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1 Bulk, surface properties and water uptake mechanisms of salt/acid

2 amorphous composite systems

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15 Abstract

Developing amorphous pharmaceuticals can be desirable due to advantageous biopharmaceutical 16 properties. Low glass transition temperature (Tg) amorphous drugs can be protected from 17 crystallisation by mixing with high Tg excipients, such as polymers, or with salt forms. 18 19 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 20 proportions of sulfathiazole and its sodium salt to produce an optimum ratio, characterised by the 21 22 best physical stability and lowest hygroscopicity. Both sulfathiazole and salt amorphised upon spray drying. At room temperature, sulfathiazole crystallised within 1 hour at <5% relative 23 humidity while the salt deliquesced when exposed to ambient humidity conditions. In the case of 24 25 composite systems, FTIR spectroscopy, thermal and surface analysis suggested interactions with 26 an acid:salt stoichiometry of 1:2. Increasing proportions of salt raised the Tg, enhancing the storage stability, however this was opposed by an enhanced hygroscopicity. The water uptake 27 mechanism within the different amorphous systems, analysed by fitting the water sorption 28 29 isotherms with the Young and Nelson equation, was dependent on the ratio employed, with the 30 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 31 the physical stability of amorphous formulations. 32

34 **1. Introduction**

The requirement to improve the bioavailability of poorly soluble active pharmaceutical 35 ingredients (API) has resulted in a growing use of processes such as milling and spray drying, 36 which reduce particle dimensions and increase specific surface area. It is well established that 37 38 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 39 al., 2011; Tajber et al., 2005; Yu, 2001). Amorphous materials are structurally disorganised and 40 41 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 42 (Newman et al., 2008), greater solubility and a higher dissolution rate (Tajber et al., 2005). 43 Although these properties are relevant from a pharmaceutical development perspective, the full 44 exploitation of amorphous drugs and formulations cannot always be achieved, mainly due to low 45 physical and chemical stability (Caron et al., 2011; Yu, 2001). Therefore a thorough 46 understanding of the properties of the amorphous state is required to develop new strategies to 47 physico-chemically stabilise amorphous compounds. 48

Previously, we studied several physicochemical properties of sulfathiazole (ST) and sulfathiazole 49 50 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 51 crystallisation of amorphous solids can be promoted by heat and therefore these materials usually 52 require storage at temperatures well below their glass transition temperature (Tg) (Caron et al., 53 2011; Hancock et al., 1995; Yu, 2001). Considerable effort has been made to address this 54 problem, either by co-processing heat labile amorphous drugs with high Tg excipients (Caron et 55 al., 2011) or by using amorphous salt forms of these compounds (Tong et al., 2002; Tong and 56

Zografi, 1999). In many cases a shift of the Tg 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 Tg compared to ST and was physically stable when stored under desiccated conditions. Nevertheless, it deliquesced when exposed to ambient RH conditions (Bianco et al., 2012).

Deliquescence together with adsorption, capillary condensation, hydrate formation and 63 absorption, is one of the known mechanisms of solid-water interactions (Airaksinen et al., 2005; 64 Hiatt et al., 2011). It is a first order phase transition that happens when a water soluble solid 65 66 generates a saturated solution by dissolving into the water sorbed from the environment at a specific relative humidity (RH₀) characteristic for that solid. Due to high void space and enlarged 67 free volume relative to the crystalline state, amorphous substances absorb water below RH0 and 68 69 undergo deliquescence at a lower RH compared to their crystalline counterparts (Mikhailov et 70 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 71 chemical reactions which may lead to product degradation (Hancock and Shamblin, 1998). 72 Furthermore, sorbed water as well as heat can promote the crystallisation of amorphous materials 73 (Baird and Taylor, 2012; Burnett et al., 2006). 74

Therefore strategies to stabilise amorphous materials should aim at both increasing the Tg 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 physicochemical 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.

86 **2. Materials and Methods**

87 **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.

91 2.2 Spray drying

92 Spray dried powders were obtained using a Buchi B-290 Mini Spray dryer (Buchi 93 Laboratoriums-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 94 95 (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 96 97 the following parameters: gas flow of 40 mm (473 L/hr); aspirator rate of 100% and feed flow 98 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 99 100 instead spray dried with an inlet of 160°C so as to produce a dry powder (Bianco et al., 2012). 101 Samples were transferred to Amebis humidity devices (Amebis Ltd., Ireland) at <5% RH (Bianco et al., 2012) and stored in a cold room at $5\pm1^{\circ}$ C immediately after spray drying. 102

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

107 **2.3 Thermal analysis**

108 Differential scanning calorimetry (DSC) runs were conducted on a Mettler Toledo DSC 821^e 109 (Mettler Toledo Ltd., Greifensee, Switzerland) using nitrogen as a purge gas. Samples (3-7 mg) 110 were placed in closed aluminium pans with three vent holes and were heated at a scanning rate of 111 10 °C/min from 25°C to 280°C. The thermograms ($n \ge 2$) were analysed by Mettler Toledo 112 STAR^e software.

