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RESEARCH PAPER

Influence of Melting and Rheological Properties of Fatty Binders on the Melt Granulation Process in a High-Shear Mixer

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ABSTRACT

The preparation of granules by melt granulation was investigated using a laboratory-scale high-shear mixer (Pellmix PL 1/8) and binary mixtures containing lactose and different lipidic binders, namely, Compritol® 888, Cutina® HR, or Precirol® ATO5. During the process, the product temperature and the impeller motor power consumption were monitored. On the other hand, the melting behavior (thermal analysis) and the rheological properties (controlled stress capillary rheometer) of the different lipophilic binders were also determined. The granule formation was shown to be quite effective at product temperatures even below the melting point of the lipidic binder, that is, when the binder is sufficiently softened to be deformed by the very high shearing forces developed in the high-shear mixer. On the other hand, the performance of lipidic binders during the melt granulation process was shown to be closely dependent on their melting and rheological properties. The granule growth rate was shown to be higher when the binder melting range is narrow and the influence of temperature on the viscosity of the unmelted product is high.

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INTRODUCTION

Melt granulation or thermoplastic granulation is known as a process in which powder agglomeration is obtained through the addition of a binder that melts or softens at a relatively low temperature. When melted, the action of the binder is similar to that occurring in a wet granulation process. As a ''one-step'' operation, melt granulation offers several advantages compared to conventional wet granulation since the liquid addition and the subsequent drying phase are omitted. Moreover, it is also a good alternative to the use of solvents, in terms of cost and safety, when granulating water-sensitive materials.

Numerous hydrophilic or fatty excipients having a melting range between 50°C and 100°C, such as polyethylene glycols (1–5), waxes (6–8), glycerol esters (9–12), fatty acids and alcohols (9,13), and hydrogenated vegetable oils (9,14–17), can be used as binders. By selecting lipophilic binders, melt granulation can be a means of producing sustained-release granules (16), pellets (8), or matrix tablets (7,9,11,14).

During melt granulation in high-shear mixers, the heat required for the granulation step is generated by friction as the powder is intensively moved by the mixer blades and/or by a heating jacket.

During the granulation process, the product temperature and the impeller motor power consumption must be monitored accurately. Indeed, the recording of the power consumption can be used as a means to follow the granule growth during the mixing process, as previously described by Bier, Leuenberger, and Sucker (18) for wet granulation in an instrumented planetary mixer. Moreover, it has been shown to be a suitable method to detect the end point of the granulation process and thus to improve the quality of the final product (14,19,20).

The purpose of the present investigation was to study the influence of three lipophilic binders (Cutina® HR hydrogenated castor oil, Henkel, Germany; Precirol® ATO 5 glyceryl palmitostearate, Gattefosse′, France; and Compritol® 888 glyceryl behenate, Gattefosse′, France) with different melting characteristics on the granule formation during the mixing process in a small-scale high-shear mixer (Pellmix, type PL 1/8, Niro A/S, Denmark). For each binder, both the product temperature and the impeller motor power consumption were monitored during the melt granulation process, and the granule size was evaluated at predetermined intervals. Then, the data obtained were correlated with the melting characteristics (thermal analysis) and the rheological properties (controlled stress capillary rheometer) of the different lipophilic binders to understand better the granule formation mechanism in high-shear mixers.

EXPERIMENTAL

Materials

Lactose 450 mesh (DMV International, Veghel, Netherlands), EP grade, was used as the diluent. Hydrogenated castor oil (Cutina HR), glyceryl palmitostearate (Precirol ATO 5) and glyceryl behenate (Compritol 888) were used as low-melting lipophilic binders. All these fatty excipients occur as fine white to slightly yellow free-flowing powders. Their typical properties, as specified by the suppliers, are summarized in Table 1.

Methods

Melt Granulation

A vertical laboratory-scale high-shear mixer (Pellmix) with a bowl capacity of 8 L was used for the production of batches of about 1 kg (14).

