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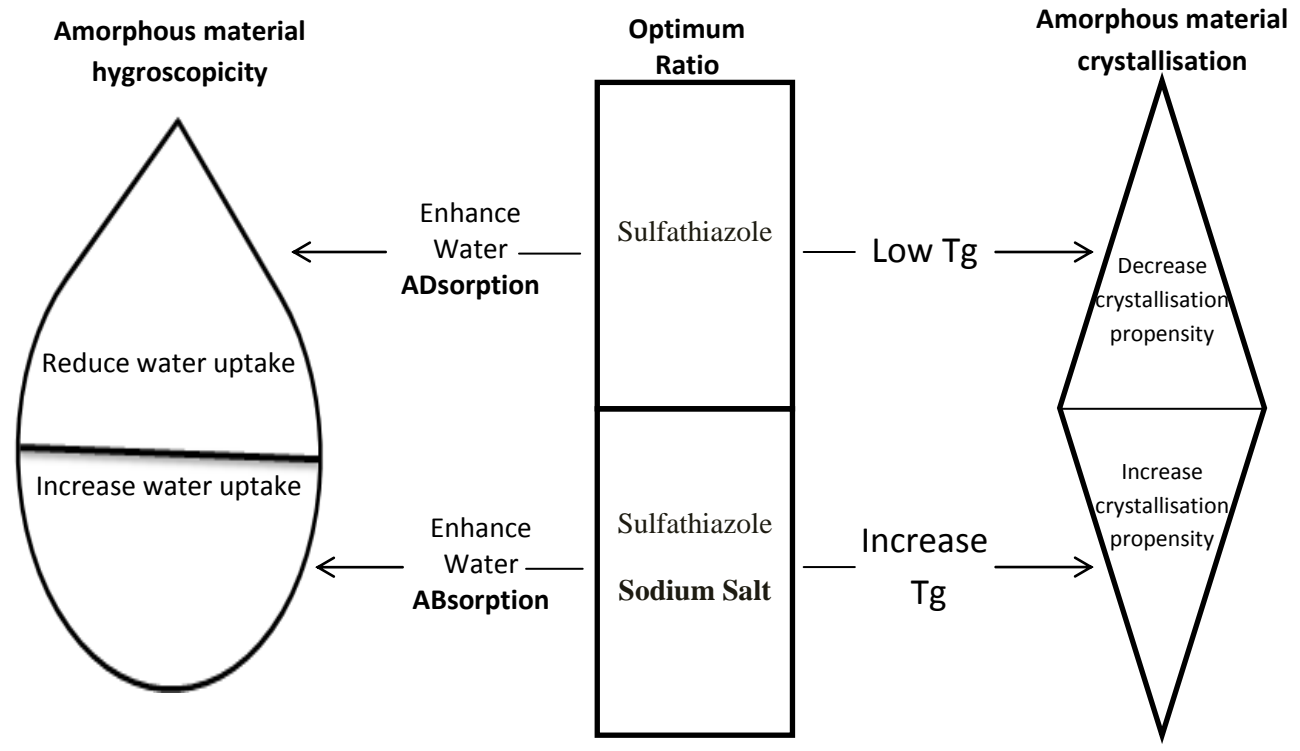
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1 **Bulk, surface properties and water uptake mechanisms of salt/acid**
2 **amorphous composite systems**

3
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14

15 **Abstract**

16 Developing amorphous pharmaceuticals can be desirable due to advantageous biopharmaceutical
17 properties. Low glass transition temperature (T_g) amorphous drugs can be protected from
18 crystallisation by mixing with high T_g excipients, such as polymers, or with salt forms.
19 However, both polymers and salts can enhance the water uptake. The aim of this study was to
20 formulate physico-chemically stable amorphous materials, by co-processing different
21 proportions of sulfathiazole and its sodium salt to produce an optimum ratio, characterised by the
22 best physical stability and lowest hygroscopicity. Both sulfathiazole and salt amorphised upon
23 spray drying. At room temperature, sulfathiazole crystallised within 1 hour at <5% relative
24 humidity while the salt deliquesced when exposed to ambient humidity conditions. In the case of
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 T_g, enhancing the
27 storage stability, however this was opposed by an enhanced hygroscopicity. The water uptake
28 mechanism within the different amorphous systems, analysed by fitting the water sorption
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
31 amorphous salt/acid composites by optimising the ratio appears potentially promising to improve
32 the physical stability of amorphous formulations.

33

34 **1. Introduction**

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

49 Previously, we studied several physicochemical properties of sulfathiazole (ST) and sulfathiazole
50 sodium (STNa), which solidify into unstable amorphous materials on spray drying (Bianco et al.,
51 2012). The acid rapidly crystallised regardless of the relative humidity (RH) conditions. The
52 crystallisation of amorphous solids can be promoted by heat and therefore these materials usually
53 require storage at temperatures well below their glass transition temperature (T_g) (Caron et al.,
54 2011; Hancock et al., 1995; Yu, 2001). Considerable effort has been made to address this
55 problem, either by co-processing heat labile amorphous drugs with high T_g excipients (Caron et
56 al., 2011) or by using amorphous salt forms of these compounds (Tong et al., 2002; Tong and

57 Zografi, 1999). In many cases a shift of the Tg to higher temperature has been achieved, which is
58 potentially a good strategy to stabilise amorphous formulations. However this is not always
59 sufficient and other influential factors affecting stability must also be considered. For instance,
60 amorphous STNa was characterised by a 60°C increase in Tg compared to ST and was
61 physically stable when stored under desiccated conditions. Nevertheless, it deliquesced when
62 exposed to ambient RH conditions (Bianco et al., 2012).

