, and might leave the pores which allow the water vapor to be released from the tablets. Thus, this result revealed that $X_3$ seemed to be well-balanced between inside and outside of the silicon dioxide in the case of Fig. 2c.

On the other hand, the DS of tablet with a low ratio of silicon dioxide decreased as $X_2$ and $X_4$ increased. This phenomenon can be explained by the dissolved mannitol in water. Since the shrunken tablets contained little silicon dioxide and a high percentage of mannitol, these formulations were sensitive to the water addition and were easy to be granulated. In general, well-granulated particles can be well packed by compression. Hence, the tablet was also efficiently compressed and the water vapor generated by microwave irradiation was confined in the tablet. The confined water vapor returned to water droplets throughout natural cooling after microwave treatment and then this water droplet dissolved mannitol, thereby causing a tablet volume decrease.

Actually, the DS of tablet with a high ratio of silicon dioxide showed no change as the water volume increase in the absence of microwave treatment ($X_4 = 0$) (Fig. 2c and d). However, the DS of tablets with a low ratio of silicon dioxide decreased when the water volume increased, and this tendency was enhanced by microwave treatment (Fig. 2a and b). This can be explained by the effect of difference in the rate of vapor generation between the two drying processes; namely, microwave
heating and draught drying, because faster drying can make vapor amount in the tablet more than
gentle draught drying which allow the release of the vapor. The dent was mainly observed at only the
center of tablet, because the vapor generated near the tablet surface was able to escape from tablet,
while it was not permitted at the center of tablet. Furthermore, the degree of dent depended on the
percentage of absorbed water by silicon dioxide, suggesting that free water retained in the pores of
silicon dioxide particles efficiently generated more vapor than that located on the surface of particles.

3.1.2. Tablet hardness

The tablet hardness increased as the water volume ($X_2$; $P < 0.0001$) increased and there was
a positive interaction between the water volume and the ratio of absorbed water ($X_2X_3$; $P = 0.0359$)
(Table 3). However, the ratio of silicon dioxide negatively affected ($X_1$; $P < 0.0001$) and a negative
interaction between the ratios of silicon dioxide and absorbed water ($X_1X_3$; $P = 0.0002$) was also
observed. Fig. 3 shows the contour plots of the tablet hardness as a function of the water volume ($X_2$)
and microwave irradiation time ($X_4$) at different ratios of silicon dioxide ($X_1$) and absorbed water
($X_3$). The all of four response surfaces obtained at different ratios of silicon dioxide and absorbed
water showed the same trend on tablet hardness; namely, the tablet hardness gradually increased as
the total water volume and microwave irradiation time increased (Fig. 3a-d). It suggests that a
common phenomenon occurred in the tablets of all batches, and this phenomenon was assumed to be
the polymorphic transformation of the mannitol crystal. As mentioned above, it has been reported
that the mannitol was able to change crystalline form from delta to beta, when it was kneaded with water or stored under high humidity conditions (Yoshinari et al, 2002 and 2003). Furthermore, the formation of new solid bridges between granules is also supposed to be occurred based on the results shown in section 3.1.1 which showed denting of the tablet surface. If denting of the tablet surface was derived from the dissolving of the mannitol, the solid bridge formation might occur during the transition from melting to cooling. To investigate whether microwave treatment promotes the crystalline change of the mannitol, powder X-ray diffraction (PXRD) patterns of obtained samples and mannitol alone were compared as shown in Fig. 4. The data show a difference between tablets which were prepared with microwave-heated (Batch no. 10) or without (Batch no. 9). As a result, both beta and delta crystalline forms of mannitol have the specific peaks at $2\theta = 10^\circ$ for beta and $20^\circ = 19^\circ$ and $23^\circ$ for delta, respectively. Comparing the two batches, differences in the peak intensity between the peaks specified for beta and delta were observed. This indicates the microwave treated tablet included a higher ratio of beta to delta of mannitol than the untreated tablets. This finding might be explained by the fact that microwave treatment promotes a transition from delta to beta crystalline form and it might contribute to an increase in the tablet hardness. In addition, the ratios of silicon dioxide ($X_1$) and absorbed water ($X_3$) determined the level of overall plot on tablet hardness. The tablets with a low ratio of silicon dioxide showed higher tablet hardness (Fig. 3a and b), whereas the tablets with high ratios of silicon dioxide and absorbed water showed lower tablet hardness (Fig. 3d). These results suggested that the silicon dioxide decreased compression
moldability, and that the high ratio of absorbed water kept adhesion of granules low and decreased compression moldability by inhibiting agglomeration of granules.