113 Modulated temperature DSC (MTDSC) scans were recorded on a QA-200 TA instruments (TA 114 instruments, United Kingdom) calorimeter using nitrogen as a purge gas. Weighed samples (1.5-115 3.5 mg, $n \ge 2$) were sealed in closed aluminium pans with one pin-hole. The method selected was 116 similar to that previously reported by (Caron et al., 2011). A scanning rate of 1°C/min, amplitude 117 of modulation of 1°C and modulation frequency of 1/60 Hz were employed for all the 118 experiments. The temperature range was from 5°C to 200°C.

120 **2.4 Powder X-ray diffraction (XRD)**

121 X-ray powder diffraction measurements were conducted using a low background silicon sample 122 holder and a Rigaku Miniflex II desktop X-ray diffractometer (Rigaku, Tokio, Japan) as 123 previously described (Caron et al., 2011; Tewes et al., 2013). The samples ($n \ge 2$) were scanned 124 over a range of 5-40° in 20 scale using a step size of 0.05°/s. The X-ray source was a Cu Ka 125 radiation ($\lambda = 1.542$ Å) and the diffractometer was operated with a voltage of 30 kV and a current 126 of 15 mA.

127 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⁻¹ over a wavenumber region of 4000-650 cm⁻¹ 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.

133 **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.

140 **2.7 Water sorption analysis**

141 Water sorption behaviour of samples was determined using a DVS Advantage 1 apparatus (DVS Surface Measurement Systems, London, UK), as previously described (Tewes et al., 2010). 142 Samples placed in a microbalance were exposed to three cycles of RH (0–90–0 %) at 25°C, with 143 144 the following steps: 3, 6, 10 and then every 10% RH (n=3). Water sorption isotherms were calculated using the equilibrated mass (dm/dt \leq 0.002 mg/min for 10 min) recorded at the end of 145 each stage and expressed as a percentage of the dry sample mass. The Young-Nelson equations 146 were used to fit experimental equilibrium sorption and desorption data of the isotherms (Tewes et 147 al., 2010): 148

149
$$M_s = A(\beta + \theta) + B\theta RH$$
(1)

150
$$M_d = A(\beta + \theta) + B\theta RH_{\text{max}}$$
 (2)

where M_s and M_d are, respectively, the mass percentage of water contents of the system at equilibrium for each %RH during sorption and desorption. *A* and *B* are constants characteristic of each system and defined by the following equations:

154
$$A = \delta W \operatorname{Vol}_{M} / (Wm) \tag{3}$$

155
$$B = \delta W \operatorname{Vol}_A / (Wm)$$
 (4)

where δw is the density of the water, Vol_M and Vol_A are respectively the adsorbed and absorbed water volumes and W*m* is the weight of the dry material.

158 In this model, θ is the fraction of the surface covered by at least one layer of water molecules. It 159 is defined as follows, with *E* a constant depending on the material.

160
$$\theta = RH/(RH + E(1 - RH))$$
(5)

161 β is defined by the following equation:

162
$$\beta = -E \times RH/(E - RH \times (E - 1)) + E^2/(E - 1) \times \ln[E - RH(E - 1)/E] - (E + 1) \times \ln(1 - RH)$$
 (6)

163 Thus, $A\theta$ is the mass of water in a complete adsorbed monolayer expressed as a percentage of the 164 dry mass of the sample. $A(\beta + \theta)$ is the total amount of adsorbed water, and $A\beta$ is the mass of 165 water which is adsorbed beyond the mass of the monolayer (i.e., in multilayer or cluster 166 adsorption). *B* is the mass of absorbed water at 100% of RH, and, hence, $B\theta$ RH is the mass of 167 absorbed water when the water coverage is θ for a given %RH. According to the model 168 characteristics, from the estimated values of *A*, *B*, and *E*, the corresponding profiles of water 169 adsorbed in monolayer ($A\theta$), multilayer ($A\beta$) and absorbed ($B\theta$ RH) were obtained.

