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1 **Small scale assays for studying dissolution of pharmaceutical cocrystals for oral**
2 **administration**

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21 **Abstract**

22 The purpose of this study was to better understand the dissolution properties and
23 precipitation behaviour of pharmaceutical cocrystals of poorly soluble drugs for the
24 potential for oral administration based on a small scale dissolution assay.
25 Carbamazepine and Indomethacin cocrystals with saccharin and nicotinamide as
26 cofomers were prepared with the sonic slurry method. Dissolution of the poorly soluble
27 drugs indomethacin and carbamazepine and their cocrystals, was studied with a small
28 scale dissolution assay installed on a SiriusT3 instrument. Two methodologies were
29 used: i.) surface dissolution of pressed tablet (3mm) in 20mL running for fixed times at
30 four pH stages (pH1.8, pH3.9, pH5.4, pH7.3), and ii.) powder dissolution (2.6 mg) in
31 2mL at a constant pH (pH2). Improved dissolution and useful insights into precipitation
32 kinetics of poorly soluble compounds from the cocrystal form can be revealed by the
33 small scale dissolution assay. A clear difference in dissolution/precipitation behaviour
34 can be observed based on the characteristics of the cofomer used.

35

36 **Keywords** indomethacin; carbamazepine; cocrystal; small-scale dissolution; precipitation

37

38 INTRODUCTION

39 Poor solubility is a major issue for the development of new compounds as it can impact on the
40 bioavailability. Several strategies have been developed in order to improve solubility and the
41 cocrystal strategy is one of them (1, 2). Cocrystals are crystalline materials comprising of at
42 least two different components but the exact definition has created a lot of discussion in the
43 literature related mainly to the properties of these components (3-6). According to the FDA,
44 cocrystals are defined as, “solids that are crystalline materials composed of two or more
45 molecules in the same crystal lattice” (7). Various approaches have been described in the
46 literature for obtaining cocrystals, such as solution evaporation, mechanical grinding, melt
47 extrusion, slurry and melt crystallization (5, 8, 9).

48 The differences in molecular arrangements and solid-state thermodynamics can lead to
49 significant changes in physicochemical and pharmacokinetic (PK) properties (10). Cocrystals
50 can significantly increase the bioavailability of poorly soluble compounds based on limited
51 animal bioavailability studies (11-14), but it should be noted that up to now, there are no human
52 bioavailability studies available to validate the cocrystal effect on human pharmacokinetics.
53 Some general conclusions concerning cocrystal effects on pharmacokinetics can be revealed
54 by an analysis performed by Shan et al (10) based on animal data from 64 cocrystals involving
55 21 APIs, with 80% of the studied APIs from BCS class II (10). Qualitative analysis between
56 PK and solubility data of cocrystals led to a relatively strong positive correlation between AUC
57 and solubility and to a strong negative correlation between solubility and Tmax for highly
58 permeable APIs. Interestingly, cocrystallization might not only impact drug absorption, but
59 also change other aspects of drug pharmacokinetics such as changes of drug distribution,
60 metabolism and excretion especially when a biologically active coformer is used (10).

61 The physical and chemical properties of cocrystals have been extensively investigated (4). The
62 selection of the coformer is a key issue and prediction of the crystal structure based solely on
63 the molecular structure of a compound remains a challenge (10). Depending on the choice of
64 coformer, the API solubility enhancement from the cocrystal may vary considerably, from less
65 than 1 to values in excess of 100 fold (2).

66 Dissolution testing can play an important role in several areas of drug development as a quality
67 control tool and as an *in vitro* surrogate for *in vivo* performance. Most of the published
68 dissolution studies with cocrystals have been reviewed by Thakuria et al 2013 (5). These are
69 mainly studies of intrinsic dissolution rates measured in simple buffers or in biorelevant media
70 and estimated on the basis of their individual molar extinction coefficients in the respective
71 medium, with the use of simple set ups or compendial apparatus (i.e. USP Apparatus 2) (15-
72 18).

73 Experimental dissolution data for cocrystals would represent many complex processes
74 occurring simultaneously, such as the change of the solid form and of the surface area of the
75 particles as cocrystals undergo solution-mediated phase transformation (8, 19). The
76 relationship between the transformation rate and the dissolution rate is critical (15). The
77 increase of the solubility of an API as a result of cocrystal formation often leads to
78 transformation back into the pure API. In the case where the solubility of the cocrystal is higher
79 than the solubility of the API, and the coformer and the API dissociate completely in solution,
80 dissolution will lead to a supersaturated solution with the likelihood of API precipitation (6).

81 An appropriately designed dissolution experiment would provide useful information relevant
82 to the transformation of cocrystals and the absorption of the API. The importance of
83 experimental set up and type of coformer for the enhanced dissolution properties of cocrystals
84 was demonstrated for carbamazepine cocrystals (9). The use of an open system (flow-through
85 cell apparatus) and media with a physiologically relevant amount of surfactant provided a

86 discriminatory dissolution method for the cocrystals, driven by the characteristics of the
87 coformer used. Additionally, there has been a trend towards using novel low volume
88 dissolution assays that are API sparing and can help with early development stage decisions
89 for candidate progression. The European Union funded OrBiTo (Oral Biopharmaceutics Tools)
90 project highlights such an initiative and brings together academia and industry in an attempt to
91 develop new in-vivo predictive dissolution methodologies (20).

