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2 Regular Article

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4 **Melt adsorption as a manufacturing method for fine particles of wax**  
5 **matrices without any agglomerates**

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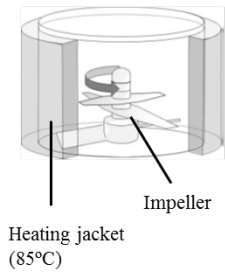
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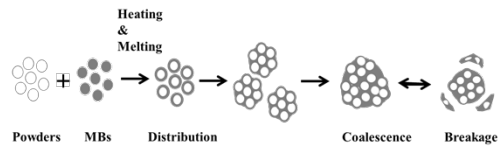
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**Manufacturing method of melt adsorption**

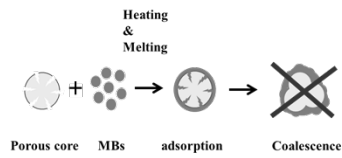


Molten	150 rpm
US2 1 <sup>st</sup> addition	150 rpm
Mixing	150 rpm 1 min
Mixing	300 rpm 1 min
US2 2 <sup>st</sup> addition	300 rpm 2 min
Mixing	300 rpm 6 min

**Granulation process of melt granulation**



**Granulation process of melt adsorption**



**Graphic Abstract**  
*Shiino et al.*

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## 25 **Summary**

26           We have focused on melt adsorption as manufacture method of wax matrices to control  
27 particles size of granules more easily than melt granulation. The purpose of present study was to  
28 investigate the possibility of identifying a hydrophobic material with a low melting point, currently  
29 used as a meltable binder of melt granulation, to apply as a novel carrier in melt adsorption.  
30 Glyceryl monostearate (GM) and stearic acid (SA) were selected as candidate hydrophobic materials  
31 with low melting points. Neusilin US2 (US2), with a particle diameter of around 100  $\mu\text{m}$  was  
32 selected as a surface adsorbent, while dibasic calcium phosphate dihydrate (DCPD), was used as a  
33 non-adsorbent control to prepare melting granules as a standard for comparison. We prepared  
34 granules containing ibuprofen (IBU) by melt adsorption or melt granulation and evaluated the  
35 particle size, physical properties and crystallinity of granules. Compared with melt granulation using  
36 DCPD, melt adsorption can be performed over a wide range of 14% to 70% for the ratio of molten  
37 components. Moreover, the particle size;  $d_{50}$  of obtained granules was 100–200  $\mu\text{m}$ , and these  
38 physical properties showed good flowability and roundness. The process of melt adsorption did not  
39 affect the crystalline form of IBU. Therefore, the present study has demonstrated for the first time  
40 that melt adsorption using a hydrophobic material, GM or SA, has the potential capability to control  
41 the particle size of granules and offers the possibility of application as a novel controlled release  
42 technique.

43

44 **Keywords:** Melt adsorption; Melt granulation; Manufacturing efficiency; Control of particle size;  
45 Neusilin US2; Ibuprofen.

## 46 **Introduction**

47           The wax matrix system is a popular controlled release technique. The main advantage of  
48 this system is that neither solvents nor drying processes are required, so the controlled release  
49 formulation can be obtained through a simple, low cost procedure, without the toxicity and  
50 environmental pollution caused by organic solvents<sup>1, 2</sup>). Melt granulation for manufacturing wax  
51 matrices uses a binding material with a low melting or softening point and after melting, the material  
52 acts as a binding liquid. The melting binder congeals at room temperature to yield a solid dosage  
53 form<sup>3</sup>). Schæfer described two mechanisms (distribution and nucleation of immersion mechanisms)  
54 for agglomerate formation and growth of granules during melt granulation<sup>4, 5</sup>). The distribution  
55 mechanism involves the nucleation of granules caused by distribution of molten binders of low  
56 viscosity and small diameter on the surface of the other powders. In contrast, the nucleation of  
57 immersion mechanism is caused by immersion of powders within molten binders of high viscosity  
58 and large diameter. After nucleation occurs through these two mechanisms, coalescence of the nuclei  
59 gradually occurs and agglomerate formation and growth progress. Thus, agglomerate formation in  
60 melt granulation depends on the physical properties of the molten binders. However, control of  
61 particle size during agglomerate formation and growth is difficult because of the high adhesion of  
62 molten binders. This problem limits the practical application of melt granulation in pharmaceutical  
63 formulation.

