Fine granules showing sustained drug release prepared by high-shear melt granulation using triglycerin full behenate and milled microcrystalline cellulose

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Abstract

This study aimed to prepare fine granules with a diameter less than 200 μm and sustained drug release properties by melt granulation. Triglycerin full behenate (TR-FB) was examined as a new meltable binder (MB) by comparison of its properties with those of glycerin monostearate (GM), a widely used as MB. The effect of milling microcrystalline cellulose (MCC), an excipient for melt granulation, on the granule properties was also investigated. TR-FB was more stable during heating and storage than GM, and produced smaller granules with narrower particle size distribution, larger yield in the 106–200 μm range, uniform roundness and better sustained drug release profile than those prepared with GM. Granules prepared with milled MCC had almost the same physicochemical properties as those produced with intact MCC. However, milled MCC produced granules with a more rigid structure and smaller void space than intact MCC. Consequently, the granules produced with milled MCC showed better sustained drug release behavior than those prepared with intact MCC. We successfully prepared fine granules with sustained drug release properties and diameter of less than 200 μm using TR-FB and milled MCC.

***Keywords*:** High-shear melt granulation; computed tomography; synchrotron X-ray radiation; milling process; internal structure; triglycerin full behenate

***Abbreviations*:** APAP, Acetaminophen; BRH, bromhexine hydrochloride; DSC, differential scanning calorimetry; GM, glycerin monostearate; IS, impeller speeds; MB, meltable binder; MCC, microcrystalline cellulose; PXRD, powder X-ray diffraction; SEM, scanning electron microscopy; TR-FB, triglycerin full behenate; X-ray CT, X-ray computed tomography

1. Introduction

Melt granulation is a granulation method that uses a material with a low melting point as a meltable binder (MB). The granules are formed by agitation or fluidization, and cooling conditions, such as ambient temperature, cause the MB to congeal to give dried granules. This simple process is one advantage melt granulation. In addition, because this method is solvent-free, it does not require a drying step or toxic solvent, so melt granulation is considered an economical and environmentally friendly process (ICH guideline, 1998) that can be applied to water-sensitive drugs. Furthermore, melt granulation can easily provide granules with sustained drug release by using hydrophobic or water-insoluble MBs (Thomsen et al., 1994, Hamdani et al., 2002, Ochoa et al., 2011). To date, numerous functional granules have been prepared by melt granulation; for example, granules with immediate drug release (Perissutti et al., 2003), improved drug solubility (Shah et al., 2013), enhanced stability of a moisture-sensitive drug (Kowalski et al., 2009), and gastroretentivity (Hamdani at al., 2006). Recently, we successfully prepared granules by melt granulation that exhibited pH-dependent drug release (Shiino et al., 2012).

Besides their functionality, fine granules with a particle diameter of less than 200 μm are desired to improve their taste and texture (Shah, Ket al., 1994). In

particular, fine granules that undergo sustained drug release have attracted considerable attention to produce orally disintegrating tablets. However, granules with sustained release properties and diameter of less than 200 μm prepared by melt granulation have not been reported. Schaefer proposed that the smaller the pharmaceutical excipients used, the smaller the granules obtained (Schaefer et al., 1997, Schaefer et al 2004). They used a MB with a mean particle diameter of 40 μm that gave granules with a diameter of approximately 500 μm. This suggests that to prepare fine granules with sustained drug release, hydrophobic or water-insoluble MBs and excipients with a particle size of less than 40 μm should be used. Operating conditions should also be improved to minimize granule size.

In the present study, we focus on triglycerin full behenate (TR-FB), which is typically used as a food additive, as a new MB. From a structural perspective, TR-FB has a long carbonyl chain and behenic acid, indicating that it can endow granules with better sustained release properties. In addition, the mean particle diameter of TR-FB is about 4 μm because it is milled by a jet mill (Kamiryo et al., 2002). The maximum acceptable daily intake of TR-FB is 25 mg/kg body weight/day, so it has similar safety to sucrose fatty acid ester, which is often used as a pharmaceutical

excipient (FAO/WHO, 1989). Therefore, TR-FB might be suitable for preparing sustained-release fine granules.