92 In this paper, we describe small-scale disk and powder dissolution assays that can be used to
93 assess cocrystal behaviour. As well as using only small quantities of material, a feature of these
94 experiments is the capability to directly control and change pH in-situ which reveals interesting
95 features with respect to dissolution and re-precipitation of the parent drug.

96 Indomethacin and carbamazepine were selected as the model compounds. They are classified
97 as BCS Class II compounds with low aqueous solubility. Saccharin (SAC; sulphonic acid
98 derivative $pK_a = 1.2$) and Nicotinamide (NIC; $pK_a 3.3$) were the cofomers selected for this
99 study. Cocrystals were prepared using the sonic slurry method (9, 21).

100

101 **MATERIALS AND METHODS**

102 **Materials**

103 Sodium dihydrogen phosphate and hydrochloric acid were purchased from Sigma-Aldrich,
104 UK, sodium acetate was purchased from Fisher Scientific, UK, and potassium chloride was
105 obtained from SureChem Ltd., UK. These reagents were used to prepare the dissolution
106 medium. Potassium hydroxide (Fisher Scientific) was used to adjust pH in the disk dissolution
107 assays.

108 Carbamazepine (99%) and saccharin (>98%) were purchased from Acros Organics and
109 indomethacin and nicotinamide were purchased from Sigma-Aldrich. Indomethacin and
110 carbamazepine cocrystals with saccharin and nicotinamide as cofomers on a 1:1 molar ratio
111 were prepared at Prosonix using the sonic slurry method whereby both API and cofomer were
112 introduced into an antisolvent and ultrasound applied. In summary, the API and the cofomer
113 were transferred to 400 mL ethyl acetate contained in a jacketed vessel with a side port for an
114 ultrasound probe. The reaction temperature was maintained at ~15 °C and an ultrasound power
115 of 30 W was applied. The slurry was stirred at a stirring rate of approximately 60 rpm and the
116 resulting slurry was filtered. The resulting solid was dried under vacuum at 35°C overnight.
117 The acoustic cavitation induces nucleation and crystallization leading to the formation of well
118 defined co-crystals as physically characterized by scanning electron microscopy, differential
119 scanning calorimetry, X-ray powder diffraction and particle size analysis (9, 22, 23).

120 **METHODS**

121 **In vitro dissolution testing**

122 Dissolution of indomethacin and carbamazepine and the two cocrystals was studied at 25 °C
123 with a small scale dissolution assay installed on a SiriusT3 instrument (Sirius Analytical
124 Instruments, East Sussex, UK) (24) (Table 1). The SiriusT3 is an automatic titration system
125 incorporating in-situ UV spectroscopy, which is specifically designed for the measurement of
126 various physiochemical properties, including pKa, log P and solubility, as well as dissolution.
127 The dissolution medium was prepared as 10mM phosphate and 10mM acetate pre-adjusted to
128 a starting pH of 1.8 or pH 2 (using HCl) and in a background of 0.15M KCl. Potassium
129 hydroxide was used to raise pH in the disk dissolution assays as described below.

130 Dissolution samples were used either directly as ~2.5mg powders or were prepared as tablets
131 with a diameter of 3 mm, requiring approximate sample weights of 5 - 10 mg. This was
132 carried out by using a modified Specac tablet press (Specac Ltd, Orpington, UK)
133 incorporating a load cell for consistent pressure readings. The press is used with a set of
134 tablet dies (3 mm diameter) to press a tablet of pure drug or cocrystal directly into a disc.
135 Tablets were prepared using a 80 kg load force applied for a period of two minutes until the
136 pressure readings remained constant, i.e., pressure readings reduce under initial compaction
137 and so the force is increased again to maintain the 80 kg load. All tablets were then visually
138 examined to ensure their surfaces were smooth and free of visible defects and the tablet discs
139 were placed in tablet disc holders and held in situ by an O-ring seal, so that only one side of
140 the tablet is exposed to the dissolution medium.

141 The powder dissolution experiments consisted of 2 mL of the phosphate-acetate buffer
142 medium adjusted to pH 2, to represent behavior at a gastric pH value, and added at the start of
143 the dissolution experiment. For the tablets, 20mL of the phosphate-acetate dissolution
144 medium was adjusted to pH 1.8 and added at the start of the dissolution experiment. The
145 dissolution of the powders or tablets was directly monitored by multi-wavelength UV-
146 absorption spectroscopy using an in-situ fibre-optic UV probe (Figure 1). Dissolution data
147 (UV spectra) were recorded for 240 minutes at pH 2, for the powders. For the tablets,
148 dissolution data were recorded for 60 minutes at gastric pH 1.8, after which the pH was
149 increased by dispensing KOH via a capillary, to simulate the pH transition occurring in the
150 gastrointestinal tract. In the intestinal pH phase, KOH solution was added to raise the pH to
151 3.9 and UV spectra were collected for a further 30 minutes. This process was continued
152 stepwise by increasing the pH to 5.4 and 7.3 and collecting UV spectra for an additional 30
153 minutes at each pH. Stirring of the solution was continuous and at a constant rate. After the

