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Triboelectrification and dissolution property enhancements of solid dispersions

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ABSTRACT

The use of solid dispersion techniques to modify physicochemical properties and improve solubility and dissolution rate may result in alteration to electrostatic properties of particles. Particle triboelectrification plays an important part in powder processing, affecting end product quality due to particle deposition and powder loss. This study investigates the use of glucosamine hydrochloride (GLU) in solid dispersions with indomethacin. Solvents selected for the preparation of the dispersions were acetone, acetone–water, ethanol and ethanol–water. Solid state characterizations (DSC, FTIR and XRPD) and dissolution were conducted. Dispersions were subjected to charge using a custom built device based on a shaking concept, consisting of a Faraday cup connected to an electrometer. All dispersions improved the dissolution rate of indomethacin. Analysis showed the method of preparation of the dispersion induced polymorphic forms of the drug. Indomethacin had a high propensity for charging (−411 nC/g). GLU had a very low charge (−1 nC/g). All dispersions had low charges (−1 to 14 nC/g). Acetone as a solvent, or in combination with water, produced samples with an electronegative charge in polarity. The same approach with ethanol produced electropositive charging. The results show the selection of solvents can influence powder charge thereby improving powder handling as well as dissolution properties.

1. Introduction

Biopharmaceutical classification system (BCS) class II drugs are characterized by high membrane permeability and low aqueous solubility. This poor aqueous solubility is problematic in pharmaceutical development and seems to be more prevalent with new drug entities (Al-Hamidi et al., 2010a; Baird and Taylor, 2012; Fahr and Liu, 2007). The solubility and dissolution rate of drugs in this category are key factors in determining their rate and extent of absorption from the gastrointestinal tract. As dissolution rates are typically the rate limiting step for bioavailability, their enhancement is often vital to attaining suitable blood concentrations for therapeutic effect.

There are several methods employed to aid the improvement of the dissolution rate of BCS class II drugs. The most common method involves particle size reduction using high pressure milling methods with the view of increasing the surface area (Rabinow, 2004; Valizadeh et al., 2004). The drawback with this method is the requirement for high energy input. Moreover, the product obtained after such high energy input is likely to increase affinity for electrostatic charging, leading to particle agglomeration and broad particle size distributions. Other methods used include complexation (Loftsson and Duchene, 2007), liquisolid techniques (Javadzadeh et al., 2007; Nokhodchi et al., 2005), salt formation (Berge et al., 1977; David et al., 2012) and solid dispersions (Al-Hamidi et al., 2010a). Despite limitations such as cost and scale

Abbreviations: GLU, glucosamine hydrochloride; DSC, differential scanning calorimetry; XRPD, X-ray powder diffraction; FTIR, Fourier transform infra-red; BCS, biopharmaceutical classification system; CBZ, carbamazepine; PXM, piroxicam; IBU, ibuprofen; IND, indomethacin; NSAID, non-steroidal anti-inflammatory drug; A, acetone; A/W, acetone–water; E, ethanol; E/W, ethanol–water; SEM, scanning electron microscopy; DE, dissolution efficiency; MDT, mean dissolution time; MDR, mean dissolution rate; ATR, attenuated total reflection; RH, relative humidity; PSD, particle size distribution; USP, United States pharmacopeia; PM, physical mixture; VIBRI, vibratory feeder; HELOS, Helium-Neon Laser Optical System.

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up with solid dispersions, adoption of cost-effective solvents along with method modifications can be selected to minimise these.

Solid dispersion formation is one of the most effective methods of improving dissolution and has had much interest in recent years (Al-Hamidi et al., 2010a; Baird and Taylor, 2012). The increased solubility and dissolution rate of drugs in solid dispersions could be the result of a reduction in particle size down to submicron (1–100 nm) levels (Manikandan et al., 2012), conversion from crystalline to amorphous form and the improved wettability of the drug particle by the dissolved hydrophilic carrier (Leuner and Dressman, 2000).

Glucosamine is a popular nutritional supplement for both humans and dogs and naturally occurring glucosamine has been shown to decrease pain and improve mobility in osteoarthritic joints of humans when given orally (da Camara and Dowless, 1998; Pujalte et al., 1980). The incorporation of glucosamine HCl (GLU) into formulations may give additional benefit to patients requiring anti-inflammatory drugs, due to glucosamine's ability to decrease pain and improve mobility in osteoarthritic joints. Al-Hamidi et al. (2010a) showed it enhanced the dissolution rate of carbamazepine (CBZ) from solid dispersion formulations when used as a hydrophilic carrier. Al-Hamidi et al., 2010b, 2013, 2014 also showed that the incorporation of glucosamine in ground piroxicam (PXM), ibuprofen (IBU) or CBZ mixtures co-ground together, significantly increased the dissolution rates of the respective drugs. They also showed that increasing the grinding time resulted in polymorphic transformation of the drugs (CBZ and PXM). Indomethacin (IND) is a non-steroidal anti-inflammatory drug (NSAID). NSAIDs are widely used for rheumatoid arthritis, osteoarthritis and a variety of other acute and chronic musculoskeletal disorders, dysmenorrhea and as ordinary analgesics (Andersson et al., 1998; Montvale, 2002). Indomethacin was selected as a model BCS class II compound due to its low solubility to establish the efficiency of the solid dispersion method employed in this work.

