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Stability of indomethacin with relevance to the release from amorphous solid dispersions studied with ATR-FTIR spectroscopic imaging

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ABSTRACT

This work presents the use of attenuated total reflection Fourier transform infrared (ATR-FTIR) spectroscopy and spectroscopic imaging to study the stability and dissolution behaviour of amorphous solid dispersions (ASDs). ASDs are employed to improve the bioavailability of drugs which are poorly soluble in aqueous solutions. Selecting the appropriate polymeric excipients for use in pharmaceutical tablets is crucial to control drug stability and subsequent release. In this study, indomethacin was used as a model poorly-aqueous soluble drug since the amorphous-form has improved dissolution properties over its crystalline forms. ASDs of indomethacin/polyethylene glycol (PEG) and indomethacin/hydroxypropyl methylcellulose (HPMC) in a 1:3 wt ratio were compared. Firstly, ATR-FTIR spectroscopy was employed to monitor the stability of indomethacin in the ASDs over 96 h. While the indomethacin/HPMC ASD showed the ability to maintain the amorphous indomethacin form for longer periods of time, ATR-FTIR spectra revealed that indomethacin in the drug/PEG ASD crystallised to the stable γ-form, via the α-form. Secondly, ATR-FTIR spectroscopic imaging was used to study the dissolution of ASD tablets in a phosphate buffer (pH 7.5). Crystallisation of amorphous indomethacin was characterised in the spectra collected during the dissolution of the indomethacin/PEG ASD which consequently hindered release into the surrounding solution. In contrast, release of amorphous indomethacin was more effective from HPMC.

1. Introduction

The bioavailability of active pharmaceutical ingredients (APIs) in a biological system is dependent upon the aqueous solubility and dissolution rate of the components within the formulation (Craig, 2002; Serajuddin, 1999). Solid oral dosage forms, tablets and capsules, are particularly common due to their relative ease of manufacture and high patient compliance. There is a need to understand the stability and dissolution properties of solid oral dosage forms to develop novel products that are more efficient for delivering the desired therapeutic effects (Siepmann et al., 2002).

Many APIs can exist in different solid state forms or polymorphs; each of these forms have different physical properties that can directly affect the rate of dissolution (Aguiar and Zelmer, 1969). In this study indomethacin was used as the model API. Indomethacin is a non-steroidal anti-inflammatory drug used to reduce pain and swelling for treatment of gout, osteoarthritis and rheumatoid arthritis. However, the stable and meta-stable crystalline forms (γ-form and α-form respectively) are considered poorly soluble in aqueous conditions resulting in low bioavailability and absorption into the biological system. The dissolution properties of indomethacin can be improved when it is in the amorphous form (Heinz et al., 2007). The amorphous form is of particular interest since it lacks long range order, i.e. no crystal lattice, hence the dissolution rate can be increased (Hancock and Parks, 2000; Hancock and Zografi, 1997). However, the amorphous form is not the favourable molecular state because of thermodynamic instability and conversion back to a more stable crystalline form can occur during the production, storage and delivery stages (Alonzo et al., 2010; Kao et al., 2012).

Amorphous solid dispersions (ASDs) stabilise amorphous APIs by the introduction of a polymeric excipient. Depending upon the excipient used, the dissolution profile (drug release over time) can be modified to influence drug release from the tablets. The resulting intermolecular interactions between the API and polymer (Miyazaki et al., 2004) and the reduced molecular mobility of API in

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the polymer (Aso et al., 2004; Matsumoto and Zografi, 1999) assist in preventing nucleation in such formulations, inhibiting crystallisation. ASDs are one of the most useful strategies employed to improve the release of poorly-aqueous soluble APIs (Leuner and Dressman, 2000; Six et al., 2004; Vasconcelos et al., 2007). When formulating an ASD, it is important to maintain the amorphous form of the API in the solid dosage form.

Fourier transform infrared (FTIR) spectroscopy is an important analytical approach allowing identification and characterisation of materials in the sample. Characteristic absorption bands, arising from interaction of infrared light with a vibrating chemical bond, can reveal chemical information about the sample. FTIR spectroscopy can also distinguish between different polymorphic forms and identify interactions occurring within the sample (Taylor and Zografi, 1997) which is particularly useful in pharmaceutical development.

FTIR spectroscopic imaging has been extensively developed over the last decade and works by combining an FTIR spectrometer with a focal plane array (FPA) detector (Kazarian and Chan, 2010). Chemical images can be obtained that reveal the spatial distribution of specific components by plotting the absorbance of characteristic absorption bands as a function of measured space. The use of FTIR spectroscopic imaging in attenuated total reflection (ATR) mode has proven very powerful to study dynamic systems, including the dissolution of pharmaceutical tablets (Kazarian and Chan, 2003; Kazarian and Ewing, 2013; Kazarian and van der Weerd, 2008; van der Weerd and Kazarian, 2005). The ability to collect both chemical and spatial information from the sample means that investigations into the behaviour of pharmaceutically relevant systems can be understood (Kimber et al., 2011, 2013; van der Weerd and Kazarian, 2004; Wray et al., 2011). Over recent years a range of different analytical imaging approaches have been used to study drug release including ultraviolet imaging (Østergaard et al., 2010; Ye et al., 2011), magnetic resonance imaging (Nott, 2010) and NIR imaging (Ishikawa et al., 2013).