154 experiment, the UV absorption data were converted to an absolute sample weight using
155 previously determined, pH-dependent, molar extinction coefficients.
156 Molar extinction coefficients and pK_as of the compounds were determined by UV-metric
157 titration using the SiriusT3. The UV-metric method allowed the determination of molar
158 extinction coefficients for neutral and ionised forms of a sample from a single experiment.
159 Samples were typically prepared as 5 mM stock solutions in DMSO and titrated between pH
160 2 and pH 12 in 1.5 mL of 0.15 M aqueous KCl. Sample concentrations were optimized in
161 order to obtain a peak UV absorbance of approximately 1 absorbance unit.

162

163 Table 1 here

164

165 **Dissolution profiles comparisons**

166 The difference between the mean dissolution data sets was assessed with the difference
167 factor, f_i as described by Moore and Flanner (25). The difference factor was evaluated for the
168 whole duration of the experiment (up to 4h). The dissolution data of the pure API were used as
169 the reference data set when comparisons between the API and the cocrystal dissolution data set
170 were performed, whereas the dissolution data of the saccharin cocrystal were used as the
171 reference data set when comparisons between the dissolution performance of the two cocrystals
172 were made. In the present study, a value of f_i higher than 15 was set as the limit for identifying
173 differences between the samples.

174

175 **RESULTS**

176

177 **Indomethacin (IND) and its co-crystals (IND-SAC, IND-NIC)**

178 Surface dissolution of pressed tablet: The dissolution profile of the tablet of indomethacin
179 shows that 4.0 ± 0.3 μg of API was released by the end of the first sector at pH 1.8. By
180 comparison, 19 ± 3 μg of indomethacin was released from the indomethacin-saccharin
181 cocrystal and 31 ± 7 μg from the indomethacin-nicotinamide co-crystal (Figure 2 and Table 2).
182 By the end of the second sector, at pH 3.9, the amounts of dissolved indomethacin increased to
183 5.1 ± 0.9 , 25 ± 2 and 33 ± 6 μg for the IND, IND-SAC and IND-NIC respectively. When the
184 pH of the dissolution medium rises above the pKa value (4.13) of indomethacin there was a
185 significant increase in the amount of indomethacin released from both the tablets of the drug
186 and of the cocrystals (21). The respective amounts dissolved at the end of the third sector (pH
187 5.4) were 17 ± 3 , 76 ± 14 and 61 ± 9 μg for the IND, IND-SAC and IND-NIC with the IND-
188 SAC showing the greatest amount released. At the end of the final pH sector (pH 7.4), the
189 indomethacin-nicotinamide once again showed the greatest release with dissolved amounts of
190 indomethacin at 141 ± 24 , 549 ± 137 and 1327 ± 252 μg for the IND, IND-SAC and IND-NIC.

191
192 Powder dissolution: The powder dissolution of all samples under constant pH (Figure 3 and
193 Table 2) revealed the solubilisation enhancement of the drug from the cocrystal samples, and
194 also provided information regarding the precipitation and kinetic solubility of the samples.
195 Dissolution of indomethacin from the indomethacin-saccharin cocrystal was similar to the
196 indomethacin-nicotinamide cocrystal reaching 26 ± 3 μg for IND-SAC versus 24 ± 1 μg for
197 IND-NIC in the first three minutes. The onset of precipitation of the free indomethacin that
198 was released at pH 2 occurred sooner for the indomethacin-saccharin cocrystal compared to
199 the indomethacin-nicotinamide cocrystal. The amount of dissolved indomethacin released from
200 the IND-SAC cocrystal peaked at 34 ± 2 μg after 7 minutes whilst it peaked at 45 ± 3 μg after
201 13 minutes from the IND-NIC cocrystal. The final concentrations of dissolved indomethacin

202 at the end of the experiments was $19 \pm 2 \mu\text{g}$ for IND-SAC and $14 \pm 1 \mu\text{g}$ for IND-NIC
203 suggesting that equilibrium solubility had been achieved for the precipitating form. By
204 comparison, the amount of dissolved indomethacin from the pure API reached only 0.3 ± 0.1
205 μg after 3 minutes and it was still dissolving by the end of the experiment where it had reached
206 a level of $4.1 \pm 0.3 \mu\text{g}$ after four hours.