3.1.3. Disintegration time

As shown in Table 3, the ratio of silicon dioxide ($X_1$) has a positive effect on disintegration time, whereas increased water volume ($X_2$) had negative impact. Additionally, the contour plots, which show responses of the disintegration time, are shown in Fig. 5, and the effects of variables on disintegration time were evaluated. In Fig. 5, the response of disintegration time is shown as a function of the water volume ($X_2$) and microwave irradiation time ($X_4$) at different ratios of silicon dioxide ($X_1$) and absorbed water ($X_3$). As for the tablet with a low ratio of silicon dioxide (Fig. 5a and b), the response showed the same tendency as that observed in tablet hardness. This tendency can be explained by the general principle that well-compressed tablets have greater hardness and lower disintegration ability. On the other hand, the tablets with a high ratio of silicon dioxide ($X_1$) showed a small increase in disintegration time when $X_2$ and $X_4$ increased. Furthermore, rapid disintegration was observed in the limited area of manufacturing conditions (Fig. 5c and d). This area is approximately consistent with the area, where the swelling phenomenon was also observed, as shown in Fig. 2. The disintegration time of obtained samples are plotted as function of the DS in Fig. 6. The fitted curve, given by an expression of the third order ($R^2 = 0.8981$) showed that the disintegration time was shortened as the DS increased. Additionally, SEM images of tablet surface of
batch numbers of 9 and 10, which were manufactured under identical conditions except for microwave treatment, are shown in Fig. 7. Batch no. 10 was microwave-treated and exhibited swelling (Table 2), whereas batch no. 9 was not microwave-treated. Especially, batch no. 10 only showed a disintegration time of less than 10 seconds and such rapid disintegration was not observed in any other batches (Table 2). In the image of batch no. 9, only small holes were shown as black spots on the surface of the tablet, while in the image of batch no. 10, some black lines which bifurcated at some points, derived from cracks were observed. Furthermore, the specific surface areas of tablets, batch no. 9 and 10, were measured and the results were 3.233 m$^2$/g and 3.399 m$^2$/g, respectively. Based on these results, it was suggested that the new channels were created during swelling phenomenon induced by microwave irradiation and improved disintegration ability.

3.2. Process optimization

The results of multiple regression analysis showed that water volume and the ratio of absorbed water in the tablet are crucially important and the limited area of the contour plot shows ideal properties of both tablet hardness and disintegration time as we expected, while the remaining other area demonstrated a common relationship between both physical properties; such as a greater tablet hardness accompanied with slower disintegration. To find the optimal manufacturing conditions to promote the swelling phenomenon, the operational conditions were established with the following criteria:
(1) The tablet hardness must be greater than 50 N.

(2) The disintegration time must be less than 30 seconds.

(3) The degree of swelling must be greater than 0.02 mm.

The optimization was carried out using the OPTIM software package. Optimized operational conditions were as follows: X₁ (ratio of silicon dioxide) = 16.7%, X₂ (water volume) = 11.7%, X₃ (ratio of absorbed water) = 50% and X₄ (microwave irradiation time) = 120 seconds (Table 4). As a result, it was found that each characteristic value was consistent with predicted values and complied with the desired product criteria. This result indicates that the experimental design was appropriate to optimize the manufacturing conditions for this method.

4. Conclusions

In the present study, we proposed an advanced method to prepare ODTs with desirable tablet properties by exploiting the swelling phenomenon. The effects of several variables on the physical tablet properties such as swelling, tablet hardness and disintegration time were evaluated using a two-factor full factorial experimental design, and then further optimized. Our results demonstrated that swelling phenomenon occurred when the ratios of silicon dioxide and absorbed water in tablet were appropriate. The tablet hardness for all microwave-treated tablets was greater than that for non-treated tablets. In addition, it was found that the change of crystalline form of mannitol was promoted by microwave irradiation; therefore this may contribute to an increase in tablet hardness.
Furthermore, our data suggested that mannitol might be partially dissolved by water vapor and formed new solid bridges. This phenomenon can be also one of reasons for an increase in tablet hardness. The disintegration time was clearly shortened in the batches accompanied with the swelling phenomenon, because channels for water uptake in tablet were reconstructed by microwave irradiation. Additional experiments performed applying an optimized conditions confirmed the validity of the tested model. The obtained tablets showed desirable tablet properties for ODTs. However, the impact of drug loading in a series of this study remains still unclear and, an evaluation of drug decomposition after microwave irradiation in drug loaded-tablets should also be examined. Therefore, in the near future, further modification in formulation and/or manufacturing conditions would be desired to be commercialized in pharmaceutical research field.
References


Table captions

Table 1. Process parameters and operating limit ranges.

