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## Three new hydrochlorothiazide cocrystals: Structural analyses and solubility studies

Item Type	Article
Authors	Ranjan, S.;Devarapalli, R.;Kundu, S.;Vangala, Venu R.;Ghosh, A.;Reddy, C.A.
Citation	Ranjan S, Devarapalli R, Kundu S et al (2017) Three new hydrochlorothiazide cocrystals: Structural analyses and solubility studies. Journal of Molecular Structure. 1133: 405-410.
DOI	<a href="https://doi.org/10.1016/j.molstruc.2016.12.019">https://doi.org/10.1016/j.molstruc.2016.12.019</a>
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**Link to publisher version:** <http://dx.doi.org/10.1016/j.molstruc.2016.12.019>

**Citation:** Ranjan S, Devarapalli R, Kundu S et al (2017) Three new hydrochlorothiazide cocrystals: Structural analyses and solubility studies. *Journal of Molecular Structure*. 1133: 405-410.

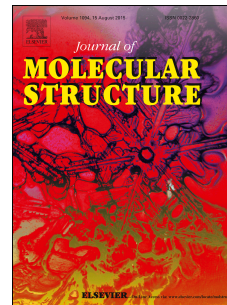
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# Accepted Manuscript

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PII: S0022-2860(16)31309-6

DOI: [10.1016/j.molstruc.2016.12.019](https://doi.org/10.1016/j.molstruc.2016.12.019)

Reference: MOLSTR 23217

To appear in: *Journal of Molecular Structure*

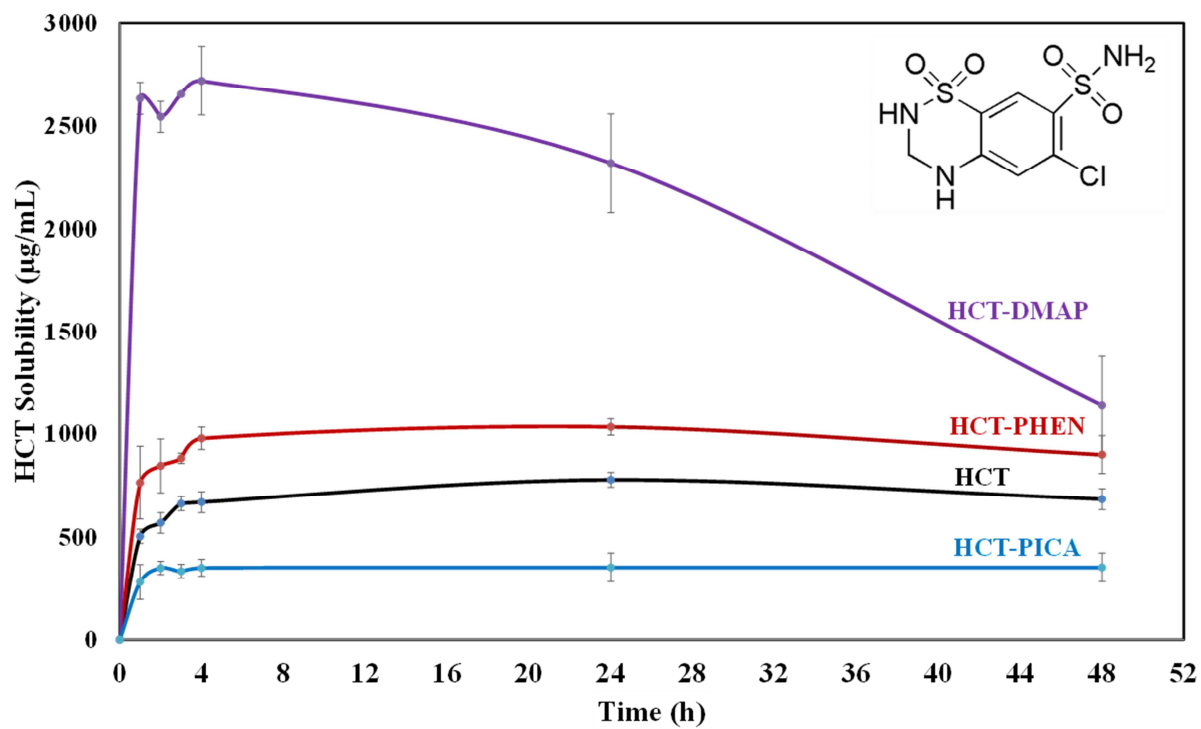
Received Date: 27 September 2016

Revised Date: 24 November 2016

Accepted Date: 6 December 2016

Please cite this article as: S. Ranjan, R. Devarapalli, S. Kundu, V.R. Vangala, A. Ghosh, C.M. Reddy, Three new hydrochlorothiazide cocrystals: Structural analyses and solubility studies, *Journal of Molecular Structure* (2017), doi: 10.1016/j.molstruc.2016.12.019.