We also investigated microcrystalline cellulose (MCC) as a pharmaceutical excipient. In general, lactose, starch and calcium hydrogen phosphate have been used as excipients for melt granulation; however, because these excipients are hydrophilic or have large particle size even after milling, they are not considered suitable excipients to prepare fine granules. In contrast, MCC is insoluble in water, easily downsized by milling and has recently been used in melt granulation (Kukec et al., 2012), indicating that it may be a suitable excipient. However, how downsized MCC affects the physicochemical properties of fine granules prepared by melt granulation has not been examined.

With the aim of preparing fine granules with sustained drug release, our two main objectives were as follows: the first was to investigate whether TR-FB acts as an MB by comparison with glycerin monostearate (GM), which is commonly used as a hydrophobic MB, and the second was to determine the effects of milling MCC on melt granulation by comparison of the granules prepared with intact and milled MCC. Differential scanning calorimetry (DSC) and powder X- ray diffraction (PXRD) were performed to determine the stability of TR-FB and GM after heat treatment. Next,

101 the physicochemical properties, including particle size distribution, roundness and
102 drug release profile, of granules prepared with either GM or TR-FB were examined.
103 The particle size distribution, roundness, morphology, internal structure, porosity and
104 drug release profile of granules prepared with either intact MCC or MCC milled at
105 different impeller speeds (IS) were then studied.
106
107

2. Materials and methods

2.1. Materials

Acetaminophen (APAP) and bromhexine hydrochloride (BRH), as model drugs, were kindly provided by Iwaki Pharmaceutical Co., Ltd. (Shizuoka, Japan) and purchased from Shiratori Pharmaceutics Inc. (Chiba, Japan), respectively. MCC PH-102 was kindly provided by Asahi Kasei Chemicals Co., Ltd. (Tokyo, Japan). GM was purchased from Taiyo Chemical Industry Co., Ltd. (Tokyo, Japan). TR-FB was kindly provided by Riken Vitamin Co., Ltd. (Tokyo, Japan). Talc was purchased from Gotoku Chemical Co., Ltd. (Tokyo, Japan).

2.2. DSC

Melting points of the MBs were determined by DSC (EXSTAR DSC 7020, SII Nano Technology Inc, Chiba, Japan). Samples (about 10 mg) were sealed in a 40-mL aluminum pan. The samples were analyzed during heating from 25 to 200 °C (first run), cooling to 25 °C, and reheating from 25 to 200 °C (second run) at a heating rate of 5 °C/min under a nitrogen atmosphere (40 mL/min).

2.3. PXRD

The MBs were analyzed by PXRD (Rigaku Rotaflex RU-200B, Rigaku Corp, Tokyo, Japan) under the following operating conditions: target: Cu; voltage: 30 kV, current: 15 mA; scanning speed: 4 °/min; 2θ range: 3–40°.

2.4. Storage stability of MB particles

GM and TR-FB particles were prepared by the spray congealing method reported in our previous paper (Nitanai et al., 2012) and then stored at 24 °C/25% RH for 6 weeks. The surface morphology of MB particles before and after storage was observed by scanning electron microscopy (SEM; JSM-5310LV, JEOL Ltd., Tokyo, Japan). The samples were placed on double-sided adhesive tape and sputter coated with platinum under vacuum prior to imaging.