207

208 Table 2 here

209

210 **Carbamazepine (CBZ) and its cocrystals (CBZ-SAC, CBZ-NIC)**

211 Surface dissolution of pressed tablet: Dissolution profiles from the tablets of the drug and of
212 the cocrystals (Figure 4 and Table 3) revealed some interesting behavior. The saccharin
213 cocrystal had the highest solubilisation followed by carbamazepine API and then the
214 nicotinamide cocrystal was the lowest. Also, there was little dependence on pH and the
215 dissolution profiles showed a continual release, as one process, over all of the pH sectors. The
216 amount of carbamazepine released from the pure drug was $368 \pm 26 \mu\text{g}$ at the end of the first
217 sector (pH 1.8), $429 \pm 42 \mu\text{g}$ at the end of the second sector (pH 3.9), and $480 \pm 61 \mu\text{g}$ and 519
218 $\pm 87 \mu\text{g}$ at the end of the third (pH 5.4) and fourth (pH 7.3) sectors. The corresponding amounts
219 of released carbamazepine from the CBZ-NIC cocrystal were $215 \pm 19 \mu\text{g}$ (pH 1.8), 261 ± 21
220 μg (pH 3.9), $301 \pm 26 \mu\text{g}$ (pH 5.4) and $340 \pm 29 \mu\text{g}$ (pH 7.3) and from the CBZ-SAC cocrystal
221 were $469 \pm 28 \mu\text{g}$ (pH 1.8), $541 \pm 26 \mu\text{g}$ (pH 3.9), $596 \pm 26 \mu\text{g}$ (pH 5.4) and $642 \pm 23 \mu\text{g}$ (pH
222 7.3). Whilst carbamazepine itself is a non-ionisable compound both the cofomers,
223 nicotinamide and saccharin, are ionisable with pKa values, measured in this work, of 3.3 (basic)
224 and 1.2 (acidic), respectively.

225

226 Powder dissolution: The powder dissolution of all samples under constant pH 2 revealed that
227 carbamazepine dissolved much more slowly from the carbamazepine sample than from the
228 cocrystal samples and also provided information regarding the precipitation and kinetic
229 solubility of the samples (Figure 5 and Table 3). The amount of dissolved carbamazepine
230 reached $152 \pm 9 \mu\text{g}$ from the CBZ-NIC cocrystal and $114 \pm 2 \mu\text{g}$ from the CBZ-SAC in the
231 first 90 seconds whilst CBZ reached only $27 \pm 4 \mu\text{g}$ in the same time. The samples continued
232 to dissolve reaching peak concentrations of $197 \pm 47 \mu\text{g}$ for CBZ-NIC after 2 minutes, $371 \pm$
233 $24 \mu\text{g}$ for CBZ-SAC after 11 minutes, and $370 \pm 5 \mu\text{g}$ after 77 minutes for pure CBZ. The drop
234 in concentration observed following dissolution of the pure CBZ is probably due to the
235 formation of the less soluble carbamazepine dihydrate form (26). The concentration decreased
236 to $285 \pm 7 \mu\text{g}$ of dissolved carbamazepine by the end of the four hour experiment. Precipitation
237 of carbamazepine from the CBZ-SAC cocrystal occurred at a much earlier time and the final
238 dissolved concentration reached a similar level at $277 \pm 10 \mu\text{g}$ after four hours. Dissolution of
239 carbamazepine from the CBZ-NIC cocrystal was faster than from the CBZ-SAC cocrystal and
240 produced a heavily turbid solution as the carbamazepine precipitated from solution after 2
241 minutes. The final amount of dissolved carbamazepine from the CBZ-NIC experiments was 70
242 $\pm 27 \mu\text{g}$ after 130 minutes.

243

244 Table 3 here

245

246 **DISCUSSION**

247 Small scale dissolution assays (24) can be used to illustrate the different behavior of the
248 cocrystals (i) with respect to pressed tablet dissolution as a function of pH and (ii) solubilization
249 capacity and precipitation behavior of powder samples at pH2.

250

251 For the dissolution of tablets, cocrystals with indomethacin dissolved faster than pure
252 indomethacin, and the greatest solubilisation occurred, in all cases, above the pKa value (4.13)
253 of indomethacin when it becomes negatively charged (Figure 2 and Table 2). A comparison of
254 the tablet dissolution profiles provided f_I values of 283 and 618 for the IND-SAC tablet and
255 the IND-NIC tablet, respectively when compared to the IND tablet. The dissolution profile of
256 the IND-NIC tablet was substantially different than the dissolution profile of the IND-SAC
257 tablet ($f_I = 90$). The tablets were prepared using an 80 kg load force applied for a period of two
258 minutes until the pressure readings remained constant and all tablets were visually examined
259 to ensure their surfaces were smooth and free of visible defects. It was therefore thought
260 unlikely that the compaction force would have a strong influence on the differences observed
261 between the dissolution profiles, as was demonstrated in a recent publication on tablet
262 dissolution of indomethacin crystalline forms (27).

263 Powder dissolution of pure indomethacin at pH 2 was very low for the duration of the assay
264 reaching only 4 μg in the 2mL volume and showing the poor solubility of the free form of the
265 API. The powders of the cocrystals had improved dissolution performance but precipitation
266 could not be prevented as the solubility limit of indomethacin was soon exceeded as it was
267 released from the cocrystal (Figure 3 and Table 2). Maximum solubilization from the IND-
268 SAC cocrystal was 17 $\mu\text{g}/\text{mL}$ and from the IND-NIC cocrystal 23 $\mu\text{g}/\text{mL}$. After precipitation,
269 both co-crystals reached a similar concentration of 7 $\mu\text{g}/\text{mL}$ for IND-NIC and 8 $\mu\text{g}/\text{mL}$ for
270 IND-SAC after ~90 minutes but this was still much higher than the solubility of the crystalline
271 form of indomethacin (2 $\mu\text{g}/\text{mL}$). A comparison of the powder dissolution profiles provided f_I
272 values of 627 and 554 for the IND-SAC powder sample and the IND-NIC powder sample,
273 respectively when compared to the IND powder sample. The dissolution profile of the IND-
274 NIC powder sample was different than the dissolution profile of the IND-SAC tablet ($f_I = 25$).

