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Influence of degassing on hot-melt extrusion process

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ABSTRACT

The present study aimed to evaluate the effect of degassing on an extrusion process, with respect to extrudate quality and drug release properties. Processed formulations were extruded with and without a degassing vent port at various locations along the barrel. All the experiments were performed under constant processing temperature, feeding rate, and screw speed. During the extrusion process, torque and pressure were monitored and recorded. The degassing process was beneficial when used over a conveying section after a mixing section. This is attributed to the large surface area available on the conveying elements, which minimizes the internal volume of the processed material, thereby facilitating the escape of entrapped gases. Degassing enhanced the homogeneity, physical appearance, and drug release properties of all the formulations. Furthermore, the degassing process also enhanced the cross-sectional uniformity of the extruded material, which is beneficial for visual monitoring during processing. Degassing considerably reduced the post-extrusion moisture content of Formula D3, which contains the highly hygroscopic polymer Kollidon® 17 PF, suggesting that the greatest influence of this process is on hygroscopic materials. The reduction in post-extrusion moisture content resulting from the inclusion of a degassing vent port, reduced fluctuations in the values of in-line monitoring parameters such as pressure and torque. Employing a degassing unit during hot-melt extrusion processing could help increase process efficacy and product quality.

1. Introduction

Hot-melt extrusion (HME) is a well-investigated technology in both the food and plastic industries and involves a continuous process where molten materials under elevated temperature and pressure are pumped along a rotating screw and out through an orifice (Crowley et al., 2007). Over the last thirty years, HME has emerged as a promising cost-effective technology for the pharmaceutical industry. The advantages of this process are that it has high throughput and relatively few processing steps compared with more conventional pharmaceutical processing technologies, and are both solvent free and potentially continuous (Repka et al., 2007). Currently, HME is widely used in the production of solid dispersions and controlled release formulations (Repka et al., 2008). Various dosage forms, such as pellets, tablets, and mucoadhesive films for transmucosal products, can be easily prepared from hot-melt extrudates (Repka et al., 2008). However, the potential for HME applications in pharmaceutical research and development has not yet been fully realized, mainly owing to the complexity of HME design and the non-Newtonian behavior of the extruded materials (Thomas and Yang, 2009). This makes it somewhat difficult to predict the behavior of materials processed by HME using mathematical modeling (Douroumis, 2012).

HME technology has been adopted primarily from the plastics industry, and therefore monitoring of the process and product quality may require adaptation to the requirements of the pharmaceutical industry. For example, the materials used in the production of plastic or food products are usually less valuable and/or sensitive than pharmaceutical products. In addition, the physicochemical properties of pharmaceutical constituents may not require the same considerations as those processed in other industries (i.e., water solubility, molecular weight, polar surface area, and partition coefficient). As a continuous process, the starting materials and processing parameters have important roles in controlling the quality of the hot-melt extrudates (Crowley et al., 2004; Sarode et al., 2013). Several reports have illustrated the significant impact of processing parameters on the physicochemical properties of the extruded drug (Verreck et al., 2003). In a study presented by Liu et al. (2010), they demonstrated the influence of extrusion temperature, screw speed, and residence time on the dissolution rate (Liu et al., 2010). The dissolution rate was significantly increased with increasing extrusion temperature and screw speed, an observation that can be explained by the enhancement of distributive mixing.

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The processing parameters that are of primary importance to the pharmaceutical industry are temperature, feeding rate, and screw speed; however, additional factors that may also affect both the process and the final product include degassing, torque, and pressure (Kolter et al., 2012). Effective degassing has been shown to have multiple effects on products in the plastic and food industries, including an increase in the free volume, reduction in the residual moisture content, improvements in odor, changes in the visual appearance, alterations in mechanical properties, prevention of bubbling or foaming, and homogeneity of mixing (Kohlgrüber, 2012). Kohlgrüber in 2012 demonstrated that proper degassing could easily be attained by changing the number, location, and geometry of the degassing vent port openings. Although the pharmaceutical literature strongly suggests that there is a definite need to investigate the influences of screw torque and degassing (Rauwendaal, 1998), pertinent studies relating to the impact of the degassing process on pharmaceutical applications are limited. Degassing is generally regarded in the pharmaceutical industry as merely an additional step in the manufacturing process (Douroumis, 2012). In the production of plastics and food, degassing has been intensely investigated and several studies have shown it to have a considerable influence on the properties of the final product (Kohlgrüber, 2008). Multiple protocols have been developed to enhance the degassing process, including the use of a vacuum equipment, addition of a stripping agent, and designing of screws specifically for degassing (Kühnle, 1986).

Degassing or venting is the process of removing gas and other volatile substance from extruded materials (Kohlgrüber, 2008) and should be considered one of the most important steps for any extrusion processes. Generally, gases may arise from the air trapped during the feeding process, or from the processed materials (Repka et al., 2013). Materials extruded with either polymers or active pharmaceutical ingredients (API) can have air trapped in the pores or adherent to their surfaces (Douroumis, 2012). The entrapped molecules may affect other processing parameters as well as the quality of the product. Under conditions of elevated temperature and pressure, melted materials are compressed and consequently, degassing is necessary to remove any residual moisture, air, polymer monomers, oligomers, solvents, reaction products, and decomposed materials, which could interfere if released during the extrusion process.