64           We have therefore focused on melt adsorption to solve this issue. Melt adsorption is known  
65 as a manufacturing method for solid dispersions in which a surface adsorbent is used to adsorb  
66 poorly water-soluble drugs and molten surfactants on its surface. Previously, Gupta et al. reported

67 that melt adsorption was a useful method for manufacturing solid dispersions of Gelucire 50/13 to  
68 enhance drug dissolution<sup>6</sup>). Moreover, they revealed that a surface adsorbent, Neusilin US2 (US2),  
69 confers good flowability and compressibility on granules, which can then be compressed into tablets  
70 without processing problems<sup>6</sup>). Other work showed that poor solubility of losartan potassium was  
71 improved by melt adsorption using Aerosil 300 as a surface adsorbent and Poloxamer 188 as a  
72 surfactant<sup>7</sup>). In these studies, surface adsorbents play the important role to adsorb the molten  
73 surfactant, thereby speculating that the sizes of granules manufactured by melt adsorption would not  
74 be increased and this technique offers the possibility to control size distribution of the granules.  
75 However, the hydrophilic characteristics of the above-mentioned surfactant cannot achieve suitable  
76 objective product properties for developing taste masking or sustained release formulations and use  
77 of hydrophobic materials alternative to surfactant would be desirable.

78         The purpose of present study was to investigate the possibility of identifying a hydrophobic  
79 material with a low melting point, currently used as a meltable binder of melt granulation, to apply  
80 as a novel carrier in melt adsorption. Glyceryl monostearate (GM) and stearic acid (SA) were  
81 selected as candidate hydrophobic materials with low melting points, and polyethylene glycol (PEG)  
82 6000 was also selected as a viscosity modifier. These materials were used as meltable binders in  
83 melt granulation to manufacture a controlled release formulation<sup>4, 5, 8, 9</sup>). Furthermore, we evaluated  
84 process parameters related to particle size control in an actual manufacturing apparatus, a high shear  
85 mixer. Most previous researches on melt adsorption were performed in a small scale apparatus like a  
86 beaker, not in an actual manufacturing apparatus<sup>7, 10, 11</sup>). It is essential to determine the effects of  
87 process conditions on the yield and the formulation on the particle size of the preparation, to develop

88 a robust manufacturing method. US2 consists of amorphous microporous granules of magnesium  
89 aluminosilicate with a high specific surface area (300 m<sup>2</sup>/g) and a particle diameter of around 100  
90 μm. US2 was selected as a surface adsorbent, while dibasic calcium phosphate dihydrate (DCPD),  
91 was used as a non-adsorbent control to prepare melting granules as a standard for comparison. We  
92 aimed at manufacturing uniform and fine granules (100–200 μm), which are desirable for imparting  
93 good handling during processing and a good mouthfeel<sup>12, 13</sup>.

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109 **Materials and methods**

110 **Materials**

111 Ibuprofen (IBU) was kindly provided from BASF Japan Ltd. (Tokyo, Japan), GM was  
112 purchased from Taiyo Chemical Industry Co. Ltd. (Saitama, Japan), SA was purchased from Wako  
113 Pure Chemical Industries Ltd. (Osaka, Japan) and PEG6000 was purchased from Wako Pure  
114 Chemical Industries Ltd. US2 was kindly provided by Fuji Chemical Industries Co. Ltd. (Tokyo,  
115 Japan), DCPD was kindly provided by Kimura Sangyo Co. Ltd. (Tokyo, Japan).

116

117 **Thermal analysis of materials**

118 Thermal analysis of materials was carried out using a differential scanning calorimeter  
119 (XSTAR DSC7020, Hitachi High-Tech Science Corp., Tokyo, Japan). The analyses were carried out  
120 over the temperature range 30–100°C at a heating rate of 10°C/min under nitrogen flow (40  
121 ml/min).