275

276 Tablet dissolution of carbamazepine and its cocrystals showed similarly shaped release profiles
277 for the amount of carbamazepine entering the solution (Figure 4 and Table 3). However, only
278 the CBZ-SAC cocrystal provided enhanced solubilisation of carbamazepine whereas the CBZ-
279 NIC cocrystal showed much less carbamazepine going into solution and a slower dissolution
280 rate, when compared to the pure carbamazepine. A comparison of the tablet dissolution profiles
281 provided f_1 values of 30 and 40 for the CBZ-SAC tablet and the CBZ-NIC tablet, respectively
282 when compared to the CBZ tablet. The dissolution profile of the CBZ-NIC tablet was
283 significantly different than the dissolution profile of the CBZ-SAC tablet ($f_1 = 54$). In this case
284 also, as for the indomethacin and the indomethacin cocrystal tablets, carbamazepine tablets and
285 carbamazepine cocrystal tablets were prepared using an 80 kg load force applied for a period
286 of two minutes until the pressure readings remained constant and all tablets were visually
287 examined to ensure their surfaces were smooth and free of visible defects. It was also thought
288 unlikely that the compaction force would have a strong influence on comparison of the release
289 profiles. Thus, the substantial difference between the amounts dissolved from the cocrystals
290 tablets and the API tablets at various time intervals (as indicated by the f_1 values), can be
291 attributed to the differences in the physicochemical properties of the samples tested.

292 Powder dissolution of carbamazepine at pH 2 reached 185 $\mu\text{g/mL}$ before precipitating after 77
293 minutes. The precipitation event probably represents transformation to the less soluble
294 dihydrate form (26). The powder of the CBZ-SAC cocrystal had a faster initial dissolution rate
295 than the CBZ powder although the peak concentration was the same (186 $\mu\text{g/mL}$) and
296 precipitation was observed at a much earlier time point (11 minutes). The final concentrations
297 after 4 hours dissolution from the carbamazepine powder sample and the CBZ-SAC cocrystal
298 powder sample were also similar at 143 $\mu\text{g/mL}$ and 139 $\mu\text{g/mL}$ (Figure 5 and Table 3). The
299 initial dissolution of the CBZ-NIC cocrystal powder was rapid (76 $\mu\text{g/mL}$ in the first 90

300 seconds) but precipitation occurred very quickly after 2 minutes and the peak concentration
301 only reached 99 µg/mL. Following precipitation, the final concentration obtained was much
302 lower at 35 µg/mL. A comparison of the powder dissolution profiles provided f_i values of 20
303 and 78 for the CBZ-SAC powder sample and the CBZ-NIC powder sample, respectively when
304 compared to the CBZ powder sample. The dissolution profile of the CBZ-NIC powder sample
305 was significantly different than the dissolution profile of the CBZ-SAC powder sample ($f_i =$
306 76).

307 The powder results and tablet results for carbamazepine, on first appearances, seem to be
308 showing different behavior to each other. The CBZ-NIC cocrystal dissolved so rapidly as a
309 powder that it released free carbamazepine that precipitated almost immediately resulting in
310 very poor solubility. The CBZ-NIC tablet dissolved slower by comparison but similarly it also
311 ended up with the lowest amount of total dissolved carbamazepine. We hypothesize that as
312 nicotinamide is released from the surface, insoluble carbamazepine is left behind and coats the
313 surface of the tablet thus retarding further dissolution. Hence, for both the tablet and powder
314 assays we ended up with the least amount of carbamazepine in solution from the CBZ-NIC
315 cocrystal. In future studies, confirmation of form changes by analysis of the solid form
316 remaining at the end of the experiment could provide a clear description of the product
317 remaining after the dissolution. Additionally, the use of in-situ Raman technology, which is
318 increasingly being used in tandem with small scale dissolution methodologies, would directly
319 reveal the nature of such form changes as the experiment progresses (28).

320

321 **CONCLUSIONS**

322 Improved dissolution and useful insights into precipitation kinetics of poorly soluble
323 compounds from the cocrystal form can be revealed by the small scale dissolution assay. A

324 clear difference in dissolution/precipitation behaviour can be observed based on the
325 characteristics of the coformer used. An increase in dissolution of indomethacin and
326 carbamazepine from cocrystals would lead to an expectation of increased oral absorption of
327 these highly permeable BCS Class II compounds due to increased solubilisation. However,
328 improved dissolution kinetics should be tempered against faster drug precipitation kinetics
329 during selection of a coformer and a balance struck to achieve optimum performance.