170 **2.8 Surface free energy measurement**

171 Surface free energy measurements were carried out using inverse gas chromatography (iGC) (SMS Ltd., London, UK), as described previously (Tewes et al., 2011). Powders were packed 172 into silanised glass columns (300mm x 3mm). The columns were pre-treated for 1 h at 30°C and 173 0% RH to remove any physisorbed molecules. Then, 250 µL of the elution mixture (probe 174 175 vapour and helium) was injected into the carrier gas (helium) flow. All injections of probe vapours were performed at 0.03% v/v of the saturated probe vapour. A flame ionization detector 176 was used to monitor the elution of probe vapours. Measurements were performed at 0, 10 and 177 20% of RH and 30°C, (n = 2). In acid-base theory, the total surface free energy of a solid (γ_s^T) has 178 2 main components: a dispersive contribution (γ_s^d) and a specific or acid-base contribution (γ_s^{AB}) , 179 which are independent and additive, according to Eq. (7). 180

$$\gamma_{s}^{T} = \gamma_{s}^{d} + \gamma_{s}^{AI}$$
(7)

In order to calculate γ_s^d of the powders, alkane probes with a known dispersive contribution (γ_p^d) 182 and a nil specific contribution (γ_p^{AB}) were used. Methane was used as inert reference to determine 183 the dead volume of the system. At this low % of saturation (0.03% v/v), iGC was used in infinite 184 dilution conditions and γ_s^d was calculated using the method developed by Schultz *et al.* (Schultz 185 et al., 1987). γ_s^{AB} was obtained indirectly via the measurement of the specific free energy of 186 adsoption (ΔG^{SP}) of 2 monopolar probes and by using the acid-base theories developed by Van 187 Oss *et al.* (vOCG) (Van Oss et al., 1988). In the vOCG theories, γ_s^{AB} is subdivided into two non-188 additive parameters γ_s^+ and γ_s^- related according to Eq. (8), representing the electron acceptor 189 (acid) and donor (base) properties, respectively. 190

191
$$\gamma_s^{AB} = 2\sqrt{\gamma_s^{+}\gamma_s^{-}}$$
 (8)

By using ethyl acetate ($\gamma_p^- = 475.67$, $\gamma_p^+ = 0 \text{ mJ/m}^2$, at 30°C) as the base probe and dichloromethane ($\gamma_p^- = 0$, $\gamma_p^+ = 124.58 \text{ mJ/m}^2$, at 30°C) as the acid probe with the acid and base component values calculated based on the Della Volpe and Siboni scale (Della Volpe and Siboni, 195 | 1997), γ_s^+ and γ_s^- of the surface of the powders were calculated. Polarity index ($\gamma_s^{AB} / \gamma_s^d$) was then calculated.

Additionally the spreading coefficient (S_{SL}) was calculated using the dispersive contribution (γ_s^d) and the acid-base contribution (γ_s^+ and γ_s^-) of the total surface free energy of the solid and of the liquid (water) by the following equation.

$$S_{SL} = 2.\sqrt{\gamma_S^d \gamma_L^d} + 2.\sqrt{\gamma_S^+ \gamma_L^-} + 2.\sqrt{\gamma_S^- \gamma_L^+} - 4.\sqrt{\gamma_L^+ \gamma_L^-} - 2\gamma_L^d$$
(9)

Where $\gamma_L^{\ d}$, $\gamma_L^{\ +}$ and $\gamma_L^{\ -}$ are respectively the dispersive contribution ($\gamma_L^{\ d}$) and the acid-base contribution ($\gamma_L^{\ +}$ and $\gamma_L^{\ -}$) of the total surface free energy of the of the liquid (water) (Zdziennicka and Jańczuk, 2010).

204 **2.9 Density measurements**

The density of spray dried ST and STNa was measured by an Accupyc 1330 Pycnometer (Micromeritics ®) using helium (99.995% purity) to determine the volume of the sample. Samples were dried prior to measurement for 24 h in a Gallenkamp vacuum oven operating at 600 mbar and 25°C.

209 **2.10 Statistical analysis**

210 Data were statistically evaluated by a two-way analysis of variance (ANOVA) test with 211 Bonferroni test as post-hoc test. Significance level was $\alpha < 0.05$.

