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The effect of mesoporous silica impregnation on tribo-electrification characteristics of flurbiprofen

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ABSTRACT

Tribo-electrification is a common occurrence within the pharmaceutical industry where solid dosage forms constitute majority of pharmaceutical formulations. Tribo-electrification of powders leads to a range of complications such as adhesion of particulate material to the processing equipment resulting in segregation, affecting the content uniformity. Flurbiprofen, a highly charging material, was used as a model drug to investigate the tribo-electrification and adhesion characteristics by impregnating the model drug inside a mesoporous silica matrix. The model drug was impregnated using i) solvent loading, and ii) physical mixing methods, at varying degree of silica to drug ratio (5–20% w/w). The resulting mixtures were tribo-charged using a custom built device based on a shaking concept inside a stainless steel capsule, consisting of a Faraday cup and connected to electrometer. The electrostatic charge and the percentage adhesion of Flurbiprofen were reduced in both drug loading methods. The solvent impregnation method using acetone was more successful at reducing the electrostatic charge build up on flurbiprofen than physical powder mixing. The percentage adhesion to the shaking capsule was reduced notably as a result of loading the drug in the SBA-15 porous network. The results illustrate that the incorporation of highly charged model drug inside a low-charging pharmaceutical carrier system to be an effective approach in control the induction of tribo-electrification phenomena during powder processing.

1. Introduction

In many industrial applications such as pharmaceutical, detergent, cosmetics and food manufacturing, powder handling is a challenging process due to complications arising during the manufacturing process. A common obstacle faced in powder handling is the powder tribo-electrification phenomenon (Watanabe et al., 2007; Kaialy 2016). The phenomenon is complex and not well understood due to many factors affecting the charge transfer process. Currently, three fundamental mechanisms contributing to charge generation by tribo-electrification are most commonly reported include material transfer, ion transfer and electron transfer. The most widely accepted theory is electron transfer, working on a principle of varying work function (∅) of material, ∅ is the minimum energy required to remove electrons in the outer electron shell of an atom. Resulting in the flow of electron from the lower work function towards the higher, inducing a potential difference across the particle surface, allowing for charge to transfer (Cross, 1987).

Tribo-electrification occurs when particles come into contact with one another or the walls of processing equipment in unit operations such as mixing, conveying, granulating or blending when these two dissimilar materials make contact by impaction or shearing and are subsequently separated, holding any charge transferred (Matsusaka et al., 2010). Charged materials have a tendency to adhere or repel powder particles, resulting in flowability issues and potentially may lead to blockages of pipes by particle adhesion to the walls of processing equipment (Matsusaka and Masuda, 2003). Within the pharmaceutical industry this can be problematic and in extreme cases, tribo-electrification of material may lead to dust explosions (Šupuk et al., 2011). These challenges are faced during common powder handling processes such as milling, filling and compaction, in addition to a rise is unit operation problems leading to segregation of materials, impacting the quality of the end product by jeopardising the content uniformity of the batch (Lakhani and Deshpande, 2013). Investigating alternative methods for charge control is therefore crucial.

SBA-15 is a highly porous material with a rising interest for its application in drug delivery (Colilla et al., 2015; Yu and Zhai, 2009). It

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is comprised of nano-sized cylinder filled with regular arranged pores, expected to provide a more versatile drug delivery material (Song et al., 2005). In this paper the principle of the highly charging material is embedded within the silica pores, to provide a low-charging carrier system. The model drug was impregnated using i) solvent loading, and ii) physical mixing methods, at different silica ratios and the drug loading ability was compared. The purpose of drug loading would allow for the API to be administered in its original form, without the need for lengthy steps to aid in material handling properties whilst maintaining physicochemical properties (Ghori, 2014; Ghori et al., 2015). Currently no work has been reported on the effects of SBA-15 upon the charging tendency of a pharmaceutical material, prompting the purpose of this study.

As many active pharmaceutical ingredients (APIs) have a propensity to become electrostatically charged, various techniques are utilised to aid material handling by improving the physicochemical properties, however, these can lead to further complications (Šupuk et al., 2013) such as extra steps increasing processing times. For the purpose of this study, FBP) was chosen as the model material due to its crystalline nature and poor adhesion properties, factors which are characteristic of materials possessing a high propensity for tribo-charging (Šupuk et al., 2013). Murtomaa et al. believe that the amorphicity has a measurable effect on the tribo-charging of powders (Murtomaa et al., 2002) A study undertaken by Carter et al. investigates the tribo-electrification of spray dried and crystalline lactose which concluded significant differences in charge values between the two lactose powders under the same conditions (Carter et al., 1998). A more recent studies have examined the tribo-electrification of amorphous salbutamol sulfate which was more electropositive than jet-milled crystalline particles (Kwok and Chan, 2008). Such results could have been seen due to different surface energies between crystalline and amorphous materials leading to varying charge values (Zhang et al., 2006). FBP is well known for its poor compaction, solubility and dissolution (Ghori et al., 2014a; Rudrangi et al., 2016) properties due to its propensity to adhere to the punch surfaces, FBP has been reported as a highly sticking compound (Paul et al., 2017). The adhesion properties may be due to the ability of the powder to withhold high levels of electrostatic charge, reducing the propensity for gaining charge may lead to an improvement in material handling as well as compaction properties (Šupuk et al., 2013). In this study we have incorporated FBP within the extremely porous SBA-15 material, which possesses a large surface area, allowing for the pores to be filled with the drug, with an aim reduce the charge propensity whilst maintaining therapeutic potency, as well as quantifying the percentage adhesion of drug material to the shaker walls. The model would then be used to explore other systems to investigate their charging tendency as a result of being loaded within the low-charging carrier system.