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# Three new hydrochlorothiazide cocrystals: Structural analyses and solubility studies

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31 **Abstract**

32 Hydrochlorothiazide (HCT) is a diuretic BCS class IV drug with poor aqueous solubility and  
33 low permeability leading to poor oral absorption. The present work explores the  
34 cocrystallization technique to enhance the aqueous solubility of HCT. Three new cocrystals  
35 of HCT with water soluble cofomers phenazine (PHEN), 4-dimethylaminopyridine (DMAP)  
36 and picolinamide (PICA) were prepared successfully by solution crystallization method and  
37 characterized by single crystal X-ray diffraction (SCXRD), powder X-ray diffraction  
38 (PXRD), fourier transform –infraredspectroscopy (FT-IR), differential scanning calorimetry  
39 (DSC) and thermogravimetric analysis (TGA). Structural characterization revealed that the  
40 cocrystals with PHEN, DMAP and PICA exists in  $P2_1/n$ ,  $P2_1/c$  and  $P2_1/n$  space groups,  
41 respectively. The improved solubility of HCT-DMAP (4 fold) and HCT-PHEN (1.4 fold)  
42 cocrystals whereas decreased solubility of HCT-PICA (0.5 fold) as compared to the free drug  
43 were determined after four hours in phosphate buffer, pH 7.4, at 25 °C by using shaking flask  
44 method. HCT-DMAP showed a significant increase in solubility than all previously reported  
45 cocrystals of HCT suggest the role of a cofomer. The study demonstrates that the selection  
46 of cofomer could have pronounced impact on the physicochemical properties of HCT and  
47 cocrystallization can be a promising approach to improve aqueous solubility of drugs.

48

49 **Keywords:** Crystal engineering, cocrystal, solubility, thermal analysis, structural analysis.

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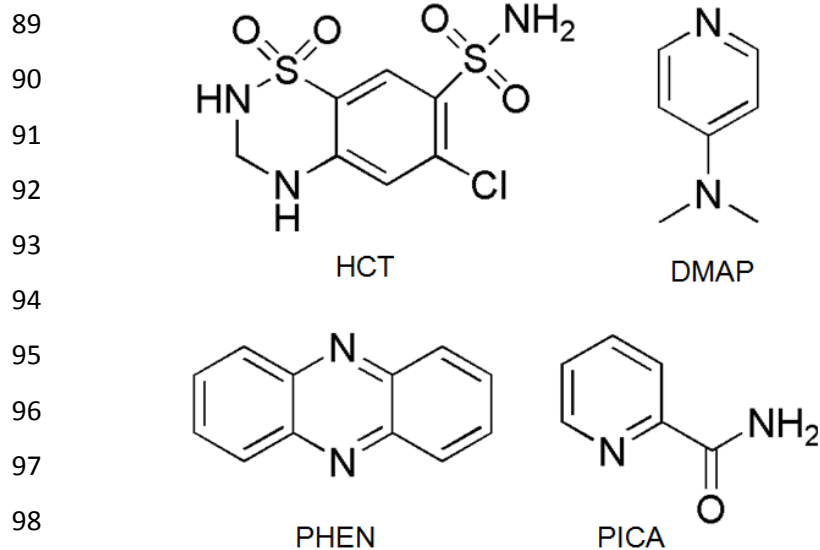
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## 56 1. Introduction