330 Small scale dissolution assays can be easily set up on the SiriusT3 to screen a selection of
331 candidate cocrystals (or salts or polymorphs) during early development under a variety of
332 conditions (powders, compacts, gastric and intestinal pH).

333 Future work should be directed towards understanding the solid-state transformations and
334 precipitation behavior in more detail and how this may impact on the oral absorption of the
335 drugs. Additionally, understanding the impact of formulation additives such as polymeric
336 precipitation inhibitors (polyvinylpyrrolidones or celluloses) would be valuable.

337

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340 in Chicago and San Antonio, October 2012, 2013.

341

342

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344

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429 Table 1: Conditions of dissolution experiments.

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Experiment	Dissolution Medium	Sector 1	Sector 2	Sector 3	Sector 4
Powder Dissolution	10mM Phosphate buffer – 10mM acetate buffer adjusted to pH 2	UV spectra recorded for 240 minutes at pH 2	n/a	n/a	n/a
Pressed tablet Dissolution	10mM Phosphate buffer – 10mM acetate buffer adjusted to pH 1.8	UV spectra recorded for 60 minutes at pH 1.8	UV spectra recorded for 30 minutes at pH 3.9*	UV spectra recorded for 60 minutes at pH 5.4*	UV spectra recorded for 60 minutes at pH 7.4*

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* Sector pH reached by in-situ addition of KOH.

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436 Table 2: Summary of tablet and powder dissolution results for indomethacin and its cocrystals

437 (n=3).

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Amount Dissolved Indomethacin	IND tablet* (µg)	IND-SAC tablet* (µg)	IND-NIC tablet* (µg)
End of Sector 1 (pH 1.8)	4.0 ± 0.3	19 ± 3	31 ± 7
End of Sector 2 (pH 3.9)	5.1 ± 0.9	25 ± 2	33 ± 6
End of Sector 3 (pH 5.4)	17 ± 3	76 ± 14	61 ± 9
End of Sector 4 (pH 7.3)	141 ± 24	549 ± 137	1327 ± 252
	IND powder# (µg)	IND-SAC powder# (µg)	IND-NIC powder# (µg)
After 3 minutes	0.3 ± 0.1	26 ± 3	24 ± 1
Peak Concentration (time)	4.1 ± 0.3 (four hours)	34 ± 2 (7 mins)	45 ± 3 (13 mins)
Final amount	4.1 ± 0.3	19 ± 2	14 ± 1

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* Experiments performed in 20mL volume.

441

Experiments performed in 2mL volume at pH 2.

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445 Table 3: Summary of tablet and powder dissolution results for carbamazepine and its cocrystals

446 (n=3).

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Amount Dissolved Carbamazepine	CBZ tablet* (μg)	CBZ-SAC tablet* (μg)	CBZ-NIC tablet* (μg)
End of Sector 1 (pH 1.8)	368 \pm 26	469 \pm 28	215 \pm 19
End of Sector 2 (pH 3.9)	429 \pm 42	541 \pm 26	261 \pm 21
End of Sector 3 (pH 5.4)	480 \pm 61	596 \pm 26	301 \pm 26
End of Sector 4 (pH 7.3)	519 \pm 87	642 \pm 23	340 \pm 29
	CBZ powder# (μg)	CBZ-SAC powder# (μg)	CBZ-NIC powder# (μg)
After 90 seconds	27 \pm 4	114 \pm 2	152 \pm 9
Peak Concentration (time)	370 \pm 5 (77 mins)	371 \pm 24 (11 mins)	197 \pm 47 (2 mins)
Final amount	285 \pm 7	277 \pm 10	70 \pm 27

449

* Experiments performed in 20mL volume.

450

Experiments performed in 2mL volume at pH 2.

