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Differential scanning calorimetry predicts the critical quality attributes of amorphous glibenclamide

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ABSTRACT

Selection of a crystallinity detection tool that is able to predict the critical quality attributes of amorphous formulations is imperative for the development of process control strategies. The main aim of this study was to determine the crystallinity detection tool that best predicts the critical quality attributes (*i.e.* physical stability and dissolution behaviour) of amorphous material. Glibenclamide (model drug) was milled for various durations using a planetary mill and characterised using Raman spectroscopy and differential scanning calorimetry (DSC). Physical stability studies upon storage at 60 °C/0% RH and dissolution studies (non-sink conditions) were performed on the milled glibenclamide samples. Different milling durations were needed to render glibenclamide fully amorphous according to Raman spectroscopy (60 min) and onset of crystallisation using DSC (150 min). This could be due to the superiority of DSC (onset of crystallisation) in detecting residual crystallinity in the samples milled for between 60 and 120 min, which were not detectable with Raman spectroscopy. The physical stability upon storage and dissolution behaviour of the milled samples improved with increased milling duration and plateaus were reached after milling for certain periods of time (physical stability — 150 min; dissolution — 120 min). The residual crystallinity which was detectable with DSC (onset of crystallisation), but not with Raman spectroscopy, adversely affected the critical quality attributes of milled glibenclamide samples. In addition, mathematical simulations were performed on the dissolution data to determine the solubility advantages of the milled glibenclamide samples and to describe the crystallisation process that occurred during dissolution in pH 7.4 phosphate buffer. In conclusion, the onset of crystallisation obtained from DSC measurements best predicts the critical quality attributes of milled glibenclamide samples and mathematical simulations based on the solvent-mediated crystallisation model were successfully performed on the dissolution data.

1. Introduction

The majority of drugs in the development pipeline are poorly water soluble. Converting crystalline drug to the amorphous form is a promising strategy to overcome the poorly water soluble challenge (Babu and Nangia, 2011; Laitinen et al., 2013). The amorphous form has a higher solubility than its crystalline counterpart. However, the amorphous form is not thermodynamically stable and has a high tendency to recrystallise (Hancock and Zografi, 1997). Recrystallisation, which may occur during processing (Ayenew et al., 2012a,2012b), storage (Mahlin and Bergström, 2013; Van Eerdenbrugh et al., 2010), and dissolution (Alonzo et al., 2010; Savolainen et al., 2009), negates the solubility advantage of the amorphous form.

There are many ways of preparing drugs in the amorphous forms and these include melt quenching, ball milling, solvent evaporating, spray drying, and freeze drying (Kawakami, 2009; Willart and Descamps, 2008). A thorough understanding of the manufacturing process of amorphous formulations is crucial for the development of process control strategies (Rathore and Winkle, 2009). In order to have a thorough understanding of the process, it is imperative to develop an understanding of the relationships between various critical process parameters and critical quality attributes and to identify the optimal operating range for the critical process variables.

Changes in the processing parameters have been shown to affect critical quality attributes (*i.e.* physical stability upon storage and dissolution behaviour) of amorphous formulations (Bøtker et al., 2011; Karmwar et al., 2011, 2012). The changes in the critical quality attributes associated with the change in the processing parameters were attributed (at least in part) to the changes in the amount of trace crystallinity. A range of analytical techniques are available for the

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detection of crystallinity and they include X-ray powder diffractometry (XRPD), thermal analysis methods, microscopy methods, and vibrational spectroscopies (Chieng et al., 2011; Mah et al., 2015). These techniques have different sensitivities to low levels of crystallinity (Shah et al., 2006). Determination of the optimal operating range for the critical process variable requires the selection of a crystallinity detection technique that best predicts the critical quality attribute of interest.

Several studies have demonstrated that some analytical techniques are able to better predict the critical quality attributes of amorphous formulations. Watanabe et al. used XRPD, DSC, and ss-NMR to monitor the amorphisation of solid dispersion of indomethacin and silica during milling (Watanabe et al., 2001). It was found that different techniques suggested different milling durations were required to render the sample fully amorphous and exhibited different recrystallisation profiles upon storage. In this study, the results of ss-NMR correlated best with the physical stability data of the samples. Ito et al. also reported that ss-NMR was better in predicting the physical stability of milled solid dispersions of troglitazone and polyvinylpyrrolidone, when compared to XRPD (Ito et al., 2010). Bøtker et al. investigated the milling of indomethacin with XRPD, DSC, and ss-NMR and also monitored the physical stability of the samples with different milling durations (Bøtker et al., 2011). DSC and ss-NMR were found to correlate best with the physical stability of milled amorphous indomethacin.