The use of solid dispersion techniques to modify physicochemical properties to improve solubility and dissolution rate may also result in changes in the electrostatic properties of particles. Particle triboelectrification plays an important part in powder processing affecting end product quality due to particle deposition and powder loss. It has been shown to give rise to segregation of binary mixtures (Supuk et al., 2011); however, very little work has been done to understand electrostatic charging characteristics of powders produced from solid dispersions.

In pharmaceutical processes, triboelectrification refers to a method of particle electrification which can take place during powder handling operations. Such charging can be regarded as a solid state electrochemistry, where there is no transport medium (electrolyte) and their action depends solely on physical contact (Matsusaka et al., 2010). Although, the exact charge transfer mechanisms in dielectric materials are still ambiguous, fundamental studies on charge transfer between an elastic sphere and a metal plate have shown the charge transfer to be completed during the unloading stage of the elastic deformation following the impact (Matsusaka et al., 2000). Therefore, essential pharmaceutical processes such as high-shear granulation are likely to influence the magnitude of charge generated as processing parameters are shown to affect the strength and size distribution of resulting granules (Rahmanian et al., 2008, 2011). Furthermore, pharmaceutical powders are usually insulators and have a relatively small particle size and low bulk density, thus providing ideal conditions for tribo-electric charging (Šupuk et al., 2012). Šupuk et al. (2013) studied the impact of the counter ion on electrostatic charge of flurbiprofen salts. The results showed the magnitude of charge and polarity of the flurbiprofen salts to be highly dependent on the type of counter ion selected for the salt formation. Ghori et al. (2014) also found cellulose ethers to reduce the charging of flurbiprofen thereby improving its flow and compaction properties.

The objective of this study was to produce indomethacin: glucosamine solid dispersions to investigate the role of solvent (ethanol and acetone and their binary mixtures with water) on dissolution enhancement and electrostatic properties. Tribo-electric properties of the solid dispersions were investigated using a custom built tribo-electric device based on a shaking concept. The present work was conducted to determine whether solid dispersions could improve the dissolution profiles and to understand their effect on charging characteristics of the indomethacin–glucosamine dispersions.

2. Materials and method

2.1. Materials

Indomethacin (γ-form) and D-(+)-glucosamine hydrochloride (GLU) were purchased from Sigma (UK). The solvents were of analytical grade and all the materials were used as obtained. The dissolution medium (pH 7.2) was prepared according to the USP 2003 method using the following materials: potassium phosphate monobasic-white crystals and sodium hydroxide (Sigma (UK)).

2.2. Hansen's solubility parameter

The Hansen solubility parameter (δ) was calculated for indomethacin and glucosamine by considering their chemical structure (Hansen, 1969). This was used to predict the miscibility of both the drug and carrier. The Hoftyzer–Van Krevelen method described below was used in the determination of the drug/carrier miscibility (Gupta et al., 2011; Hansen, 1969; Hoftyzer and Krevelen, 1976; Maniruzzaman et al., 2014).

$$\delta_d = \frac{\sum F_{\mathrm{di}}}{V}, \tag{1}$$

$$\delta_p = \frac{(\sum F_{\mathrm{pi}})^{0.5}}{V}, \tag{2}$$

$$\delta_h = \left(\frac{\sum E_{\mathrm{hi}}}{V}\right)^{0.5}, \tag{3}$$

and

$$\delta_t^2 = \delta_d^2 + \delta_p^2 + \delta_h^2, \tag{4}$$

where F_{di} and F_{pi} are molar attraction constants due to dispersion ($\mathrm{J}^{1/2}\,\mathrm{cm}^{3/2}\,\mathrm{mol}^{-1}$) and polar ($\mathrm{J}^{1/2}\,\mathrm{cm}^{3/2}\,\mathrm{mol}^{-1}$) components, respectively and E_{hi} is the hydrogen bonding energy (J/mol). δ_d, δ_p and δ_h are the dispersive ($\mathrm{MPa}^{1/2}$), electrostatic polar ($\mathrm{MPa}^{1/2}$) and hydrogen bonding forces ($\mathrm{MPa}^{1/2}$), respectively with V being the molar volume (cm^3/mol). δ_t is known as the total solubility parameter also known as the Hansen solubility parameter. The molar volume of the drug and carrier were calculated based on their density and molecular weight, as determined from literature.

2.3. Preparation of physical mixtures of drug-carrier

Physical mixtures of indomethacin were prepared by mixing indomethacin and D-(+)-glucosamine hydrochloride in a Turbula blender (Type T2C, Switzerland) for 10 min. Different ratios of drug:carrier (2:1, 1:3, 1:5 and 1:10) were prepared for comparison.