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454 LEGEND TO FIGURES

455 Figure 1: Small scale dissolution assay (Sirius system)

456 Figure2: Dissolution of indomethacin and cocrystal pressed tablets (n=3) over four pH sectors.

457 Figure 3: Dissolution of indomethacin and cocrystal powders (n=3) at pH2.

458 Figure 4: Dissolution of carbamazepine and cocrystal pressed tablets (n=3) over four pH
459 sectors.

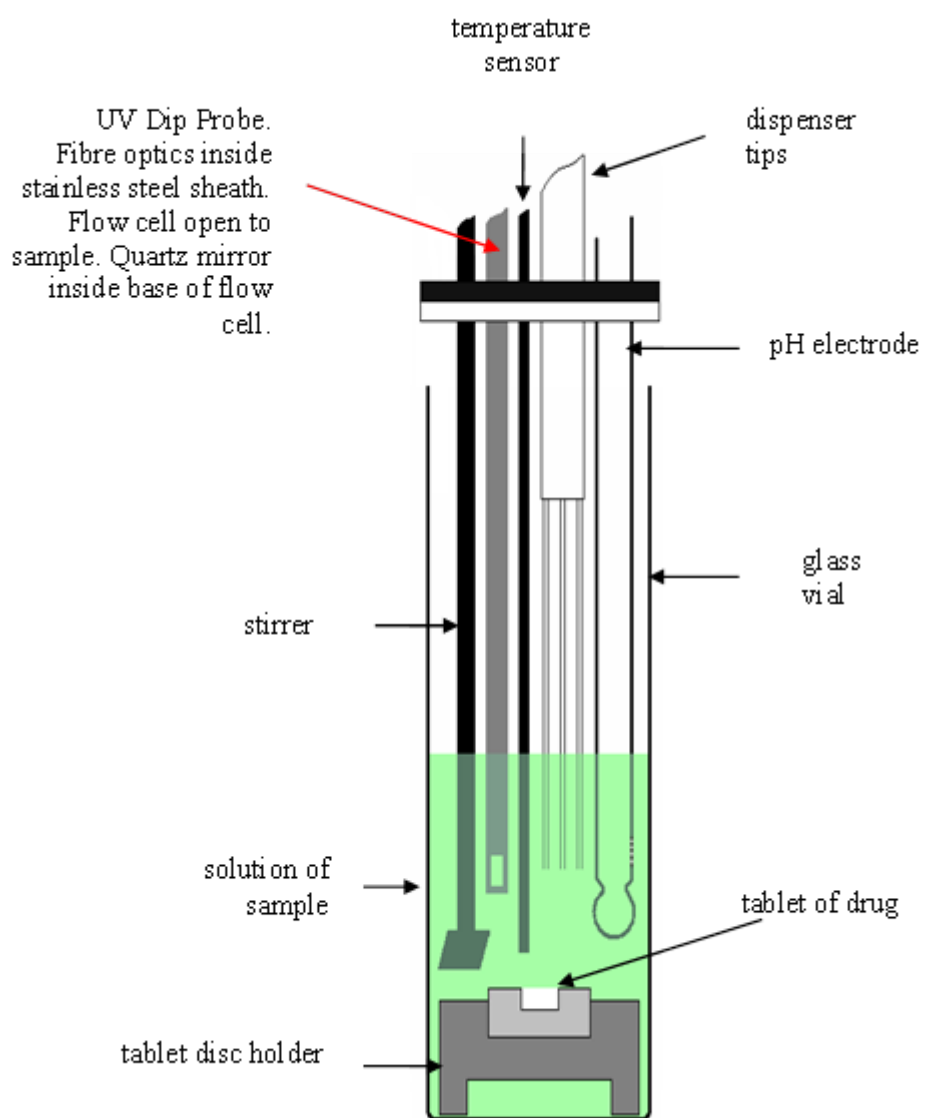
460 Figure 5: Dissolution of carbamazepine and cocrystal powders (n=3) at pH2.

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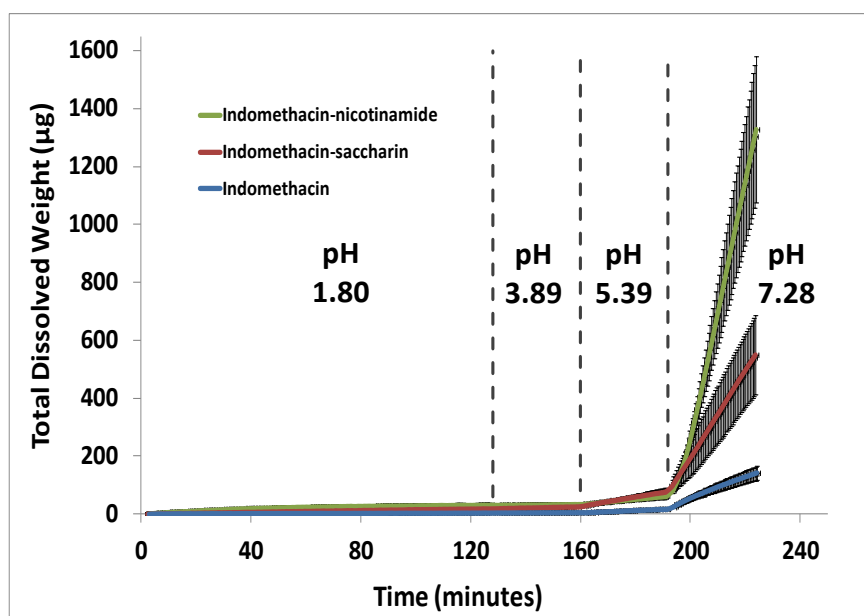
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466 Figure 1: Small scale dissolution assay (Sirius system)