We previously characterised milled glibenclamide samples using XRPD, Raman spectroscopy coupled with principal component analysis (PCA), and DSC (onset of crystallisation) and studied the dissolution behaviour of glibenclamide milled for different durations in sink conditions (Mah et al., 2013). It was found that the onset of crystallisation temperature (detected using DSC) best correlated with the dissolution properties of milled glibenclamide samples in sink conditions, with XRPD being the least accurate predictor. To the best of our knowledge, no studies have investigated the usefulness of analytical tools to predict both the physical stability and dissolution behaviour of amorphous materials. The aim of the present study was to determine the analytical tool that best predicts the physical stability and dissolution behaviour (in non-sink conditions) of a milled amorphous material. Previous studies have found that dissolution testing in non-sink conditions resulted in a better *in vitro–in vivo* correlation and was also better at discriminating different formulations (Dong et al., 2007; Liu et al., 2013). Glibenclamide which is a poorly water soluble antidiabetic drug (Mah et al., 2013), was used as a model drug. Mathematical simulations were also performed on the dissolution data in order to determine the solubility advantages (in conditions with limited crystallisation) and also to describe the crystallisation process that occurred during dissolution in pH 7.4 phosphate buffer.

2. Materials & Methods

2.1. Materials

Glibenclamide (Berlin Chemie, Berlin, Germany) and phosphorous pentoxide (Sigma-Aldrich, Steinheim, Germany) were used as received. Potassium dihydrogen phosphate (Riedel-de Haein, Seelze, Germany), sodium hydroxide (Eka Nobel, Bohus, Sweden) and hydroxypropyl methylcellulose (HPMC) E5 (Dow Chemical Company, Michigan, USA) were used to prepare the buffer for the dissolution experiments.

2.2. Milling

Milling was performed using the planetary ball mill Pulverisette 6 (Fritsch GmbH, Idar-Oberstein, Germany). Glibenclamide form I powder (1.5 g) was placed in an 80 ml volume stainless steel bowl, containing 15 stainless steel balls (10 mm in diameter). The bowl containing the sample was pre-cooled in an ice bath prior to milling. Milling was performed at 400 rpm for 30, 60, 90, 120, 150, and 180 min. The sample in the milling bowl was scraped down from the wall and lid of the bowl after every 15 min of milling to ensure milling homogeneity. The bowl containing the sample was cooled in an ice bath for 15 min after every 15 min of milling to avoid the sample from heating up.

2.3. Scanning Electron Microscopy

Scanning electron microscopy (SEM) images of the particles were recorded using the FEI Quanta 250 FEG (FEI Inc., Eindhoven, The Netherlands) scanning electron microscope equipped with the Everhart–Thornley detector (ETD). The samples were mounted on aluminium stubs with double-sided carbon tape and were then coated with platinum before imaging. The particle size of the various samples was estimated by averaging the apparent maximum linear dimension of 150 particles randomly selected from three SEM images. Image analyses to determine the particle size of the samples were performed using the Fiji Is Just ImageJ 1.48 software (University of Wisconsin-Madison, Wisconsin, USA).

2.4. Raman Spectroscopy

Raman spectra were collected using the PhAT system (Kaiser Optical Systems, Ann Arbor, MI, USA) which was equipped with a 785 nm excitation laser source, a probe which consisted of an array of 50 optical fibres and an air-cooled charge-coupled device (CCD) detector. The sampling spot size of this system was 6 mm in diameter and the size of the area illuminated was 28.3 mm^2. The integration time used was 5 s and the final spectrum was the mean of 5 scans. Each sample was measured in triplicate. Data collection and conversion was performed using the HoloGRAMS™ 4.1 (Kaiser Optical Systems) software.

The Raman spectra were truncated so that only the spectral region between 764 and 1288 cm^{-1} was included in the analysis. The spectra were subsequently subjected to 64-point rubber band correction (OPUS software v.5.0, Bruker Optik, Ettlingen, Germany) to remove baseline differences. Finally, the spectra underwent standard normal variate (SNV) transformation in order to remove intensity differences. The preprocessed spectra were then subjected to principal component analysis (PCA) to investigate the differences in the samples. SNV transformation and PCA were performed using the Unscrambler® X software (v. 10.1, Camo Software AS, Norway).

A partial least square (PLS) model was constructed using the Raman spectra of physical mixtures containing 0%, 20%, 40%, 60%, 80%, and 100% crystallinity. Two thirds of the calibration spectra was used to construct the calibration model and the final third used to test the model. Full cross validation was performed. Multivariate analysis was performed using the Unscrambler® X software (v. 10.1, Camo Software AS, Norway).

2.5. Differential Scanning Calorimetry (DSC)

DSC thermograms were recorded using the Mettler DSC 823e (Mettler-Toledo AG, Greifensee, Switzerland). Samples (1–2 mg) were crimped in aluminium pans with pierced lids, equilibrated at 0 °C for 5 min and finally heated up to 200 °C at a heating rate of 10 °C/min. The measurement cell was purged with dry nitrogen gas at a flow rate of 50 ml/min during the measurements. The glass transition temperature (T_g), onset of crystallisation and enthalpy of crystallisation were determined using the STAR^e software (Mettler-Toledo AG, Greifensee, Switzerland). The T_g was defined as the mid-point change in heat capacity of the sample. Each sample was measured in triplicate.

2.6. Stability

Samples were stored in open vials at 60 °C over phosphorous pentoxide (0% RH) and monitored on a daily basis using Raman spectroscopy.