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Melt Adsorption as a Manufacturing Method for Fine Particles of Wax Matrices without Any Agglomerates

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We have focused on melt adsorption as manufacture method of wax matrices to control particles size of granules more easily than melt granulation. The purpose of present study was to investigate the possibility of identifying a hydrophobic material with a low melting point, currently used as a meltable binder of melt granulation, to apply as a novel carrier in melt adsorption. Glyceryl monostearate (GM) and stearic acid (SA) were selected as candidate hydrophobic materials with low melting points. Neusilin US2 (US2), with a particle diameter of around 100 μm was selected as a surface adsorbent, while dibasic calcium phosphate dihydrate (DCPD), was used as a non-adsorbent control to prepare melting granules as a standard for comparison. We prepared granules containing ibuprofen (IBU) by melt adsorption or melt granulation and evaluated the particle size, physical properties and crystallinity of granules. Compared with melt granulation using DCPD, melt adsorption can be performed over a wide range of 14 to 70% for the ratio of molten components. Moreover, the particle size; d50 of obtained granules was 100–200 μm, and these physical properties showed good flowability and roundness. The process of melt adsorption did not affect the crystalline form of IBU. Therefore, the present study has demonstrated for the first time that melt adsorption using a hydrophobic material, GM or SA, has the potential capability to control the particle size of granules and offers the possibility of application as a novel controlled release technique.

Key words melt adsorption; melt granulation; manufacturing efficiency; particle size control; Neusilin US2; ibuprofen

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

We have therefore focused on melt adsorption to solve this issue. Melt adsorption is known as a manufacturing method for solid dispersions in which a surface adsorbent is used to adsorb poorly water-soluble drugs and molten surfactants on its surface. Previously, Gupta *et al.* reported that melt adsorption was a useful method for manufacturing solid dispersions of Gelucire 50/13 to enhance drug dissolution.[6] Moreover, they revealed that a surface adsorbent, Neusilin US2 (US2), confers good flowability and compressibility on granules, which can then be compressed into tablets without processing problems.[6] Other work showed that poor solubility of losartan potassium was improved by melt adsorption using Aerosil 300 as a surface adsorbent and Poloxamer 188 as a surfactant.[7] In these studies, surface adsorbents play the important role to adsorb the molten surfactant, thereby speculating that the sizes of granules manufactured by melt adsorption would not be increased and this technique offers the possibility to control size distribution of the granules. However, the hydrophilic characteristics of the above-mentioned surfactant cannot achieve suitable objective product properties for developing taste masking or sustained release formulations and use of hydrophobic materials alternative to surfactant would be desirable.

The purpose of present study was to investigate the possibility of identifying a hydrophobic material with a low melting point, currently used as a meltable binder of melt granulation, to apply as a novel carrier in melt adsorption. Glyceryl monostearate (GM) and stearic acid (SA) were selected as candidate hydrophobic materials with low melting points, and polyethylene glycol (PEG) 6000 was also selected as a viscosity modifier. These materials were used as meltable binders in melt granulation to manufacture a controlled release formulation.[2,4,5,8] Furthermore, we evaluated process parameters

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related to particle size control in an actual manufacturing apparatus, a high shear mixer. Most previous researches on melt adsorption were performed in a small scale apparatus like a beaker, not in an actual manufacturing apparatus.[7,9,10] It is essential to determine the effects of process conditions on the yield and the formulation on the particle size of the preparation, to develop a robust manufacturing method. US2 consists of amorphous microporous granules of magnesium aluminosilicate with a high specific surface area (300 m^2/g) and a particle diameter of around 100 μm. US2 was selected as a surface adsorbent, while dibasic calcium phosphate dihydrate (DCPD), was used as a non-adsorbent control to prepare melting granules as a standard for comparison. We aimed at manufacturing uniform and fine granules (100–200 μm), which are desirable for imparting good handling during processing and a good mouthfeel.[11,12]

Experimental

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

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

Manufacturing Melt adsorption was conducted with a high shear mixer (MECHANOMiLL, Okada Seiko Co., Ltd., Tokyo, Japan) equipped with a heating jacket (rubber heater) and temperature sensor. A representation of the MECHANOMiLL apparatus is shown in Fig. 1. The particle size of DCPD was reduced using a Sample Mill (TI-300, Cosmic Mechanical Technology Co., Ltd., Fukushima, Japan), and the milled DCPD were passed through a 177-μm sieve (Tokyo Screen Co., Ltd., Tokyo, Japan). To manufacture the granules by melt adsorption or melt granulation, IBU, GM, PEG6000 and SA were placed into the apparatus, heated at approximately 85°C by the rubber heater and mixed at an impeller speed of 150 rpm until the mixture components were fully melted. The impeller speed was set to prevent from excessive scattering of the molten component in the chamber and achieve uniform mixing. US2 or DCPD was then added to the molten mixture in the apparatus under continuous mixing by impeller, and the granules were prepared by adsorption or agglomerate formation. Each manufacturing experiments was conducted three times.