213 **3. Results and discussion**

214 **3.1 PXRD, DSC and FTIR analysis of spray dried systems**

215	Previous experiments showed that ST and STNa solidified into amorphous materials on spray
216	drying. However, both spray dried substances were physically unstable. Amorphous ST started
217	to crystallise to polymorph I ~30 minutes after the end of the spray drying process regardless of
218	the temperature and RH of storage. In contrast, spray dried STNa remained amorphous when
219	stored for over a year in desiccated conditions at 5±1°C. Nevertheless, amorphous STNa rapidly
220	deliquesced at ambient conditions (18-22°C and 40-80% RH) (Bianco et al., 2012).
221	All ST: STNa spray dried composites presented a diffuse halo pattern, characteristic of XRD
222	amorphous materials (Fig. 1).
223 224 225	Figure 1: PXRD patterns of: (a) unprocessed ST (form III); b) spray dried ST; c) spray dried ST 9:1; d) spray dried ST 3:1; e) spray dried ST 1:1; f) spray dried ST 1:3; g) spray dried STNa; h) unprocessed STNa.
226	The ST: STNa ratio employed and the storage conditions influenced the physical stability of the
227	processed powders. For example, in desiccated conditions at 5°C, by using just 10% w/w of the
228	salt form, the resulting composite remained amorphous for ~2 months as observed by PXRD.
229	Higher amounts of salt in the composites increased the stability by up to 5 months for ST 3:1 and
230	by six months for ST 1:1 and ST 1:3.
231	SEM images showed that ST: STNa composite samples were homogeneous and consisted of
232	spherical smooth particles with surface indentations for systems comprising up to 50% w/w

- 233 STNa (Fig. 2a-b-c). In contrast, no discrete particles were detected by SEM for a higher STNa
- content. Both ST 1:3 (Fig. 2d) and STNa deliquesced, indicating a higher affinity of these two
- samples for water compared to the other systems.

Figure 2: SEM micrographs of: a) spray dried ST 9:1; b) spray dried ST 3:1; c) spray dried ST1:1;
d) spray dried ST1:3.

Previously reported thermal analysis of pure spray dried ST showed an exotherm of 238 crystallization at 79±0.5°C followed by an endotherm of melting at 201±0.5°C while the 239 amorphous salt crystallised above 160°C and melted at 268±0.2°C (Bianco et al., 2012). Spray 240 dried ST 9:1, ST 8:2, ST 3:1 and ST 15:85 (Fig. 3) presented one endothermic event of melting. 241 242 These composites also showed one exotherm of crystallisation with onset ranging between those of the pure materials. In contrast ST 6:4, ST 1:1, ST 4:6 and ST 1:3 did not show either 243 exothermic or melting peaks on the thermograms. The inhibition of crystallisation upon heating 244 (at 1 or 10° C/min) for these mixtures could be due to the development of molecular interactions 245 between ST: STNa for these specific ST: STNa ratios (Tong and Zografi, 2001). 246

Figure 3: Heat flow thermograms of: (a) unprocessed ST (form III); b) spray dried ST; c) spray dried ST 9:1; d) spray dried ST 3:1; e) spray dried ST 1:1; f) spray dried ST 1:3; g) spray dried ST 15:85 h) spray dried STNa; i) unprocessed STNa.

The glass transition temperature (Tg) for pure ST and STNa were previously found to be \sim 59°C 250 and ~120°C, respectively (Bianco et al., 2012). To determine the Tgs of the various composites 251 252 and distinguish between thermal events which could happen simultaneously upon heating, MTDSC was employed in this work. All reversing heat flow thermograms recorded for the 253 different spray dried systems showed a single Tg, with values between those of the pure 254 materials and increasing with the STNa content. According to several authors (Bosma et al., 255 1988; Caron et al., 2011; Tong and Zografi, 2001) the detection of a single Tg is indicative of 256 homogeneous amorphous phases (molecular dispersions). Therefore, thermal analysis revealed 257 that the increase of physical stability was due to the introduction of STNa in the mixture which 258 shifted the Tgs to higher temperatures. Measured Tgs and Tg values calculated using the Gordon 259

Taylor with Simha-Boyer rule (GT – equation 10) (Caron et al., 2011; Tajber et al., 2005) were
plotted versus STNa weight fraction (Fig. 4).

262
$$T_g(mix) = \frac{w_1 T_{g1} + K_{GT} w_2 T_{g2}}{w_1 + K_{GT} w_2} \text{ where } K_{GT} = \frac{d_1 T_{g1}}{d_2 T_{g2}}$$
 (10)

263 $T_{g_{i}}$ w and d are the glass transition temperature in degrees Kelvin, the weight fraction, and

264 density of the subscripts 1 — first component, 2 — second component, respectively.

The true densities for the pure amorphous components of 1.52 g/cm³ and 1.57 g/cm³ for ST and STNa respectively, were used in the calculation of theoretical Tg values. The Tgs of the composites were found to deviate positively from the GT predicted values.

Figure 4: Glass transition temperatures of ST: STNa systems as a function of STNa content (squared markers). The solid line represents the Tg predictions based on the Gordon-Taylor with Simha-Boyer rule equation.

