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Humidity induced phase transformation of poloxamer 188 and its effect on physical stability of amorphous solid dispersion of AMG 579, a PDE10A inhibitor

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ABSTRACT

Poloxamer 188, a commonly used emulsifying and solubilizing agent, was found to be the cause of crystallization of an investigational drug, AMG 579, from its amorphous solid dispersion at accelerated storage conditions. Investigation of this physical stability issue included thorough characterization of poloxamer 188 at non-ambient conditions. At 40 °C, poloxamer 188 becomes deliquescent above relative humidity of 75%. Upon returning to ambient conditions, the deliquescent poloxamer 188 loses water and re-solidifies. The reversible phase transformation of poloxamer 188 may cause physical and chemical stability issues and this risk should be assessed when selecting it as an excipient for formulation development.

1. Introduction

Amorphous solid dispersions (ASD) have now been established as the formulation strategy of choice for overcoming solubility-limited bioavailability of pharmaceutical compounds (Dahan et al., 2013; Miller et al., 2012; Van den Mooter, 2012). As ASDs are high energy systems, they offer the promise of higher "apparent solubility" and dissolution rate thereby providing an avenue to improve oral exposure. The main risk associated with this formulation approach is the potential physical and chemical instability of the amorphous drug. In order to address the issue of physical stability, numerous studies have been conducted in the past two decades. For example, the type of polymer to be used with drug to make the ASD and its impact of physical stability (Konno et al., 2008; Wegiel et al., 2013), the method of manufacture of the ASD (Paudel et al., 2013; Van den Mooter, 2012), and the ability of the chosen polymer to sustain supersaturation *in-vivo* have been studied (Friesen et al., 2008).

Pharmaceutical dosage forms comprise of active pharmaceutical ingredients and excipients that are added to aid the formulation and the manufacturing process (York, 1983). Thus in order to convert the ASD into a usable dosage form, it has to be mixed with excipients and processed using routine manufacturing techniques. As excipients are an integral part of the final drug product, excipient-induced phase transformation of the active pharmaceutical ingredient (API) and/or phase transformation of the excipient itself during manufacturing, stability testing, and storage can be potentially detrimental to the product quality (Airaksinen et al., 2005; Buckton and Darcy, 1995; Landín et al., 1994). Thorough understanding of the physicochemical properties of excipients and their impact on the physical form of the API is therefore essential to successful drug product development. While the influence of excipients on the physical stability of crystalline compounds has been well studied (Zhang et al., 2004), there have been only a few studies undertaken to understand the impact of downstream processing and excipients on the physical stability of the ASD (Démuth et al., 2015). Ayenew et al. showed that compression induces amorphous phase separation in 30 and 40 weight percent ASDs of naproxen with polyvinylpyrrolidone (Ayenew et al., 2012). Leane and coworkers studied the effect of formulation composition of the physical stability of ibipinabant/polyvinylpyrrolidone (PVP) ASD (Leane et al., 2013). They found that commonly used fillers such as mannitol and lactose induced crystallization of the ASD under accelerated conditions while microcrystalline cellulose (MCC) led to only minimal crystallization. Based on this finding, they designed a formulation composition with MCC as the only filler. Demuth et al. showed that magnesium stearate acts as a crystallization promoter in electrospuns ASD of itraconazole with PVP-VA. However, this problem could be mitigated by replacing Magnesium stearate with sodium steryl fumarate (Démuth et al., 2016). Ghebremeskel et al. studied the effect of addition of

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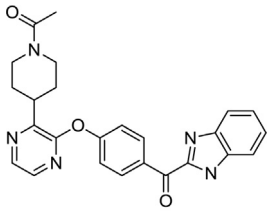
surfactant/plasticizer (Tween 80) on the physical stability of ASDs of a poorly soluble drug with PVP-K30, Plasdone-S630, and HPMC-C-E5 (Ghebremeskel et al., 2006). They showed that addition of Tween 80 to the ASD with HPMC-E5 led to increased amount of crystallization of the API while Tween 80 had no discernable effect on physical stability of ASDs made from PVP-K30 and Plasdone-S630. Mosquera-Giraldo and coworkers studied the impact of surfactant on the crystal growth rates of amorphous celecoxib and showed that surfactants increased the growth rate of the crystals in amorphous celecoxib (Mosquera-Giraldo et al., 2014). However, the addition of PVP to celecoxib to form an ASD led to the reduction in crystal growth rates. Gumaste et al. showed that the addition of poloxmer 188 led to crystallization of the itraconazole API from its ASD with Soluplus® even at a low drug loading, however addition poloxmer 188 to the ASD of itraconazole with HPMC-AS did not lead to physical instability (Gumaste et al., 2016). In addition to impact on physical stability, surfactants can also impact *in-vivo* performance due to interaction with the ASD in solution. For example addition of sodium lauryl sulfate to a posoconazole/HPMC-AS ASD led to a 70% reduction in *in-vivo* exposure when compared to the ASD alone (Chen et al., 2016). The examples provided above clearly show that the effect of excipient and processing on the physical stability and performance of the ASD has to be carefully considered when designing the formulation composition and process. Moreover the examples provided also show that the effect of commonly used excipients such as surfactants on physical stability and performance of ASD can be complex and produce contradictory results due to the ternary nature of the system.