2.5. High-shear melt granulation

2.5.1. Granules containing APAP

Size reduction of APAP and MCC was carried out using a sample mill (TI-300, Cosmic Mechanical Technology Co., Ltd., Fukushima, Japan) for 15 min. The milled materials were passed through a 149-μm sieve (Tokyo Screen Co. Ltd., Tokyo, Japan), and then milled APAP, TR-FB and intact MCC or milled MCC were

144 manually pre-mixed in a polyethylene bag for 5 min. Granulation was conducted
145 with a high-shear mixer (MECHANOMiLL, Okada Seiko Co., Ltd., Tokyo, Japan)
146 equipped with a rubber heater and temperature sensor as previously reported (Shiino
147 et al, 2012). The batch size was 130 g for all formulations; the formulation of each
148 batch is summarized in **Table 1**. To manufacture granules, the jacket temperature was
149 fixed at approximately 85 °C, and the IS was set to 1200 rpm. After the product
150 temperature reached 77 °C, the rubber heater was turned off, the lid was removed
151 and mixture was agitated at various IS for 1 min. To cool the obtained products, the
152 mixture was removed from the bed of the mixer, and spread into thin layers on metal
153 trays.
154
155 ***2.5.2. Granules containing BRH***
156 Granules containing BRH were prepared by almost the same method as
157 APAP granules. Only two processes were different. One is that the size reduction of
158 BRH was performed using a different-type sample mill (SK-M, Kyoritsu-riko Co.,
159 Ltd., Tokyo, Japan) for 90 s. The other is that granulation was performed with
160 various IS as summarized in **Table 1**.
161

2.6. Particle size distribution

The particle size distribution of granules was evaluated by sieve analysis using standard sieves (Tsutsui Scientific Instruments Co., Ltd., Tokyo, Japan) with aperture sizes ranging from 54 to 1000 μm. The relative width of the particle size distribution (R_w) was calculated by the following equation,

$$R_w = \frac{d_{90} - d_{10}}{d_{50}} \qquad [1]$$

where d_{10}, d_{50}, and d_{90} are 10%, 50%, and 90% of the accumulated particle size under a screen, respectively.

2.7. Roundness

One hundred granules with diameters in the range of 250–297 μm were chosen randomly. Images of these granules were captured using an Olympus BHS microscope (Olympus, Tokyo, Japan) connected to a digital imaging camera (Nikon D80, Nikon, Tokyo, Japan). These images were analyzed with WinROOF image analysis software (Version 5.5, Mitani, Fukui, Japan) to determine the exact diameters and shapes of the granules. The shapes of the granules were defined by their roundness (P_t/P_r), where P_t is the theoretical perimeter length of a perfectly

spherical granule with the same area as the one being analyzed, and P_r is the actual perimeter length.

2.8. SEM observation of granules

The surface morphology of MB particles and granules with a diameter range of 250–297 μm was assessed by SEM as described above in section 2.4.

2.9. Drug release test

The release behavior of APAP from granules with a diameter of 420–590 μm for each formulation was examined in accordance with the paddle method listed in the Japanese Pharmacopoeia 16th Edition (JP 16th). The test medium was 900 mL of distilled water. The medium temperature was set to 37.0±0.5 °C and the paddle speed was 100 rpm. At each time point, a 5-mL aliquot of the test solution was withdrawn and replaced with an equal volume of buffer solution, and the aliquot was passed through a membrane filter (Pore size: 0.45 μm, Toyo Roshi Kaisha Ltd., Tokyo, Japan). The amount of APAP released into the medium was quantitatively determined by UV absorptiometry (UV-mini, Shimadzu, Kyoto, Japan) at 243 nm.

For BRH, granules with a diameter of 250–297 μm were tested. The test medium was hydrochloride buffer solution (pH 1.2), and UV absorptiometry was carried out at 245 nm. A series of dissolution tests for BRH granules was the same as that for APAP granules.

2.10. Synchrotron X-ray computed tomography (CT) measurement

BRH granules with diameters of 250–297 μm were put in Lindemann glass capillaries with a diameter of 0.2–0.3 mm. X-ray CT measurements were performed using a micro-CT instrument (Uesugi et al., 2012; Suzuki et al., 2011) installed at the undulator beamline BL37XU of SPring-8 (Hyogo, Japan). The X-ray energy was set to 8 keV, and flux density was approximately 6×10^{12} photons/s/mm^2. Nine hundred transmission X-ray images, with parallel projection geometry, were recorded in 0.2° steps with continuous rotation of the sample (on-the-fly scan mode). During measurement, each sample was continuously irradiated with X-rays, and the exposure time for each projection was 150 ms. The distance from the sample to the area detector was 2 mm. CT measurement of one sample was accomplished within 5 min. All CT measurements were performed at room temperature. Tomographic reconstruction was performed by the convolution-back-projection method using the

