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Solid-state, triboelectrostatic and dissolution characteristics of spray-dried piroxicam-glucosamine solid dispersions

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ABSTRACT

This work explores the use of both spray drying and D-glucosamine HCl (GLU) as a hydrophilic carrier to improve the dissolution rate of piroxicam (PXM) whilst investigating the electrostatic charges associated with the spray drying process. Spray dried PXM:GLU solid dispersions were prepared and characterised (XRPD, DSC, SEM). Dissolution and triboelectric charging were also conducted. The results showed that the spray dried PXM alone, without GLU produced some PXM form II (DSC results) with no enhancement in solubility relative to that of the parent PXM. XRPD results also showed the spray drying process to decrease the crystallinity of GLU and solid dispersions produced. The presence of GLU improved the dissolution rate of PXM. Spray dried PXM: GLU at a ratio of 2:1 had the most improved dissolution. The spray drying process generally yielded PXM-GLU spherical particles of around 2.5 μm which may have contributed to the improved dissolution. PXM showed a higher tendency for charging in comparison to the carrier GLU (−3.8 *versus* 0.5 nC/g for untreated material and −7.5 *versus* 3.1 nC/g for spray dried materials). Spray dried PXM and spray dried GLU demonstrated higher charge densities than untreated PXM and untreated GLU, respectively. Regardless of PXM:GLU ratio, all spray dried PXM:GLU solid dispersions showed a negligible charge density (net-CMR: 0.1–0.3 nC/g). Spray drying of PXM:GLU solid dispersions can be used to produce formulation powders with practically no charge and thereby improving handling as well as dissolution behaviour of PXM.

1. Introduction

The physiochemical properties of a drug can influence the choice of dosage form in which it is delivered. Properties such as stability, pK_a, partition coefficient and salt forms are all taken into consideration during pre-formulation studies [1]. In addition, it is important to assess the aqueous solubility, dissolution rate and intestinal permeability of a drug. These three factors have been used to classify drugs in the Biopharmaceutical Classification System (BCS) into four different classes [2]. BCS class II drugs are characterised by high membrane permeability but low aqueous solubility therefore; there is a low drug concentration gradient between the gut and the blood vessels limiting drug transport and oral bioavailability. The poor solubility of drugs has always been a major problem in pharmaceutical development and this problem is now more prevalent with more than 40% of the new chemical entities being practically insoluble in water or lipophilic in nature [3–7]. As dissolution rates are typically the rate-limiting step for bioavailability, especially for poorly soluble drugs, enhancement of solubility is vital to attaining suitable systemic concentrations for therapeutic effect [8].

Despite the recent advances in particle engineering, one of the most common method employed to aid the improvement of the dissolution rate of poorly soluble drugs is particle size reduction using high shear milling methods [9,10]. This enhancement of dissolution

Abbreviations: GLU, D-glucosamine hydrochloride; DSC, differential scanning calorimetry; XRPD, X-ray powder diffraction; FTIR, fourier transform infra-red; BCS, biopharmaceutical classification system; CBZ, carbamazepine; PXM, piroxicam; NSAID, non-steroidal anti-inflammatory drug; DE, dissolution efficiency; MDT, mean dissolution time; MDR, mean dissolution rate; ATR, attenuated total reflection; PSD, particle size distribution; USP, United States pharmacopoeia; PM, physical mixture.

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rate by size reduction is due to the fact that solubility of drugs in intrinsically related to particle size of the drug [7]. As the particle size of the drug is reduced, the surface area available for solvation also increases. Particle size reduction is a safe method of increasing drug dissolution without altering the chemical nature of the drug. However, although particle size reduction leads to an increase in the effective surface area of the drug available to interact with the solvent, it does not increase equilibrium solubility of the drug [11] unless the sizes of particles are reduced to below 1 micrometre [12]. In addition, micronization may cause agglomeration and thus may negatively impact on the solubility and bioavailability during the storage of the final product [13]. Moreover, milled particles usually exhibit a high level of electrostatic charge; such high level of charge can increase the inter-particle cohesive forces leading to poor product performance [14–16].

Other methods used to improve drug solubility include complexation [17], liquisolid techniques [18,19] and salt formation [20,21]. Several authors have classed the solid dispersion approach as one of the most effective method of improving dissolution of drugs [5,8,22]. It involves the dispersion of one or more active ingredients in an inert excipient or carrier, where the active ingredients could exist in a finely crystalline, solubilised or amorphous state [23,24]. Solid dispersion also enhances the absorption and efficacy of drugs in a dosage form, despite limitations such as cost, scale up and physicochemical instabilities of the dispersions under normal storage conditions [25–27]. Al-Hamidi and co-workers have studied the rate of carbamazepine (CBZ), ibuprofen (IBU) and PXM (PXM) in solvent evaporated and co-ground solid dispersions [3,22,28,29]. Asare-Addo et al. [8], also studied the effect of GLU on indomethacin (IND) dissolution and charging properties using a solvent evaporation process. All these authors showed that incorporation of GLU in PXM, IBU, CBZ and IND using either the solvent evaporation or grinding method significantly increased the dissolution rates of these drugs. They attributed the increased solubility and dissolution rate of drugs observed to be due to particle size reduction to sub-micron levels, change in polymorphic forms and the improved wettability of the drug particle by the dissolved hydrophilic carrier [28,30].