After mixing the binary materials containing lactose and 16% w/w of each meltable binder at 400 rpm for 1 min, the speed of the impeller was adjusted to 1200 rpm. The heat required to increase the product temperature and promote the formation of granules was produced solely

Table 1

Physicochemical Properties of Lipophilic Binders

Lipidic Binder	Acid Value	Iodine Value	Saponification Value	Hydroxyl Value	Melting Range[a] (°C)
Cutina HR	<4.0	<5	±180	±155	80–85
Compritol 888	<4.0	<3	145–165	—	69–74
Precirol ATO 5	<6.0	<3	175–195	60–115	53–57

[a] Drop point.

by friction. During processing, the time, temperature, and impeller motor power consumption were all monitored. Granule samples of approximately 50 g were withdrawn at predetermined intervals to follow the formation of granules during the process. The granules were allowed to cool at room temperature and, granule size (geometric weight mean diameter $\bar{d}_{gw}$) and size distribution (geometric standard deviation s_{gw}) were determined by sieve analysis. The granulation process with each binder and the granule size determinations were performed in triplicate.

Differential Scanning Calorimetry

The melting behavior of the lipophilic binders was estimated by a Perkin-Elmer DSC-7 differential scanning calorimeter (DSC)/TAC-7 thermal analysis controller (Perkin-Elmer Corp., Norwalk, CT). Samples were previously melted in the DSC by heating at a temperature at least 10°C higher than their melting point, and then they were rapidly cooled and solidified, thus avoiding effects due to previous thermal history (freshly solidified samples). Samples of about 5 mg were sealed in a 30-μl aluminum pan and were scanned between 20°C and 100°C at a heating rate of 5°C/min using nitrogen as the effluent gas. To detect the possibility of any polymorphic changes, especially on storage, samples were also stored up to 10 days at 40°C, and the DSC curves were recorded. All experiments were performed in triplicate.

Rheological Measurements

The rheological properties of the lipophilic binders on the solid or the softened material were determined at different temperatures close to their melting points using a Rheograph 2002 (Göttfert, Buchen, Germany) controlled stress capillary rheometer. With this instrument, pressures as high as 2×10^8 N · m^{-2} (±2000 bar) may be used to produce the flow (extrusion) of the lipophilic material at a constant speed through a stainless steel capillary tube (inner diameter 1.0 mm; length 20 mm; piston diameter 12.0 mm).

The force necessary to produce this constant flow rate was recorded at each temperature (45°C to 80°C) versus time and the shear rate, and the shear stresses at the capillary wall were calculated using Rabinowitch's equation [21,22]. Viscosities η_{app} in the range of about 10 to 2×10^5 Pa · s can be measured with the fatty substances. The type of flow can be deduced from the shape of the recorded curve, and a rheogram can be constructed when various constant flow rates of the material are produced through the capillary tube.

RESULTS AND DISCUSSION

The DSC heating curves of the three freshly solidified lipophilic binders are shown in Fig. 1. As can be seen,

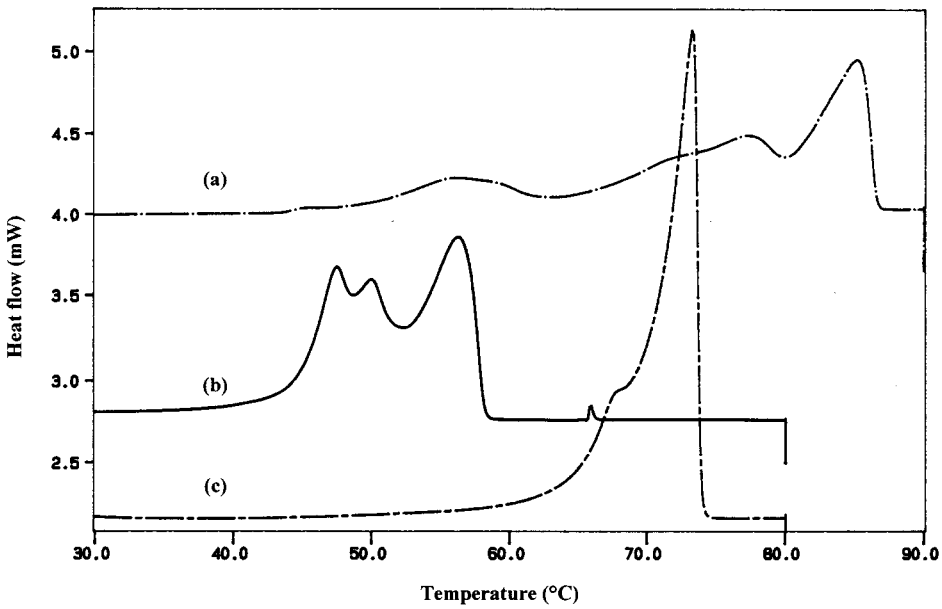

Figure 1. The DSC heating curves obtained from the freshly solidified (a) Cutina HR, (b) Precirol, and (c) Compritol.

