European Journal of Pharmaceutics and Biopharmaceutics 119 (2017) 56–67

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Research paper

Processing thermally labile drugs by hot-melt extrusion: The lesson with gliclazide ☆

Siyuan Huang [a,b], Kevin P. O'Donnell [c], Sophie M. Delpon de Vaux [a], John O'Brien [d], John Stutzman [d], Robert O. Williams III [a,*]

[a] Division of Pharmaceutics, College of Pharmacy, The University of Texas at Austin, 2409 University Avenue, Mail Stop A1920, Austin, TX, United States
[b] Small Molecule Design and Development, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, United States
[c] The Dow Chemical Company, Dow Food, Pharma & Medical, Midland, MI, United States
[d] The Dow Chemical Company, Analytical Sciences, Midland, MI, United States

ARTICLE INFO

Article history:
Received 15 February 2017
Revised 25 April 2017
Accepted in revised form 29 May 2017
Available online 3 June 2017

Keywords:
Melt extrusion
Process optimization
AFFINISOL HPMC HME
Solid dispersion
Degradation
Arrhenius kinetics
Amorphous

ABSTRACT

The formation of molecularly dispersed amorphous solid dispersions by the hot-melt extrusion technique relies on the thermal and mechanical energy inputs, which can cause chemical degradation of drugs and polymeric carriers. Additionally, drug degradation may be exacerbated as drugs convert from a more stable crystalline form to a higher energy amorphous form. Therefore, it is imperative to study how drug degrades and evaluate methods to minimize drug degradation during the extrusion process. In this work, gliclazide was used as a model thermally labile drug for the degradation kinetics and process optimization studies. Preformulation studies were conducted using thermal analyses, and liquid chromatography–mass spectroscopy to identify drug degradation pathways and to determine initial extrusion conditions. Formulations containing 10% drug and 90% AFFINISOL™ HPMC HME 100LV were then extruded using a twin screw extruder, and the extrudates were characterized using X-ray powder diffraction, modulated dynamic scanning calorimetry, and potency testing to evaluate physicochemical properties. The energies of activation for both amorphous gliclazide, crystalline gliclazide, and gliclazide solution were calculated using the Arrhenius equation to further guide the extrusion optimization process. Preformulation studies identify two hydrolysis degradation pathways of gliclazide at elevated temperatures. The activation energy study indicates a significantly higher degradation rate for the amorphous gliclazide compared to the crystalline form. After optimization of the hot-melt extrusion process, including improved screw designs, machine setup, and processing conditions, gliclazide amorphous solid dispersion with ~95% drug recovery was achieved. The ability to process thermally labile drugs and polymers using hot-melt extrusion will significantly expand the possible applications of this manufacturing process.

1. Introduction

The hot-melt extrusion (HME) technique has gained increasing popularity in the pharmaceutical industry due to its widespread applications as a drug delivery option, including device shaping [1], taste-masking [2], controlled release [3], and solubility enhancement [4]. In particular, the manufacture of amorphous solid dispersions (ASDs) to improve the bioavailability of BCS Class II and Class IV drugs has been widely studied and has been commercially proven as an effective formulation strategy [5]. However, during extrusion the conversion of the drug from the crystalline to amorphous form relies on thermal and mechanical energy inputs from the extruder, and this energy input can degrade the active ingredient or excipients [6]. Therefore, the application of HME with thermally labile materials is challenging. Thermal energy input during the extrusion process is normally supplied by heat conduction from the barrel and the friction of the material against the kneading elements and interior wall of the extruder barrel [7]. Thermally induced chemical degradation has been widely reported to occur during HME process [8–10]. Moreover, mechanical energy input is also supplied by the machine motor, and it is delivered through the interaction of the screw elements and the extruded materials [11]. Part of the mechanical energy can be converted to thermal energy, especially in large-scale extruders. However, when kneading elements are used, the relatively high-shear energy generated can still result in degradation of shear-sensitive materials [12].

☆ This work was presented in part as a poster at the American Association of Pharmaceutical Scientists Annual Meeting, November 2016, Denver, CO.

* Corresponding author.
E-mail address: bill.williams@austin.utexas.edu (R.O. Williams III).

http://dx.doi.org/10.1016/j.ejpb.2017.05.014
0939-6411/

Due to the wide diversity of drugs and excipients, many may be susceptible to different degradation pathways during the extrusion process, including hydrolysis, oxidation, dehydration, isomerization, and photo-degradation [13]. Among the different pathways, oxidation [14] and hydrolysis [15] are considered the most common degradation reactions. Chemical degradation can be triggered by some of the conditions involved in HME, such as elevated temperature [16], excipient incompatibility [17], the presence of oxygen [18], moisture [19], and pH level [20]. Temperature, which is an important processing parameter in HME, is well known to significantly affect chemical degradation kinetics as predicted by the Arrhenius equation [21]. Moreover, because of the high molecular mobility of amorphous materials, amorphous drugs are more prone to chemical degradation compared to their crystalline counter-parts [22,23].

Therefore, it is important to find the optimum balance between providing enough energy for amorphous conversion and generating excess energy that triggers chemical degradation [24]. Formulation approaches such as decreasing the melting point, viscosity, and mixing temperature of the extruded materials [25,26] have been used to achieve less aggressive extrusion conditions. Processing approaches, on the other hand, have also shown some success in minimizing degradation by optimizing barrel temperature, screw speed, machine throughput, and screw geometry [9,27,28]. However, these studies fail to provide a sufficiently detailed explanation of how and where drug degradation took place during the process, or a systematic strategy to solve the degradation problem during HME.

