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Development of an analytical method for crystalline content determination in amorphous solid dispersions produced by hot-melt extrusion using transmission Raman spectroscopy: A feasibility study

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ABSTRACT

The development of a quantitative method determining the crystalline percentage in an amorphous solid dispersion is of great interest in the pharmaceutical field. Indeed, the crystalline Active Pharmaceutical Ingredient transformation into its amorphous state is increasingly used as it enhances the solubility and bioavailability of Biopharmaceutical Classification System class II drugs. One way to produce amorphous solid dispersions is the Hot-Melt Extrusion (HME) process. This study reported the development and the comparison of the analytical performances of two techniques, based on backscattering and transmission Raman spectroscopy, determining the crystalline remaining content in amorphous solid dispersions produced by HME.

Principal Component Analysis (PCA) and Partial Least Squares (PLS) regression were performed on preprocessed data and tended towards the same conclusions: for the backscattering Raman results, the use of the DuoScan™ mode improved the PCA and PLS results, due to a larger analyzed sampling volume. For the transmission Raman results, the determination of low crystalline percentages was possible and the best regression model was obtained using this technique. Indeed, the latter acquired spectra through the whole sample volume, in contrast with the previous surface analyses performed using the backscattering mode. This study consequently highlighted the importance of the analyzed sampling volume.

1. Introduction

In the last decades, more and more Biopharmaceutical Classification System (BCS) class II drugs were implemented in pharmaceutical manufacturing processes. The issue of such drugs is their poor solubility and bioavailability leading to restrictive integration in conventional pharmaceutical formulations. One way to enhance this lack of solubility is to transform the crystalline Active Pharmaceutical Ingredient (API) in its amorphous state. Indeed, an amorphous drug has a higher molecular mobility inducing a higher solubility and dissolution rate but has a lower chemical and physical stability. Several techniques were developed to manufacture amorphous APIs in the pharmaceutical field such as milling, melting, quenching, spray drying, freeze drying and solid dispersions. The production of solid dispersions by a Hot-Melt Extrusion (HME) process is discussed in this work. During the HME process, the API is encompassed in a polymeric carrier and transformed in its amorphous state by manufacturing a solid dispersion. The aim of an adequate formulation is consequently to reduce the recrystallization of the amorphous API and stabilize the latter using appropriate polymers and

Abbreviations: API, active pharmaceutical ingredient; BCS, Biopharmaceutical classification system; DSC, differential scanning calorimetry; EMCCD, electron multiplying charged couple device; FTIR, Fourier transform infrared spectroscopy; HME, hot-melt extrusion; ITZ, itraconazole; PCA, principal component analysis; PCs, principal components; PLS, partial least squares; SEM, scanning electron microscopy; TGA, thermogravimetric analysis.

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excipients. Indeed, amorphous APIs tend to convert into the most stable form during storage, which induces solid-state changes, leading to lower dissolution rates and poorer dosage form effectiveness (Kanaujia et al., 2015; Kogermann et al., 2013; Li et al., 2014; Sarode et al., 2013a,b; Shah et al., 2013; Van Den Mooter, 2012).

As can be read in the literature (Agrawal et al., 2016; Bochmann et al., 2016; Engers et al., 2010; Fule and Amin, 2014; Gumaste et al., 2016; Janssens et al., 2007; Lim et al., 2017; Tian et al., 2014), more and more scientific teams explored the development of solid dispersions to solve this issue. In this context, several thermal analyses techniques such as Differential Scanning Calorimetry (DSC) and Thermogravimetric analysis (TGA) were developed to characterize the solid dispersion by measuring the state of the API and thus its recrystallization that should be avoided (Agrawal et al., 2016; Bochmann et al., 2016; Engers et al., 2010; Fule and Amin, 2014; Gumaste et al., 2016; Janssens et al., 2007; Lim et al., 2017; Tian et al., 2014). The development of vibrational spectroscopic techniques spread out as it performs analyses able to distinguish the amorphous and crystalline API state (Croker et al., 2012; Hennigan and Ryder, 2013; Li et al., 2011; Mah et al., 2015; Netchacovitch et al., 2015; Nikowitz et al., 2016; Saerens et al., 2014a, 2014b). Moreover, the analyses of solid dispersions by Raman microscopy are in real expansion since it also studies the spatial drug distribution inside the formulation. In this case, multivariate analyses are most often performed to extract the relevant information (Amigo, 2010; Docoslis et al., 2007; Fule et al., 2014; Gendrin et al., 2008; Sacré et al., 2014; Scoutaris et al., 2014; Vajna et al., 2011; Vigh et al., 2014; Widjaja et al., 2011). The ability to use Raman mapping and adequate chemometric tools to characterize pharmaceuticals was demonstrated by Vajna et al. (2011). They compared the spatial distribution of melt extruded and conventional Isoptin formulations by analyzing their internal structure and concluded that melt extrusion was able to manufacture sustained release products with a better dissolution profile than the one produced by wet granulation. Scoutaris et al. (2014) characterized paracetamol – Compritol® extrudates, as well qualitatively as quantitatively, using Energy Dispersive X-ray (EDX) and confocal Raman microscopy by means of multivariate analyses. They studied the drug distribution and concluded that a better uniformity and distribution of paracetamol in pre-mixed extruded formulations was obtained compared to direct compressed tablets. Vigh et al. (2014) developed a model to determine the drug crystallinity in extrudates. They analyzed real samples, based on a factorial design experiment, to study the relationship between process parameters and residual drug crystallinity content using confocal Raman mapping and transmission Raman spectrometry. They found that Raman spectroscopy may be a suitable tool for the prediction of drug degradation, the determination of glass transition temperature (T_g) and the determination of drug crystallinity content.

