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Solubility and dissolution rate enhancement of ibuprofen by co-milling with polymeric excipients

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ABSTRACT

The aim of this study was to enhance the kinetic solubility and dissolution rate of ibuprofen by co-milling with different excipients and to establish the underlying mechanism(s) for such enhancement. In the first-part, two excipients (HPMC and soluplus) were selected from seven, and the optimal ball-milling parameters of speed and time (18 Hz, 15 min) were determined based on solubility-enhancement and flow-ability criteria. In the second-part, co-milling of different weight-ratios of ibuprofen-to-excipient was carried out and solubility and dissolution rates were determined. Mechanisms of biopharmaceutical enhancement were studied by SEM, laser diffraction, DSC, and FTIR analysis of the co-mixtures. Ibuprofen solubility (0.09 mg/mL for un-milled) was increased by factors of 4–5 and 10–20 for HPMC and soluplus, respectively. The weakening of crystals, stabilization of the amorphous phase and an increase in solid-state hydrogen bonding are the likely mechanisms for this enhancement. Reductions in Q70% dissolution time were also observed, by a factor of 4 and 7 for ibuprofen:HMPC and ibuprofen:soluplus co-milled mixtures, respectively. Although, there were similar reductions in particle size, dispersibility and degree of amorphization in both mixtures, the higher dissolution rate for soluplus, over that for HPMC, must be due to the additional solubilization contribution to the kinetic solubility provided by soluplus.

1. Introduction

Milling and co-milling (which is defined as milling in the presence of an excipient) are well known techniques that have a positive influence on the kinetic solubility and dissolution rate of sparingly soluble drugs (Jagadish et al., 2010; Szafraniec et al., 2017). These procedures have been shown to provide a simple, efficient and economical method that does not require any particularly sophisticated equipment (Fisher, 2007). Moreover, the method has less environmental impact as it does not require the use any organic solvent (Friedrich et al., 2005). Co-milling combines the advantages of a reduction in particle size and the amorphization of a crystalline drug substance, which are the benefit of conventional milling of single materials, and have the additional benefits of improved wettability and solubilization that are provided by the co-milled excipient (Mosharraf and Nyström, 1995). Furthermore, it may also; i) prevent aggregation by the surface coverage of the charged particles (produced by milling), ii) stabilize the amorphous phase in the solid state and iii) reduce the mechanical/thermal degradation of drugs by moderating the effect of the heat generated on milling (Lin et al., 2010).

Solubility is a physicochemical property of substance, which depends on the thermodynamic properties of the crystal lattice (i.e. the bonding energies which define the melting point) and the balance between solute-solute and solute-solvent (solvation) interactions in the solution state. The solute-solvent interactions may be changed by adding other chemicals to the solvent, for example surfactants which provide a micellar environment for the solubilization of the drug. It is also important to remember that the solubility of a milled crystalline material, containing metastable (partially amorphous) phase, represents the kinetic solubility rather than thermodynamic/equilibrium solubility (Brittain, 2014).

The rate of dissolution, which defines the rate of mass transfer from the crystalline state to the dissolved (solution state) is coupled to the solubility but is also impacted by attributes of the material such as the

Abbreviations: PM, physical mixture; mPM, milled physical mixture; A, absorbance

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particle size distribution (surface to volume ratio), surface tension (which influences the wettability of the surface) and the physical form (i.e. whether in a crystalline or amorphous state). In the case of an amorphous solid (which is often present in a milled material) the supersaturated solution (i.e. one which exceeds the thermodynamic equilibrium solubility) can be obtained for a short time until the system relaxes and returns to the thermodynamic equilibrium (when the excess drug precipitates from solution). The presence of an excipient in the solution or from co-milling with excipient can affect both the solubility of drug (due to the alteration of the liquid medium and presence of more complex interactions between solvent, excipient and drug molecules) and the dissolution rate (including the relaxation time of oversaturated solution). An extension of the oversaturated state of the solution for few hours is desirable in order to increase the bioavailability of drug. Co-milling process may have an impact on all three aspects: a reduction in drug particles size, a partial conversion to amorphous state and the alterations to the molecular interactions between drug and solvent.

The focus of this study is the model drug Ibuprofen. It is one of many propionic acid derivatives that provide analgesia through the inhibition of the enzyme cyclooxygenase (COX). It is widely used in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and acute gouty arthritis (Brunton et al., 2006). Ibuprofen is practically insoluble in an aqueous or acidic medium (Saleh et al., 2008) resulting in poor bioavailability when administered as a conventional dosage form. The poor solubility of ibuprofen has been addressed using a variety of approaches. One of them is to reduce the particle size by milling (Plakkot et al., 2011), however; the milling of ibuprofen alone is difficult as it is a highly ductile material with a low melting point (Larsson and Kristensen, 2000). Nevertheless, the size reduction of ibuprofen has been achieved by co-milling with variety of excipients, i.e. aluminium hydroxide, kaolin and PVP (Mallick et al., 2008a; Mallick et al., 2008b). Other approaches to improve the solubility of ibuprofen include the preparation of solid dispersions with PEG (Hasnain and Nayak, 2012) or poloxamer (Newa et al., 2008b; Passerini et al., 2002) and the complexation with β-cyclodextrin (Chowdary and Susmitha, 2012; Salústio et al., 2011). In the majority of these studies, size reduction or the dispersion of the drug in an amorphous matrix were the underlying mechanisms for solubility and dissolution rate enhancement. Among the excipients used in the co-milling of ibuprofen in aforementioned studies, none would be expected to solubilise the drug.