The purpose of this study is to investigate the behaviour and stability of amorphous indomethacin in two different polymers, polyethylene glycol (PEG) and hydroxypropyl methylcellulose (HPMC). Fig. 1 shows the chemical structure of the materials studied, which are widely used in pharmaceutical tablets. The aim is to investigate and highlight the importance of selecting appropriate excipients to maintain the desired structural form of indomethacin in the ASDs. The behaviour of indomethacin crystallisation and dissolution have been studied and it was reported that ATR-FTIR spectroscopy provided the most reliable assessment among the analytical techniques used (Priemel et al., 2012). Recent studies also state that the stability of amorphous drugs change depending on the polymer employed (Konno et al., 2008; Priemel et al., 2013).

This investigation demonstrates the applicability of ATR-FTIR spectroscopy and spectroscopic imaging to observe the intermolecular interactions between indomethacin and polymers within different ASDs. ATR-FTIR spectroscopic imaging was also employed here to monitor the behaviour of amorphous indomethacin during *in situ* dissolution experiments, where its release into the surrounding solution was observed.

2. Materials and methods

2.1. Sample preparation

A phosphate buffer of pH 7.5 was used as the aqueous media at a flow rate of 5 ml/min for the dissolution experiments in this study. The phosphate buffer was prepared by mixing a solution of 0.1 M sodium hydroxide solution to 0.1 M potassium dihydrogen phosphate solution in a 8:10 ratio. Both chemicals were products of Sigma–Aldrich (UK).

Indomethacin (γ-form) and PEG (4000 g/mol) were purchased from Sigma–Aldrich (UK). HPMC (K100 LV) was supplied from Colorcon (UK). Pure samples of different indomethacin were prepared by the following: γ-indomethacin was used as received; α-indomethacin was prepared using a solvent evaporation method (Kaneniwa et al., 1985) and amorphous indomethacin using the hot-melt method described below but without introduction of the polymer.

ASDs were prepared by a hot-melt method followed by quench cooling with liquid nitrogen. Two different tablet formulations containing 25% (w/w) loading of indomethacin were prepared: indomethacin with PEG (1:3 wt ratio); and indomethacin with HPMC (1:3 wt ratio). Amorphous indomethacin was heated to 165 °C followed by addition of the polymer. This temperature was maintained for 5 min whilst the molten formulation was stirred to achieve an even dispersion of both components in the mixture. The melts were removed from the heat and flash-cooled using liquid nitrogen. After measurements by conventional ATR-FTIR spectroscopy, the resulting ASDs were stored in a desiccator at room temperature until further use.

Model pharmaceutical tablets, 3 mm in diameter, were prepared by grinding the ASDs, sieving to select particles between 90 and 125 μm and compacting the resulting powder using a metal cell that was attached to the diamond ATR accessory (van der Weerd and Kazarian, 2004, 2005).

2.2. FTIR spectroscopy and spectroscopic imaging

An FTIR spectrometer (Alpha-P, Bruker, UK) in ATR mode with a single element detector was used to obtain conventional ATR-FTIR spectra presented in this manuscript. A spectral resolution of 8 cm^{-1} with 32 co-added scans was used throughout this investigation.

ATR-FTIR spectroscopic images in macro imaging mode (without the use of a microscope) were collected using an FPA detector with an array size of 64 × 64 pixels giving an approximate image size of 638 × 525 μm^2 with a spatial resolution of ~10 μm. The accessory used was a diamond ATR accessory (Specac Ltd., UK) fitted within the macrochamber linked to a spectrometer (Equinox 55, Bruker, UK). 8 cm^{-1} spectral resolution and 32 co-added scans

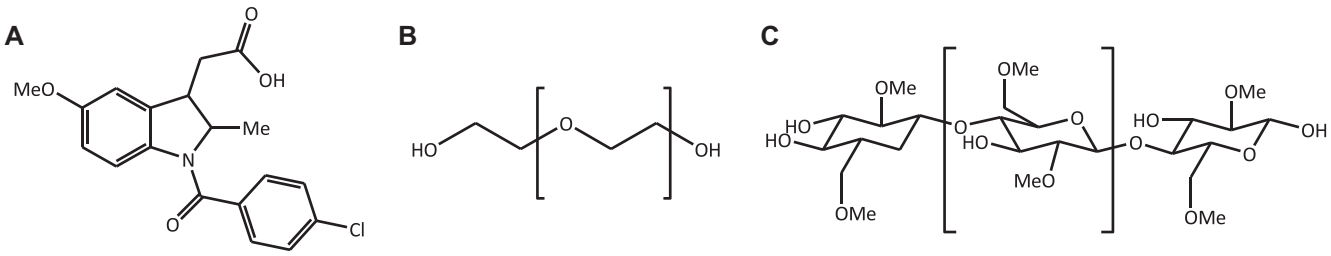

Fig. 1. Chemical structures of (A) indomethacin, (B) polyethylene glycol (PEG) and (C) hydroxypropyl methylcellulose (HPMC).