International Journal of Pharmaceutics 463 (2014) 89–97

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Effect of binders on the release rates of direct molded verapamil tablets using twin-screw extruder in melt granulation

David Cheng Thiam Tan, William Wei Lim Chin [1], En Hui Tan, Shiqi Hong, Wei Gu [2], Rajeev Gokhale *

AbbVie Pte Ltd, 11 Biopolis Way, Helios, #05-06, Singapore 138667, Singapore

ARTICLE INFO

Article history:
Received 8 October 2013
Received in revised form 4 December 2013
Accepted 27 December 2013
Available online 7 January 2014

Keywords:
Melt granulation
Hot melt extruder
Direct mold
Modified release
Hydrophobic
Hydrophilic

ABSTRACT

Conventional manufacturing of pharmaceutical tablets often involves single processes such as blending, granulation, milling and direct compression. A process that minimizes and incorporates all these in a single continuous step is desirable. The concept of omitting milling step followed by direct-molding of tablets utilizing a twin-screw extruder in a melt granulation process using thermoplastic binders was explored. The objective of this study was to investigate the effect of combining hydrophilic binder (HPMC K4M, PEO 1M), and hydrophobic binder (Compritol® ATO 888, Precirol® ATO 5) on the release profiles of direct-molded tablets and direct-compressed tablets from milled extrudates using a quality-by-design approach. It was identified that hydrophilic binder type and process significantly affects ($p = 0.005$) the release profiles of verapamil. Moreover, two-way interaction analysis demonstrated that the combination of process with type of hydrophilic polymer ($p = 0.028$) and the type of hydrophilic polymer with polymer ratio ($p = 0.033$) significantly affected the release profiles. The formulation release kinetics correlated to Higuchi release model and the mechanism correlated to a non-Fickian release mechanism. The results of the present study indicated that direct-molded tablets with different release profiles can be manufactured without milling process and through a continuous melt granulation using twin-screw extruder with appropriate thermoplastic binder ratio.

1. Introduction

In recent years, many novel granulation techniques were reported such as spray granulation (Loh et al., 2011), foam granulation (Thompson et al., 2012) and ultrasonic spray congealing (Passerini et al., 2006). One of the more viable granulation processes in the pharmaceutical industry is melt granulation. In melt granulation, a binder with low melting point is added to the powder blend. This powder blend is then mixed at appropriate temperature and the formed granules are allowed to cool to room temperature. Melt granulation is more advantageous than wet granulation as it does not require drying or solvent removal process. Moreover, the granules produced by melt processing contained less fines compared to wet and dry granulation (Dalziel et al., 2013). Melt granulation can also be optimized to produce direct-molded tablets with omission of milling process. Direct molded tablets can be produced using continuous manufacturing process and is advantageous over batch processing as the former saves cost and time. Furthermore, continuous melt granulation using twin-screw extruder has gained greater mileage in pharmaceutical application. A twin-screw extruder is characterized by the screw length-to-diameter ratio and either counter or co-rotating screws mechanism. The twin-screw extrusion process can be further optimized by varying the types and number of conveying elements, kneading blocks and combing elements within the screw configuration.

One of the early applications of twin-screw extruder for continuous granulation followed by milling was for an effervescent formulation (Lindberg et al., 1988). Elimination of the milling step was feasible by modifying the twin-screw configuration to yield reasonably sized granules (Keleb et al., 2002). In addition, optimal granulation temperature is also important in modulating the agglomeration characteristic of drug-polymer in the twin-screw extruder (Van Melkebeke et al., 2006). The application of optimal parameters in the twin-screw extruder melt granulation had successfully developed formulations with a relatively high drug load (>50%). This process was also proven feasible for development of poorly compactible drug substance at a high drug load of 90% (Lakshman et al., 2011). Using the same technology, another study also gained success in developing a robust high-dose

* Corresponding author. Tel.: +65 65915759; fax: +65 64789426.
E-mail addresses: cheng.tan@abbvie.com (D.C.T. Tan), rajeev.gokhale@abbvie.com (R. Gokhale).
[1] Present address: Theodor-Heuss Platz 16, 30175 Hannover, Germany.
[2] Present address: Blk 74A, Redhill Road, #27-38, Singapore 151074, Singapore.

0378-5173/$ – see front matter © 2014 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ijpharm.2013.12.053

Table 1
Design of experiment (DOE).

Independent variables	Level 1	Level 2
Process	Direct molding	Milling
Hydrophobic binder	Compritol® ATO 888	Precirol® ATO 5
Hydrophilic binder	HPMC K4M	PEO 1M
Ratio (hydrophobic:hydrophilic)	30:10	35:5

modified-release formulation with uniform distribution and stable solid state (Krause et al., 2009; Reitz and Kleinebudde, 2007; Vasanthavada et al., 2011)