214 *CBP* package (Uesugi , 2004), and 1920 × 1920 pixel cross-sectional images were
215 obtained. One pixel is equivalent to 0.444 × 0.444 μm. 3-D analyses of the
216 cross-sectional images were performed using the *SLICE* package (Nakano et al.,
217 2006) and *ImageJ* (Schneider et al., 2012). X-ray linear attenuation coefficient
218 (LAC) values between 0 and 70 cm^{-1} are shown in 8-bit grayscale in the images of
219 granules, and LAC values higher than 70 cm^{-1} are in white.
220

221 ***2.11. Calculation of the void voxel ratio of granules***

222 To evaluate the porosity of the granules, the void voxel ratio (VVR) was
223 calculated from slice images of X-ray CT. VVR is defined as follows:

$$\mathrm{VVR} = (\text{number of voxels regarded as void in the sample}) \,/\, (\text{number of total voxels in the sample})$$

224 Voxels with LAC values less than 0.3 cm^{-1} were regarded as voids.
225

3. Results and discussion

3. 1. Evaluation of TR-FB as an MB

3. 1. 1. Heat and storage stability of GM and TR-FB

First, to determine whether TR-FB works as an MB, the crystal states of TR-FB and GM, which is generally used as an MB, were evaluated by DSC and PXRD. **Figure 1** shows DSC curves of GM and TR-FB. In the first heating cycle, GM and TR-FB exhibited endothermic peaks at 73.2 and 71.9 °C, respectively, and both melted at a similar temperature. In the second heating cycle, the endothermic peak of GM decreased to 67.5 °C because of the crystal transition from the stable β form to the metastable α form, as reported by Yajima et al. (2002). GM also transforms from the metastable form (α) to the stable form (β) through another metastable form (β') during storage at ambient temperature (Windbergs et al., 2009). This crystal transition is likely to change the drug dissolution profile of granules prepared with GM after storage. In contrast, the endothermic peak of TR-FB did not shift in the second heating cycle. The PXRD pattern of TR-FB was the same before and after melting (**Fig. 2**). This indicates that TR-FB does not show any crystal transition in the investigated temperature range. **Figure 3** shows SEM images of the surface of GM and TR-FB particles prepared by a spray congealing method. After storage at

24 °C/25% RH for 6 weeks, acicular crystals were observed on the surface of GM particles (**Fig. 3b**), consistent with previous observations (Windbergs et al., 2009). Conversely, the TR-FB particle remained smooth even after storage (**Fig. 3d**). From these results, TR-FB might be more stable as an MB than GM and should be suitable for use in melt granulation.

3. 1. 2. Effect of GM and TR-FB on granulation properties

Figure 4 shows the particle size distribution of granules prepared using GM and TR-FB as an MB. In both types of granules, as the amount of GM or TR-FB increased, the particle size of the granules also increased. **Table 2** shows the physicochemical properties of the granules, such as d_{50}, R_w, yield of particles in the 106–210 μm range and roundness. The roundness of both types of granules was high (over 0.83). When comparing the same amount of MB, d_{50} of TR-FB granules was larger than that of GM granules; however, R_w of TR-FB granules was smaller, and yield of particles in the 106–210 μm range of TR-FB is higher than that of GM granules. This is because of the difference in the particle size and viscosity of melted GM and TR-FB. The mean particle sizes of GM and TR-FB powders were 41 and 3.8 μm, respectively, while the viscosities of GM and TR-FB at 80 °C are 27.3 and 31.3

