International Journal of Pharmaceutics 505 (2016) 107–114

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

# Impact of polymer type on bioperformance and physical stability of hot melt extruded formulations of a poorly water soluble drug

Amitava Mitra[a,*], Li Li[b], Patrick Marsac[c,e], Brian Marks[b], Zhen Liu[c], Chad Brown[d]

[a] Biopharmaceutics, Pharmaceutical Sciences and Clinical Supply, Merck & Co. Inc., West Point, PA 19486, United States
[b] Analytical Sciences, Pharmaceutical Sciences and Clinical Supply, Merck & Co. Inc., West Point, PA 19486, United States
[c] Preformulation, Pharmaceutical Sciences and Clinical Supply, Merck & Co. Inc., West Point, PA 19486, United States
[d] Formulation Sciences, Pharmaceutical Sciences and Clinical Supply, Merck & Co. Inc., West Point, PA 19486, United States
[e] College of Pharmacy, University of Kentucky, United States

ARTICLE INFO

*Article history:*
Received 23 October 2015
Received in revised form 13 March 2016
Accepted 20 March 2016
Available online 21 March 2016

*Keywords:*
Hot melt extrusion
Dissolution
Pharmacokinetics
Stability
Solid dispersion
Anti-nucleation

ABSTRACT

Amorphous solid dispersion formulations have been widely used to enhance bioavailability of poorly soluble drugs. In these formulations, polymer is included to physically stabilize the amorphous drug by dispersing it in the polymeric carrier and thus forming a solid solution. The polymer can also maintain supersaturation and promote speciation during dissolution, thus enabling better absorption as compared to crystalline drug substance. In this paper, we report the use of hot melt extrusion (HME) to develop amorphous formulations of a poorly soluble compound (FaSSIF solubility = 1 μg/mL). The poor solubility of the compound and high dose (300 mg) necessitated the use of amorphous formulation to achieve adequate bioperformance. The effect of using three different polymers (HPMCAS-HF, HPMCAS-LF and copovidone), on the dissolution, physical stability, and bioperformance of the formulations was demonstrated. In this particular case, HPMCAS-HF containing HME provided the highest bioavailability and also had better physical stability as compared to extrudates using HPMCAS-LF and copovidone. The data demonstrated that the polymer type can have significant impact on the formulation bioperformance and physical stability. Thus a thorough understanding of the polymer choice is imperative when designing an amorphous solid dispersion formulation, such that the formulation provides robust bioperformance and has adequate shelf life.



## 1. Introduction

The use of amorphous solid dispersion (ASD) formulations to enhance bioavailability of poorly soluble drugs has been widely published (Serajuddin, 1999; Newman et al., 2012; Paudel et al., 2013; Lang et al., 2014). The ASDs typically enhance bioavailability due to higher kinetic solubility of the drug substance and increased dissolution rate of the formulation, by the virtue of the fact that the drug molecule exists in the formulation in a high energy amorphous state. The hot melt extrusion (HME) process has been successfully used in pharmaceutical applications to produce ASDs and several of these products have been approved by the FDA including Noxafil®, Kaletra™, and Norvir™ (Lang et al., 2014; Crowley et al., 2007; Repka et al., 2007). Briefly, in the HME process the drug substance and stabilizing polymer are melt compounded in an extruder forming a solid solution. Upon exiting the extruder the molten mixture is quickly quenched such that the temperature drops below its glass transition temperature thus kinetically inhibiting recrystallization. These extrudates are then processed to produce the final tablet product. While the HME process has certainly been a great addition in the pharmaceutical scientist's repertoire to formulate poorly soluble drugs, the successful development of a product using HME is determined by careful consideration of material properties (drug and polymer), process (temperature, shear) and equipment design. For a more detailed description of the HME process and operations, interested readers are referred to several in-depth reviews on this topic (Lang et al., 2014; Crowley et al., 2007; Repka et al., 2007). Most often, unique formulations yield unique physical stability, dissolution performance, and ultimately bioperformance. The number of formulation options makes the production of ASDs particularly complex – each formulation may require unique processing conditions given

* Corresponding author.
*E-mail address:* amitava_mitra@merck.com (A. Mitra).

http://dx.doi.org/10.1016/j.ijpharm.2016.03.036
0378-5173/

the differences in the material properties and the associated phase diagrams. A balance must be struck between processing, physical stability, and measures of in vitro performance without compromising bioperformance. Although there are reports which focus on physical stability, dissolution, and other measures of in-vitro performance (Ilevbare et al., 2013; Sarode et al., 2014), relatively few reports highlight the influence of formulation on bioperformance.

The amorphous nature of the active pharmaceutical ingredient (API) could lead to physical instability in the drug product such as conversion to the crystalline state. One common approach to physically stabilize the amorphous drug is to disperse the API in a polymeric carrier and thus form a solid solution of the drug and the polymer. Another goal of using the polymer matrix is to maintain the supersaturation achieved during dissolution over an extended period of time so as to better enable absorption of the solubilized API i.e. the higher energy amorphous form of the drug substance transiently increases solubility relative to that of the stable crystalline form and the polymer inhibits nucleation and crystal growth and maintains supersaturation for an extended time period (Guzmán et al., 2007; Brouwers et al., 2009; Augustijns and Brewster, 2012). The polymer can also promote speciation during dissolution, which also would enhance bioperformance of the formulation (Friesen et al., 2008). Several polymers have been reported in literature for use in pharmaceutical ASDs, interested readers are referred to the following references (Paudel et al., 2013; Lang et al., 2014; Konno et al., 2008; Curatolo et al., 2009; Rumondor et al., 2009; Tajarobi et al., 2011).

