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Integrated hot-melt extrusion – injection molding continuous tablet manufacturing platform: Effects of critical process parameters and formulation attributes on product robustness and dimensional stability

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ABSTRACT

This study provides a framework for robust tablet development using an integrated hot-melt extrusion-injection molding (IM) continuous manufacturing platform. Griseofulvin, maltodextrin, xylitol and lactose were employed as drug, carrier, plasticizer and reinforcing agent respectively. A pre-blended drug-excipient mixture was fed from a loss-in-weight feeder to a twin-screw extruder. The extrudate was subsequently injected directly into the integrated IM unit and molded into tablets. Tablets were stored in different storage conditions up to 20 weeks to monitor physical stability and were evaluated by polarized light microscopy, DSC, SEM, XRD and dissolution analysis. Optimized injection pressure provided robust tablet formulations. Tablets manufactured at low and high injection pressures exhibited the flaws of sink marks and flashing respectively. Higher solidification temperature during IM process reduced the thermal induced residual stress and prevented chipping and cracking issues. Polarized light microscopy revealed a homogeneous dispersion of crystalline griseofulvin in an amorphous matrix. DSC underpinned the effect of high tablet residual moisture on maltodextrin-xylitol phase separation that resulted in dimensional instability. Tablets with low residual moisture demonstrated long term dimensional stability. This study serves as a model for IM tablet formulations for mechanistic understanding of critical process parameters and formulation attributes required for optimal product performance.

1. Introduction

The pharmaceutical community has realized the need for new manufacturing technologies and is advancing towards the next phase of modernization by shifting from batch to continuous manufacturing (Desai et al., 2015; Rantanen and Khinast, 2015). Minimization of scale up requirements, reduced space, energy and carbon foot-print, reduced processing time, minimized manufacturing cost and an increase in process efficiency, and product quality are well reported benefits of this paradigm (Sacher and Khinast, 2016; Van Snick et al., 2017). Regulatory agencies, such as United States Food and Drug Administration (US-FDA) and European Medicines Agency (EMA), have also echoed this initiative firmly (Meng et al., 2016). Pharmaceutical industries, regulatory agencies, academicians and researchers have reached the consensus that the continuous manufacturing can often have a significant edge over batch manufacturing (Badman and Trout, 2015; Baxendale et al., 2015; Byrn et al., 2015). Traditional batch methods of drug product conversion often involve multiple costly and time consuming powder handling steps such as milling, wet or dry granulation, drying, sieving, and tableting to produce a uniform product (Byrn et al., 2015). Continuous drug product manufacturing decreases process and handling steps via innovative integration of excipients and APIs. Toward this goal, the Novartis-MIT Center for Continuous Manufacturing has developed an integrated hot-melt extrusion (HME) and injection molding (IM) process (Mascia et al., 2013).

HME is a continuous melt processing technology that is widely used in the plastic industry and involves the mixing of polymers, carriers and other constituents with the application of heat and shear (Eggenreich et al., 2016). It is now a well understood solvent-free technique utilized in the pharmaceutical industry to produce homogeneous mixtures of APIs and excipients under elevated temperatures and shear (Patil et al., 2016; Verstraete et al., 2016b). HME Process parameters (particularly

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barrel temperature, screw design, screw speed and feed rate) in addition to the native formulation attributes influence API melting and dispersion in a polymer matrix (Van Renterghem et al., 2017; Zhang et al., 2017). HME processing can often increase the solubility and bioavailability of poorly soluble APIs such as by transforming the API to an amorphous state (Ashour et al., 2016). However, it is understood that the amorphous form is often thermodynamically unstable which can spontaneously transform to a more stable crystalline form upon storage or *in vivo* after ingestion. Crystalline solid dispersion, on the other hand, would be more stable and a well dispersed crystalline API in water soluble or hydrophilic polymer matrix (in other words, microfine crystalline dispersions) could still improve the dissolution of API.

IM is a rapid, melt processing-based and versatile technology to manufacture products of diverse and intricate three dimensional shapes with high precision. The quality of an IM product relies on different factors such as part design, mold design, material attributes and process parameters (Moayyedian et al., 2017). Process parameters such as injection pressure, hold pressure, mold surface temperature, and cooling time are critical in achieving a robust IM product (Huang and Lin, 2017). This complicated multi-physical process imparts thermal and mechanical history including molding defects, like dimensional deviations, flashing, short shot, etc. (Wang et al., 2017). Although IM has been extensively used in the plastic industry, it has recently gained traction in pharmaceutical production (Alhijjaj et al., 2015; Bouman et al., 2015; Claeys et al., 2015; Eggenreich et al., 2016; Melocchi et al., 2015; Quinten et al., 2012, 2009a, 2011; Verstraete et al., 2016a,b). In previous work at the Novartis-MIT Center of Continuous Manufacturing, Mascia et al. (2013) reported an integrated multistep process for the API synthesis, purification, and tablet production. Later, the feasibility of an integrated HME-IM continuous manufacturing platform and the manufacture of a suitable immediate release tablet formulation was demonstrated (Puri et al., 2017). However, the HME-IM platform is relatively new and critical process parameters (CPPs) and formulation attributes affecting IM products have not been thoroughly explored. A systematic investigation of these process parameters and formulation attributes could prevent common tableting defects associated with IM tableting. Tablets manufactured from the optimized formulation (Puri et al., 2017) also experienced dimensional instability and as per our best knowledge, the root causes behind this issue have not been studied. These deviations could be detrimental to subsequent downstream pharmaceutical processing steps such as coating, where coating defects could appear due to the core tablet expansion (Cahyadi et al., 2012; Ruotsalainen et al., 2002). Considering the HME process perspective for pharmaceutical applications, the physical instability and phase separation of solid dispersions have always been an associated concern and it would be imperative to study how this plausible phase separation phenomenon affects injection molded tablets. Furthermore, studies of storage conditions and subsequent tablet stability (manufactured by the integrated HME-IM platform) have been scarce. Additionally, HME and IM operations were accomplished separately in most reported cases (Melocchi et al., 2015; Quinten et al., 2009b; Verstraete et al., 2016a). To achieve a successful integrated HME-IM continuous manufacturing platform, these shortfalls must be addressed.