mPa·s, respectively. Previous literature suggested that a difference of viscosity of about 4 mPa·s caused differences of physicochemical properties such as d_{50} and R_w (Eliasen et al., 1999). The granule growth mechanism of melt granulation is shown in **Fig. 5a**. Melted MB particles adhere to the powder, allowing the powder particles to bond with each other to make core particles (distribution phase). Then, these core particles adhere to each other (coalescence phase) and the granules become larger by adhering repeatedly, suggesting that when the core particle is larger, the resulting granules are larger. When the product is cooled and the temperature is close to the melting point of the MB, the MB starts to congeal, and granules are sheared by the impeller blade (**Fig. 5b**). Eliasen reported that when the viscosity of an MB is less than 50 mPa·s, adhesion and breakage occur simultaneously during the coalescence and agglomeration phase (Eliasen et al., 1999), so the particle size of granules depends on the balance between adhesion and breakage. Therefore, in GM with a large particle size, the core particles were large so the granules were also large. Moreover, because of the low viscosity of GM, breakage frequently occurred in the agglomeration phase to produce a large amount of finely crushed granules. As a result, GM granules had a small d_{50} and large R_w. In contrast, for TR-FB with smaller particle size and higher viscosity than those of GM, the core particles were smaller

and less breakage occurred, so the TR-FB granules had lower R_w and a larger yield of fine granules with a particle size range of 106 to 210 μm than those of GM. **Figure 6** shows drug dissolution profiles of GM and TR-FB. TR-FB granules showed more sustained release than GM granules. Because the hydrophile-lipophile balance values of GM and TR-FB are 4.0 and 2.1 respectively, TR-FB is more hydrophobic than GM. Taken together, these findings suggest that TR-FB is a better MB than GM for preparing fine granules with sustained drug release properties.

3.2. Effect of MCC milling on granule properties

3. 2. 1. Particle size and external structure of granules

Figure 7 shows SEM images of intact and milled MCC particles. Intact MCC particles were acicular, and their mean diameter was approximately 90 μm **(Fig. 7a)**. After milling, the MCC particles had an undefined shape and their mean diameter was approximately 10 μm **(Fig. 7b)**.

Figure 8 shows the particle size distributions of granules prepared with intact and milled MCC. **Table 3** shows physicochemical properties of the granules, The granules containing 22.5% TR-FB and intact MCC **(Fig. 8a, Batch 7)** showed similar particle size distribution to that of granules containing 17.5% TR-FB and

298 milled MCC **(Fig. 8b, Batch 12)**. This indicates that even a small amount of TR-FB
299 was sufficient to prepare granules when milled MCC was used. For milled MCC,
300 addition of a larger amount of TR-FB and increasing IS increased granule size
301 compared with use of intact MCC, suggesting that careful control of operating
302 conditions is needed to prepare fine granules smaller than 200 μm. The roundness of
303 both types of granules was almost the same (**Table 3**). In both types of granules,
304 addition of a smaller amount of TR-FB and lower IS were found to make granules
305 rounder and *vice versa*. The granules prepared with either intact or milled MCC
306 using different binder concentration and IS had a similar appearance (**Fig. 9**).
307
308 ***3. 2. 2. Drug dissolution from granules***
309 **Figure 10** shows dissolution profiles of BRH from granules containing
310 intact or milled MCC. For the milled MCC granules, it took about 30–60 min for
311 80% of the BRH to dissolve (**Fig. 10B**), while it took only about 15–30 min for 80%
312 of the BRH to dissolve from the intact MCC granules (**Fig. 10A**). Although the
313 appearance of these granules was almost the same (**Fig. 9**) and a larger amount of
314 TR-FB was present in the intact MCC granules than in the milled MCC ones, the
315 milled MCC granules exhibited more sustained drug release than the intact MCC