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

75 Therefore strategies to stabilise amorphous materials should aim at both increasing the Tg and
76 protecting the amorphous system from water uptake. Co-formulation of a deliquescent salt form
77 (sodium ascorbate) with excipients (maltodextrins) was seen to reduce the moisture sorption and
78 enhance the physical stability of this salt (Hiatt et al., 2011). It was also observed that the

79 production of molecular dispersions of indomethacin and indomethacin sodium via evaporation
80 under vacuum influenced the physicochemical characteristics of each species (Tong and Zografi,
81 2001).

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

85

86 **2. Materials and Methods**

87 **2.1 Materials**

88 Sulfathiazole (ST) form III and sulfathiazole sodium (STNa) anhydrous were purchased from
89 Sigma Ireland. Ethanol (99.5% v/v) was purchased from Corcoran Chemicals (Ireland) and
90 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
94 using air as the drying gas. 0.5% w/v feed solutions were prepared by dissolving the APIs
95 (Table 1) in a mixture of ethanol and deionised water at a v/v ratio of 9:1, as previously
96 described (Bianco et al., 2012). Spray drying of ST and ST-STNa systems was performed using
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
99 employed in the system ranging from 85 to 90°C and reported in table 1. The salt alone was
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
102 (Bianco et al., 2012) and stored in a cold room at 5±1°C immediately after spray drying.

103

104 **Table 1: Spray drying parameters for ST: STNa systems. (An inlet temperature higher**
105 **than 85°C for ST 9:1 resulted in partially crystalline materials. For the other systems an**
106 **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 ($n \geq 2$) 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, $n \geq 2$) 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.

119

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, Tokyo, Japan) as
123 previously described (Caron et al., 2011; Tewes et al., 2013). The samples ($n \geq 2$) were scanned
124 over a range of $5-40^\circ$ in 2θ scale using a step size of $0.05^\circ/s$. The X-ray source was a Cu $K\alpha$
125 radiation ($\lambda = 1.542 \text{ \AA}$) 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)**

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

133 **2.6 Scanning electron microscopy (SEM)**

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

139

140 2.7 Water sorption analysis

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

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

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

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

$$154 \quad A = \delta_w \text{Vol}_M / (Wm) \quad (3)$$

$$155 \quad B = \delta_w \text{Vol}_A / (Wm) \quad (4)$$

156 where δ_w is the density of the water, Vol_M and Vol_A are respectively the adsorbed and absorbed
157 water volumes and Wm 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.

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

161 β is defined by the following equation:

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

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 adsorbed water at 100% of RH, and, hence, $B\theta RH$ is the mass of
167 adsorbed 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 adsorbed ($B\theta RH$) were obtained.

170 **2.8 Surface free energy measurement**

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

$$181 \quad \gamma_s^T = \gamma_s^d + \gamma_s^{AB} \quad (7)$$

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

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

192 By using ethyl acetate ($\gamma_p^- = 475.67$, $\gamma_p^+ = 0$ mJ/m², at 30°C) as the base probe and
 193 dichloromethane ($\gamma_p^- = 0$, $\gamma_p^+ = 124.58$ mJ/m², at 30°C) as the acid probe with the acid and base
 194 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
 196 then calculated.

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

$$200 \quad S_{SL} = 2\sqrt{\gamma_s^d \gamma_L^d} + 2\sqrt{\gamma_s^+ \gamma_L^-} + 2\sqrt{\gamma_s^- \gamma_L^+} - 4\sqrt{\gamma_L^+ \gamma_L^-} - 2\gamma_L^d \quad (9)$$

201 Where γ_L^d , γ_L^+ and γ_L^- are respectively the dispersive contribution (γ_L^d) and the acid-base
202 contribution (γ_L^+ and γ_L^-) of the total surface free energy of the of the liquid (water) (Zdziennicka
203 and Jańczuk, 2010).

204 **2.9 Density measurements**

205 The density of spray dried ST and STNa was measured by an Accupyc 1330 Pycnometer
206 (Micromeritics ®) using helium (99.995% purity) to determine the volume of the sample.
207 Samples were dried prior to measurement for 24 h in a Gallenkamp vacuum oven operating at
208 600 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 $\alpha < 0.05$.

212

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 $5\pm 1^\circ\text{C}$. 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 **Figure 1: PXRD patterns of: (a) unprocessed ST (form III); b) spray dried ST; c) spray dried ST**
224 **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)**
225 **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
234 content. Both ST 1:3 (Fig. 2d) and STNa deliquesced, indicating a higher affinity of these two
235 samples for water compared to the other systems.

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

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

247 **Figure 3: Heat flow thermograms of: (a) unprocessed ST (form III); b) spray dried ST; c) spray**
248 **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**
249 **15:85 h) spray dried STNa; i) unprocessed STNa.**

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

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

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

263 T_g , 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.

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

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

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

280 FTIR spectroscopy has been used to investigate molecular interaction between species, included
281 in composites (Caron et al., 2011; Tong and Zografis, 2001). FTIR spectra (1800-1000 cm⁻¹) of
282 spray dried ST, STNa and ST mixed in different proportions with STNa are shown in Fig. 5A.

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

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

299 The stretching peak shifts of N-H₂ and C-S for the different composites were plotted against the
300 mole fraction of STNa to create a Job plot representation (Fig 5B) in order to determine the
301 stoichiometry of the interaction involving -NH₂ and -SO₂ groups (Likussar and Boltz, 1971).