2. Materials and methods

2.1. Materials

Flurbiprofen was purchased from Aesica Pharmaceutical Ltd. (Cramlington, UK) and Mesoporous silica (SBA-15) was obtained from ACS Material (California, USA). The solvent used was Acetone, purchased from Fisher Scientific (Loughborough, UK).

2.2. Methods

2.2.1. Fractionation of SBA-15 and FBP particle size

Particle size fractions of SBA-15 (150–250 μm) and Flurbiprofen (38–63 μm) were obtained through mechanical sieving. All the powders were stored at ambient temperature (18–24 °C) and humidity (RH 36%–44%) before any further investigations.

2.2.2. Development of SBA-15: FBP powder mixtures

The binary mixtures of SBA-15 and FBP of varying SBA-15 to FBP ratios (5–20%w/w) were prepared using two loading methods; solvent impregnation and powder impregnation, allowing for a comparison of drug distribution throughout the mesoporous silica matrix.

2.2.2.1. Solvent impregnation method. SBA-15: FBP mixtures were prepared by dissolving 1.5 g of pure drug in 5 ml of acetone. After the drug has completely dissolved, the ratio dependant quantity of SBA-15 was added, and the solution was stirred for 5 min. The samples were initially dried at room temperature for 24 h followed by a further 24 h drying at 40 °C using conventional oven.

2.2.2.2. Powder physical mixing. SBA-15: FBP physical mixtures were prepared by placing 5 g of drug and the relevant ratio of SBA-15 in a glass container and mixed for 10 min at 49 rpm using a Turbula mixer (Glen Creston Ltd, UK). The container was left for 2 days for any potential charge to dissipate.

2.2.3. Physicochemical characterisation of powder mixtures

2.2.3.1. Differential scanning Calorimetry (DSC) studies. Differential Scanning Calorimetry (DSC) was undertaken using Mettler Toledo SC 821, Mettler-Toledo Ltd., Leicester, UK. Specimens of 5–10 mg were placed in vented aluminium pans under nitrogen purge at 50 ml min^{-1}, over a range of 25–300 °C at a heating rate of 10 °C min^{-1}. An estimated percent crystallinity of the binary mixtures was assessed using Eq. (1), relative to the melting enthalpy of crystalline FBP as a reference.

$$\%Relative\ crystallinity = \left(\frac{melting\ enthalpy\ of\ the\ sample}{melting\ enthalpy\ of\ the\ reference\ standard}\right) \times 100 \quad (1)$$

2.2.3.2. Thermogravimetric analysis (TGA). Thermogravimetric analysis (TGA) was performed using a Mettler Toledo TGA, Mettler-Toledo Ltd., Leicester, UK, samples between 5 and 10 mg and a temperature range of 25–500 °C at a heating rate of 5 °C min^{-1} were used. The process was carried out under a nitrogen purge at a constant flow rate of 50 ml min^{-1}.

2.2.3.3. Powder X-Ray diffraction (XRD). The Bruker D_2 Phaser XRD diffractometer by Bruker, Coverntry, UK was used to obtain patterns for the parent drug (FBP) and SBA-15 as well as the powder mixes. The sample powders were scanned at a *2 θ (5°–100°)* at a scanning rate of 1.5 min^{-1}.

2.2.3.4. Content uniformity analysis. The concentration of FBP was quantified by UV–Vis spectrophotometry, (Jenway 6305 UV–Vis Spectrophotometer, λ max = 247 nm) (Verma et al., 2016) where 10 mg of sample was randomly obtained from each batch (n = 3), dissolved in 100 ml of phosphate buffer at pH 7.2 for 24 h (Ghori et al., 2014b). The sample was then filtered using a 0.45 ml PTFE syringe filter. The acceptance limit was in the 95–105% range (BP, 2012).

2.2.3.5. Brunauer–Emmett–Teller (BET) analysis. Pore size and surface area was analysed using the Micromeritics 2020 apparatus. The study was carried out at 77 K, prior to analysis the samples were de-gassed in a vacuum oven at 100 °C for 10 h, using a FlowPrep 060. The surface area of the sample was calculated using Brunauer–Emmett–Teller (BET) equation from the adsorption data (Brunauer et al., 1938). The pore-size distribution results are generated from the adsorption branches of the nitrogen isotherms using the BJH model (Barrett et al., 1951). Each sample was analysed in duplicate.

2.2.4. Tribo-electrification studies

The charge to mass ratio (*Q/M*) of the materials was obtained using a shaking concept originally described by (Šupuk et al., 2009) and