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Development and characterisation of sustained release solid dispersion oral tablets containing the poorly water soluble drug disulfiram

Mandip Shergill[a], Mina Patel[a], Siraj Khan[a], Ayesha Bashir[a], Christopher McConville[b,*]

[a] School of Pharmacy, Faculty of Science and Engineering, University of Wolverhampton, Wulfrana Street, Wolverhampton WV1 1LY, UK
[b] School of Pharmacy, Institute of Clinical Sciences, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK

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ABSTRACT

Administration of drugs via the oral route is the most common and preferred route due to its ease of administration, cost-effectiveness and flexibility in design. However, if the drug being administered has limited aqueous solubility it can result in poor bioavailability. Furthermore, the low pH of the stomach as well as enzymatic activity can result in drugs delivered via the oral route being rapidly metabolised and degraded. Here we demonstrate the development and characterisation of sustained release solid dispersion oral tablets, containing the poorly water-soluble drug disulfiram (DSF). The tablets, which are manufactured from two different polymers (Kolliphor® P 188 and P 237) specifically designed for the manufacture of solid dispersions and two different polymers (Kollidon® SR and HPMC) specifically designed to provide sustained release, can enhance the solubility of DSF, sustain its release, while protecting it from degradation in simulated gastric fluid (SGF). The paper demonstrates that when using the hot melt method at 80 °C the DSF loading capacity of the Kolliphor® P 188 and P 237 polymers is approximately 43 and 46% respectively, with the DSF completely in an amorphous state. The addition of 80% Kollidon® SR to the formulation completely protected the DSF in SGF for up to 70 min with 16% degradation after 120 min, while 75% degradation occurred after 120 min with the addition of 80% HPMC. The release rate of DSF can be manipulated by both the loading and type of sustained release polymer used, with HPMC providing for a much faster release rate compared to Kollidon® SR.

1. Introduction

Due to their ease of administration, cost-effectiveness and flexibility in design, oral tablets are the most common and preferred drug delivery dosage form (Yellela 2010). However, as result of low aqueous solubility and drug permeability drugs delivered via the oral route can have poor bioavailability (Savjani et al., 2012).

More and more class II of the Biopharmaceutical Classification System (BCS) are being developed, which means they have a low solubility and high tissue permeability and therefore bioavailability is dependent on solubility (Krishnaiah, 2010). This has resulted in a number of issues for the pharmaceutical industry as a result of limited flexibility in formulation and administration of poorly water soluble drugs (Mukherjee and Plakogiannis, 2010). A range of formulation approaches such as co-solvent systems; cyclodextrin complexation; salt-forming techniques; self-microemulsifying drug delivery systems (SMEDDS); prodrug formation and particle size reduction have been used to improve the water solubility of hydrophobic drugs (Brewster and Loftsson, 2007; Fleisher et al., 1996; Hintzen et al., 2014; McConville and Friend 2013; Millard et al., 2002; Miyako et al., 2010; Serajuddin 2007).

Solid dispersions, which are defined as the dispersion of one or more active ingredients in a matrix at solid state (Chaudhari, 2006), have been used to enhance the solubility of orally administered poorly water soluble drugs (Cho et al., 2014; Tran et al., 2014; Ramadhani et al., 2014). The enhancement in solubility can be attributed to increased wettability, reduction in particle size, reduction in agglomeration, changes in the physical state of the drug from crystalline to amorphous and even dispersion of the drug on a molecular level (Janssens and Van den Mooter, 2009). They offer a number of advantages over other types of solubility enhancement techniques, such as reducing the particle size to the molecular level, prevention of agglomeration of the drug particles through interactions between the drug and carrier, as well as enhancing absorption due to the drug being released in a supersaturated state (Muhrer et al., 2006; Karavas et al., 2006; Pouton, 2006; Moschwitzer, 2012). However, only a few solid dispersion based formulations are currently on the market as

* Corresponding author. Tel.: +44 121 414 4094.
E-mail address: C.McConville.2@bham.ac.uk (C. McConville).

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result issues relating to scale-up, phase separation and crystallisation during manufacture or storage (Chauhan et al., 2005; Pokharkar et al., 2006; Van den Mooter et al., 2006; Vasanthavada et al., 2004). There are a number of techniques, each with their own advantages and disadvantages, which can be used to manufacture solid dispersions: (1) the hot melt or fusion method, (2) the solvent evaporation method and (3) the hot melt extrusion method (Gupta et al., 2004; Abdul-Fattah and Bhargava, 2002; Sinha et al., 2010).