AMG 579 (**1**) is being developed as a PDE10A inhibitor for the treatment of schizophrenia. As solubility limited bioavailability has been observed in pre-clinical species, **1** was converted to a 50% w/w amorphous solid dispersion with HPMC-AS, in order to achieve desired bioavailability in clinical studies. Physical instability (Crystallization of API) was observed at 40 °C, 75% RH for some poloxamer 188-containing prototype tablet formulations of the amorphous dispersion of **1**. Typical properties of commonly used excipients, such as poloxamer 188, a tri-block copolymer used as a wetting or solubilizing agent, are well documented in the Handbook of Pharmaceutical Excipients (Collett, 2003). Polaxamers are described as being "hygroscopic" (Newman et al., 2008) in the handbook only at relative humidity greater than 80%, with the statement supported by a plot of the equilibrium moisture content of poloxamer 188 at 25 °C as a function of relative humidity. This plot shows that poloxamer 188 adsorbs about 40% of moisture between 80% to 90% relative humidity at 25 °C, suggesting deliquescence. Although hygroscopicity at 25 °C is useful information, equilibrium moisture content and physical stability of poloxamer 188 at other pharmaceutically relevant conditions, such as 40 °C, 75% RH, the ICH recommended accelerated drug stability testing condition, have not been reported in the handbook or elsewhere, to our best knowledge. In this paper, we report the moisture content of poloxamer 188 as a function of relative humidity at 40 °C. This moisture isotherm indicates that at 40 °C, poloxamer 188 is hygroscopic at relative humidity of 75%, adsorbing 15% of water and becoming deliquescent. Upon returning to ambient conditions, the deliquescent poloxamer 188 loses water and re-solidifies. We propose that the reversible phase transformation of polaxmer 188 is the underlying cause of physical instability observed at 40 °C, 75% RH for these formulations. Whether such reversible phase transformation of poloxamer 188 will lead to stability issues of the drug product depends on the properties of the active pharmaceutical ingredients. Nonetheless, this important physical property of poloxamer 188 should be made available to pharmaceutical researchers as part of the risk assessment when using poloxamer 188 in formulation development.



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2. Material and methods

The development compound **1** (1-4-(3-(4-(1*H*-benzo[d]imidazol-2-carbonyl)phenoxy]pyrazin-2-yl)piperidin-1-yl)ethanone) was synthesized by Amgen Inc. It was received as a crystalline white to off-white powder. The solid dispersion of **1** and the prototype tablets were prepared by Amgen Inc. The amorphous solid dispersion of 50% (w/w) **1** in hypromellose acetate succinate (HPMC-AS, Shin-Etsu Chemical Co., Ltd., Japan) was obtained by spray drying 50% (w/w) **1** and 50% (w/w) HPMC-AS from a solution of 25% (w/w) methanol in tetrahydrofuran. Excipients used in the prototype tablets were Lutrol® F68 (poloxamer 188, BASF Corporation, USA), Pharmaburst® 500 (a rapidly-dissolving, co-processed excipient comprised predominantly of a proprietary mixture of sugar alcohol excipients manufactured by SPI Pharma, USA), Explotab® (JRS Pharma, Germany) and magnesium stearate (Macron Fine Chemicals, USA). The prototype tablets were prepared manually using a compaction simulator, Presster (Measurement Control Corporation, East Hanover, New Jersey, USA). The mixture of 5:1 w/w **1** HPMC-AS ASD and poloxamer 188 was prepared by mixing the pre-sieved poloxamer 188 (200 mesh) and the ASD in Turbula Type T2F (Glen Mills Inc. Clifton, New Jersey, USA) at 96 rpm for 2 min.

2.1. X-ray diffraction

Powder X-ray diffraction (pXRD) patterns were collected with a PANalytical (Almedo, the Netherlands) X-ray powder diffractometer (X'Pert PRO) equipped with a real-time-multiple-strip detector, using Ni filtered Cu Kα radiation at 45 kV, 40 mA. The diffractometer employs a divergence slit of 1/4°, an anti-scatter slit of 1/2°, and soller slits of 0.04 radian at both the incident and the diffraction sides. Each sample was scanned between 4 and 40° 2θ. Powder patterns of ambient humidity samples were collected on zero background wafers. Controlled humidity samples were mounted on a sample holder of 0.2 mm depth, which was placed in an Anton Paar THC chamber connected to a VTI RH-200 humidity generator (VTI Corporation, Hialeah, Florida, USA) for data collection at specific relative humidities.

2.2. Moisture sorption

Moisture sorption isotherms were generated with a VTI SGA-100 sorption analyzer (VTI Corporation, Hialeah, Florida, USA). Isotherms were generated at 25 °C and 40 °C. The material was pre-dried at 40 °C under dry nitrogen until either less than 0.01% weight change was observed over 10 min or a maximum drying time of 120 min was reached. The moisture sorption isotherm was taken at an interval of 5 or 10% RH from 5% to 95% RH. The equilibrium criterion for each step was less than 0.01% weight change over 5 min. The maximum equilibration time of 180 min if the equilibrium criterion was not reached. Moisture sorption at