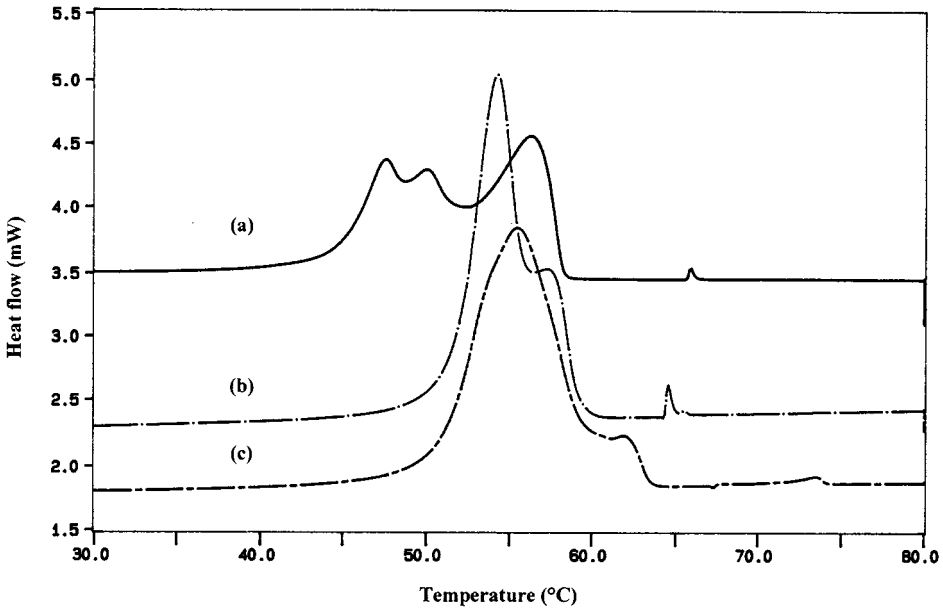

Figure 2. DSC heating curves obtained for Precirol from (a) the freshly solidified sample, (b) the previous sample stored for 10 days at 40°C, and (c) the untreated sample.

Cutina HR and Precirol ATO5 are characterized by quite a complex melting behavior as they melt over a relatively wide range of temperatures, showing at least three endothermic peaks. Indeed, the DSC curves obtained for Cutina HR and Precirol already show an endothermic deviation of the baseline at approximately 45°C, while the melting is only ended at approximately 85°C and 60°C, respectively. In contrast, the DSC curve obtained from Compritol is characterized by a more limited melting range that shows only one important melting endotherm at approximately 72°C. In this case, the endothermic deviation of the baseline occurs at approximately 65°C and corresponds, most probably, to the softening of the lipophilic binder.

The comparison of DSC scans obtained from the untreated sample (initial), the freshly solidified sample, and the previous sample stored for 10 days at 40°C (Fig. 2) permitted finding the presence of at least two different polymorphic forms for Precirol. Indeed, as can be seen in Fig. 2, the two low-melting endotherms (45°C–50°C), corresponding to the less-stable polymorphic forms, can be detected only on the freshly solidified samples. Moreover, as it is usually observed for polymorphic changes, the low-melting endotherms are lost during storage, with an increase in height and sharpness of the higher-melting endotherm. This phenomenon was not observed for Cutina HR, for which the lower-temperature endothermic peaks observed in the DSC melting curve (Fig. 1), probably correspond to a partial melting and/or softening of the lipophilic binder rather than to the presence of any polymorphism. As described below, both the polymorphism and the melting range may influence the rheological properties of the lipophilic binders at temperature values below their melting point and even may influence the granule formation in high-shear mixers.

