International Journal of Pharmaceutics 478 (2015) 530–539

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

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

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ARTICLE INFO

Article history:
Received 30 September 2014
Received in revised form 14 November 2014
Accepted 26 November 2014
Available online 27 November 2014

Keywords:
High-shear melt granulation
Computed tomography
Synchrotron X-ray radiation
Milling process
Internal structure
Triglycerin full behenate

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), 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.

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 of 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 environment 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 et 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 and Chafetz, 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 and Mathiesen, 1996; 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.

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.

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http://dx.doi.org/10.1016/j.ijpharm.2014.11.058
0378-5173/

Table 1
Formulations of granules and operating conditions.

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

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 and Harada, 2004). 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, the physicochemical properties, including particle size distribution, roundness and drug release profile, of granules prepared with either GM or TR-FB were examined. The particle size distribution, roundness, morphology, internal structure, porosity and drug release profile of granules prepared with either intact MCC or MCC milled at different impeller speeds (IS) were then studied.

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).

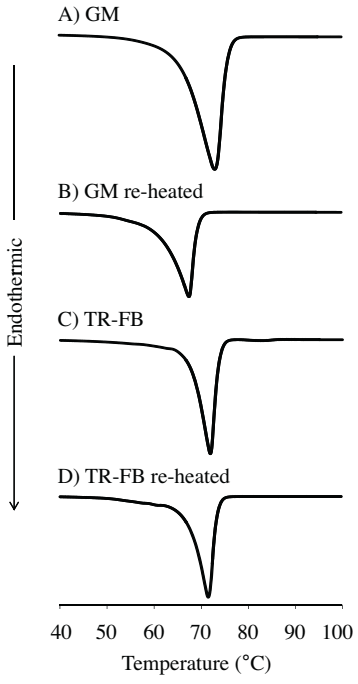

Fig. 1. DSC curves of GM (A and B) and TR-FB (C and D) measured on first (A and C) and second (B and D) heating cycles.