302 This approach using solid ATR-FTIR was adapted from the study of Osmani *et al.* (Osmani et
303 al., 2008) who generated a Job plot from FTIR C=O band shifting frequency in solution. The

304 STNa molar fraction associated to the maximum of the Job plots, obtained at two wavenumbers,
305 were between 0.6 and 0.7. The ST: STNa molar ratio of 1:2 lies between these two molar
306 fractions. Therefore, from the plot, it appears that one molecule of ST interacted with two

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

310 **3.2 iGC and DVS analysis**

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

325 **Figure 6: Total surface free energy for the different weight ratios (ST: STNa) at different %RH.**
326 **Statistical analysis compares data obtained at the same RH value. System ST 1:3 was taken as**
327 **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

330 and four different composites were analysed by iGC. The γ_s^T values measured for ST 9:1 and ST
331 3:1 were not significantly different, and were found to be the highest among the systems studied,
332 at $\sim 53 \text{ mJ/m}^2$ (Fig. 6). The increase in STNa content to the ST 1:3 system decreased significantly
333 the γ_s^T values, down to $\sim 41 \text{ mJ/m}^2$ ($P < 0.001$). Then γ_s^T rose up again for the pure amorphous salt,
334 reaching $\sim 48 \text{ mJ/m}^2$ (Fig. 6). The minimum of γ_s^T obtained for ST 1:3 could be due to a different
335 organisation and/or to the development of interactions between the molecules at the surface of
336 the particles, decreasing the number of chemical groups available to interact with external
337 molecules such as the probe molecules. Moreover, changes in ST: STNa ratio also influenced the
338 polarity of the powder surfaces as shown by the variation in the polarity index ($\gamma_s^{AB} / \gamma_s^d$) in Fig.
339 7A.

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

343
344 An increase in salt content from ST 9:1 to ST 3:1 raised the polarity index, reaching a value
345 similar to that obtained for pure amorphous STNa. However, a further increase (in salt content)
346 to ST 1:1 and ST 1:3 reduced the surface polarity. The ST: STNa molar ratio 1:2 falls between
347 that of these two systems (i.e. ST 1:1 and ST 1:3), which supports the concept of the
348 development of 1:2 interactions, as previously suggested by FTIR spectroscopy. Therefore, ST-
349 STNa interaction should involve polar bonding, decreasing the amount of polar chemical groups
350 available at the surface to interact with the probe molecules.

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

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

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

370 The overlaid DVS 1st sorption isotherm plots of the systems indicated that the whole/entire
371 water uptake increased with the increase of salt content over the entire RH range (Fig. 8). The
372 mass gain recorded at 90% RH was linearly proportional to the STNa content in the composites.
373 The coefficient of determination (r^2) of the linear fit was 0.99. For instance, spray dried STNa
374 mass uptake was 36% w/w of the dry mass and decreased to 3.6% w/w for ST 9:1. As previous

375 studies on the hygroscopicity of ST after spray drying indicated that the API had a maximum
376 water uptake of only 0.5% at 90% RH (Bianco et al., 2012), the water uptake for the blends is
377 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
382 decrease in mass. A similar behaviour was also seen for ST 1:3 but the decrease in mass was
383 lower, recorded at a lower RH and in two steps at 30% and 40% RH (Fig. 9B). A decrease in
384 mass versus time with increasing RH for amorphous substances corresponds to the crystallisation
385 of the material (Burnett et al., 2006). The mass loss is attributed to water loss due to the reduced
386 hygroscopicity of a new crystalline phase compared to the amorphous form. Therefore the
387 content of salt in the mixtures influenced the RH at which crystallisation took place by
388 promoting the water uptake which acts as a plasticiser for the mixture.

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

391 In contrast the kinetics for the pure amorphous STNa did not show any mass loss but a
392 continuous increase in mass with increasing RH (Fig. 9C). Generally, crystalline solids with high
393 solubility such as salts may deliquesce at a RH value lower than 100%, defined as RH_0 , which is
394 characteristic of the material. RH_0 of a compound can be determined from the moisture sorption
395 isotherm as a sharp break due to a sudden change in water uptake which takes place at
396 deliquescence (Hiatt et al., 2011). In contrast, when dealing with amorphous solids,
397 deliquescence can be regarded as a non-equilibrium phase transition because water uptake by

398 amorphous substances proceeds in a gradual way and their transformation from solid to liquid
399 state may involve intermediate semi-solid stages (Mikhailov et al., 2009). It was not possible to
400 determine the RH of deliquescence for amorphous STNa either from the water sorption isotherm
401 (Figure 9C) or the corresponding kinetics (Figure 9C').

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

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

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

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

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

441 Therefore the ratio ST:STNa influenced not only the total hygroscopicity but also the water
442 distribution in the different systems and this may have an important impact on the physical
443 stability of the powders. Several authors have attributed the water uptake by amorphous
444 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
449 from crystallisation by co-spray drying it with its corresponding sodium salt form. In particular
450 the addition of just 10% w/w salt was enough to delay the crystallisation of the resulting powder
451 from 1 to 60 days of storage under desiccated conditions. Increasing the proportion of salt in the
452 composite further improved the storage stability; however this was opposed by an increased
453 hygroscopicity. The increased physical stability may be attributed to interactions between the
454 species which cause the shift of T_g to higher temperature. FTIR spectroscopy, iGC and thermal
455 analysis suggested interactions between the species with a stoichiometry of 1 molecule of acid
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
458 adsorption or by absorption depending on the chemical nature of the material, with the salt
459 facilitating water absorption. Therefore controlling the physico-chemical properties of the
460 composites by varying the ratio of the components can be beneficial to stabilise amorphous
461 formulations. For example among the ST: STNa composites an optimum mixture which
462 provided the best compromise between hygroscopicity and stability was the 1:1 w:w system. In
463 this ratio the amorphous powder was characterised by good physical stability, intermediate water
464 uptake and low surface free energy.