The main objective of this study was to determine the influence of extrusion degassing on the properties of the extrudate such as dissolution rate, physical stability, and chemical stability as well as to monitor other parameters while evaluating the visible effects on the product. In this study, the effect of a vent port open to the atmosphere, with a large opening to release gas while retaining molten materials was evaluated.

2. Materials and Methods

2.1. Materials

Carbamazepine was purchased from Afine Chemicals Limited, Zhejiang, China. Polyvinylpyrrolidone (Kollidon® 17 PF) was received as a gift sample from BASF Chemical Co. (Ludwigshafen, Germany). Hydroxypropylcellulose (Klucel™ ELF) was received as a gift sample from Ashland Inc. (Wilmington, DW 19808, USA). All other chemicals used were of analytical grade and obtained from Thermo Fisher Scientific (Fair Lawn, NJ 07410, USA).

2.2. Methods

2.2.1. Thermal Characterization Studies

2.2.1.1. Thermogravimetric Analysis. A Perkin Elmer Pyris 1 thermogravimetric analyzer (TGA) equipped with Pyris manager software (PerkinElmer Life and Analytical Sciences, 719 Bridgeport Ave., Connecticut, USA) was used for thermogravimetric analyses of the samples. Each sample was weighed and heated from 20–220 °C at a heating rate of 10 °C/min under an inert nitrogen atmosphere and monitored for the percent weight loss with temperature increase.

2.2.1.2. Differential Scanning Calorimetry. A Perkin Elmer Diamond Differential Scanning Calorimeter (DSC) (Perkin Elmer Life and Analytical Sciences, 710 Bridgeport Ave., Connecticut, USA) equipped with Pyris manager software (Shelton, CT, USA) was used to perform polymer–drug miscibility studies. Each test formulation in this study was weighed (approximately 2–5 mg) and was hermetically sealed in an aluminum pan. The samples were then heated from 20 °C to 220 °C at a linear heating rate of 10 °C/min under an inert nitrogen atmosphere. The extrudates were also evaluated in a similar manner to assess the morphology of the API.

2.2.1.3. Moisture Content. Moisture content was examined by measuring loss on drying (LOD) using a halogen moisture analyzer balance (MB45 moisture analyzer, Ohaus, USA). Each formulation was analyzed before and after extrusion. The percentage of moisture was estimated by drying 5 to 8 g of each mixture at 105 °C for 15 min.

2.2.2. Non-thermal Characterization Studies

2.2.2.1. Chromatography System and Conditions. The drug content was determined on a Waters high-performance liquid chromatography (HPLC) system consisting of a Water 600 binary pump, Waters 2489 UV/ detector, and Waters 717 Plus autosampler (Waters Technologies Corporation, 34 Maple St., Milford, MA 0157). Empower 2 software was used to analyze the data. A Phenomenex Luna® C18 reverse phase column (5 μm 100 Å, 250 × 4.6 mm) was used as the stationary phase. The mobile phase was water, methanol, and acetic acid (34:65:1% v/v/v), and the UV detector was set at a wavelength of 285 nm. The flow rate was maintained at 1.0 mL/min, and 20 μL of each sample was injected. The uniformity of the drug content was assessed by dissolving a weighed quantity of the carbamazepine extrudate in methanol with subsequent analysis by the HPLC procedure outlined above. All studies were performed in triplicate. Samples from the dissolution studies (Section 2.2.2.3) were filtered and 20 μL was injected for analysis by the same protocol.

2.2.2.2. Fourier Transform Infrared Spectroscopy (FTIR) and Chemical Imaging. Mid-infrared spectra from 4000–650 cm^{-1} were collected on an FTIR (Agilent Technologies, Cary 660 & 620 IR) apparatus equipped with a sampling accessory (MIRacle ATR, Pike Technologies), fitted with a single bounce diamond coated ZnSe internal reflection element. Chemical images were collected using an infrared microscope, which was equipped with a Ge micro ATR. The spectra were analyzed using Agilent's software suite (Resolutions Pro Version 5.2.0).

2.2.2.3. In-vitro Dissolution Study. Extruded samples were accurately weighed (100 mg carbamazepine) and put into hydroxypropyl methylcellulose (HPMC) capsules. In vitro release studies (n = 3) were carried out at 37 ± 0.5 °C using a Hanson SR8-Plus™ dissolution test station (Chatsworth, CA) operated at 100 rpm paddle speed with 900 mL of distilled water as the dissolution medium (Alshahrani et al., 2015). Samples were collected at 10-, 20-, 30-, 45-, 60-, 90-, and 120-min intervals and were then filtered and analyzed using the HPLC method described in Section 2.2.2.1.

2.2.2.4. Stability Study. Extruded samples were stored in a stability chamber at 40 °C and 75% relative humidity (RH) for three months. Stability studies were then performed to test the crystalline content (using DSC), chemical stability (HPLC), and in vitro release parameters. The drug release profiles were compared using a mathematical