Characterization of the Granules

Yield and Available Yield

The total yield of the final product (%, w/w) was calculated by dividing the mass of the product by that of the initial materials, multiplied by 100. The granules obtained with a 500-μm sieve pass were defined as the available fraction in this study. The available yield (%, w/w) was calculated by dividing the mass of the available fraction by that of the starting material, multiplied by 100.

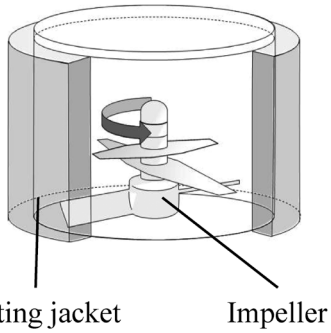

Fig. 1. Representation of MECHANOMiLL Apparatus

Particle Size Distribution

The size distribution of granules with a 500-μm sieve pass was measured using a laser diffractometer with free fall or dry dispersing system (LDSA-1500A, MicrotracBEL Corp., Osaka, Japan) under the following conditions: focal length, 300 mm; measurement time, 2.0 s; dispersive air pressure of dry dispersing system, 1.5 kgf/cm^2.

Physical Properties

The angle of repose and shapes of granules were evaluated as their physical properties. The angle of repose of granules was measured as per a standard procedure.[13] Fifty granules with diameters in the 74–210 μm range were chosen randomly to measure the sphericity of the granules. Images of granules were captured using a microscope (BHS, Olympus Optical Co., Ltd., Tokyo, Japan) connected to a digital imaging camera, and sphericities were analyzed with image analysis software (WinROOF, Mitani Co., Ltd., Fukui, Japan). The sphericities were defined by their roundness (Pt/Pr), where Pt is the theoretical perimeter length of a perfectly spherical granule having the same area as the particle under analysis, and Pr is the actual perimeter length of the particle.

Powder X-Ray Diffraction Analysis The crystalline form of IBU in granules was measured using a powder X-ray diffractometer (Rigaku Rotaflex RU-200B, Rigaku Corp., Tokyo, Japan) under the following conditions: target: Cu; current: 30 mA; scanning speed: 2°/min; and 2θ range: 3–40°.

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

Results and Discussion

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

Optimum Manufacturing Conditions for Attaining High Yield When US2 is added to the molten mixture in one step, the temperature of product will be immediately decreased. This may then cause the risk of adhesion to the apparatus and extreme agglomeration, resulting in a reduction in available yield. Therefore, addition of US2 was divided in two steps, as shown in Fig. 3. We selected each amount of US2 (1st and 2nd

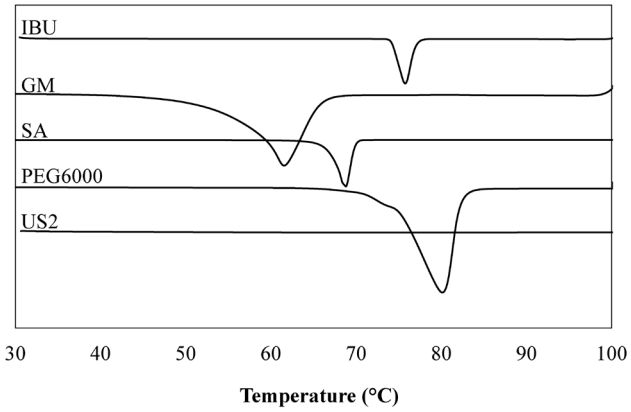

Fig. 2. Differential Scanning Calorimetric Thermograms of IBU, GM, SA, PEG6000 and US2

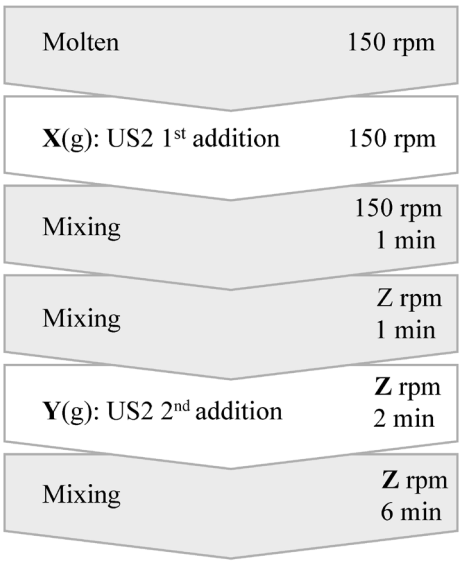

Fig. 3. The Melt Adsorption Process Flowchart

additions) as two of the three process parameters.