465

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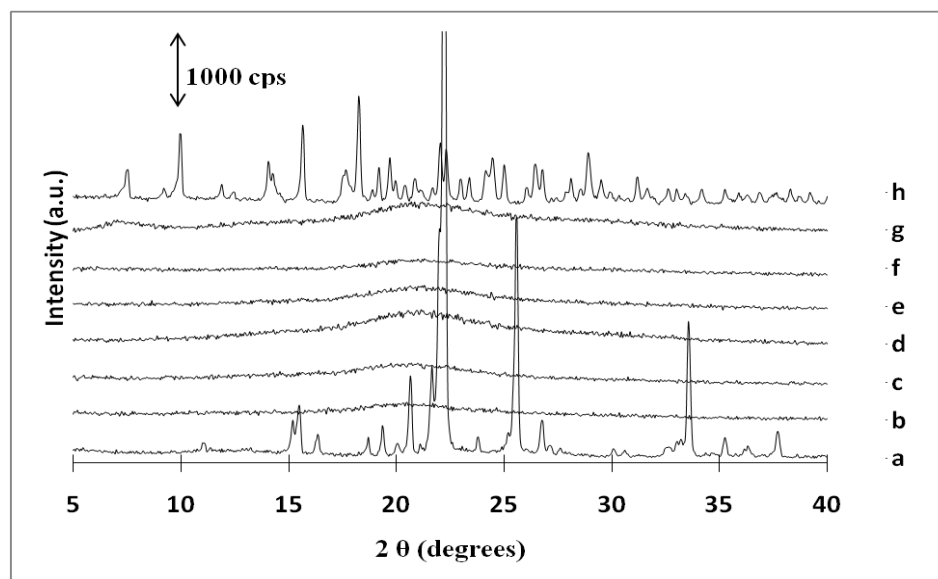


Figure 1: PXRD patterns of: (a) unprocessed ST (form III); b) spray dried ST; c) spray dried ST 9:1; d) spray dried ST 3:1; e) spray dried ST 1:1; f) spray dried ST 1:3; g) spray dried STNa; h) unprocessed STNa.

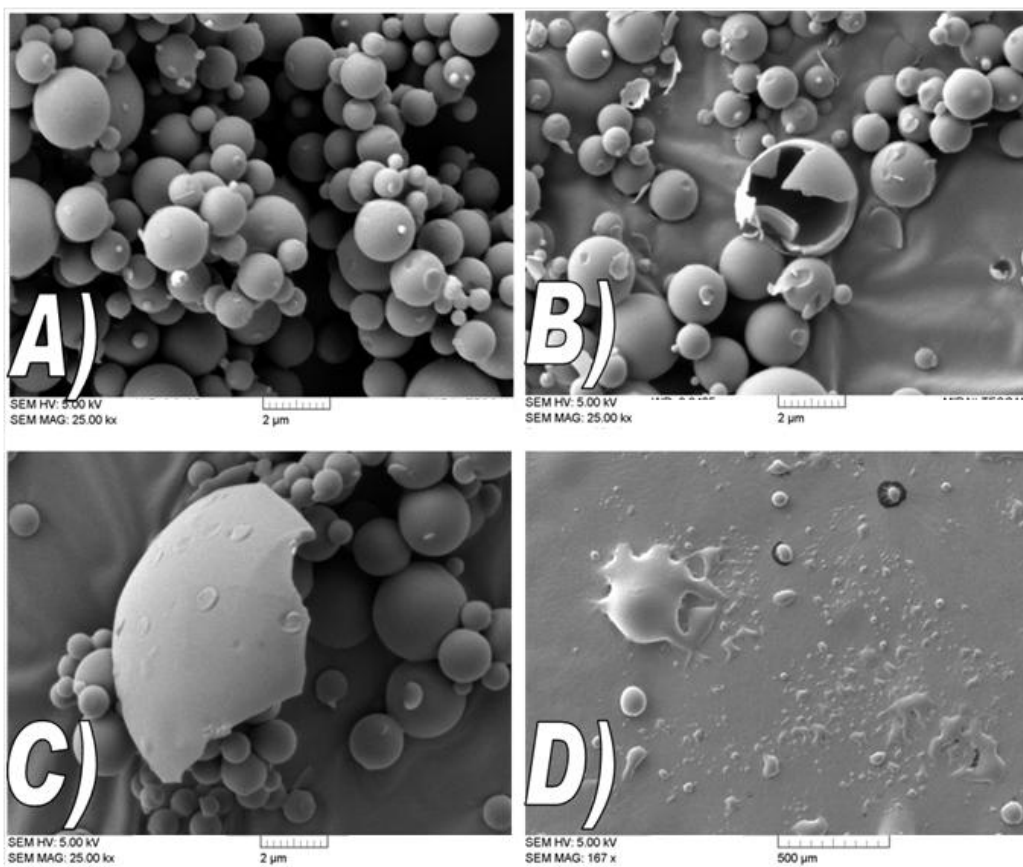


Figure 2: SEM micrographs of: a) spray dried ST 9:1; b) spray dried ST 3:1; c) spray dried ST1:1; d) spray dried ST1:3.