122

123 **Manufacturing**

124 Melt adsorption was conducted with a high shear mixer (MECHANOMiLL, Okada Seiko  
125 Co. Ltd., Tokyo, Japan) equipped with a heating jacket (rubber heater) and temperature sensor. A  
126 representation of the MECHANOMiLL apparatus is shown in **Fig. 1**. The particle size of DCPD was  
127 reduced using a Sample Mill (TI-300, Cosmic Mechanical Technology Co. Ltd., Fukushima, Japan),  
128 and the milled DCPD were passed through a 177- $\mu$ m sieve (Tokyo Screen Co. Ltd., Tokyo, Japan).  
129 To manufacture the granules by melt adsorption or melt granulation, IBU, GM, PEG6000 and SA

130 were placed into the apparatus, heated at approximately 85°C by the rubber heater and mixed at an  
131 impeller speed of 150 rpm until the mixture components were fully melted. The impeller speed was  
132 set to prevent from excessive scattering of the molten component in the chamber and achieve  
133 uniform mixing. US2 or DCPD was then added to the molten mixture in the apparatus under  
134 continuous mixing by impeller, and the granules were prepared by adsorption or agglomerate  
135 formation. Each manufacturing experiments was conducted three times.

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### 137 **Characterization of the granules**

#### 138 **Yield and available yield**

139 The total yield of the final product (% w/w) was calculated by dividing the mass of the  
140 product by that of the initial materials, multiplied by 100. The granules obtained with a 500- $\mu\text{m}$   
141 sieve pass were defined as the available fraction in this study. The available yield (% w/w) was  
142 calculated by dividing the mass of the available fraction by that of the starting material, multiplied  
143 by 100.

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#### 145 **Particle size distribution**

146 The size distribution of granules with a 500- $\mu\text{m}$  sieve pass was measured using a laser  
147 diffractometer with free fall or dry dispersing system (LDSA-1500A, MicrotracBEL Corp., Osaka,  
148 Japan) under the following conditions: focal length, 300 mm; measurement time, 2.0 s; dispersive  
149 air pressure of dry dispersing system, 1.5 kgf/cm<sup>2</sup>.

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151 **Physical properties**

152           The angle of repose and shapes of granules were evaluated as their physical properties. The  
153 angle of repose of granules was measured as per a standard procedure<sup>14</sup>). Fifty granules with  
154 diameters in the 74–210  $\mu\text{m}$  range were chosen randomly to measure the sphericity of the granules.  
155 Images of granules were captured using a microscope (BHS, Olympus Optical Co. Ltd., Tokyo,  
156 Japan) connected to a digital imaging camera, and sphericities were analyzed with image analysis  
157 software (WinROOF, Mitani Co. Ltd., Fukui, Japan). The sphericities were defined by their  
158 roundness ( $P_t/P_r$ ), where  $P_t$  is the theoretical perimeter length of a perfectly spherical granule having  
159 the same area as the particle under analysis, and  $P_r$  is the actual perimeter length of the particle.

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161 **Powder X-ray diffraction analysis**

162           The crystalline form of IBU in granules was measured using a powder X-ray diffractometer  
163 (Rigaku Rotaflex RU-200B, Rigaku Corp., Tokyo, Japan) under the following conditions: target: Cu;  
164 current: 30 mA; scanning speed:  $2^\circ/\text{min}$ ; and  $2\theta$  range:  $3\text{--}40^\circ$ .

165

166 **Statistics**

167           Statistical analyses were performed by using Student's t-test, where a probability value of  $p$   
168  $< 0.05$  was considered to indicate statistical significance.

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## 172 **Results and discussion**

### 173 **Determination of jacket temperature**

174 The DSC spectrums of IBU, SA, GM, PEG6000 and US2 are shown in **Fig. 2**. For IBU,  
175 GM, SA and PEG6000, the endothermic peaks corresponding to each melting point were observed at  
176 76, 62, 69 and 83°C, respectively. However, no peak was observed for US2 so US2 is stable over the  
177 temperature range 30 to 100°C. Taking the thermographic properties of materials into consideration,  
178 the jacket temperature of the high shear mixer was set at 85°C, which is higher than the melting  
179 point of PEG6000.

180

### 181 **Optimum manufacturing conditions for attaining high yield**

182 When US2 is added to the molten mixture in one step, the temperature of product will be  
183 immediately decreased. This may then cause the risk of adhesion to the apparatus and extreme  
184 agglomeration, resulting in a reduction in available yield. Therefore, addition of US2 was divided in  
185 two steps, as shown in **Fig. 3**. We selected each amount of US2 (1<sup>st</sup> and 2<sup>nd</sup> additions) as two of the  
186 three process parameters.