In the recent works using soluplus for solubility enhancement by the way of hot melt extrusion (Albadarin et al., 2017), electro-spinning (Nagy et al., 2012), micellization (Ke et al., 2017), spray drying (Herbrink et al., 2017) and freeze drying (Nagy et al., 2012), it was suggested that this excipient may be used to advantage when co-milled with drugs, as previously used to form amorphous solid dispersion (Caron et al., 2013). In addition, there are many other prospective candidate excipients, which have not been investigated to date for their potential to enhance the solubility and dissolution rate of ibuprofen. Examples of such excipients include HPMC, MCC, PVP and lactose, which are the widely used materials owing to their hydrophilicity and wetting properties for many other drugs (Garg et al., 2009; Vogt et al., 2008a; Vogt et al., 2008b).

The objectives of this study are the enhancement of solubility and dissolution rate of ibuprofen and to understand the mechanisms involved. The development of method for assaying ibuprofen in the presence of interfering substance was also an objective of this study.

There are two phases to this work; In the first **(screening) phase**, a sub-set of excipient type and processing conditions (including the speed and time of milling) were selected on the basis of best outcomes in terms of processing properties (like flowability) and solubility of the drug. In the second **(extended) phase**, the optimal process parameters of speed and time were applied to prepare co-milled binary mixtures of ibuprofen with the sub-set of excipient and the effect on solubility and dissolution rate of ibuprofen determined. These co-milled mixtures were then characterized by various analytical techniques in order to establish the mechanism of solubility and dissolution rate enhancement.

2. Materials and methods

Ibuprofen was purchased from Fischer chemical, UK. Soluplus (a graft co-polymer of PEG) and lutrol F-68 (a block co-polymer non-ionic surfactant consisting of Poly-oxyethylene-(POE-) and Polyoxypropylene-(POP-) units) were obtained from BASF, UK as gift samples. Polyvinyl pyrrolidone (PVP K30) (Jiaozou Fine Chemical, China), hydroxy-propylmethyl cellulose (HPMC-E5) (Ashland, US), micro-crystalline cellulose (MCC), PEG-6000, lactose monohydrate were obtained from Merck, Germany. All excipients were of pharmaceutical grade and were used as received from the suppliers.

2.1. Assay of ibuprofen in co-milled mixtures

A 0.05% w/v solution of the un-milled ibuprofen in phosphate buffer of pH 7.4 was prepared and its UV spectrum was measured between 200 and 400 nm in UV spectrophotometer (2550, Schimadzou, Japan). From this spectrum, the wavelength of maximum absorbance (λ_{max}) was selected based on the highest clear peak (see Section 3.1).

In order to determine any interference in UV absorbance of ibuprofen by co-milled excipients, the UV spectrum of each excipient (0.05% w/v) was also measured and overlaid on the spectrum of ibuprofen (see Appendix 1). The interference as detected by soluplus was corrected by applying two wavelength assay approach or multivariate least square approach (see Section 3.3).

2.2. Screening phase

2.2.1. Co-milling of ibuprofen with excipients

At the initial stage of this study, an optimum milling speed and time was determined and a sub-set of excipients selected based on the binary mixtures that provided highest solubility while maintaining optimal flowability (Section 3.5).

For this purpose soluplus was used as trial excipient (as it was the only excipient that has shown the prominent effect on solubility of drug on changing the concentration while maintaining the flowability) and it was co-milled with ibuprofen in an oscillatory ball mill (MM 301, Retsch, Germany), according to following protocol.

i) For the selection of milling speed, Ibuprofen and soluplus (1:0.5 ratio) were co-milled at three different speeds, viz. 15, 18 and 25 Hz, for 15 min. The milling time of 15 min was selected on hit and trail basis to avoid melting of this drug.
ii) For the selection of milling time, the mill speed was fixed (i.e. 18 Hz, see results in Section 3.5) and ibuprofen was co-milled with soluplus (1:0.5 ratio) for 5, 10, 15 and 30 min.
iii) For the selection of best excipient for co-milling, Ibuprofen was co-milled with different excipients (soluplus, HPMC, lutrol, PVP, MCC, lactose and PEG-6000) with 1:1 ratio at the selected speed and time (18 Hz and 15 min, see results Section 3.1).

The solubility of co-milled mixtures was determined as per method described in Section 2.2.2.

2.2.2. Solubility studies

The well-known shake-flask method (Nandi et al., 2003) was used to determine the solubility of ibuprofen in distilled water (pH 6.1). For this purpose, an excess quantity of ibuprofen or its mixtures equivalent to 200 mg ibuprofen was added to a 100 mL conical flask containing 50 mL of the distilled water. The flasks were capped and shaken at 100 rpm on a multi-flask shaker (Heidolph Unimax 2010, Germany) at ~25 °C temperature. The samples were collected after 24 h, filtered