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

The results for yield under each condition are shown in Table 2. From Condition Nos. 1, 2 and 3, yield increased with increasing the amount of US2 in the 1st addition step. Adhesion to the chamber was observed after examination of Condition Nos. 1 and 2. This was probably caused by a reduction in the temperature of the molten component through an excessive amount of US2 in the 2nd addition, resulting in congealing of the molten component and enhancing adhesion to the chamber. In contrast, pulverized powder and clusters were found without adhesion under Condition No. 3. In this case, the non-uniform adsorption of the molten component by excess US2 in the 1st addition may have resulted in a wider size distribution of granules. Taking yield and visual observation into consideration, we decided that the optimum ratio between 1st and 2nd addition of US2 is 10 : 30. We then attempted to determine the optimum impeller speed for the yield under Condition Nos. 4, 5 and 6 in Table 1. However, the adhesion tendency was so strong that a high yield could not be obtained under all conditions, as shown in Table 2. In particular, with respect to Condition No. 4, granulation could not be completed because of extreme adhesion to the chamber through insufficient stirring. An increment in pulverized powder and clusters caused a reduction in yield in the case of Condition No. 6. That is to say, a reduction in yield at high impeller speed was presumably caused by an increase in collision frequency between the granules and the chamber, leading to the enhancement of adhesion. Moreover, this uneven distribution of molten components in the chamber at high impeller speed was considered to hinder the adsorption and binding between particles, re-

Table 1. Manufacturing Conditions Used in Melt Adsorption to Investigate the Effect of Process Parameters

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

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[a)]	Pulverized powder[b)]	Cluster[c)]
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	✓	✓	✓

a) "Adhesion to the chamber" was defined as a large amount of adhesion over 1 g. *b*) "Pulverized powder" means the powders scattered after manufacturing process. *c*) "Cluster" was defined as large aggregates with particle size of over 10 mm. *d*) "—" indicated that the granulation could not be completed. *$p<0.05$ as compared with No. 1.

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

Table 4. Yields and Available Yield of Granules Prepared by Melt Adsorption and Melt 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#	1.6	68.6#	1.5
D3	—a)	—a)	—a)	—a)

a) "—" indicated that the granulation could not be completed. *$p<0.05$ as compared with U1. #$p<0.05$ as compared with D1.

sulting in an increase in pulverized powder. From the above considerations, we determined the optimum impeller speed as 300 rpm. Subsequent procedures for melt adsorption were conducted under the optimum Condition No. 5 (1st addition: 10%, 2nd addition: 30%, impeller speed: 300 rpm).

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

The results of yield and available yield for various formulations are shown in Table 4. As the molten component ratio (the total amounts of IBU, GM, PEG6000 and SA) increased, available yield decreased. In particular, the reduction of available yield in D formulations was larger than that in U formulations. The available yield of U3 comprised of 16.7% IBU, 15% GM, 3.3% PEG6000 and 35% SA) was larger than U2 comprised of 50% IBU, 10% GM and 10% PEG6000, even though each molten component ratio was same. A possible reason for this discrepancy might be the difference in viscosity between the molten materials. The viscosities of molten GM, PEG6000 and SA at 80°C were 26, 701 and 6 mPa·s, respectively.[5] The agglomerate growth is supposed to be promoted by a higher viscosity, which is known for theory of Stokes' number.[14] Therefore, as for U3, the viscosity of molten components was reduced due to low amount of PEG and high amount of SA, and granules with a diameter of smaller than 500 μm were obtained, resulting in high available yield.

Table 5 shows the particle size; d10, d50 and d90, of each granule. As the content of IBU increased, the particle size of both D and U formulations increased. The particle size of U1 was almost equivalent to that of intact US2, but that of U2 and U3 were much larger. These results indicate that the molten components in U2 and U3 were completely occupied in the adsorption sites of US2, and accordingly excess molten components on the surface of US2 enhanced the growth of particle. Although increases in particle size of granules were observed in U formulations, d50 of obtained all granules meet the criteria (100–200 μm). In contrast, the size of granules in D formulations was significantly increased by changing the ratio of molten components in the narrow range from 12 to 14%. That is to say, the addition of US2 prevented particle growth by molten components compared with DCPD. From the above results, melt adsorption using US2 was a superior method for controlling particle size and loading significantly more API, with a lower melting point than conventional melt granulation using DCPD.