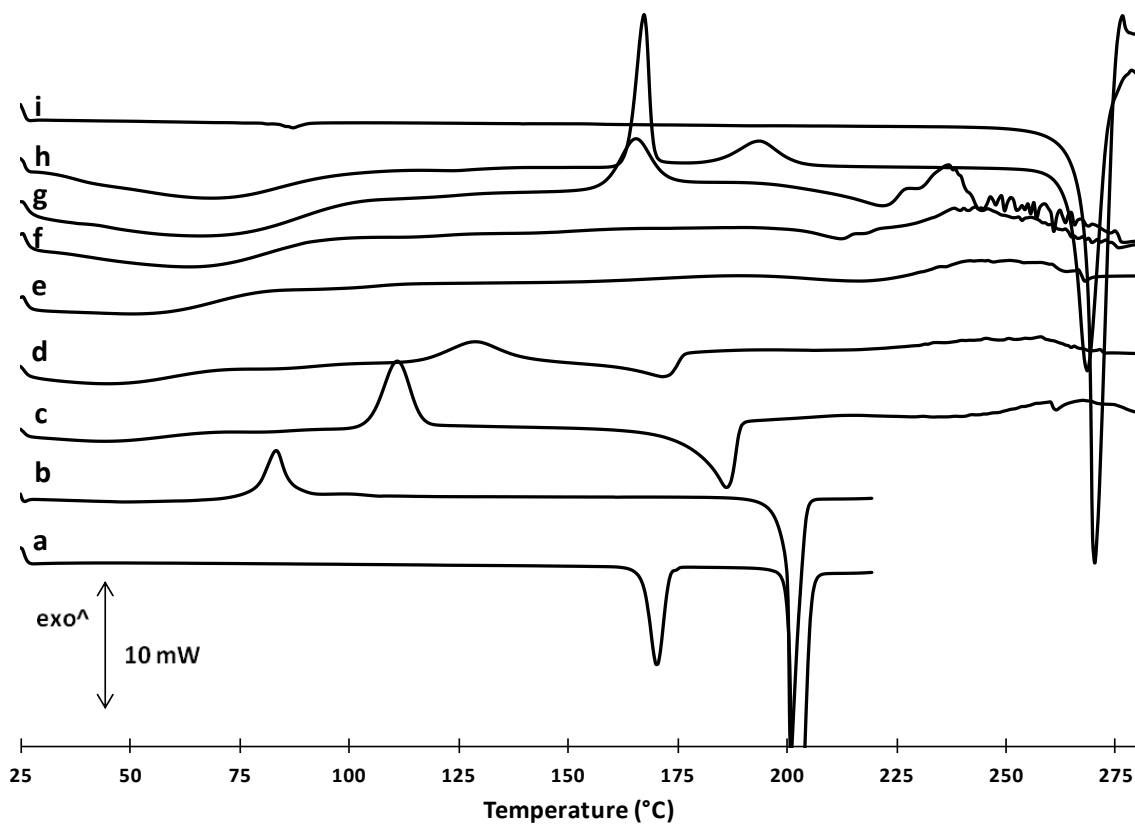


Figure 3 Heat flow thermograms of: (a) unprocessed ST (form III); b) spray dried ST; c) spray dried ST 9:1; d) spray dried ST 3:1; e) spray dried ST 1:1; f) spray dried ST 1:3; g) spray dried ST 15:85 h) spray dried STNa; i) unprocessed STNa.

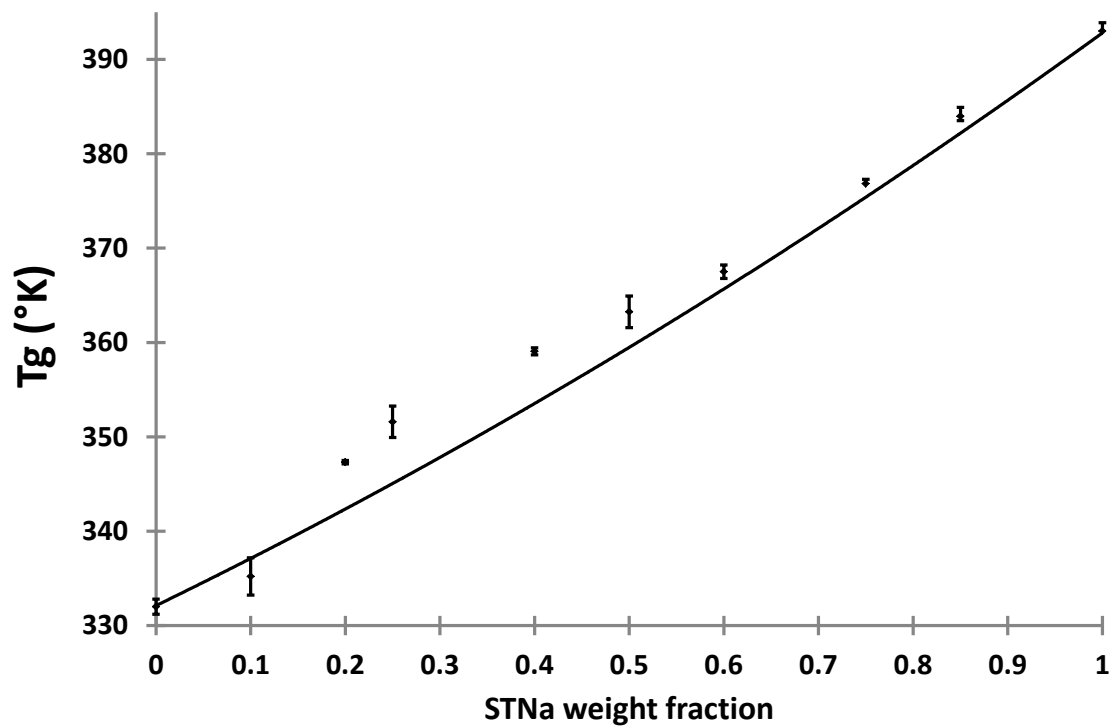


Figure 4: Glass transition temperatures of ST:STNa systems as a function of STNa content (squared markers). The solid line represents the Tg predictions based on the Gordon-Taylor with Simha-Boyer rule equation.

