



## Bulk, surface properties and water uptake mechanisms of salt/acid amorphous composite systems



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### ABSTRACT

Developing amorphous pharmaceuticals can be desirable due to advantageous biopharmaceutical properties. Low glass transition temperature ( $T_g$ ) amorphous drugs can be protected from crystallisation by mixing with high  $T_g$  excipients, such as polymers, or with salt forms. However, both polymers and salts can enhance the water uptake. The aim of this study was to formulate physico-chemically stable amorphous materials, by co-processing different proportions of sulfathiazole and its sodium salt to produce an optimum ratio, characterised by the best physical stability and lowest hygroscopicity. Both sulfathiazole and salt amorphised upon spray drying. At room temperature, sulfathiazole crystallised within 1 h at <5% relative humidity while the salt deliquesced when exposed to ambient humidity conditions. In the case of composite systems, FTIR spectroscopy, thermal and surface analysis suggested interactions with an acid:salt stoichiometry of 1:2. Increasing proportions of salt raised the  $T_g$ , enhancing the storage stability, however this was opposed by an enhanced hygroscopicity. The water uptake mechanism within the different amorphous systems, analysed by fitting the water sorption isotherms with the Young and Nelson equation, was dependent on the ratio employed, with the salt and the acid facilitating absorption and adsorption, respectively. Tuning the properties of amorphous salt/acid composites by optimising the ratio appears potentially promising to improve the physical stability of amorphous formulations.

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### 1. Introduction

The requirement to improve the bioavailability of poorly soluble active pharmaceutical ingredients (API) has resulted in a growing use of processes such as milling and spray drying, which reduce particle dimensions and increase specific surface area. It is well established that partial or full amorphisation of an API can occur as a result of these processes and that changes in the solid state nature can alter the physicochemical and biopharmaceutical properties (Caron et al., 2011; Tajber et al., 2005; Yu, 2001). Amorphous materials are structurally disorganised and have different bulk and surface properties compared to the corresponding crystalline materials. They typically display higher surface free energy (Newell et al., 2001b), higher hygroscopicity (Newman et al., 2008), greater solubility and a higher dissolution rate (Tajber et al., 2005). Although these properties are relevant from a pharmaceutical development perspective, the full exploitation of amorphous drugs and formulations cannot always be achieved, mainly due to low

physical and chemical stability (Caron et al., 2011; Yu, 2001). Therefore a thorough understanding of the properties of the amorphous state is required to develop new strategies to physico-chemically stabilise amorphous compounds.

Previously, we studied several physicochemical properties of sulfathiazole (ST) and sulfathiazole sodium (STNa), which solidify into unstable amorphous materials on spray drying (Bianco et al., 2012). The acid rapidly crystallised regardless of the relative humidity (RH) conditions. The crystallisation of amorphous solids can be promoted by heat and therefore these materials usually require storage at temperatures well below their glass transition temperature ( $T_g$ ) (Caron et al., 2011; Hancock et al., 1995; Yu, 2001). Considerable effort has been made to address this problem, either by co-processing heat labile amorphous drugs with high  $T_g$  excipients (Caron et al., 2011) or by using amorphous salt forms of these compounds (Tong et al., 2002; Tong and Zografis, 1999). In many cases a shift of the  $T_g$  to higher temperature has been achieved, which is potentially a good strategy to stabilise amorphous formulations. However this is not always sufficient and other influential factors affecting stability must also be considered. For instance, amorphous STNa was characterised by a 60 °C increase in  $T_g$  compared to ST and was physically stable when stored under desiccated

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**Table 1**

Spray drying parameters for ST:STNa systems (an inlet temperature higher than 85 °C for ST 9:1 resulted in partially crystalline materials. For the other systems an inlet temperature lower than 90 °C resulted in wet powders).

ST:STNa weight ratio (w/w)	Code	Inlet (°C)
9:1	ST 9:1	85
8:2	ST 8:2	90
3:1	ST 3:1	90
3:2	ST 6:4	90
1:1	ST 1:1	90
4:6	ST 4:6	90
1:3	ST 1:3	90
15:85	ST 15:85	90

conditions. Nevertheless, it deliquesced when exposed to ambient RH conditions (Bianco et al., 2012).

Deliquescence together with adsorption, capillary condensation, hydrate formation and absorption, is one of the known mechanisms of solid-water interactions (Airaksinen et al., 2005; Hiatt et al., 2011). It is a first order phase transition that happens when a water soluble solid generates a saturated solution by dissolving into the water sorbed from the environment at a specific relative humidity (RH<sub>0</sub>) characteristic for that solid. Due to high void space and enlarged free volume relative to the crystalline state, amorphous substances absorb water below RH<sub>0</sub> and undergo deliquescence at a lower RH compared to their crystalline counterparts (Mikhailov et al., 2009). The amount of water absorbed into amorphous materials is proportional to the volume/weight of the amorphous solid and high absorption and retention of water can enhance chemical reactions which may lead to product degradation (Hancock and Shamblin, 1998). Furthermore, sorbed water as well as heat can promote the crystallisation of amorphous materials (Baird and Taylor, 2012; Burnett et al., 2006).