Effect of Surface Adsorbent on Physical Properties of the Granules The angle of repose and the roundness of the granules are summarized in Table 6. Carr suggested that powders with an angle of repose less than 41° are required to avoid cross-linking during storage in Carr's index.[13] Therefore, we decided that the reference value of the angle of repose for good flowability was less than 41°. The angle of repose of DCPD formulations was decreased from 43.3 to 36.0° by increasing the ratio of molten components from 12 to 14%. This improvement in flowability caused by growth of particle, as can be also seen during conventional granulation. In contrast, the angle of repose of all US2 formulations was less than 41°, which can be explained by the preservation of the characteristics of intact US2, which has good flowability.[6] The roundness of U formulations was thus higher than that of D formulations, indicating a difference in the granule formation mechanism between melt adsorption and melt granulation. In melt adsorption (US2 formulations), US2 is used as a core and this adsorbs molten components so that the shape is maintained. However, in melt granulation (DCPD formulations), the pulverized DCPD is used as an excipient, and this is granulated with the binder of molten components. From the physical property results of U formulation, it is evident that granules with good flowability and roundness can be manufactured over a wide range (14 to 70%) of the ratio of molten components.

Crystalline Form of IBU in the Granules Powder X-ray diffraction analysis was performed to investigate the crystalline form of IBU in granules. Figure 4(A) shows X-ray diffraction patterns of each raw material. Four strong diffraction peaks at 2θ values of 5.8, 16.4, 19.9 and 22.1° were observed in UBU. The characteristic peaks of each crystalline form were observed in other materials, PEG6000, GM and SA, without US2. The 2θ values of GM peaks (19.7, 23.0°) match that of the β form, which is the most stable crystalline form of

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$^{\#}$	9.7	98.5$^{\#}$	24.1	186.5$^{\#}$	59.7
D3	—$^{a)}$	—$^{a)}$	—$^{a)}$	—$^{a)}$	—$^{a)}$	—$^{a)}$

a) "—" indicated that the granulation could not be completed. *$p<0.05$ as compared with U1. $^{\#}p<0.05$ as compared with D1.

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$^{\#}$
	S.D.	1.7	1.2	3.6	2.1	2.0
Roundness	Average	0.876*	0.864*	0.785	0.591	0.758$^{\#}$
	S.D.	0.079	0.057	0.098	0.172	0.068

*$p<0.05$ as compared with D2. $^{\#}p<0.05$ as compared with D1.

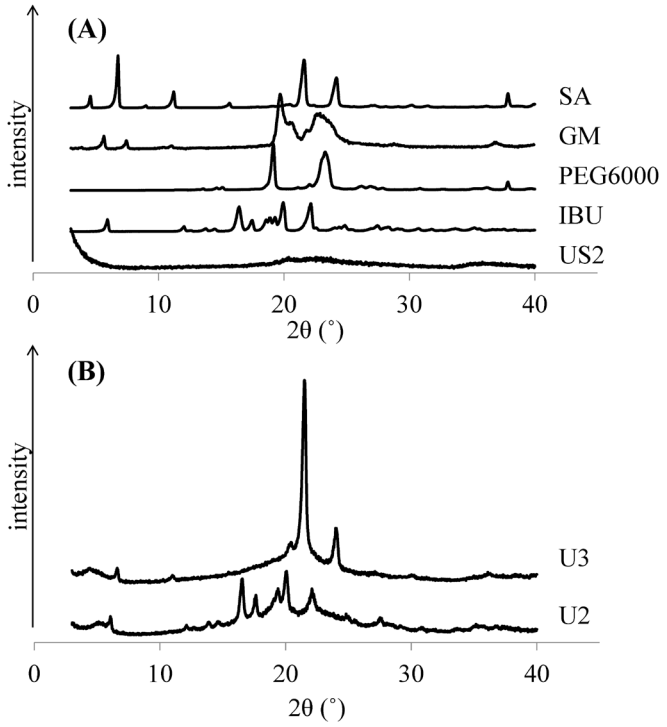

Fig. 4. X-Ray Diffraction Patterns of (A) Raw Materials and (B) Granules Prepared by Melt Adsorption

GM.[15] The absence of peaks in US2 confirmed its amorphous nature. Figure 4(B) shows the X-ray diffraction patterns for U2 and U3. Two strong diffraction peaks at 2θ values of 21.5 and 24.1° were observed in U3 and these diffraction peaks were also identified as SA. The diffraction peaks seen in crystalline IBU of Fig. 4(A) were not observed in U3, because they may be obscured by the strong peaks resulting from the high content of SA. On the other hand, four strong diffraction peaks of crystalline IBU were clearly observed in U2 because this contained high amount of IBU (50%). Therefore, these results indicated that the process of melt adsorption might not affect the crystalline form of IBU.

Conclusion

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

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Conflict of Interest The authors declare no conflict of interest.

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