187 The third parameter, impeller speed, was selected because it is a critical factor in  
188 determining the yield during conventional granulation in a high shear mixer. The ratio of each US2  
189 quantity and well as the impeller speed were varied and the manufacturing conditions shown in  
190 **Table 1** were set up, where total amount of US2 added was fixed at 40 g.

191 The results for yield under each condition are shown in **Table 2**. From Condition Nos. 1, 2  
192 and 3, yield increased with increasing the amount of US2 in the 1<sup>st</sup> addition step. Adhesion to the

193 chamber was observed after examination of Condition Nos. 1 and 2. This was probably caused by a  
194 reduction in the temperature of the molten component through an excessive amount of US2 in the  
195 2<sup>nd</sup> addition, resulting in congealing of the molten component and enhancing adhesion to the  
196 chamber. In contrast, pulverized powder and clusters were found without adhesion under Condition  
197 No. 3. In this case, the non-uniform adsorption of the molten component by excess US2 in the 1<sup>st</sup>  
198 addition may have resulted in a wider size distribution of granules. Taking yield and visual  
199 observation into consideration, we decided that the optimum ratio between 1<sup>st</sup> and 2<sup>nd</sup> addition of  
200 US2 is 10:30. We then attempted to determine the optimum impeller speed for the yield under  
201 Condition Nos. 4, 5 and 6 in **Table 1**. However, the adhesion tendency was so strong that a high  
202 yield could not be obtained under all conditions, as shown in **Table 2**. In particular, with respect to  
203 Condition No. 4, granulation could not be completed because of extreme adhesion to the chamber  
204 through insufficient stirring. An increment in pulverized powder and clusters caused a reduction in  
205 yield in the case of Condition No. 6. That is to say, a reduction in yield at high impeller speed was  
206 presumably caused by an increase in collision frequency between the granules and the chamber,  
207 leading to the enhancement of adhesion. Moreover, this uneven distribution of molten components  
208 in the chamber at high impeller speed was considered to hinder the adsorption and binding between  
209 particles, resulting in an increase in pulverized powder. From the above considerations, we  
210 determined the optimum impeller speed as 300 rpm. Subsequent procedures for melt adsorption  
211 were conducted under the optimum Condition No. 5 (1<sup>st</sup> addition: 10%, 2<sup>nd</sup> addition: 30%, impeller  
212 speed: 300 rpm)

213

## 214 **Effect of surface adsorbent on the growth of particle**

215           After the analysis of process parameters, we evaluated yield, particle size and physical  
216 properties of several formulations manufactured under the optimal conditions. Specifications for  
217 formulations are summarized in **Table 3**, where U and D indicate formulations containing US2 and  
218 DCPD, respectively. We investigated the effect of the presence or absence of adsorbent on the size  
219 distribution of the granules by comparing U and D formulations.

220           The results of yield and available yield for various formulations are shown in **Table 4**. As  
221 the molten component ratio (the total amounts of IBU, GM, PEG6000 and SA) increased, available  
222 yield decreased. In particular, the reduction of available yield in D formulations was larger than that  
223 in U formulations. The available yield of U3 comprised of 16.7% IBU, 15% GM, 3.3% PEG6000  
224 and 35% SA) was larger than U2 comprised of 50% IBU, 10% GM and 10% PEG6000, even though  
225 each molten component ratio was same. A possible reason for this discrepancy might be the  
226 difference in viscosity between the molten materials. The viscosities of molten GM, PEG6000 and  
227 SA at 80°C were 26, 701 and 6 mPa·s, respectively<sup>15)</sup>. The agglomerate growth is supposed to be  
228 promoted by a higher viscosity, which is known for theory of Stokes' number<sup>16)</sup>. Therefore, as for U3,  
229 the viscosity of molten components was reduced due to low amount of PEG and high amount of SA,  
230 and granules with a diameter of smaller than 500 µm were obtained, resulting in high available  
231 yield.