Disulfiram (DSF), which has been used as an anti-alcoholism drug for over 60 years, has demonstrated a have high cytotoxicity to a wide range of cancers with limited toxicity to normal cells (Brar et al., 2004; Cen et al., 2002, 2004; Chen et al., 2006; Lljin et al., 2009; Ketola et al., 2012; Liu et al., 2012; Yip et al., 2011). DSF has also been shown to increase the cytotoxicity of other anticancer drugs while protecting normal cells (Dufour et al., 1993; Verma et al., 1990). The anticancer effect of DSF has been shown to be copper (Cu) dependent (Cen et al., 2002; Cen et al., 2004) and due to cancer cells having increased copper levels compared to normal cells (Gupte and Mumper, 2009) DSF demonstrates selectivity towards cancer cells compared to normal cells. Its poor oral bioavailability and rapid metabolism in vivo has limited the clinical use of DSF as an anti-cancer drug (Agarwal et al., 2007). The solubility of DSF is 4.09 mg/L and it has a log P of 3.88, which makes it a BCS class II drug with poor water solubility. It is this poor water solubility that is limiting its clinical use as anti-cancer drug because it reduces its absorption rate from the stomach and thus increases its residence time within the stomach where it is rapidly metabolised (Johansson 1992). Therefore, we recently investigated the preparation and characterisation of DSF solid dispersion oral tablets in an attempt to significantly improve its solubility and thus oral bioavailability, with the possibility of improving its clinical use as an anticancer drug. We demonstrated that the solubility of DSF was significantly increased by formulating it into a solid dispersion (Ramadhani et al., 2014). We used the hot melt/fusion method and the solvent evaporation method, due to their simplicity and potential for scale-up, to manufacture solid dispersions of DSF in Kolliphor® P 188 and P 237 polymer matrices, which have been specifically designed for the manufacture of solid dispersions. The results demonstrated that the DSF solid dispersion tablets had an enhanced release rate of DSF, under non-sink conditions, compared to control tablets. Furthermore, we also showed that the hot melt/fusion method, with a processing temperature of 80 °C, was the best method, in relation to solubility enhancement and stability for manufacturing DSF solid dispersions (Ramadhani et al., 2014).

Sustained release polymers have been used to increase the stability of drugs in the stomach by protecting them from hydrolysis in the gastrointestinal fluid (Ratnaparkhi and Gupta, 2013). Sustained-release tablets are designed to slowly release drug at a rate governed predominately by the design of the delivery system. Many sustained release formulations are specifically designed for once-daily per-oral administration and have been shown to improve patient compliance and acceptability compared with conventional multiple daily dosing regimens (Claxton et al., 2001).

In this study we investigate the preparation and characterisation of sustained release DSF-loaded solid dispersion oral tablets in an attempt to significantly improve the solubility and thus oral bioavailability of DSF, while protecting it in the stomach from degradation. We believe that this strategy has the potential to improve the clinical use of DSF as an anticancer drug. The drug loading capacity of the solid dispersions was determined using melt rheology, while the solid dispersions were subsequently characterised for their crystallinity using PXRD and DSC. The solid dispersions were blended with either of the sustained release polymers HPMC or Kollidon® SR and subsequently tested for their powder flow and compressibility, then compressed into oral tablets. The tablets were then characterised for their hardness, friability, protection of DSF in simulated gastric fluid (SGF) and drug release into both sink and non-sink conditioned release media.

2. Materials and methods

2.1. Materials

Disulfiram (DSF), magnesium stearate, ethanol, sodium chloride, hydrochloric acid and hydroxypropylmethylcellulose (HPMC) were purchased from Sigma–Aldrich (Dorset, England). Kollidon® SR, Kolliphor® P 188 and P 237 were provided by BASF (Ludwigshafen, Germany).

2.2. Melt rheology

Continuous flow rheological assessment of the drug loading capacity of the Kolliphor® P 188 and P 237 polymers was carried out using a TA Instruments AR 2000 rotational Rheometer fitted with a 40 mm diameter steel parallel plate (Ramadhani et al., 2014). The appropriate amount of DSF and the appropriate amount of either Kolliphor® P 188 or P 237 was mixed together to produce a total of 3 g and placed onto the lower stationary plate of the rheometer, which was set to 80 °C. The blend was allowed to melt and further mixed the the upper plate was lowered to produce a gap between the plates of 1000 μm. Excess material was removed before initiating the test. Flow rheology was conducted in temperature sweep mode with the temperature decreased from 80 °C to 40 °C at a rate of 5 °C per minute.

2.3. Preparation of the 40% w/w DSF-loaded solid dispersions using the hot melt method

40 g of DSF and 60 g of either Kolliphor® P 118 or P 237 were ground together, using a pestle and mortar, to produce a fine powder and poured onto a glass plate heated to 80 °C. The resulting yellow liquid was mixed for 5 min using a heated palette knife, before being removed from the heat and allowed to cool. The powdered solid dispersion was scraped into the mortar and ground into a fine powder.

2.4. Powder X-ray diffraction (PXRD)

The PXRD analysis was performed on DSF, Kolliphor® P 188 and P 237 as well as the 40 and 50% w/w DSF-loaded solid dispersions using a Panalytical Empyrean diffractometer (PANanalyical, Almelo, The Netherlands) with Cu Kα radiation ($\lambda = 1.54060$) at 40 kV and 40 mA between 5° and 80° (2Theta) at 25 °C.

2.5. Differential scanning calorimetry

Thermal analysis of Kolliphor® P 188 and P 237 as well as the 40 and 50% w/w DSF-loaded solid dispersions was conducted using a Q200 TA Instruments differential scanning calorimeter (DSC). Approximately 10 mg of each sample ($n = 10$) was added to a DSC pan and placed in the thermal chamber of the DSC. The DSC analysis was performed between 30 and 90 °C at a heating rate of 10 °C/min.

2.6. Preparation of the 40% w/w DSF-loaded sustained release solid dispersion blends

0.5% w/w of magnesium stearate was blended into each of the solid dispersions to improve powder flow. The appropriate amount