271 The Gordon-Taylor equation is widely accepted to predict the Tg of mixtures. The theory affirms that in the ideal mix free volumes are additive and no interaction between the components takes 272 place during mixing (Caron et al., 2011). However, because of the presence of interacting groups 273 in either species, the ST-STNa mixture could, in theory, result in the formation of intermolecular 274 bonds, such as hydrogen or ion-dipole bonding, which should cause an increase in Tg compared 275 to the predicted values. Tong and Zografi also showed positive deviations of Tg from GT 276 predicted values when indomethacin was co-processed with its corresponding sodium salt, 277 suggesting a stronger acid-salt interaction in the amorphous state than that between acid-acid and 278 279 salt-salt (Tong and Zografi, 2001).

FTIR spectroscopy has been used to investigate molecular interaction between species, included

in composites (Caron et al., 2011; Tong and Zografi, 2001). FTIR spectra (1800-1000 cm⁻¹) of

spray dried ST, STNa and ST mixed in different proportions with STNa are shown in Fig. 5A.

Figure 5A: FTIR spectrum in the 1800-1000 cm⁻¹ range of a) spray dried ST; b) to f) spray dried ST:STNa in the ratios 9:1, 3:1, 1:3, 15:85 and g) FTIR spectrum of spray dried STNa. 5B: Job plot representation

Peak shifts of different magnitudes were recorded, depending on the STNa content, indicative of 286 interactions between the two species (Caron et al., 2011; Tong and Zografi, 2001). For example, 287 in the 3000-3500 cm⁻¹ region, the N-H₂ asymmetric stretch peak, which in the spectrum of pure 288 amorphous ST appears at \sim 3462 cm⁻¹, shifted to lower wavenumbers (data not shown). The shift 289 to lower wavenumbers can be due to weakening of the N-H bond as a result of a stronger 290 involvement in H-bondings (Kaushal et al., 2008; Tang et al., 2002). The simultaneous shift to 291 higher wavenumbers of the C-NH₂ stretching peak (~ 1417 cm⁻¹ on the spectrum of ST), 292 confirmed the NH2 group being increasingly involved in H-bonds (Fig. 5A). In the 1000-1600 293 cm⁻¹ region, shifts to lower wavenumbers were seen for the peaks at 1140 and 1084 cm⁻¹, 294 characteristic of the stretching of both symmetric SO₂ and C-S peaks (Hu et al., 2010). These 295 shifts to lower wavenumbers suggested the SO₂ group as the H-bond acceptor and the 296 297 development of $N-H^{\cdot \cdot \cdot \cdot O}$ bondings. This type of interaction was previously described to link 298 dimers of ST in polymorph I (Parmar et al., 2007).

The stretching peak shifts of N-H₂ and C-S for the different composites were plotted against the 299 mole fraction of STNa to create a Job plot representation (Fig 5B) in order to determine the 300 stoichiometry of the interaction involving -NH₂ and -SO₂ groups (Likussar and Boltz, 1971). 301 This approach using solid ATR-FTIR was adapted from the study of Osmani *et al.* (Osmani et al.) 302 al., 2008) who generated a Job plot from FTIR C=O band shifting frequency in solution. The 303 STNa molar fraction associated to the maximum of the Job plots, obtained at two wavenumbers, 304 were between 0.6 and 0.7. The ST: STNa molar ratio of 1:2 lies between these two molar 305 306 fractions. Therefore, from the plot, it appears that one molecule of ST interacted with two

molecules of STNa. This interaction between ST and STNa could be responsible for the lack of
thermal events observed on the DSC thermograms obtained for the ST 4:6 and ST 1:3, as the ST:
STNa molar ratio of 1:2 falls between these two composites.

310 **3.2 iGC and DVS analysis**

iGC was used to more fully investigate the surface of the systems and to assess the possibility of 311 interactions between ST and STNa at the surface of the spray dried particles. Several phenomena 312 of pharmaceutical importance start at the surface, and are critically affected by the surface 313 properties of the substances involved (Buckton and Gill, 2007; Puri et al., 2010). Surface solid-314 liquid interactions for example, besides affecting processes such as dissolution, can have a deep 315 impact on the stability of the solid, powder flow etc., and are, above all, governed by solid 316 surface free energy (y_s^T) (Puri et al., 2010). Generally a substance in its amorphous form has a 317 higher γ_s^T than the corresponding crystalline form because of a more random orientation of 318 molecules exposing higher surface energy groups at the particle surface (Brum and Burnett, 319 2011; Newell et al., 2001a). This γ_s^T differences can have a significant impact on the behaviour 320 of the two solid states (amorphous versus crystalline) upon processing. Differences in the γ_s^T can 321 also be displayed by amorphous samples of the same material obtained with different processing 322 techniques and changes with time due to relaxation can affect the γ_s^T of amorphous material upon 323 storage (Buckton and Gill, 2007). 324