316 ones. This may be caused by differences in the internal structure of the granules, so
317 we conducted synchrotron X-ray CT measurements to obtain cross-sectional images
318 of the granules.
319
320 ***3. 2. 3. Internal structure of granules***
321 **Figure 11** shows cross-sectional X-ray CT images of the granules. White
322 and black areas in each figure represent BRH (calculated LAC = 75.5 cm^{-1}) and void
323 space, respectively. Brighter gray and darker gray areas represent MCC (12.4 cm^{-1})
324 and TR-FB (4.1 cm^{-1}), respectively. TR-FB in intact MCC granules was present
325 mainly near the surface of the granules and adhered to MCC particles, which
326 produced voids inside the granules (**Fig. 11A-E**). Conversely, in the milled MCC-
327 granules, TR-FB surrounded milled MCC particles, and no large voids were
328 observed (**Fig. 11F-J**). This indicates that because intact MCC particles became core
329 particles and adhered to each other to form granules, voids were caused by the
330 acicular shape of intact MCC. In contrast, in milled MCC granules, because the
331 MCC particles were non-acicular and small, they were surrounded by TR-FB
332 efficiently, and granules with rigid structure were formed. Focusing on the
333 distribution of BRH, in intact MCC granules, BRH was found near the surface of the

334 granules, while BRH was uniformly distributed throughout milled MCC granules.
335 This is because the high hydrophobicity of BRH means that it has a high affinity for
336 hydrophobic TR-FB, indicating that the drug distribution in the granules depends on
337 the characteristics of the MB.

338 The VVR of each granule was then calculated (**Fig. 12**). In intact MCC
339 granules, VVR is significantly lower (26–27% to 15–17%) when the amount of MB
340 is higher (22.5% to 27.5%) ($p<0.01$, compared with batch No. 7). Conversely, in
341 milled MCC granules, all of the granules exhibited markedly lower VVR (5–8%)
342 compared with that of the intact MCC granules (15–27%) ($p<0.001$, compared with
343 batch No. 7). This difference of the porosity of the granules might cause the
344 difference of the drug release profiles of intact and milled MCC granules. **Figure 13**
345 shows the relationship between VVR and 80% drug release time from each granule.
346 Although these granules were prepared by different binder ratios, which affect the
347 drug dissolution ratio and by various impeller speeds while granulation, high
348 correlation coefficient value of liner regression was obtained. This is to say, because
349 of the higher porosity of intact MCC granules, test solution entered the granules
350 more readily, so the area where BRH was in contact with the test solution was larger

than that in the milled MCC granules. As a result, intact MCC granules released BRH faster than milled MCC granules.

Up to now, it has been thought that melt granulation generally produces granules with rigid structure because of the high speed of the impeller and high centrifugation force regardless of formulation and operating conditions. However, our results demonstrate that the milling process of the excipient affects the distribution of drug particles and void space ratio in granules formed by high-shear melt granulation, and these differences in the inner structure of granules affect drug release.

4. Conclusions

We investigated TR-FB as an MB and the effect of milling MCC with the objective of preparing fine granules with sustained drug release properties. TR-FB was more stable during heating and storage than GM, a commonly used as MB. Granules prepared with TR-FB were smaller, had a narrower particle size distribution, and showed a better-sustained drug release profile compared with those formed with GM. In addition, granules prepared with milled MCC had rigid structure, whereas those produced with intact MCC had large void space. Consequently, the granules prepared with milled MCC showed better-sustained drug release behavior than that of granules formed with intact MCC, because penetration of test solution into granules was limited. Our results reveal that TR-FB is suitable as an MB and milling MCC affects the physicochemical properties and drug dissolution behavior of granules. Fine granules with a diameter of less than 200 μm and sustained drug release behavior were successfully prepared using TR-FB and milled MCC. In the near future, after adding functional polymers to enhance the sustained release properties, further in vivo studies would be necessary.

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Table captions

Table 1.

Formulations of granules and operating conditions.

Table 2.

Properties of particles prepared with GM (Batch No. 1-3) and TR-FB (Batch No. 4-6).

Table 3.

Properties of particles prepared with intact MCC (Batch No. 7-11) and milled MCC (Batch No. 12-16).