Therefore strategies to stabilise amorphous materials should aim at both increasing the  $T_g$  and protecting the amorphous system from water uptake. Co-formulation of a deliquescent salt form (sodium ascorbate) with excipients (maltodextrins) was seen to reduce the moisture sorption and enhance the physical stability of this salt (Hiatt et al., 2011). It was also observed that the production of molecular dispersions of indomethacin and indomethacin sodium via evaporation under vacuum influenced the physico-chemical characteristics of each species (Tong and Zografi, 2001).

The aim of the current research was to improve the physical stability of amorphous ST/STNa mix in terms of crystallisation and deliquescence by adjusting the salt/acid ratio in the composite systems.

## 2. Materials and methods

### 2.1. Materials

Sulfathiazole (ST) form III and sulfathiazole sodium (STNa) anhydrous were purchased from Sigma Ireland. Ethanol (99.5%, v/v) was purchased from Corcoran Chemicals (Ireland) and deionised water produced by a Millipore Elix Advantage water purification system.

### 2.2. Spray drying

Spray dried powders were obtained using a Buchi B-290 Mini Spray dryer (Buchi Laboratories-Technik AG, Flawil, Switzerland) operating in an open cycle mode configuration using air as the drying gas. 0.5% (w/v) feed solutions were prepared by dissolving the APIs (Table 1) in a mixture of ethanol and deionised water at a v/v ratio of 9:1, as previously described (Bianco et al., 2012). Spray drying of ST and ST-STNa systems was performed using the following

parameters: gas flow of 40 mm (473 L/h); aspirator rate of 100% and feed flow rate of 30% (8 ml/min). The inlet temperature for the mixtures was adapted to the amount of salt employed in the system ranging from 85 to 90 °C and reported in Table 1. The salt alone was instead spray dried with an inlet of 160 °C so as to produce a dry powder (Bianco et al., 2012). Samples were transferred to Amebis humidity devices (Amebis Ltd., Ireland) at <5% RH (Bianco et al., 2012) and stored in a cold room at  $5 \pm 1$  °C immediately after spray drying.

### 2.3. Thermal analysis

Differential scanning calorimetry (DSC) runs were conducted on a Mettler Toledo DSC 821<sup>e</sup> (Mettler Toledo Ltd., Greifensee, Switzerland) using nitrogen as a purge gas. Samples (3–7 mg) were placed in closed aluminium pans with three vent holes and were heated at a scanning rate of 10 °C/min from 25 °C to 280 °C. The thermograms ( $n \geq 2$ ) were analysed by Mettler Toledo STAR<sup>e</sup> software.

Modulated temperature DSC (MTDSC) scans were recorded on a QA-200 TA instruments (TA instruments, United Kingdom) calorimeter using nitrogen as a purge gas. Weighed samples (1.5–3.5 mg,  $n \geq 2$ ) were sealed in closed aluminium pans with one pin-hole. The method selected was similar to that previously reported by (Caron et al., 2011). A scanning rate of 1 °C/min, amplitude of modulation of 1 °C and modulation frequency of 1/60 Hz were employed for all the experiments. The temperature range was from 5 °C to 200 °C.

### 2.4. Powder X-ray diffraction (XRD)

X-ray powder diffraction measurements were conducted using a low background silicon sample holder and a Rigaku Miniflex II desktop X-ray diffractometer (Rigaku, Tokio, Japan) as previously described (Caron et al., 2011; Tewes et al., 2013). The samples ( $n \geq 2$ ) were scanned over a range of 5–40° in  $2\theta$  scale using a step size of 0.05°/s. The X-ray source was a Cu K $\alpha$  radiation ( $\lambda = 1.542$  Å) and the diffractometer was operated with a voltage of 30 kV and a current of 15 mA.

### 2.5. Attenuated total reflection Fourier transform infra-red spectroscopy (ATR-FTIR)

Infrared spectra were produced using a PerkinElmer Spectrum one FT-IR Spectrometer and evaluated using Spectrum v5.0.1 software as previously described (Grossjohann et al., 2012; Tewes et al., 2011). An average of 6 scans with a resolution of 4 cm<sup>-1</sup> over a wavenumber region of 4000–650 cm<sup>-1</sup> was used for each sample. All spectra were baseline corrected. The spectrum of pure STNa was subtracted from the mixture spectra, considering their molar ratio.

### 2.6. Scanning electron microscopy (SEM)

SEM micrographs of samples were taken using a Tescan Mira XMU (Brno, Czech Republic) SEM. The dry powder samples were fixed on aluminium stubs with double-sided adhesive tape and a 10 nm-thick gold film was sputter coated on the samples before visualisation. Primary electrons were accelerated under a voltage of 5 kV. Images were formed from the collection of secondary electrons.

### 2.7. Water sorption analysis

Water sorption behaviour of samples was determined using a DVS Advantage 1 apparatus (DVS Surface Measurement Systems,

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