Figure 6: Total surface free energy for the different weight ratios (ST: STNa) at different %RH. Statistical analysis compares data obtained at the same RH value. System ST 1:3 was taken as reference of comparison for statistical post-hoc analysis. *** P<0.001

328 As a consequence of the development of interactions between the species included in the 329 processed mixtures, variations of the γ_s^T among the various systems would be expected. STNa

and four different composites were analysed by iGC. The γ_s^T values measured for ST 9:1 and ST 330 3:1 were not significantly different, and were found to be the highest among the systems studied, 331 at \sim 53 mJ/m² (Fig. 6). The increase in STNa content to the ST 1:3 system decreased significantly 332 the γ_s^T values, down to ~41 mJ/m² (P<0.001). Then γ_s^T rose up again for the pure amorphous salt, 333 reaching ~48 mJ/m² (Fig. 6). The minimum of γ_s^T obtained for ST 1:3 could be due to a different 334 organisation and/or to the development of interactions between the molecules at the surface of 335 the particles, decreasing the number of chemical groups available to interact with external 336 molecules such as the probe molecules. Moreover, changes in ST: STNa ratio also influenced the 337 polarity of the powder surfaces as shown by the variation in the polarity index $(\gamma_{S}^{AB}/\gamma_{S}^{d})$ in Fig. 338 339 7A.

Figure 7: Polarity index (A) and spreading coefficient (B) changes for different weight ratios and
%RH. Statistical analysis compares data obtained at the same RH value. System ST 1:3 was taken
as reference of comparison for statistical post-hoc analysis *** P<0.001, ** P<0.01, * P < 0.05.

An increase in salt content from ST 9:1 to ST 3:1 raised the polarity index, reaching a value similar to that obtained for pure amorphous STNa. However, a further increase (in salt content) to ST 1:1 and ST 1:3 reduced the surface polarity. The ST: STNa molar ratio 1:2 falls between that of these two systems (i.e. ST 1:1 and ST 1:3), which supports the concept of the development of 1:2 interactions, as previously suggested by FTIR spectroscopy. Therefore, ST-STNa interaction should involve polar bonding, decreasing the amount of polar chemical groups available at the surface to interact with the probe molecules.

Water adsorption is strongly influenced by surface polarity (Bradley et al., 2010). In particular,
water vapor molecules can interact with solids through specific hydrogen-bonding with surface

polar groups. Furthermore, when the solid is ionic, water molecules can interact with the components of the solid through ion-dipole interaction. For amorphous solids, the wettability and interaction with water are fundamental aspects to be studied because they can affect both dissolution properties (Puri et al., 2010) and physical stability (Hancock and Zografi, 1994; Puri et al., 2010). Both STNa and ST 1:3 deliquesced when exposed to ambient humidity conditions. Hence, the interaction of the composites with water was investigated by calculating the powder wettability and analysing the water vapor sorption isotherms.

The wettability of a powder by water depends on both the work of adhesion of the water onto the 360 powder surface (W_A) and on the water work of cohesion (W_C) . Complete spreading of the water 361 362 over a powder is possible if the work of adhesion onto the surface is equal to or higher than the 363 work of cohesion among the water molecules (Zdziennicka and Jańczuk, 2010). This difference equals the spreading coefficient (S_{SL}) . The S_{SL} of water over the composites, for various %RH, is 364 reported in Fig. 7B. For all systems the S_{SL} was negative, indicating that the spreading of water 365 on the powder surface is not favoured and requires work. For each system, S_{SL} was not affected 366 by a change in the %RH from 0% to 20% but changed depending on the ST: STNa ratio. An 367 increase in salt content from ST 3:1 to ST 1:3 decreased the S_{SL} , indicating a decrease in water 368 affinity for the powder surfaces. 369

The overlayed DVS 1st sorption isotherm plots of the systems indicated that the whole/entire water uptake increased with the increase of salt content over the entire RH range (Fig. 8). The mass gain recorded at 90% RH was linearly proportional to the STNa content in the composites. The coefficient of determination (r^2) of the linear fit was 0.99. For instance, spray dried STNa mass uptake was 36% w/w of the dry mass and decreased to 3.6% w/w for ST 9:1. As previous studies on the hygroscopicity of ST after spray drying indicated that the API had a maximum
water uptake of only 0.5% at 90% RH (Bianco et al., 2012), the water uptake for the blends is
primarily due to the salt.