232           **Table 5** shows the particle size; d10, d50 and d90, of each granule. As the content of IBU  
233 increased, the particle size of both D and U formulations increased. The particle size of U1 was  
234 almost equivalent to that of intact US2, but that of U2 and U3 were much larger. These results

235 indicate that the molten components in U2 and U3 were completely occupied in the adsorption sites  
236 of US2, and accordingly excess molten components on the surface of US2 enhanced the growth of  
237 particle. Although increases in particle size of granules were observed in U formulations, d50 of  
238 obtained all granules meet the criteria (100–200  $\mu\text{m}$ ). In contrast, the size of granules in D  
239 formulations was significantly increased by changing the ratio of molten components in the narrow  
240 range from 12% to 14%. That is to say, the addition of US2 prevented particle growth by molten  
241 components compared with DCPD. From the above results, melt adsorption using US2 was a  
242 superior method for controlling particle size and loading significantly more API, with a lower  
243 melting point than conventional melt granulation using DCPD.

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#### 245 **Effect of surface adsorbent on physical properties of the granules**

246 The angle of repose and the roundness of the granules are summarized in **Table 6**. Carr  
247 suggested that powders with an angle of repose less than  $41^\circ$  are required to avoid cross-linking  
248 during storage in Carr's index<sup>14</sup>). Therefore, we decided that the reference value of the angle of  
249 repose for good flowability was less than  $41^\circ$ . The angle of repose of DCPD formulations was  
250 decreased from  $43.3^\circ$  to  $36.0^\circ$  by increasing the ratio of molten components from 12% to 14%. This  
251 improvement in flowability caused by growth of particle, as can be also seen during conventional  
252 granulation. In contrast, the angle of repose of all US2 formulations was less than  $41^\circ$ , which can be  
253 explained by the preservation of the characteristics of intact US2, which has good flowability<sup>6</sup>). The  
254 roundness of U formulations was thus higher than that of D formulations, indicating a difference in  
255 the granule formation mechanism between melt adsorption and melt granulation. In melt adsorption

256 (US2 formulations), US2 is used as a core and this adsorbs molten components so that the shape is  
257 maintained. However, in melt granulation (DCPD formulations), the pulverized DCPD is used as an  
258 excipient, and this is granulated with the binder of molten components. From the physical property  
259 results of U formulation, it is evident that granules with good flowability and roundness can be  
260 manufactured over a wide range (14% to 70%) of the ratio of molten components.

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### 262 **Crystalline form of IBU in the granules**

263 Powder X-ray diffraction analysis was performed to investigate the crystalline form of IBU  
264 in granules. **Figure 4 (A)** shows X-ray diffraction patterns of each raw material. Four strong  
265 diffraction peaks at  $2\theta$  values of  $5.8^\circ$ ,  $16.4^\circ$ ,  $19.9^\circ$  and  $22.1^\circ$  were observed in UBU. The  
266 characteristic peaks of each crystalline form were observed in other materials, PEG6000, GM and  
267 SA, without US2. The  $2\theta$  values of GM peaks ( $19.7^\circ$  and  $23.0^\circ$ ) match that of the  $\beta$  form, which is  
268 the most stable crystalline form of GM<sup>17</sup>). The absence of peaks in US2 confirmed its amorphous  
269 nature. **Figure 4 (B)** shows the X-ray diffraction patterns for U2 and U3. Two strong diffraction  
270 peaks at  $2\theta$  values of  $21.5^\circ$  and  $24.1^\circ$  were observed in U3 and these diffraction peaks were also  
271 identified as SA. The diffraction peaks seen in crystalline IBU of Fig. 4(A) were not observed in U3,  
272 because they may be obscured by the strong peaks resulting from the high content of SA. On the  
273 other hand, four strong diffraction peaks of crystalline IBU were clearly observed in U2 because this  
274 contained high amount of IBU (50%). Therefore, these results indicated that the process of melt  
275 adsorption might not affect the crystalline form of IBU.

276

277 **Conclusions**

278 In the present study, we prepared granules containing hydrophobic materials, GM and SA,  
279 by melt adsorption, and evaluated the particle size, physical properties and crystallinity of granules.  
280 The investigation of the effect of process parameters on yield indicated that the optimum  
281 manufacturing conditions to prevent the formation of adhesion and clusters are a 1<sup>st</sup> addition of US2  
282 of 10%, a 2<sup>nd</sup> addition of US2 of 30% and an impeller speed of 300 rpm. Compared with melt  
283 granulation using DCPD, melt adsorption can be performed over a wide range of 14% to 70% for  
284 the ratio of molten components. Moreover, the particle size; d50 of obtained granules was 100–200  
285 µm, and these physical properties showed good flowability and roundness. The process of melt  
286 adsorption did not affect the crystalline form of IBU. Therefore, the present study has demonstrated  
287 for the first time, that melt adsorption using a hydrophobic material, GM or SA, has the potential  
288 capability to control the particle size of granules and offers the possibility of application as a novel  
289 controlled release technique.