In this paper, we report the development of an HME formulation, in-vitro characterization including dissolution and physical stability, as well as preclinical pharmacokinetics (PK) data for Merck compound A. In addition, we also report the impact of three different polymers used in the HME formulation-Copovidone, HPMCAS-HF, and HPMCAS-LF, on the physical stability and bioperformance. Compound A is a low solubility and high permeability (BCS class 2) compound (Table 1) with a fairly high efficacious dose projection of approximately 300 mg. This results in a very high dose to volume ratio i.e. high dose number (Do = dose/FaSSIF solubility/250 mL) of 1200 indicating significant solubility limited absorption for this compound (Oh et al., 1993). Hence there was a need to develop an enabled formulation such as an ASD so as to transiently increase the concentration in solution and the dissolution rate. Further, the data shown in this paper also demonstrates that the choice of polymer can have a significant impact on the performance (physical stability and bioavailability) of the ASD formulation. It is the aim of this publication to highlight the influence that formulation selection has on bioperformance and physical stability of amorphous formulation so as to facilitate improved approaches and methodologies employed in the careful balance between process, formulation, and performance.

**Table 1**
Physicochemical properties of compound A.

| |
|---|
| Melting point (crystalline anhydrous form II) = 140 °C |
| Caco-2 permeability = $14.6 \times 10^{-6}$ cm/s |
| Solubility (crystalline anhydrous form II): |
| Simulated Gastric Fluid (SGF, pH 1.2) = 0.001 mg/mL |
| Fasted State Simulated Intestinal Fluid (FaSSIF, pH 6.5) = 0.001 mg/mL |
| Fed State Simulated Intestinal Fluid (FeSSIF, pH 5.0) = 0.002 mg/mL |
| Water = 0.001 mg/mL |

## 2. Materials and methods

### 2.1. Preparation of hot melt extrusion (HME) formulations of compound A

The melting point (Tm) of compound A is approximately 140 °C and it is thermally stable up to approximately 220 °C by thermal gravimetric analysis (TGA), making the compound a prime candidate for HME. Thus, formulations of compound A were extrusion compounded at a 20% drug load in a custom built co-rotating 7.5 mm twin screw extruder with L/D = 15 and 1 cm slit die (MP&R, Hackensack, NJ) with three individual polymers- copovidone (Kollidon VA-64™, BASF), hydroxypropyl methyl cellulose LF grade (HPMCAS-LF, Shin Etsu), hydroxypropyl methyl cellulose HF grade (HPMCAS-HF, Shin Etsu). These three polymers were chosen based on high-throughput screening to assess compatibility of the drug and the polymer. This was achieved by film-casting of the drug with several polymers, and analysis of the film casts by XRD, DSC and dissolution studies (data not shown). The extruder was equipped with all conveying screws and heated to target a product temperature of 145 °C to ensure facile processing of each polymer. This temperature was above the Tm of compound A thus making this a facile compounding process as the drug was completely melted. The screw speed was set at 50 revolutions per minute. Approximately 7.5 g of feed stock for each formulation was pre-blended in a turbula blender for 10 min prior to extrusion to help ensure compositional homogeneity. A VIBRI (SympaTec, Germany) vibratory feeder was used to convey the formulation into the extruder. The gap width was set to 8 mm and a V-shaped tray was used to convey the material to the feed port on the extruder. The vibration setting was set at 35% to provide a feed rate of approximately 1 g/min. Initial breakthrough of the extruded formulation through the slit die (1 mm × 10 mm) was approximately 3.5 min after the start of feeding. Strands of clear, glassy extrudate were collected on a custom built take-off belt equipped with a dual nozzle cold air gun Vortec™ (AiRTX, Cincinnati, OH) to provide rapid quenching. Extrudates of each composition (20% compound A and 80% polymer) were milled in a coffee grinder (Krups, Milville, NJ) on the fine setting for approximately 30 s. The particle size of the extrudates was approximately 200 μm and 100 μm for the HPMCAS and copovidone based extrudates, respectively. Approximately 300 mg of extrudate (60 mg potency) were hand-filled into hard gelatin capsules (size 00) for dosing to beagle dogs and for biorelevant dissolution testing. An overall yield of approximately 55% for the process was achieved. The low yield from this process is primarily because of the small batch size (~7.5 g), which results in fixed losses such as approximately 2 g loss in the extruder due to free volume and approximately 1 g loss during milling. This yield is not representative of large scale HME process.

### 2.2. Physical characterization of the extrudates

Milled extrudate were tested by X-ray diffraction (XRD) and differential scanning calorimetry (DSC) to ensure a single phase, amorphous solid dispersion was formed. XRD was performed on a Philips X'Pert with a 1 h scan over a 2Θ of 2-40 (PANalytical, Westborough, MA). Modulated differential scanning calorimetry (DSC) was conducted on a TA instrument Q2000 over a temperature range of 0° C to 130° C or 145° C (TA Instruments, New Castle, DE). The heating rate was 2° C/min with a modulation frequency of ±0.5° C every 60 s. Solid dispersions prepared with HPMCAS-L and HPMCAS-H were placed on stability at 40 °C/35%RH and 40 °C/75%RH in open containers and analyzed after 4 weeks of storage. The copovidone systems were stored at 30 °C/65%RH and 40 °C/35%RH. For the stability studies a combination of