378 Figure 8 Water sorption isotherms for spray dried systems with different ST: STNa weight ratios.

379 The kinetic profiles obtained for systems ST 9:1 (Fig. 9A), ST 3:1 and ST 1:1 showed 380 continuous water uptake versus time before reaching equilibrium for each % RH steps up to 40% 381 RH. For these systems during the 50% RH step an initial mass increase was followed by a decrease in mass. A similar behaviour was also seen for ST 1:3 but the decrease in mass was 382 383 lower, recorded at a lower RH and in two steps at 30% and 40% RH (Fig. 9B). A decrease in mass versus time with increasing RH for amorphous substances corresponds to the crystallisation 384 of the material (Burnett et al., 2006). The mass loss is attributed to water loss due to the reduced 385 386 hygroscopicity of a new crystalline phase compared to the amorphous form. Therefore the content of salt in the mixtures influenced the RH at which crystallisation took place by 387 promoting the water uptake which acts as a plasticiser for the mixture. 388

Figure 9 DVS kinetics (A, B, C) and isotherms (A', B', C') of: A-A') spray dried ST 9:1; B-B') spray dried ST 1:3; C-C') spray dried STNa.

In contrast the kinetics for the pure amorphous STNa did not show any mass loss but a continuous increase in mass with increasing RH (Fig. 9C). Generally, crystalline solids with high solubility such as salts may deliquesce at a RH value lower than 100%, defined as RH_0 , which is characteristic of the material. RH_0 of a compound can be determined from the moisture sorption isotherm as a sharp break due to a sudden change in water uptake which takes place at deliquescence (Hiatt et al., 2011). In contrast, when dealing with amorphous solids, deliquescence can be regarded as a non-equilibrium phase transition because water uptake by amorphous substances proceeds in a gradual way and their transformation from solid to liquid
state may involve intermediate semi-solid stages (Mikhailov et al., 2009). It was not possible to
determine the RH of deliquescence for amorphous STNa either from the water sorption isotherm
(Figure 9C) or the corresponding kinetics (Figure 9C').

Both ST 1:3 and STNa recorded mass uptake of respectively ~4.3% and 7% at the end of the first 402 cycle. The water uptake for amorphous STNa was previously attributed to the crystallisation of 403 the amorphous salt to a sesquihydrate (Bianco et al., 2012). PXRD analysis performed at the end 404 of the water sorption isotherm confirmed that the composites converted to the same 405 406 sesquihydrate form. Additional mass losses were detected in the kinetics for all composites in the second DVS sorption cycle (Fig. 9). These mass losses were of lower magnitude compared those 407 in the first cycles. These mass losses indicated a not complete (i.e. partial) crystallisation of the 408 amorphous systems at the end of the first sorption cycle. Full crystallisation following exposure 409 to a first full 0-90% RH cycle was not achieved and this may be attributed to water not 410 completely penetrating the bulk of the composites. 411

If we consider the adsorption process as the only mechanism of interaction between water and 412 the powders, the higher the surface energy, surface polarity and spreading coefficient the greater 413 414 is the expected water uptake. However, the surface properties measured for the different composites examined did not correlate with the whole water uptake isotherms. The γ_s^T of ST 9:1 415 and ST 3:1 were greater than those of STNa, ST 1:1 and ST 1:3, respectively. Nonetheless, ST 416 9:1 and ST 3:1 were characterised by lower water uptake compared to the other systems. Despite 417 having the lowest γ_s^T profile (Fig. 6) among all systems examined, the water uptake of ST 1:3 418 419 was the second highest, lower only than STNa. However amorphous materials can either adsorb water, or absorb it in the bulk of the material (Agrawal et al., 2004; Alvarez-Lorenzo et al., 2000; 420

421 Bravo-Osuna et al., 2005). Hence, the distribution of water in the different systems was determined by establishing quantitative correlations between equilibrium moisture content and 422 the %RH using the Young and Nelson equations (Agrawal et al., 2004; Alvarez-Lorenzo et al., 423 2000; Bravo-Osuna et al., 2005; Tewes et al., 2010). Fitting DVS data with the Young–Nelson 424 equations indicated that the water distribution within the different systems was dependent on the 425 426 ST:STNa ratio. For ST 9:1, adsorption was the main process of water uptake, as can be confirmed by the high value of the A parameter, compared to the B parameter of the Young-427 Nelson equations (Fig. 10). 428

Figure 10: Moisture distribution patterns for 1:3 (A) and 3:1 (B) samples obtained by fitting experimental DVS results with the Young and Nelson equations. Estimated A, B, E Young and Nelson parameters and fit correlation coefficient for all the composites investigated are inserted in the chart (A).

