Journal of Drug Delivery Science and Technology 29 (2015) 189–198

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

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

Research paper

Influence of molecular weight of carriers and processing parameters on the extrudability, drug release, and stability of fenofibrate formulations processed by hot-melt extrusion

Bader B. Alsulays [a], Jun-Bom Park [b], Sultan M. Alshehri [a], Joseph T. Morott [a], Saad M. Alshahrani [a], Roshan V. Tiwari [a], Abdullah S. Alshetaili [a], Soumyajit Majumdar [a], Nigel Langley [c], Karl Kolter [d], Andreas Gryczke [e], Michael A. Repka [a, f, *]

[a] Department of Pharmaceutics and Drug Delivery, School of Pharmacy, The University of Mississippi, University, MS, 38677, USA
[b] College of Pharmacy, Sahm Yook University, Seoul, 139-742, Republic of Korea
[c] BASF Corporation, 500 White Plains Road, Tarrytown, NY, 10591, USA
[d] BASF SE, R&D Project, Management Excipients, Ludwigshafen, 67056, Germany
[e] BASF SE, Global Development and Technical Marketing, Ludwigshafen, 67056, Germany
[f] Pii Center for Pharmaceutical Technology, School of Pharmacy, The University of Mississippi, University, MS, 38677, USA

ARTICLE INFO

Article history:
Received 14 May 2015
Received in revised form
17 July 2015
Accepted 17 July 2015
Available online 18 July 2015

Keywords:
Fenofibrate
PVP grades
Processing parameters
Hot-melt extrusion
Stability

ABSTRACT

The objective of this study was to investigate the extrudability, drug release, and stability of fenofibrate (FF) formulations utilizing various hot-melt extrusion processing parameters and polyvinylpyrrolidone (PVP) polymers of various molecular weights. The different PVP grades selected for this study were Kollidon® 12 PF (K12), Kollidon® 30 (K30), and Kollidon® 90 F (K90). FF was extruded with these polymers at three drug loadings (15%, 25%, and 35% w/w). Additionally, for FF combined with each of the successfully extruded PVP grades (K12 and K30), the effects of two levels of processing parameters for screw design, screw speed, and barrel temperature were assessed. It was found that the FF with (K90) was not extrudable up to 35% drug loading. With low drug loading, the polymer viscosity significantly influenced the release of FF. The crystallinity remaining was vital in the highest drug-loaded formulation dissolution profile, and the glass transition temperature of the polymer significantly affected its stability. Modifying the screw configuration resulted in more than 95% post-extrusion drug content of the FF–K30 formulations. In contrast to FF–K30 formulations, FF release and stability with K12 were significantly influenced by the extrusion temperature and screw speed.

1. Introduction

Hot-melt extrusion (HME) is a continuous, solvent free, and cost-effective method, which makes it a viable processing technology for use in the pharmaceutical industry [1]. One of the most common applications of HME processing is enhancing the solubility of poorly water soluble active pharmaceutical ingredients (APIs) via the preparation of amorphous solid dispersions in numerous polymeric carriers [2–4]. Crystalline APIs are commonly changed to the amorphous phase by the high shear conditions and temperature typically employed in the extrusion process. This generally results in increased solubility of poorly water soluble APIs, particularly in the case of biopharmaceutics classification system (BCS) class II compounds, and subsequently improves their bioavailability [1,2]. However, the high energy input from the applied shear forces and elevated temperature could lead to drug instability [5,6]. Therefore, researchers have investigated these stability issues by using carefully selected carriers and processing parameters [7,8].

The primary processing parameters for HME are barrel temperature, screw speed, feeding rate, and screw design [1]. The extrusion temperature influences the melt viscosity of the material and the extrusion process. Screw speed is also one of the factors that affects the dispersion and the residence time of the material within the barrel [9]. The screws themselves can be configured into

* Corresponding author. Department of Pharmaceutics and Drug Delivery Director, Pii Center for Pharmaceutical Technology School of Pharmacy, The University of Mississippi, University, MS, 38677, USA.
E-mail address: marepka@olemiss.edu (M.A. Repka).

http://dx.doi.org/10.1016/j.jddst.2015.07.011
1773-2247/

various designs by changing the number, orientation, and order of the kneading and conveying elements, as well as altering the overall screw length. These processing parameters play a vital role in the extrusion process and should be chosen based on the physiochemical properties of the API and the carrier, as well as the desired outcome [2].

In this study, various grades of polyvinylpyrrolidone (PVP), commonly referred as povidone, were used as the polymeric carriers. PVP is water soluble and is primarily used for immediate release formulations [9]. Additionally, PVP has been observed to function as a recrystallization inhibitor [10,11]. The various grades of PVP are typically characterized by their molecular weight and glass transition temperatures (T_g). For example, Kollidon® 12 PF (K 12), Kollidon® 30 (K 30), and Kollidon® 90 F (K 90) possess average molecular weights of approximately 2500, 50,000, and 1,250,000 g/mol, and T_gs of 90 °C, 149 °C, and 156 °C, respectively [9]. These grades of PVP can be utilized to study the effect of polymer molecular weight on the extrudability, *in vitro* drug release, and stability of an API when processed by HME.