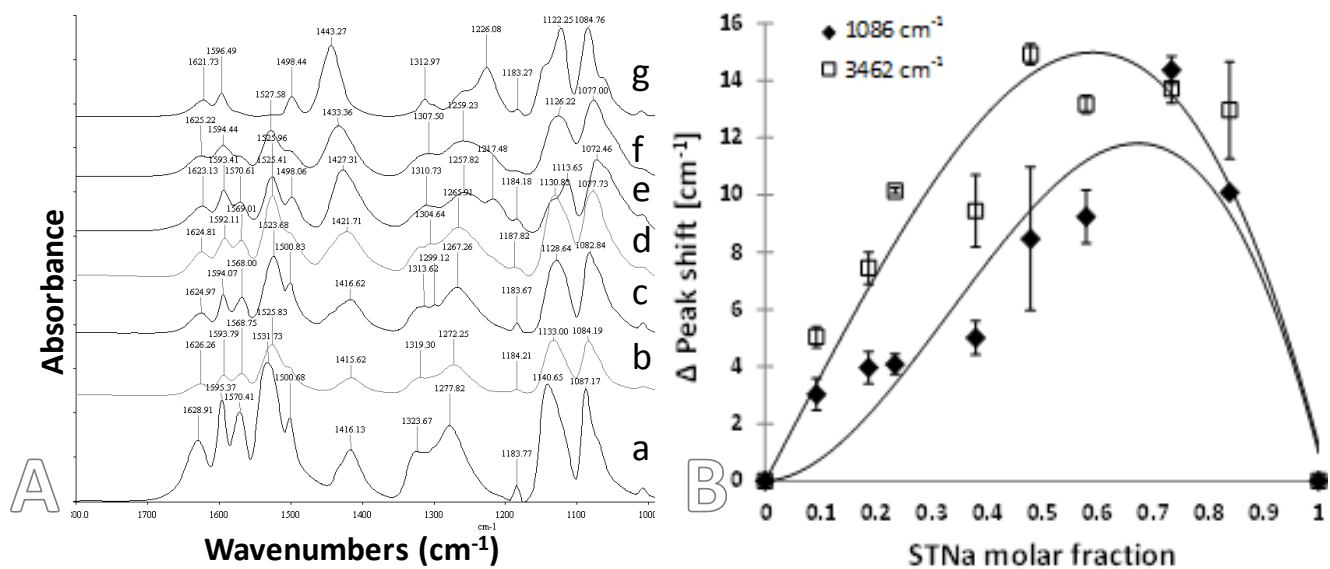


Figure 5A: FTIR spectrum in the 1800-1000 cm⁻¹ range of a) spray dried ST; b) to f) spray dried ST:STNa in the ratios 9:1, 3:1, 1:3, 15:85 and g) FTIR spectrum of spray dried STNa. 5B: Job plot representation

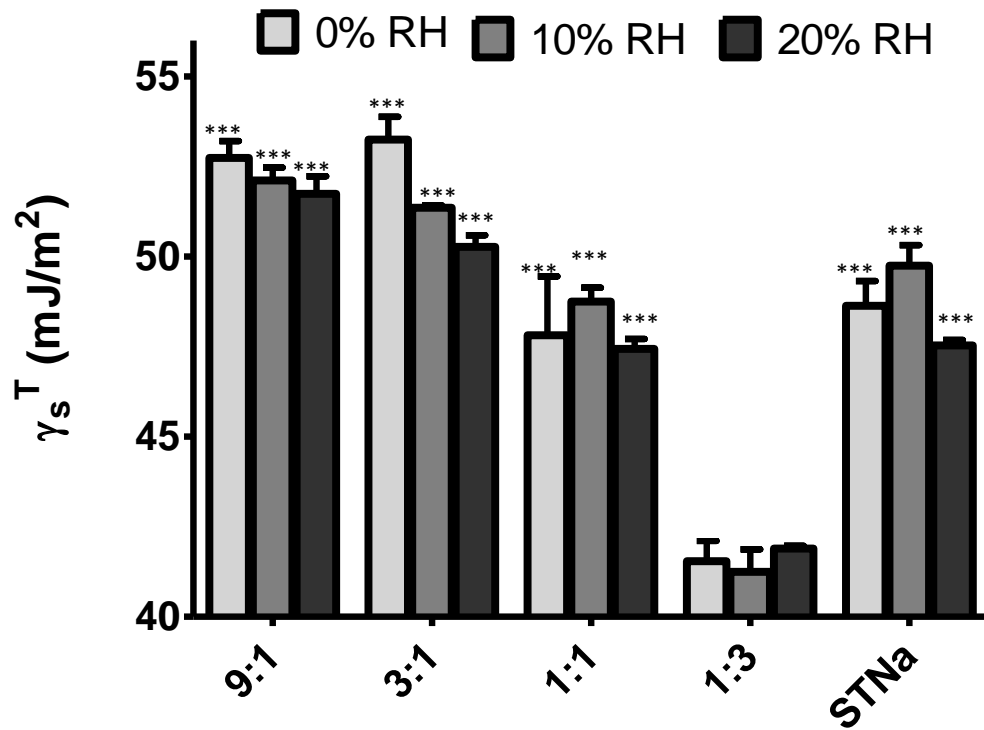


Figure 6: Total surface free energy for the different weight ratios (ST:STNa) at different %RH. Statistical analysis compares data obtained at the same RH value. System ST 1:3 was taken as reference of comparison for statistical post-hoc analysis. * P<0.001**