It was found that an increase in STNa content increased the proportion of water absorbed, and 433 water sorption for ST 1:1 and ST 1:3 was mainly by absorption. Fig. 10 shows a comparison of 434 the Young and Nelson distribution patterns of water obtained by fitting DVS results for two 435 systems (A) ST 1:3 and (B) ST 3:1 which are characterised respectively by low and high surface 436 437 free energy. Most of the water uptake by ST 1:3 was absorbed in the bulk while only a minute amount was adsorbed on the surface. In contrast the water uptake for the higher γ_s^T system ST 438 439 3:1 was due to both adsorption and absorption. The higher amount of water adsorbed by ST 3:1 440 compared to ST 1:3 is consistent with the surface profiles for the two different systems.

Therefore the ratio ST:STNa influenced not only the total hygroscopicity but also the water distribution in the different systems and this may have an important impact on the physical stability of the powders. Several authors have attributed the water uptake by amorphous materials mainly to absorption processes (Alvarez-Lorenzo et al., 2000; Bravo-Osuna et al.,

- 445 2005; Hancock and Shamblin, 1998). However, according to this study the main water sorption
- 446 mechanism for the system ST 9:1 was by adsorption, with a minimal amount of water absorbed.

447 4. Conclusions

448 This study showed that an extremely unstable amorphous API like sulfathiazole can be protected from crystallisation by co-spray drying it with its corresponding sodium salt form. In particular 449 the addition of just 10% w/w salt was enough to delay the crystallisation of the resulting powder 450 451 from 1 to 60 days of storage under desiccated conditions. Increasing the proportion of salt in the composite further improved the storage stability; however this was opposed by an increased 452 hygroscopicity. The increased physical stability may be attributed to interactions between the 453 species which cause the shift of Tg to higher temperature. FTIR spectroscopy, iGC and thermal 454 analysis suggested interactions between the species with a stoichiometry of 1 molecule of acid 455 456 for 2 molecules of salt. For the systems investigated, by analysing the hygroscopic properties it 457 has also emerged that water uptake by an amorphous material could either be mainly by adsorption or by absorption depending on the chemical nature of the material, with the salt 458 459 facilitating water absorption. Therefore controlling the physico-chemical properties of the composites by varying the ratio of the components can be beneficial to stabilise amorphous 460 formulations. For example among the ST: STNa composites an optimum mixture which 461 provided the best compromise between hygroscopicity and stability was the 1:1 w:w system. In 462 this ratio the amorphous powder was characterised by good physical stability, intermediate water 463 464 uptake and low surface free energy.

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Figure 1: PXRD patterns of: (a) unprocessed ST (form III); b) spray dried ST; c) spray dried ST 9:1; d) spray dried ST 3:1; e) spray dried ST 1:1; f) spray dried ST 1:3; g) spray dried STNa; h) unprocessed STNa.



Figure 2: SEM micrographs of: a) spray dried ST 9:1; b) spray dried ST 3:1; c) spray dried ST1:1; d) spray dried ST1:3.



Figure 3 Heat flow thermograms of: (a) unprocessed ST (form III); b) spray dried ST; c) spray dried ST 9:1; d) spray dried ST 3:1; e) spray dried ST 1:1; f) spray dried ST 1:3; g) spray dried ST 15:85 h) spray dried STNa; i) unprocessed STNa.



Figure 4: Glass transition temperatures of ST:STNa systems as a function of STNa content (squared markers). The solid line represents the Tg predictions based on the Gordon-Taylor with Simha-Boyer rule equation.



Figure 5A: FTIR spectrum in the 1800-1000 cm⁻¹ range of a) spray dried ST; b) to f) spray dried ST:STNa in the ratios 9:1, 3:1, 1:3, 15:85 and g) FTIR spectrum of spray dried STNa. 5B: Job plot representation



Figure 6: Total surface free energy for the different weight ratios (ST:STNa) at different %RH. Statistical analysis compares data obtained at the same RH value. System ST 1:3 was taken as reference of comparison for statistical post-hoc analysis. *** P<0.001



Figure 7: Polarity index (A) and spreading coefficient (B) changes for different weight ratios and %RH. Statistical analysis compares data obtained at the same RH value. System ST 1:3 was taken as reference of comparison for statistical post-hoc analysis *** P<0.001, ** P<0.01, * P<0.05.



Figure 8: Water sorption isotherms for spray dried systems with different ST:STNa weight ratios.



Figure 9 DVS kinetics (A, B, C) and isotherms (A', B', C') of: A-A') spray dried ST 9:1; B-B') spray dried ST 1:3; C-C') spray dried STNa.



Figure 10: Moisture distribution patterns for 1:3 (A) and 3:1 (B) samples obtained by fitting experimental DVS results with the Young and Nelson equations. Estimated A, B, E Young and Nelson parameters and fit correlation coefficient for all the composites investigated are inserted in the chart (A).