Fenofibrate (FF) is used as an antilipidemic agent for decreasing cholesterol and triglyceride levels in the blood. It is a BCS class II drug, which indicates poor solubility and high permeability. It can be considered as a melt-extrudable API [10,12] with a melting point of 80.5 °C and a low T_g of −20 °C [13,14]. FF can be easily processed by melt extrusion; however, it subsequently exhibits rapid recrystallization behaviors due to its low T_g [10]. Therefore, FF is a good candidate for the investigation of the effects of the molecular weight of the carrier, extrusion processing parameters, and drug loading.

The objective of this study was to investigate the effects of different molecular weights of polymeric carriers and processing parameters on the extrudability, *in vitro* drug release, and stability of FF utilizing HME technology. K12, K30, and K90 were used as the polymeric carriers with three different drug loadings of 15%, 25%, and 35% (w/w) to study the effect of the molecular weight of the carrier. Additionally, design of experiments was utilized to assess the effects of the processing parameters on the extrudability, *in vitro* drug release, and stability of the FF–PVP matrices based on the molecular weight of PVP used.

2. Materials and methods

2.1. Materials

The various grades of PVP (K12, K30, and K90) were generously donated by BASF SE (Ludwigshafen, Germany). FF was obtained from Ria International (East Hanover, NJ, USA). All other reagents used in this study were of analytical grade.

2.2. Methods

2.2.1. Thermogravimetric analysis

A Perkin Elmer Pyris 1 TGA (PerkinElmer Life and Analytical Sciences, CT, USA) was used to conduct the thermogravimetric analysis (TGA). The drug and polymer samples (3–4 mg) were heated over a temperature range of 30–200 °C at a heating rate of 20 °C/min. The data were analyzed using Pyris manager software (PerkinElmer Life and Analytical Sciences, CT, USA).

2.2.2. Differential scanning calorimetry

A Perkin Elmer Diamond DSC (PerkinElmer Life and Analytical Sciences, CT, USA) was utilized to study the formation of solid dispersions as well as to calculate the percent crystallinity. The drug and polymer samples (3–5 mg) were hermetically sealed in an aluminum pan and analyzed at a heating rate of 10 °C/min under an inert nitrogen atmosphere at a flow rate of 20 ml/min over a temperature range of 30–200 °C. The data was analyzed using Pyris manager software.

The percentage crystallinity was calculated using the following formula [10]:

$$\text{Crystallinity } \% = \left[\Delta H_{\text{extrudate}} \Big/ \left(\Delta H_{\text{fenofibrate}} \times \text{w}\%\right)\right] \times 100$$

where w% is concentration of the drug in the extrudates (%w/w), and $\Delta H_{\text{fenofibrate}}$ is 90 J/g.

2.2.3. HPLC analysis

The dissolution study and the drug content samples were analyzed using a Waters HPLC-UV system (Waters Corp., Milford, MA, USA) with a Phenomenex Luna®RP C18 (250 × 4.6 mm, 5 μm) column and a detection wavelength of 286 nm. The mobile phase was acetonitrile:water:trifluoroacetic acid at a ratio of 700:300:1 (v:v:v) [15]. The flow rate was 1 ml/min and the injection volume was 20 μL. All of the HPLC data were analyzed using Empower V software (Milford, MA, USA).

2.2.4. Hot-melt extrusion

Three different drug loadings (15, 25, and 35% w/w) of FF with three grades of PVP (K 12, K 30, and K 90) were blended in a small V-blender prior to extrusion using a batch size of around 50 gm for each formulation. The blends were melt extruded at the temperatures and screw speeds shown in Table 1. The processing temperatures were selected based on the T_g of each polymer and the plasticizing effect of FF in order to obtain well-solidified extrudates. The screw speed and the feeding rate were adjusted to keep the torque below 70%.

To study the effect of the processing parameters, FF at a drug load of 25% (w/w) was mixed with K12 and K30 individually, and then extruded using a standard and a modified screw design (Fig. 1) utilizing the processing parameters shown in Table 2 (FF–K12) and Table 3 (FF–K30). The drug and individual polymers were sieved through an USP #35 mesh to remove any agglomerates and then mixed using a V-Shell blender (MaxiBlend™, GlobePharma, North Brunswick, NJ, USA) for 10 min at 25 rpm. A co-rotating twin-screw extruder (11 mm Process 11, Thermo Fisher Scientific, Pittsburgh, PA, USA) was used for the extrusion process. The drug content uniformity of the physical mixtures and extrudates was analyzed using HPLC. The drug content analysis was evaluated by dissolving an accurate amount of FF from the extrudates or the physical mixtures in 20 ml of acetonitrile, then 1 ml was transferred to another bottle and diluted with 9 ml of acetonitrile. Samples were taken from the diluted solution and centrifuged followed by the analysis using the HPLC. The drug content analysis was performed using six replicates from different position of the extrudates or the physical mixture.

2.2.5. In vitro dissolution studies

The dissolution studies were conducted using a USP type II dissolution apparatus. An amount equivalent to 54 mg of FF was filled into capsules and the capsules were then placed in the dissolution medium within the apparatus for 2 h. The dissolution studies were performed under sink conditions and the medium was 0.025 M sodium lauryl sulfate (SLS) in 1000 ml of water maintained at 37 ± 0.5 °C and the paddle rotation speed was 75 rpm [16]. At various time points, the samples were withdrawn and an equal amount of fresh medium was added to the ongoing dissolution medium vessel. The % of the drug release was calculated based on the actual post-processing drug content. HPLC was used to analyze the samples and the % of drug release vs. time (min) profile