Until now, the influence of the binder viscosity on the melt granulation process was generally evaluated on the molten material by considering the viscosity of the molten binder at experimental temperatures several degrees above its melting point (4). Nevertheless, the presence of very high shearing forces in high-shear mixers may provoke the deformation and the flow of the low-melting binder at product temperatures still below the melting point when the binder softens and/or melts partially.

For this purpose, the rheological properties of the lipophilic binders were determined on the solid or the softened material at different temperatures close to their melting points using a controlled stress capillary rheometer. All the three lipophilic binders evaluated show pseudoplastic flow as the log-log rheograms obtained are linear ($r \geq .989$) and are characterized by N values less than

Table 2

Apparent Viscosities, Calculated at 40 s^{-1}, for Binders at Temperatures Below Their Melting Points

	Apparent Viscosity, η_{app} (Pa.s)							
Lipidic Binder	45°C	50°C	55°C	60°C	65°C	70°C	75°C	80°C
Cutina HR	—	MB[a]	9236	4238	3595	1139	972	44.8
Compritol	—	—	MB[a]	5537	1677	19.4	melted	—
Precirol	5196	665	melted	—	—	—	—	—
Precirol[b]	4182	318	melted	—	—	—	—	—

[a] Manual breaking off (material not extruded).
[b] Freshly solidified sample.

1 (shear thinning) according to the ''power law'' (23). The apparent viscosity η_{app} results, calculated at a shear rate of 40 s^{-1}, for Cutina HR, Compritol, and Precirol at different temperatures below their melting points are summarized in Table 2. As can be seen, the apparent viscosities of the unmelted lipidic binders can be determined from experimental temperature values of 55°C, 60°C, and 45°C for Cutina HR, Compritol, and Precirol, respectively. Indeed, at lower temperature values, the material was too hard to be extruded through the rheometer capillary. Moreover, the temperature range at which a lipidic material flows (extrusion) appears to be variable and dependent on its melting properties. In accordance with the DSC results, the unmelted Cutina HR flows within a wider temperature range than Compritol and Precirol as it is characterized by the widest melting range. Obviously, the viscosity decreases when the temperature increases, as the material softens, but no linear correlation was observed between the temperature ($1/T$) and the logarithm of the viscosity. Finally, the viscosity of the freshly solidified Precirol is substantially lower than that of the untreated material, resulting most probably from the polymorphism of this lipidic material, as discussed above.

Figures 3 and 4 show, respectively, the evolution of the product temperature and the geometric weight mean diameter d_{gw} during the granulation process with binary mixtures containing Compritol, Cutina HR, and Precirol. The granule size d_{gw}, determined from sieve analysis, grows during the granulation process, from about 50 μm to approximately 300 μm, 400 μm, and 500 μm for Cutina HR, Compritol, and Precirol, respectively. Granules

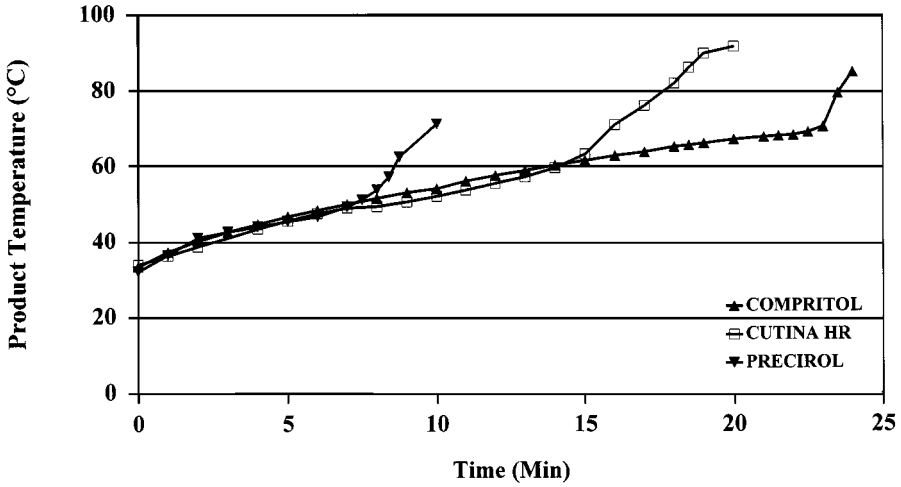

Figure 3. The evolution of the product temperature during the melt granulation process in a high-shear mixer with Compritol, Cutina HR, and Precirol.