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295 **References and Notes**

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321 **Table 1. Manufacturing conditions used in melt adsorption to investigate the effect of process**  
 322 **parameters**

No.	Formulation				Process parameter		
	IBU (%)	GM (%)	PEG (%)	US2 (%)	X (g): 1 <sup>st</sup> addition of US2	Y(g): 2 <sup>nd</sup> addition of US2	Z(rpm): Impeller speed
1					5	35	500
2					10	30	500
3					14	26	500
4	10	25	25	40	10	30	150
5					10	30	300
6					10	30	700

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334 **Table 2. Effect of process parameters on yield and visual observation**

No.	X	Y	Z	Yield (%)		Visual observation		
				Average	S.D.	Adhesion to the chamber <sup>a</sup>	Pulverized powder <sup>b</sup>	Cluster <sup>c</sup>
1	5	35	500	72.1	6.6	✓		
2	10	30	500	77.1	2.1	✓		
3	14	26	500	86.9*	3.0		✓	✓
4	10	30	150	_d	_d	_d	_d	_d
5	10	30	300	81.6	1.6	✓		
6	10	30	700	73.2	7.2	✓	✓	✓

335 <sup>a</sup>,"Adhesion to the chamber" was defined as a large amount of adhesion over 1 g.

336 <sup>b</sup>,"Pulverized powder" means the powders scattered after manufacturing process.

337 <sup>c</sup>,"Cluster" was defined as large aggregates with particle size of over 10 mm.

338 <sup>d</sup>,"\_" indicated that the granulation could not be completed.

339 \*  $p < 0.05$  as compared with No.1.

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349 **Table 3. Formulation of granules prepared by melt adsorption and melt granulation**

Formulation	IBU (%)	GM (%)	PEG6000 (%)	SA (%)	US2 (%)	DCPD (%)
U1	10.0	2.0	2.0	0.0	86.0	0.0
U2	50.0	10.0	10.0	0.0	30.0	0.0
U3	16.7	15.0	3.3	35.0	30.0	0.0
D1	8.6	1.7	1.7	0.0	0.0	88.0
D2	10.0	2.0	2.0	0.0	0.0	86.0
D3	12.3	2.5	2.5	0.0	0.0	82.7

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362 **Table 4. Yields and available yield of granules prepared by melt adsorption and melt**  
 363 **granulation**

Formulation	Yield (%)		Available yield (%)	
	Average	S.D.	Average	S.D.
U1	95.2	1.2	94.8	1.2
U2	90.3*	2.0	72.8*	1.4
U3	93.9	5.2	84.4*	5.2
D1	95.0	2.8	92.3	0.9
D2	84.1 <sup>#</sup>	1.6	68.6 <sup>#</sup>	1.5
D3	- <sup>a</sup>	- <sup>a</sup>	- <sup>a</sup>	- <sup>a</sup>

364 <sup>a</sup>,"-" indicated that the granulation could not be completed.

365 \*  $p < 0.05$  as compared with U1. <sup>#</sup>  $p < 0.05$  as compared with D1.

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375 **Table 5. Particle size of US2 and granules prepared by melt adsorption and melt granulation**

Formulation	d10 (µm)		d50 (µm)		d90 (µm)	
	Average	S.D.	Average	S.D.	Average	S.D.
US2	27.9	8.9	95.2	6.0	172.5	41.5
U1	32.0	14.2	91.0	8.6	180.0	16.0
U2	60.1*	6.6	118.6	22.4	226.6	80.8
U3	57.8*	4.4	119.4*	2.8	217.3*	24.0
D1	33.6	3.1	59.9	6.4	90.6	16.8
D2	49.5 <sup>#</sup>	9.7	98.5 <sup>#</sup>	24.1	186.5 <sup>#</sup>	59.7
D3	_a	_a	_a	_a	_a	_a

376 <sup>a</sup>,"\_" indicated that the granulation could not be completed.

377 \*  $p < 0.05$  as compared with U1. <sup>#</sup>  $p < 0.05$  as compared with D1.