57 The properties of an active pharmaceutical ingredient (API) are broadly determined by  
58 the molecular arrangement in three-dimensional crystal lattice.<sup>1</sup> In recent times, many  
59 effective APIs are appearing eventually less in the market place due to poor  
60 biopharmaceutical properties.<sup>2</sup> Poor aqueous solubility is one of the crucial problems,<sup>3</sup>  
61 which affects the dissolution and bioavailability. Therefore, designing a new solid  
62 form with desired physicochemical properties is essential for its progress in the  
63 advanced stage of research and development. Exploitation of non-covalent interactions  
64 of the molecules in the crystal lattice, thereby altering the molecular arrangement may  
65 aid in the development of crystal with desirable physicochemical properties.<sup>4</sup> The  
66 various solid forms such as amorphous solids,<sup>5</sup> polymorphs,<sup>6</sup> salts,<sup>7</sup> hydrates<sup>8</sup> and  
67 solvates<sup>9</sup> have been utilized in tailoring specific physicochemical properties to  
68 overcome the difficulties associated with poor aqueous solubility. The most common  
69 approaches that are used for improving the delivery of poorly soluble drugs includes  
70 salt formation,<sup>10</sup> micronisation,<sup>11</sup> solid-lipid nanoparticles carrier,<sup>12</sup> solid dispersion,<sup>13</sup>  
71 solubilization of drugs in co-solvents,<sup>14</sup> complexation with cyclodextrins,<sup>15</sup> etc.  
72 Cocrystallization of API with water soluble cofomers is an emerging strategy to  
73 achieve the spring and parachute nature of aqueous solubility. It involves the  
74 formation of a homogenous crystalline material of two or more molecules with defined  
75 stoichiometry in a single crystal lattice.<sup>16</sup> Non-covalent interactions such as hydrogen  
76 bonding, halogen bonding,  $\pi$ - $\pi$  stacking, and van der Waals forces are the most  
77 common type of interactions utilized for engineering of cocrystals.<sup>17</sup>  
78 Biopharmaceutical properties such as solubility, dissolution, bioavailability, moisture  
79 uptake, chemical stability, mechanical properties have been altered by  
80 cocrystallization.<sup>18</sup> Amongst these, solubility and dissolution are the most frequently  
81 studied properties.

82 Hydrochlorothiazide (HCT, 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiazine-7-  
83 sulfonamide) (Scheme 1) is a diuretic antihypertensive drug of the thiazide family,  
84 widely prescribed for the management of edema and hypertension. However, this API  
85 as per biopharmaceutical classification system (BCS) class IV drug, has poor water  
86 solubility (0.7 g/L) and low permeability (Caco-2 permeability: -6.06) which is a  
87 major barrier in making it bioavailable (65 %) in the body.<sup>19</sup>

88



100 **Scheme 1.** Chemical structures of hydrochlorothiazide (HCT) and the cofomers used  
101 in this study.

102  
103 Several researchers have attempted to improve the solubility of HCT by complexation  
104 with cyclodextrins,<sup>20</sup> solid dispersions,<sup>21</sup> liquid–solid compacts,<sup>22</sup> lecithin/chitosan  
105 nanoparticles,<sup>23</sup> pluronic® nanoaggregates,<sup>24</sup> etc. It reveals that these formulations  
106 could favorably impact an aqueous solubility of HCT. Recently, HCT has also been  
107 investigated for its cocrystallization tendencies where there is a potential for solubility  
108 enhancement at the molecular level. HCT cocrystals involving some cofomers were  
109 reported and they exhibited improved aqueous solubility and dissolution than the drug  
110 itself.<sup>19,25</sup>

111 Hydrochlorothiazide moiety, the principal functional unit i.e. two sulfonamide and one  
112 aromatic amine group is expected to form  $S=O \cdots H$  and  $N-H \cdots O$  hetero-synthons. On  
113 this basis several cofomers including aromatic acids and amides were attempted for  
114 cocrystallization with HCT (see Table S1, Electronic Supplementary Information, ESI  
115 for complete list of cofomers tested). However, the cocrystals were identified with  
116 only three cofomers, phenazine (PHEN), 4-dimethylaminopyridine (DMAP) and  
117 picolinamide (PICA) and are reported herein. From the literature it has been found that  
118 the cofomers phenazine (PHEN),<sup>26</sup> picolinamide (PICA)<sup>28</sup> could form cocrystals or a  
119 cofomer, 4-dimethylaminopyridine (DMAP),<sup>29</sup> forms salt with APIs and have altered  
120 the physicochemical properties of the API. Thus in this study, we undertaken these  
121 cofomers and investigated the solubility of all three HCT cocrystals.

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## 2. Experimental section

### 2.1 Materials

Hydrochlorothiazide and all cocrystal formers (phenazine, 4-dimethylaminopyridine and picolinamide) were purchased from Sigma-Aldrich chemicals, Bangalore, India. All the solvents were used (for crystallization) as received without any further purification.