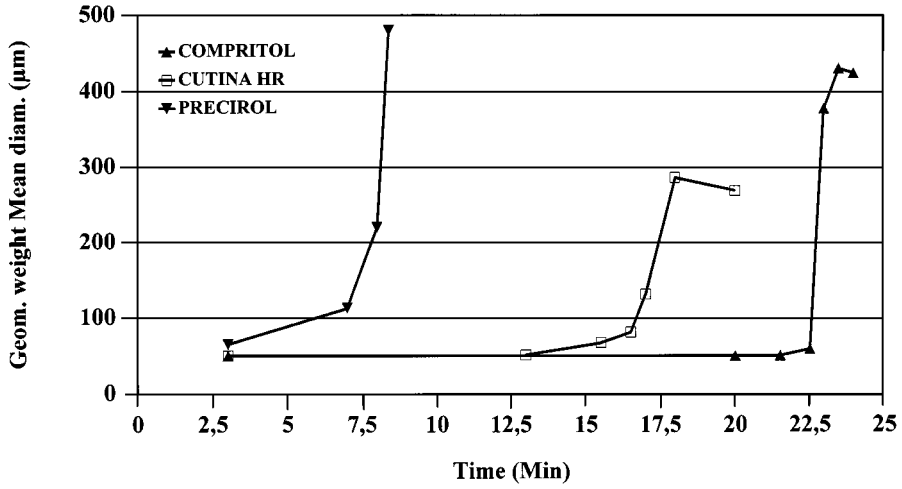

Figure 4. The evolution of the granule size (geometric weight mean diameter $\bar{d}_{gw}$) during the melt granulation process in a high-shear mixer with Compritol, Cutina HR, and Precirol.

show relatively narrow size distributions, and the geometric standard deviations s_{gw} are similar for the three binders and vary from 1 to 3.5 within all sample sets. As can be seen in Fig. 3, the product temperature increases very slowly in a first step, during which the granule formation does not take place yet as there are only few interactions between the particles. After this initial lag time, which lasts about 7, 15, and 23 min for Precirol, Cutina HR, and Compritol, respectively, the product temperature increases rapidly as the granule formation occurs. The granulator was then stopped without further delay to avoid any overwetting phenomenon and the formation of lumps, which are likely to occur when prolonged massing times are adopted. The overall granulation process is relatively rapid and lasts about 8, 18, and 24 min with Precirol, Cutina HR, and Compritol, respectively.

These results seem to be contradictory at first sight, as the granule formation occurs more rapidly with Cutina HR than with Compritol despite the higher value of the main melting peak of the former (see Fig. 1). This can be explained by the differences observed below between the melting and the rheological properties of the lipophilic binders. Indeed, the granule formation may take place only when the product reaches a temperature sufficiently high to soften and thus to promote the binder deformation and flow. Figure 1 and Table 2 indicate that Cutina HR is softened at a lower temperature than Compritol (about 55°C and 65°C, respectively). On the other hand, the granule growth appears also to be dependent on the melting and rheological properties of the binders. Indeed, the granule growth is faster with Compritol and Precirol (lower melting range and strong influence of temperature on viscosity) than with Cutina HR (wider melting range and little influence of temperature on viscosity) since the granule formation step is prolonged from about 1 min for the former binders to about 5 min for the latter (Figs. 3 and 4).

The influence of the melting and rheological properties of the binders on the granulation process in high-shear mixers can be understood better by considering the granule formation, as well as the impeller motor power consumption, in function of the product temperature (see Figs. 5 and 6). Changes of granule size and motor power consumption in the function of the product temperature are quite similar, despite the fact that the granule formation is slightly shifted to higher temperature values. This phenomenon is particularly evident for Cutina HR, as the granule formation is more progressive with this binder than with the other two. Moreover, in accordance with thermal and rheological determinations, the granule formation occurs through a relatively limited temperature range and is effective from approximately 50°C and 70°C with Precirol and Compritol, respectively. Therefore, the use of binding agents like Cutina HR, with a wide melting range (between approximately 60°C and 80°C), rather than those with a more narrow melting range like Compritol, permits better control of the granule size and of the granulation end point during the granulation process.