Melt granulation process requires the utilization of polymers as meltable binders. However, polymers can initiate or propagate chemical or physical interactions with drug compounds which may compromise the melt granulation process and the quality of the drug product. Therefore, the thermoplastic characteristics of polymer such as glass transition and melting temperature are imperative for the processability of the formulation. Polymers for melt granulation are categorized into hydrophilic and hydrophobic binders. Hydrophilic binder controls the drug release by swelling into viscous gel layer when water penetrates the matrix system (Maderuelo et al., 2011). In contrast, hydrophobic binder controls the drug release through pore diffusion and erosion. Hydrophobic binders, such as wax or lipid-based excipients are advantageous due to its low cost, ease of manufacture and chemical inertness (Reitz and Kleinebudde, 2007; Windbergs et al., 2009). In addition, these excipients can provide taste masking applications (Breitkreutz et al., 2003; Suzuki et al., 2004), enhancement of drug bioavailability (Prabhu et al., 2005) and floating dosage forms (Chauhan et al., 2005). Hence, by utilizing different binder types, binder ratio and physico-chemical properties of the drug, the modulation of drug release kinetics can be optimized (Quadir et al., 2003; Reza et al., 2003; Windbergs et al., 2009).

Verapamil hydrochloride is a BCS Class I compound with the water solubility of 82 mg/ml at pH 2.32 and 0.44 mg/ml at pH 7.32 in the crystalline form (Vogelpoel et al., 2004). Verapamil has a short biological half life (4–6 h) and requires more frequent administration. Thus, verapamil serves as a good model compound for modified release evaluation. Literature data have reported several approaches to formulate modified release verapamil (Bhardwaj et al., 1995; Passerini et al., 2003; Sipahigil and Dortunc, 2001; Soppimath et al., 2001; Vaithiyalingam and Khan, 2002). Nevertheless, limited literature data is available in the application of continuous direct-molding process for high drug load, modified release verapamil formulation. Thus, a one-step direct process that develops tablets from the extruder without milling is crucial to attain a broader understanding of modified release formulations.

In this study, we formulated a modified release verapamil using direct-molding melt granulation process with the twin-screw extruder. A design of experiment (DOE) consisted of four-factors and two-levels were conducted to investigate the influence of hydrophilic and hydrophobic binder types in different ratios on the dissolution profiles. We also compared the kinetics and mechanism of drug release of direct-compressed tablets from milled extrudate and direct molded tablets.

2. Materials and methods

2.1. Materials

Verapamil Hydrochloride (crystalline form and melting point of 140 °C), was purchased from Sequoia Research Products (Reading, United Kingdom). Glyceryl behenate (Compritol® ATO 888) and glyceryl palmitostearate (Precirol® ATO 5) were obtained from Gattefosse (Seoul, Korea). Hypromellose K4M (HPMC K4M) and Polyethylene oxide 1 M (PEO 1M) were obtained from Colorcon (Shanghai, China) as samples. Colloidal Silicon dioxide was supplied by Cabot Corporation (MA, United States).

2.2. Design of experiments

A 2^4 full factorial design (Table 1) was employed to study the effect of process, hydrophilic binder type, hydrophobic binder type and hydrophobic:hydrophilic ratios on the material properties, solid state characteristics, assay, impurities and release profiles of verapamil. Statistical analysis of data obtained was conducted utilizing Minitab 15.1.0.0 (Minitab Inc., United States). The data analysis allowed us to separate main effects and interactions among the factors at $p < 0.05$.

2.3. Hot melt granulation

The co-rotating twin screw extruder (Leistritz, Nano 16, NJ, United States) with volumetric feeder (Schenck Accurate, WI, United States) was used to process direct molded verapamil tablets and milled extrudates for direct compression. The process flow chart is as depicted in Fig. 1. Prior to granulation, 60% verapamil and

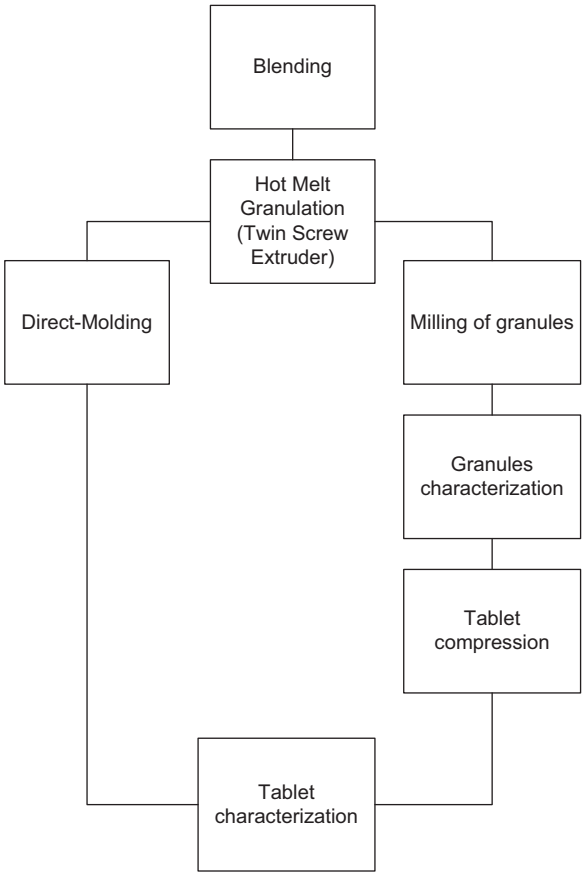

Fig. 1. Process flow chart for hot melt granulation using twin-screw extruder. Information in bracket depicts the type of equipment used for each unit of operation.