As reported in the literature, the qualitative and quantitative characterization of amorphous solid dispersions spread out during these last decades. These dispersions are of great interest in the pharmaceutical field enhancing the solubility and bioavailability of BCS class II drugs. In this context, this study reported the comparison of the analytical performances of a backscattering and a transmission Raman spectroscopic technique, analyzing tablets containing different crystalline/amorphous ITZ ratio, determining the crystalline remaining ITZ content in amorphous solid dispersions produced by HME.

2. Materials and methods

2.1. Chemicals

Itraconazole (ITZ) was purchased from Lee Pharma Ltd. (Andhra, Pradesh, India), Soluplus® and AcDiSol® were provided from BASF (Ludwigshaven, Germany) and FMC Biopolymer (Brussels, Belgium), respectively.

2.2. Hot-melt extrusion process

A Hot-Melt Extrusion process was performed to obtain extrudates with and without Itraconazole (ITZ). These extrudates were milled, compressed and used as validation matrix to obtain samples with different degrees of crystallinity as close as possible to the real future samples (extrudates). In this context, 12 independent batches (6 with ITZ and 6 without ITZ) were produced based on an optimized formulation containing 25% ITZ, 72.5% Soluplus® and 2.5% AcDiSol® (Thiry et al., 2016). The hot-melt extruded samples with ITZ were used to obtain amorphous solid dispersions. Indeed, the extrudates with ITZ contained 100% amorphous API and the ones without ITZ contained the polymeric matrix (Thiry et al., 2016).

For the HME process, mixtures with and without ITZ, based on the optimized formulation, were premixed in a *TURBULA*® Shaker-Mixer for 20 min and then put inside the volumetric feeder for extrusion. An 18 mm twin screw hot-melt extruder was used (L/D = 32, Scamex®, Crosne, France) with a common screw configuration containing two kneading zones. The temperature gradient (70–135–145–155 °C) was applied to the four heating zones of the barrel. The rotational screw speed was set at 100 rpm. A volumetric feeder was used and the feeding rate was set at 4 rpm corresponding with the formulation mixture to 6 g min^{-1}. The extrudates were collected after cooling to ambient temperature for off-line analyses. The batches were then grinded using an Ultra Centrifugal Mill, type ZM 200 (Retsch GmbH, Haan, Germany) apparatus.

2.3. Tablet preparation

Based on the 12 HME productions (6 with ITZ and 6 without ITZ), tablets comprising different percentages of crystalline/amorphous ITZ ratio were prepared on three series to obtain training and test sets, as presented in Table 1. The training sets included three levels of concentration (0%, 10% and 50% crystalline ITZ) and the test sets included five levels of concentration (0%, 5%, 10%, 25% and 50% crystalline ITZ). These tablets contained crystalline ITZ powder, grinded extrudates with ITZ (amorphous samples) and grinded extrudates without ITZ (polymeric matrix) as presented in Fig. 1 and Table 2.

Table 1
Training and test sets preparation on three series.

Series 1	Series 2	Series 3
Training set 1 (production 1)	Training set 1 (production 3)	Training set 1 (production 5)
Training set 2 (production 1)	Training set 2 (production 3)	Training set 2 (production 5)
Test set 1 (production 2)	Test set 1 (production 2)	Test set 1 (production 2)
Test set 2 (production 4)	Test set 2 (production 4)	Test set 2 (production 4)
Test set 3 (production 6)	Test set 3 (production 6)	Test set 3 (production 6)