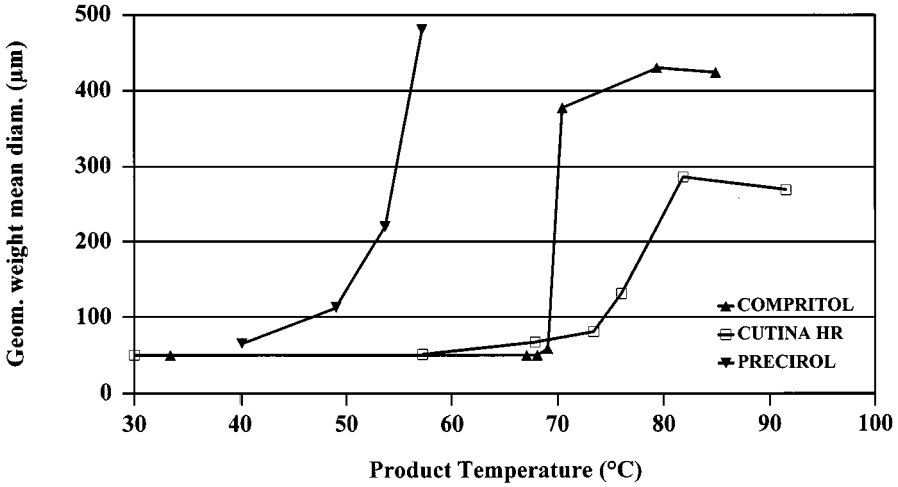

Figure 5. The evolution of the granule size (geometric weight mean diameter $\bar{d}_{gw}$) in function of the product temperature during the melt granulation process in a high-shear mixer with Compritol, Cutina HR, and Precirol.

CONCLUSION

The granule formation in high-shear mixers using low-melting fatty binders is quite effective at product temperatures even below their melting point, that is, when the binder is sufficiently softened to be deformed under the action of very high shearing forces. The performance of such binders during the melt granulation process is closely dependent on their melting and rheological properties. Generally, the granule growth rate is higher when the binder melting range is narrow and the influence of temperature on the viscosity of the unmelted product is high.

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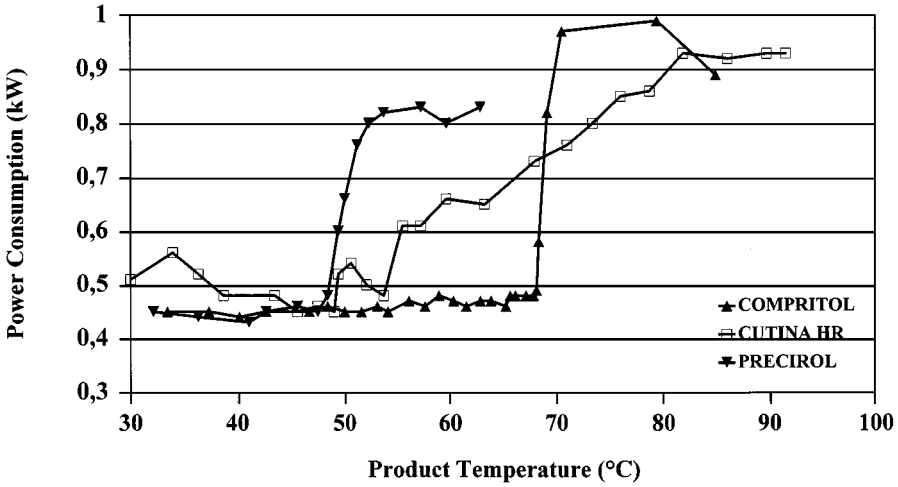

Figure 6. The evolution of the impeller motor power consumption (W) in function of the product temperature during the melt granulation process in a high-shear mixer with Compritol, Cutina HR, and Precirol.

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