PXM (4-hydroxy-2-methyl-*N*-(2-piridyl) 2H-1,2-benzothiazine-3-carboxamide-1, 1-dioxide) is one of the most potent non-steroidal anti-inflammatory and analgesic drugs used in treatment of various acute and chronic musculoskeletal and joint disorders [31]. This drug was used as the model BCS class II drug. In addition, GLU was the preferred hydrophilic carrier due to its popular use as a nutritional supplement for humans in decreasing pain and improving mobility in osteoarthritic joints of humans when administered orally [32,33]. The limited solubility of PXM leads to a delayed onset of therapeutic effect. Oral absorption is slow and gradual with maximum absorption occurring 3–5 h after administration and a long half-life of elimination [34].

Spray drying of poorly soluble drugs could potentially enhance their solubility [35]. The state of the final spray dried product depends on the nature of the drug as the process may result in the amorphous, partially crystalline, metastable crystal forms [36]. The ability of a pure drug substance to convert into its amorphous form during spray drying depends mainly on its inherent glass forming ability and crystallization tendency [37] and to a lesser extent on the preparation methods [38,39]. In the amorphous state, the drug exhibits high levels of super-saturation in aqueous media compared to the crystalline drug, thereby achieving higher apparent solubility [40]. Spray drying works by providing a large surface area where heat transfer and atomization of the solution or suspension into small droplets can occur. It is also good at producing a uniform product that is spherical in shape [41]. By spraying the substance into a steam of hot air, the droplet will dry to form individual solid particles at a fast drying rate within milliseconds to a few seconds as a result of the high surface to volume ratio, which prevents phase separation between the drug and polymer components [42].

In pharmaceutical development field, characterization of the electrostatic properties of powders has become a subject of extensive research [43]. Electrostatic charging within powders is generated from inter-particulate contacts and collisions (particle–particle and particle-surface collisions) in a gaseous environment; *i.e.* two different materials brought to contact and then separated [44]. To date, there are no pharmacopoeial methods for charge characterization [45]. Although bipolar charging commonly takes place in industrial processes of pharmaceutical particulates [46], the most prevalent assessment of tribocharging is gained from the Faraday pail method, which provides only limited information in the form of net charge-to-mass ratio [47]. In this work, a novel instrument recently developed in the Wolfson Centre [48] (Fig. 1a) to characterise the charge properties of the particulate materials under investigation in the form of charge distribution is used. The major advantages of this method of charge sensing include its high sensitivity (charges on the particles equal or more than to 30×10^{-15} C are detectable), quick measurement (<1 min) and the lack of the particle flow disturbance. Kaialy et al. [16] applied the latter method to characterise the charge distribution of several size fractions of spray dried mannitol. In this study, the efficiency of the spray drying process in enhancing the dissolution rate of the PXM using GLU as a hydrophilic carrier is investigated. Recently, Adebisi et al. [49], also utilized this methodology in determining the charge distribution in co-ground solid dispersions. The charging propensity of the solid dispersions produced as a result of the spray drying process is also assessed to determine its effect on the handling of these dispersions. To the best of our knowledge, there is no reported work that has investigated the use of GLU in spray dried solid dispersions and the charge distributions from resulting samples.

2. Materials and methods

2.1. Materials

PXM was purchased from TCI Chemicals (Japan). GLU was purchased from Sigma-Aldrich (UK). The solvent used (acetone) was obtained from Fischer Scientific (UK) was of analytical grade and was used as obtained. The dissolution medium (pH 1.2) was prepared according to the USP 2003 method using the following materials: KCl (Sigma, UK) and concentrated HCl (Fisher, UK).

2.2. Preparation of PXM-GLU physical mixtures

Physical mixtures (PM) of PXM were prepared by mixing PXM and GLU in a Turbula® blender (Type T2C, Switzerland) for 10 min. Different PXM:GLU ratios (2:1, 1:1 and 1:2) were prepared for comparison. The powders were stored in screw-capped glass vials in a desiccator at room temperature until required after the mixing process.

2.3. Preparation of spray dried solid dispersions of drug-carrier

The spray drier (SD-06AG laboratory spray dryer, LabPlant UK) was set up in a closed mode configuration with an inlet temperature of 70 °C, a feed flow rate set to 10 mL min^{-1} and a nozzle size of 0.5 mm. Suspensions of PXM and GLU were made at three different drug:carrier ratios: 1:1 (Sample A) 1:2 (Sample B) and 2:1 (Sample C). When making the 1:1 ratio, 1.5 g of PXM was dissolved in a beaker containing 600 mL of acetone whereas 1.5 g of GLU was dissolved in a beaker containing 600 mL of deionised water under stirring conditions. The two solutions were then mixed together to