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387 **Table 6. Physical properties of granules prepared by melt adsorption and melt granulation**

		U1	U2	U3	D1	D2
Angle of repose (°)	Average	27.0*	33.7	37.0	43.3	36.0 <sup>#</sup>
	S.D.	1.7	1.2	3.6	2.1	2.0
Roundness	Average	0.876*	0.864*	0.785	0.591	0.758 <sup>#</sup>
	S.D.	0.079	0.057	0.098	0.172	0.068

388 \*  $p < 0.05$  as compared with D2. <sup>#</sup>  $p < 0.05$  as compared with D1.

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390 **FIGURE CAPTIONS**

391 **Fig. 1. Representation of MECHANOMiLL apparatus**

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393 **Fig. 2. Differential scanning calorimetric thermograms of IBU, GM, SA, PEG6000 and US2**

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395 **Fig. 3. The melt adsorption process flowchart**

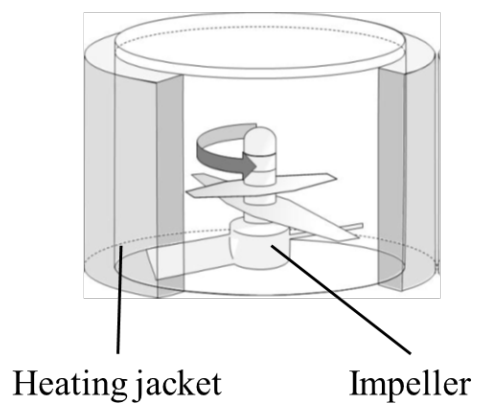
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397 **Fig. 4. X-ray diffraction patterns of (A) raw materials and (B) granules prepared by melt**  
398 **adsorption**

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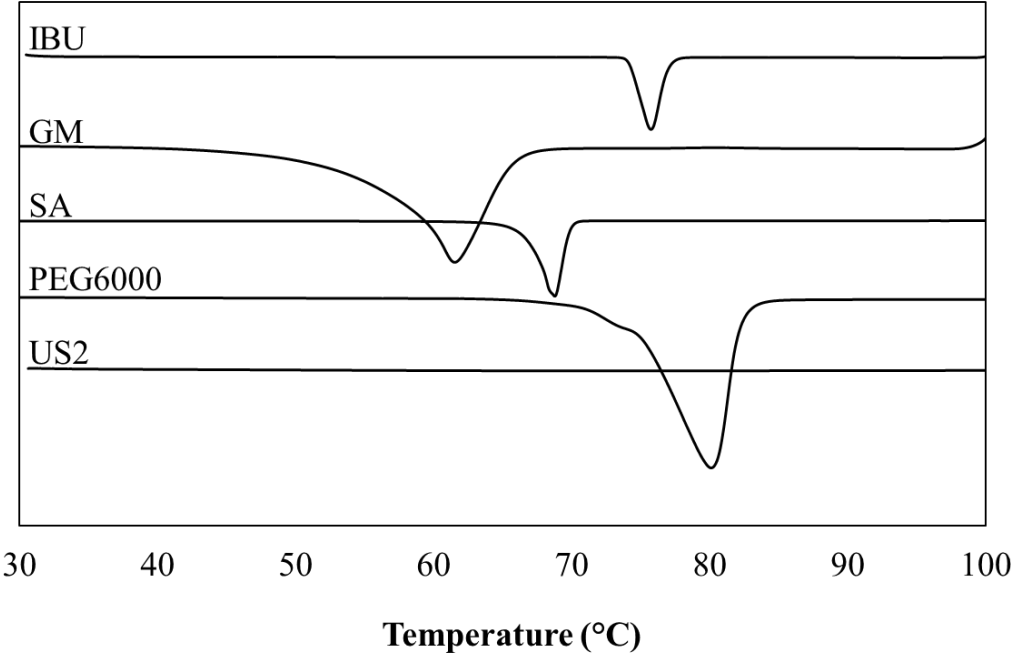
Fig.1.



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Fig.2.



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Fig.3.

Molten	150 rpm
X(g): US2 1 <sup>st</sup> addition	150 rpm
Mixing	150 rpm 1 min
Mixing	Z rpm 1 min
Y(g): US2 2 <sup>st</sup> addition	Z rpm 2 min
Mixing	Z rpm 6 min

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Fig.4.