The aim of this study was to investigate the factors that directly contribute to the degradation of gliclazide (GLZ) during the HME process, and to investigate the degradation kinetics of different forms of GLZ. This information was then used to guide the optimization of the extrusion process parameters in order to minimize its chemical degradation, which has not been addressed previously in the thermal processing of GLZ [29]. Additionally, activation energies were used to compare the thermal stability of GLZ in crystalline and amorphous forms, which provided a risk assessment method for the development of ASD formulation by fusion process in pharmaceutical industry. The results learned in this study for GLZ are applicable to other thermally labile drugs.

2. Materials and methods

2.1. Materials

Crystalline GLZ and AFFINISOL™ HPMC HME 100LV were donated by The Dow Chemical Company (Midland, MI). Soluplus® (Soluplus) and Kollidon® VA 64 (PVP VA64) were donated by BASF Corporation (Florham Park, NJ). Indigo carmine was obtained from Acros Organics (Geel, Belgium). HPLC–grade acetonitrile and water were purchased from Fisher Scientific Co. (Houston, TX). All other chemicals used in this study were of American Chemical Society (ACS) grade. All percentages are based on w/w unless otherwise noted.

2.2. Methods

2.2.1. Hot melt extrusion and milling

HME processing was conducted on a co-rotating Leistritz Nano-16 twin-screw extruder (American Leistritz Extruder Corp., Somerville, NJ, USA) with a twin-screw volumetric feeder (Brabender Technology, Duisburg, Germany). Three screw designs were used to provide different levels of shear input. Blends with 10% GLZ loading were processed at temperatures ranging from 100 to 160 °C, feed rate from 2.3 g/min to 4.3 g/min, and with screw speeds set at 100 rpm, 200 rpm, and 300 rpm with or without a die. Extrudates were cooled to room temperature before milling. A Fitzpatrick L1A Fitzmill (Fitzpatrick, Inc., Elmhurst, IN, USA) operating at 9000 rpm in the impact configuration with a 0.033-in. screen was used to mill HME materials. Powders retained between 37 μm (400 US mesh) and 44 μm (325 US mesh) were collected and stored in a desiccator over phosphorus pentoxide for further analysis.

2.2.2. Residence time studies

The residence time of GLZ formulations at different processing conditions was determined after the processing torque was stable. The time at which 0.2 g of indigo carmine was charged into the extruder feed port and into the sampling port was denoted as $t = 0$. The time at which colored extrudate emerged from the die was noted as the residence time. A calibrated timer was utilized to determine the time.

2.2.3. High-Performance Liquid Chromatography (HPLC)

GLZ content was analyzed with a Dionex Ultimate 3000 HPLC system (Thermo Fisher Scientific Inc., Waltham, MA) equipped with a Waters Spherisorb® ODS-2 250 mm (5 μm, 4.6 mm × 250 mm) column. The HPLC system also included an Ultimate 3000 autosampler to consistently inject 20 μL samples, an Ultimate RS variable wavelength detector extracting at a wavelength of 235 nm, and dual Ultimate 3000 pumps. The system was operated under isocratic flow at 1 mL/min using a mobile phase consisting of 60% ammonium acetate buffer (0.025 M, with pH adjusted to 3.1 using acetic acid) and 40% acetonitrile. The mobile phase was filtered through a 0.45-μm filter and degassed under vacuum with sonication before use. The column was kept at 30 °C. Chromeleon Version 6.80 software (Thermo Fisher Scientific Inc., Waltham, MA) was used to process all chromatography data.

Finely ground powder samples were accurately weighed to 20.0 ± 1.0 mg and transferred directly into a 20-mL scintillation vial. Measured powder samples were dissolved using 20 mL 1:1 acetonitrile:water diluent solution. Samples were then filtered using 13-mm 0.2-μm PTFE filters (Wheaton, Millville, NJ) and transferred into HPLC vials for analysis (Phenomenex, Torrance, CA) for analysis.

2.2.4. X-ray Powder Diffraction (XRD)

XRD studies were performed with a Rigaku Miniflex 600 (Rigaku, Tokyo, Japan) X-ray Diffractometer equipped with Cu Kα radiation at 40 kV, 15 mA. Data were collected in a scan mode with a step size of 0.02° and a step time of 2 s over a 2θ range of 5–50°. Data analysis was performed with Bruker DIFFRAC^{plus} EVA diffraction software, version 15.0 (Billerica, MA, USA).

2.2.5. Liquid Chromatography-Mass Spectroscopy (LC–MS)

Analytes were analyzed using an Agilent 1290 Infinity binary liquid chromatograph and a 6538 UHD Accurate-Mass quadruple time of flight (QTOF) mass spectrometer (Santa Clara, CA). Analyte solutions were subjected to liquid separation on an Agilent Atlantis dC18 4.6 mm × 150 mm (3 μm particle size) column at a flow rate of 0.7 mL/min. Mobile phases were composed of 0.1% formic acid (aqueous) and 0.1% formic acid in acetonitrile (organic). Starting conditions were held at 2% organic for 4 min and then ramped to 95% over 20 min, and the organic was held at 95% for 10 min. Analyte effluent was analyzed using electrospray ionization in the positive and negative ion modes. Mass spectra were subjected to an external calibration during the MS analysis to generate accurate mass assignments within ±1 mDa. Agilent MassHunter Qualitative Analysis software (version B.03.01) was used to interpret the collected results.