Table 2. Characterization results.

Table 3. Results of multiple regression analysis for tablet properties.

Table 4. Process optimization and statistical model validation.
### Table 1.

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<th>Low (-1)</th>
<th>Center (0)</th>
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<td>$X_2$: Total water volume (%)</td>
<td>11.7</td>
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<td>$X_3$: Ratio of absorbed water (%)</td>
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<td>$X_4$: Microwave irradiation time at 500 W (sec)</td>
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### Table 2.

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Table 3.

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<td>R²</td>
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Table 4.

Process parameters
: X₁ = 16.7%, X₂ = 11.7%, X₃ = 50%, X₄ = 120 sec

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<thead>
<tr>
<th></th>
<th>Predicted value</th>
<th>Experimental value</th>
<th>Deviation (%)</th>
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<td>Tablet hardness</td>
<td>46.5</td>
<td>50.7</td>
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<td>Disintegration time</td>
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<tr>
<td>Degree of swelling</td>
<td>0.821</td>
<td>0.845</td>
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Figure captions

Figure 1. Illustration of swelling induced by microwave irradiation.

Figure 2. Response surface plots of the degree of swelling as a function of total water volume ($X_2$) and microwave irradiation time ($X_4$) with different ratios of silicon dioxide ($X_1$) and absorbed water ($X_3$).

Figure 3. Response surface plots of tablet hardness as a function of total water volume ($X_2$) and microwave irradiation time ($X_4$) with different ratios of silicon dioxide ($X_1$) and absorbed water ($X_3$).

Figure 4. Effect of microwave irradiation on the crystalline form of mannitol. Figure shows power X-ray diffraction data for beta and delta forms of mannitol, and ground tablets manufactured with (batch no. 10) and without (batch no. 9) microwave treatment.

Figure 5. Response surface plots of the degree of swelling as a function of total water volume ($X_2$) and microwave irradiation time ($X_4$) with different ratios of silicon dioxide ($X_1$) and absorbed water ($X_3$).

Figure 6. Relationship between the degree of swelling and disintegration time.
Figure 7. Scanning electron microscopy images of tablet surface. Surface of tablets (a) batch no. 9 (not microwave-treated) and (b) no. 10 (microwave-treated).
Figure 1

Sugar alcohol
Water carrier

Microwave heating
Water vapor generation

Wet molded tablet
Figure 2

Sano S. et al.

a) $X_1$: Ratio of silicon dioxide 12%
$X_2$: Ratio of absorbed water 50%

b) $X_1$: Ratio of silicon dioxide 12%
$X_3$: Ratio of absorbed water 80%

c) $X_1$: Ratio of silicon dioxide 22%
$X_3$: Ratio of absorbed water 50%

d) $X_1$: Ratio of silicon dioxide 22%
$X_3$: Ratio of absorbed water 80%
**Figure 3**

**a)** $X_1$: Ratio of silicon dioxide 12%  
$X_3$: Ratio of absorbed water 50%

**b)** $X_1$: Ratio of silicon dioxide 12%  
$X_3$: Ratio of absorbed water 80%

**c)** $X_1$: Ratio of silicon dioxide 22%  
$X_3$: Ratio of absorbed water 50%

**d)** $X_1$: Ratio of silicon dioxide 22%  
$X_3$: Ratio of absorbed water 80%
Figure 4

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Mannitol (β form)

Mannitol (δ form)

Batch no. 9

Batch no. 10
Figure 5

a) $X_1$: Ratio of silicon dioxide 12%
$X_3$: Ratio of absorbed water 50%

b) $X_1$: Ratio of silicon dioxide 12%
$X_3$: Ratio of absorbed water 80%

c) $X_1$: Ratio of silicon dioxide 22%
$X_3$: Ratio of absorbed water 50%

d) $X_1$: Ratio of silicon dioxide 22%
$X_3$: Ratio of absorbed water 80%
Figure 6

\[ y = 13439x^3 + 1342.5x^2 - 508.06x + 34.682 \]

\[ R^2 = 0.8981 \]

Degree of swelling (mm)
Disintegration time (sec)

Figure 7

a) Batch no. 9

b) Batch no. 10