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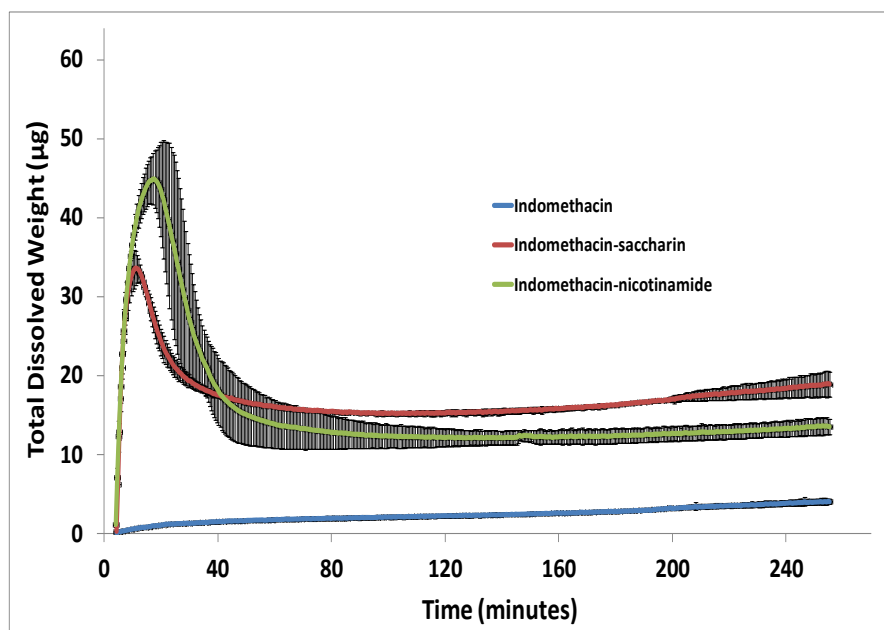
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472 Figure 2: Dissolution of indomethacin and cocystal pressed tablets (n=3) over four pH sectors.

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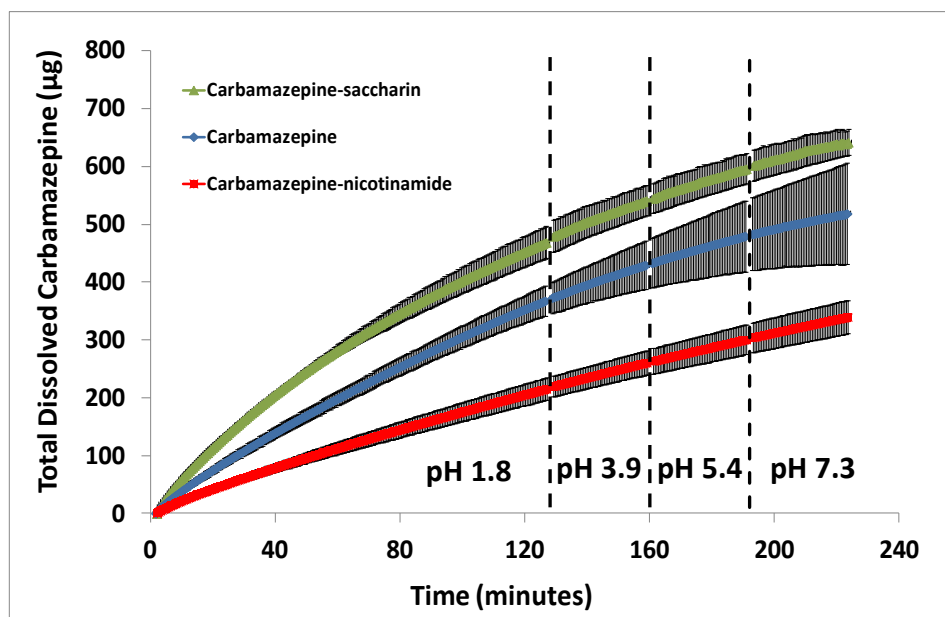
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477 Figure 3: Dissolution of indomethacin and cocrystal powders (n=3) at pH2.

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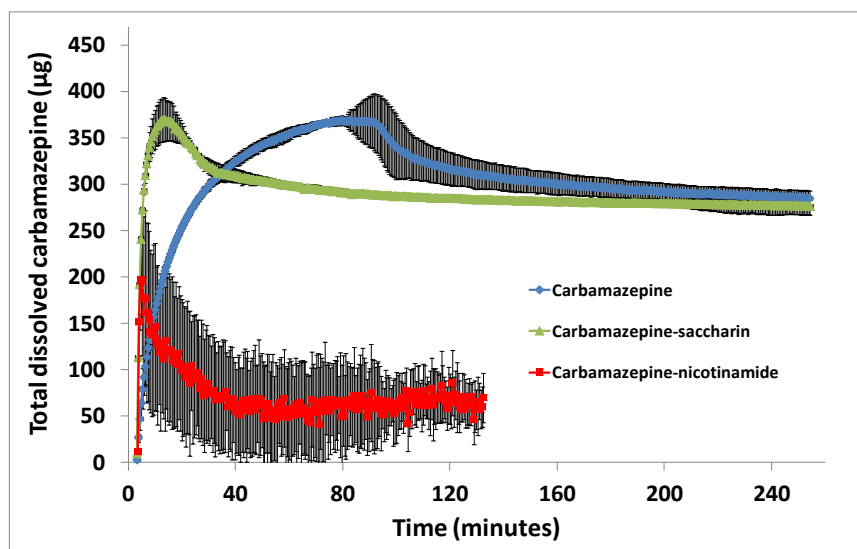
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482 Figure 4: Dissolution of carbamazepine and cocrystal pressed tablets (n=3) over four pH

483 sectors.

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488 Figure 5: Dissolution of carbamazepine and cocrystal powders (n=3) at pH2.

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