In this examination, an integrated HME-IM platform was used to continuously manufacture tablets. Griseofulvin, maltodextrin, xylitol and lactose were employed as model drug, polymer matrix, plasticizer and reinforcing agent, respectively. CPPs and key performance metrics of this recently introduced platform were identified and rigorously evaluated to achieve robust tablet manufacturing with acceptable product properties and performance. Herein, dimensional changes of the injection molded tablets were thoroughly analyzed and root causes responsible for these changes were underpinned in detail. This study employed a wide combination of microscopic, thermal and spectroscopic characterization tools to evaluate phase transition and separation phenomena. Lastly, we investigated the effect of environmental conditions on the overall stability of the formulated product.

2. Materials and methods

2.1. Materials

Griseofulvin (USP) was purchased from Jinlan Pharm-Drugs Technology Co. Limited. (Hangzhou, China). Maltodextrin (Glucidex IT 12) and xylitol (Xylisorb® 90) were donated by Roquette America Inc. (Geneva, IL, USA). Anhydrous lactose (SuperTab 24AN) was obtained from DFE Pharma (Paramus, NJ, USA). Potassium acetate and magnesium nitrate hexahydrate were purchased from Sigma-Aldrich, Co. (St. Louis, MO, USA).

2.2. Methods

2.2.1. IM tablet manufacturing by HME-IM processing

Integrated HME-IM was performed with a formulation based on (a physical mixture of) griseofulvin (10% w/w), maltodextrin (54.4% w/w), xylitol (32.6% w/w) and lactose (3% w/w). The components (batch size, 400 g) were screened through an 800 μm sieve and mixed using a shaker mixer (Turbula®T2F, Glen Mills Inc, Clifton, NJ, USA) for 10 min. Then, the mixture was fed through a gravimetric (loss-in-weight) feeder at 80 g/h into an intermeshing co-rotating 16-mm twin screw extruder (Nano 16, Leistritz, Somerville, NJ, USA). The screw speed was set to 90 rpm while the inlet zone temperature was set to 8 °C, to prevent premature melting of the mixture. Zones one, two, three and four of the barrel were heated to 80 °C, 155 °C, 155 °C and 155 °C, respectively. The screw design (Supplementary Fig. A.1) consisted of different segmented conveying elements and kneading blocks (described in the supplementary section) along the length of the screw. This screw configuration provided sufficient mechanical shear to the mixture. The melt temperature, melt pressure and torque values were monitored in real time throughout the run. The outlet of the extruder was coupled to an IM unit (MHS Hot Runner Solutions, Ontario, Canada) via a 0.6 cm cylindrical exit die. The IM unit consists of two main temperature controlled regions: a reservoir and a hot-runner section. The hot-runner zone can be further divided into manifold, injection nozzle, and valve gate area. The molten extrudate mass were directly flushed through this cylindrical exit die into the heated reservoir. The mass would further travel from the reservoir to manifold, injection nozzles and six valve gates and shape into the tablets inside the six mold cavities. The reservoir, manifold and injection nozzle were set at 150 °C, 145 °C and 130–135 °C respectively.

IM is a repeated processing and can be divided into four phases: filling phase, packing phase, holding phase, and cooling phase. In the filling phase, material is injected into the mold cavity at a particular injection pressure. In the packing phase, material will continue to flow into the cavity to fill any voids which form due to material shrinkage resulting from the transformation of a melt to a solid. Next is the holding phase where the injected material, present inside the cavity, will be held at particular pressure and time. Finally, in the cooling phase, the molten material sufficiently solidifies so that the final product can be ejected from the cavity. In this study, injection pressure and mold surface temperature were the critical parameters and therefore were studied in detail. Both parameters were varied at different levels and the resultant IM product was evaluated. After preliminary studies, it was found that the injection time, hold pressure and hold time did not affect IM processing and product quality and were therefore kept constant. The reservoir back pressure and cooling time were adjusted in a particular range, to control the reservoir filling and solidification of the tablets. Table 1 summarizes the process parameters and their values used throughout the study. In a nutshell, a single parameter method was used where only injection pressure or mold surface temperature were varied one parameter at a time, keeping other parameters constant. This provided valuable guidance about high quality product