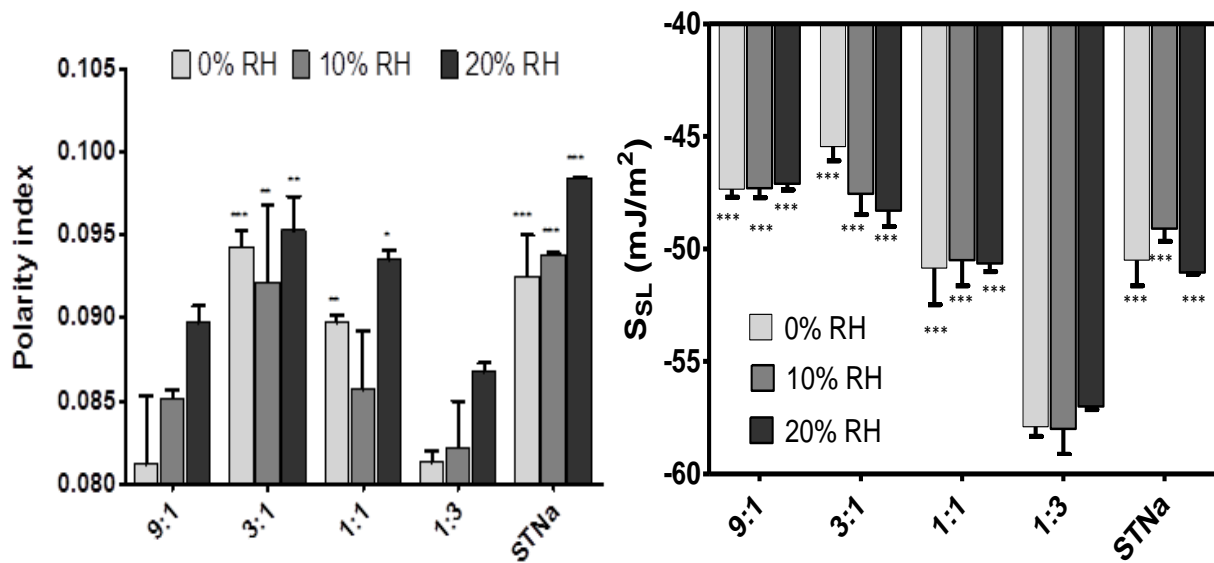


Figure 7: Polarity index (A) and spreading coefficient (B) changes for different weight ratios and %RH. Statistical analysis compares data obtained at the same RH value. System ST 1:3 was taken as reference of comparison for statistical post-hoc analysis * P<0.001, ** P<0.01, * P < 0.05.**

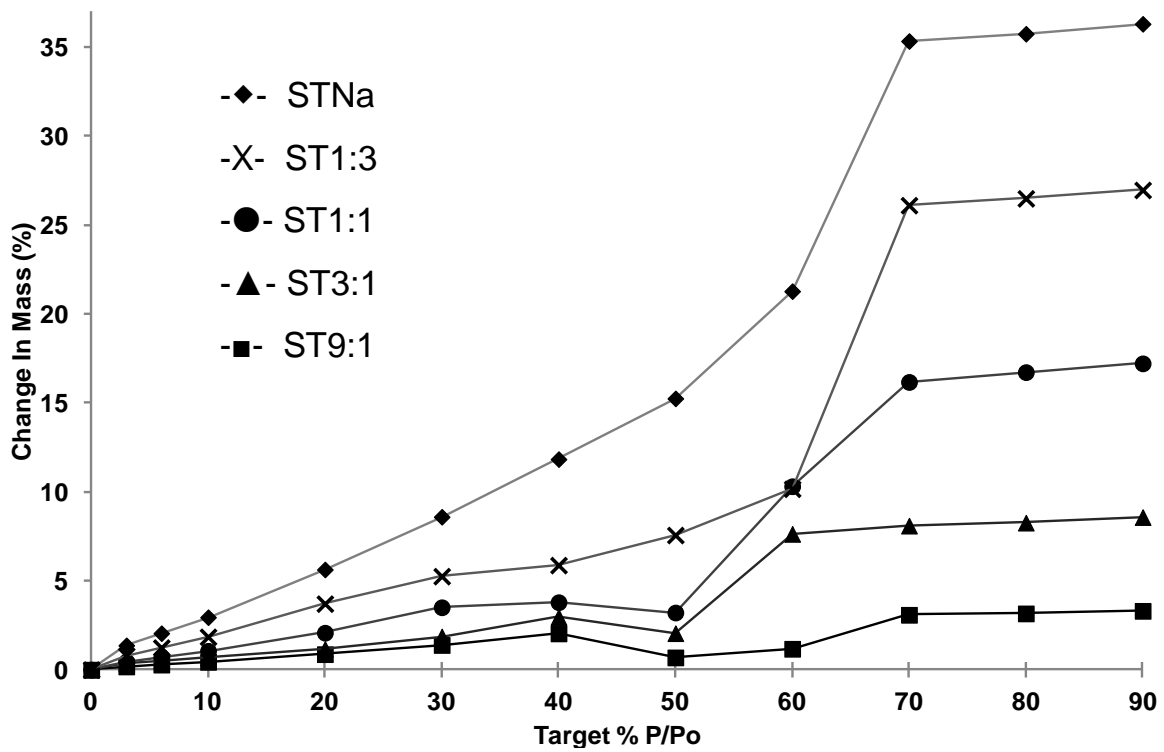


Figure 8: Water sorption isotherms for spray dried systems with different ST:STNa weight ratios.