457 **Table 1.**

Batch No.	Formulation						Operation
	APAP (%)	BRH (%)	GM (%)	TR-FB (%)	Intact MCC (%)	Milled MCC (%)	IS (rpm)
1	10	—	20.0	—	—	70.0	400
2	10	—	22.5	—	—	67.5	400
3	10	—	25.0	—	—	65.0	400
4	10	—	—	20.0	—	70.0	400
5	10	—	—	22.5	—	67.5	400
6	10	—	—	25.0	—	65.0	400
7	—	10	—	22.5	67.5	—	400
8	—	10	—	22.5	67.5	—	1200
9	—	10	—	27.5	62.5	—	400
10	—	10	—	27.5	62.5	—	1200
11	—	10	—	27.5	62.5	—	1600
12	—	10	—	22.5	—	67.5	400
13	—	10	—	22.5	—	67.5	1200
14	—	10	—	27.5	—	62.5	1600
15	—	10	—	27.5	—	62.5	400
16	—	10	—	27.5	—	62.5	1200

458

459

460 **Table 2.**

Batch No.	**1**	**2**	**3**	**4**	**5**	**6**
MB Concentration (%)	GM			TR-FB		
	20	22.5	25	20	22.5	25
d_{50} (μm)	101	105	195	125	160	290
R_w	4.16	3.41	2.91	1.92	1.78	2.27
Yield (%) (106-210 μm)	17.2	21.9	38.6	50.0	59.4	25.9
Roundness	0.86	0.89	0.88	0.86	0.86	0.83

461

462

463 **Table 3.**

Batch No.	**7**	**8**	**9**	**10**	**11**
Excipient	Intact MCC				
Binder (%)	22.5	22.5	27.5	27.5	27.5
IS (rpm)	400	1200	400	1200	1600
d_{50} (μm)	155	154	180	187	197
R_w	0.93	0.93	1.21	1.45	1.26
Yield (%) (106-210 μm)	66.7	66.9	56.9	51.5	47.0
Roundness	0.88	0.85	0.83	0.78	0.78

464

Batch No.	**12**	**13**	**14**	**15**	**16**
Excipient	Milled MCC				
Binder (%)	17.5	17.5	17.5	22.5	22.5
IS (rpm)	400	1200	1600	400	1200
d_{50} (μm)	149	197	185	351	421
R_w	1.28	1.90	2.25	1.90	1.53
Yield (%) (106-210 μm)	61.2	45.8	47.3	17.6	9.6
Roundness	0.89	0.81	0.83	0.80	0.79

Figure legends

Fig. 1. DSC curves of GM (**A, B**) and TR-FB (**C, D**) measured on first (**A, C**) and second (**B, D**) heating cycles.

Fig. 2. PXRD patterns of TR-FB before (**A**) and after (**B**) heating.

Fig. 3. SEM images of the surface of MB particles prepared by a spray congealing method using (**A, B**) GM and (**C, D**) TR-FB (**A, C**) before and (**B, D**) after storage for 6 weeks.

Fig. 4. Effect of binder concentration on the particle size distributions of granules prepared with (**A**) GM or (**B**) TR-FB.

Fig. 5. Diagram of the granulation mechanism in melt granulation (**A**) above and (**B**) near the melting temperature of the MB.

Fig. 6. Drug dissolution profile from granules prepared with GM or TR-FB.

Fig. 7. SEM images of MCC (**A**) before and (**B**) after milling.

Fig. 8. Particle size distribution of granules prepared with (**A**) intact or (**B**) milled MCC with various IS.

Fig. 9. SEM images of granules prepared with (**A-E**) intact or (**F-J**) milled MCC with various IS.

Fig. 10. Drug dissolution profiles of granules prepared with (**A**) intact or (**B**) milled MCC with various IS.

Fig. 11. X-ray CT images of granules prepared with (**A-E**) intact or (**F-J**) milled MCC with various IS.

Fig. 12. VVR of granules prepared with intact or milled MCC with various IS. *: $p<0.01$ and **: $p<0.001$, compared with VVR of batch No. 7.

Fig. 13. Relationship between VVR and 80% drug release time.