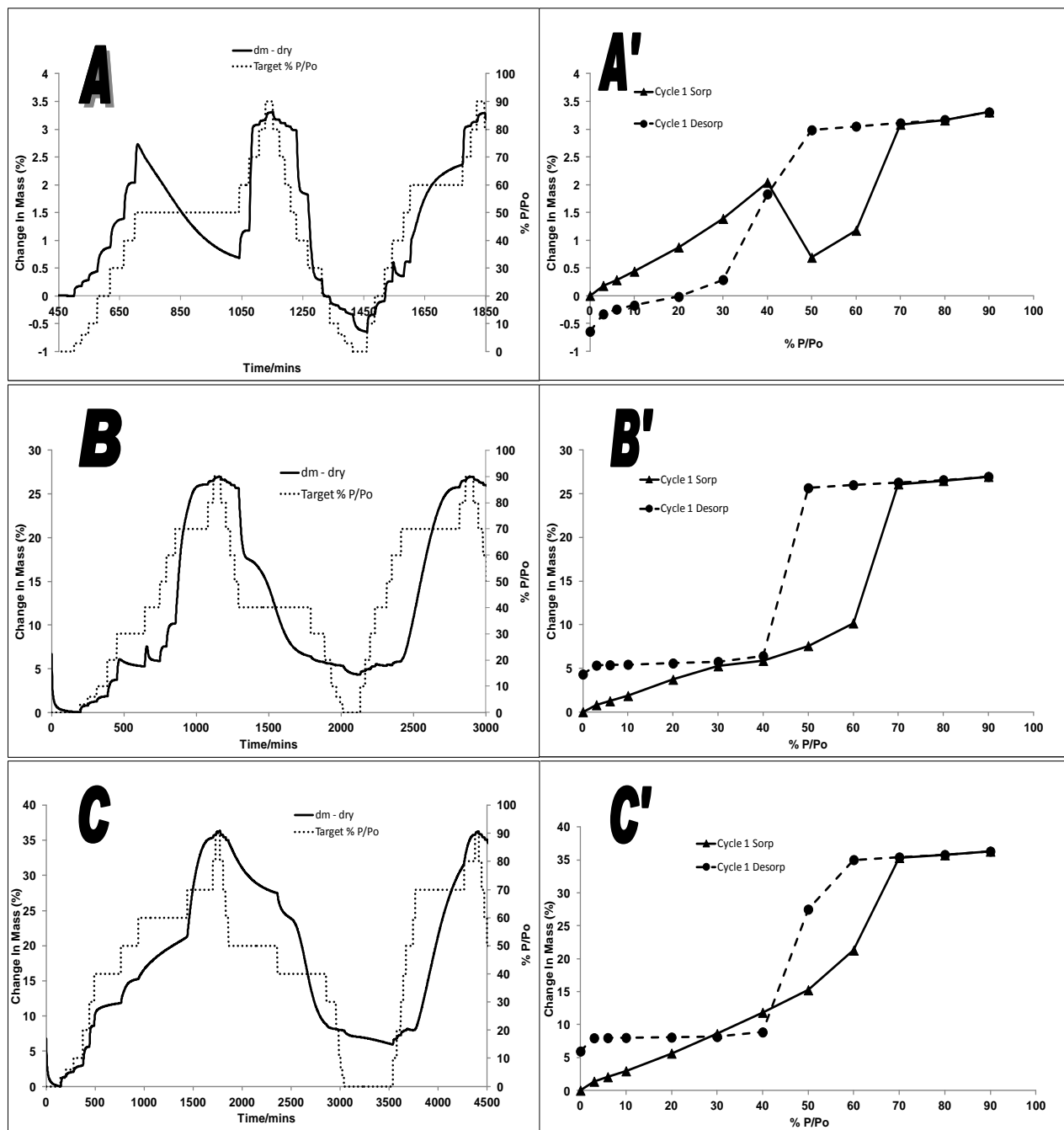


Figure 9 DVS kinetics (A, B, C) and isotherms (A', B', C') of: A-A') spray dried ST 9:1; B-B') spray dried ST 1:3; C-C') spray dried STNa.

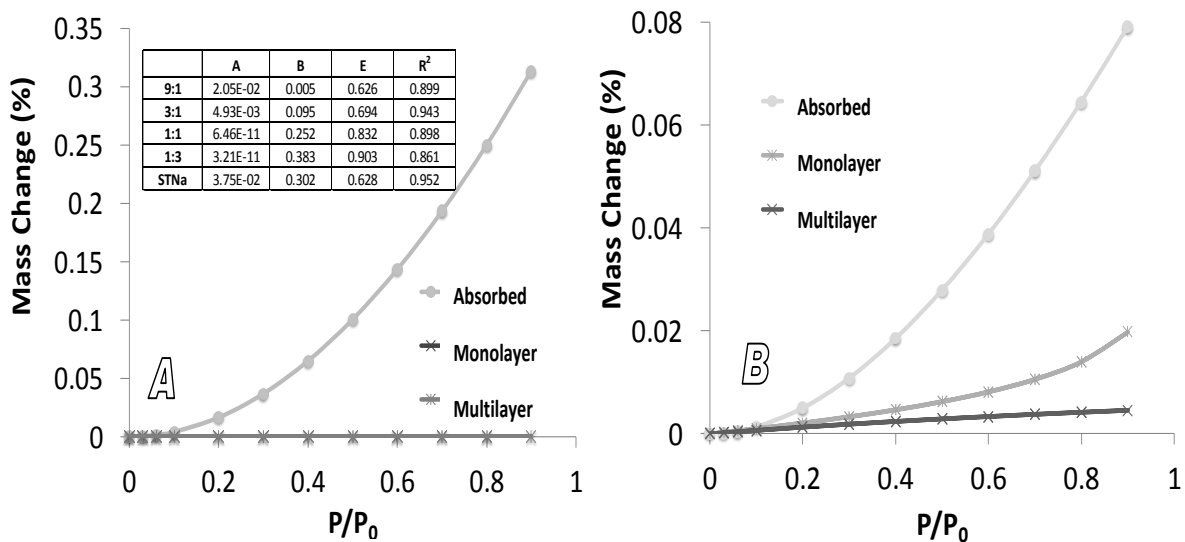


Figure 10: Moisture distribution patterns for 1:3 (A) and 3:1 (B) samples obtained by fitting experimental DVS results with the Young and Nelson equations. Estimated A, B, E Young and Nelson parameters and fit correlation coefficient for all the composites investigated are inserted in the chart (A).