### 2.2 Methodology

#### 2.2.1 Cocrystals preparation method

HCT and cocrystal former in a definite stoichiometric ratio were subjected to grinding using an agate mortar and pestle for about 6 to 8 min with the addition of few drops of methanol. The Liquid Assisted Grinding (LAG) was used because it is expected to increase cocrystallization kinetics and for polymorph control.<sup>30</sup> After grinding, the mixture was dissolved in ethanol (or methanol) and the suspension was heated until a clear solution was obtained. Then the solution was filtered to remove any undissolved particles into a fresh conical flask and the filtrate was left to evaporate slowly at ambient conditions. The single crystals suitable for X-ray diffraction studies were obtained in 4 to 6 days.

#### 2.2.2 Single crystal X-ray diffraction (SXRD)

X-ray diffraction data for all the cocrystals of HCT were recorded on a SuperNova, Eos diffractometer using monochromatic Mo-K $\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ). The data collection was carried out at 246 K for HCT-PHEN, 291 K for HCT-DMAP, and 296 K for HCT-PICA cocrystals respectively. The structure was solved using Olex<sup>2,31</sup> with Superflip<sup>32</sup> structure solution program using Charge Flipping solution method and refined with the ShelXL<sup>33</sup> refinement package using Least Squares minimization.

#### 2.2.3 Powder X-ray diffraction (PXRD)

The PXRD patterns were collected on a RigakuSmartLab with a Cu-K $\alpha$  radiation (1.540  $\text{\AA}$ ). The tube voltage and amperage were set at 20 kV and 35 mA, respectively. Each sample was scanned between 5 and 50° 2 $\theta$  with a step size of 0.02°. Before performing the experiments, the instrument was calibrated using a silicon standard.

#### 2.2.4 Fourier transform-infrared spectroscopy (FT-IR)

156 Transmission infrared spectra of all the cocrystals and coformers including HCT were  
157 obtained using a Fourier-transform infrared spectrometer (PerkinElmer502). Before  
158 measuring the spectra for samples, background scan was performed with pure KBr pellet.  
159 Later the samples were pelleted with the help of 2 mg in 15 mg of KBr and 8 scans were  
160 collected at  $4\text{ cm}^{-1}$  resolutions for each sample. The spectra were measured over the range of  
161  $4000 - 400\text{ cm}^{-1}$ .

### 162

### 163 **Differential scanning calorimetry (DSC)**

164 DSC was conducted on a Mettler-Toledo DSC11 STAR<sup>e</sup> instrument. Accurately weighed  
165 samples (4–5 mg) were placed in hermetically sealed 40  $\mu\text{L}$  aluminium crucibles and scanned  
166 from 50 to 300  $^{\circ}\text{C}$  at a heating rate of 10  $^{\circ}\text{C}/\text{min}$  under a dry nitrogen atmosphere (flow rate  
167 60 ml/min). The data was managed by STAR<sup>e</sup> software.

### 168

### 169 **2.2.5 Thermogravimetric analysis (TGA)**

170 TGA was carried out using a Perkin Elmer, Diamond TG/DTA analyzer, operated under  
171 nitrogen atmosphere with a heating rate of 10  $^{\circ}\text{C}/\text{min}$  and in the range of 30-300  $^{\circ}\text{C}$ .

### 172

### 173 **2.2.6 Solubility studies**

174 The solubility of HCT, HCT-PHEN, HCT-DMAP and HCT-PICA were measured in  
175 phosphate buffer, pH 7.4, at 25  $^{\circ}\text{C}$  by using shaking flask method.<sup>19</sup> An excess amount of the  
176 drug and cocrystals were added to 20 mL of buffer. The resulting slurry was shaken in a  
177 water bath shaker, maintained at 25  $^{\circ}\text{C}$  for 48 h. Aliquots (0.5 mL) of the slurry were  
178 withdrawn at different time intervals for a period of 48 h to confirm that the solution has  
179 achieved equilibrium. The samples were assayed after suitable dilution for drug content by  
180 HPLC at 227 nm. The amount of drug dissolved in each time interval was calculated using  
181 the standard curve (linearity range: 2-32  $\mu\text{g}/\text{mL}$ ) which was prepared in phosphate buffer (pH  
182 7.4). The experiment was performed in triplicate and values were expressed as mean  $\pm$   
183 standard deviation.

### 184

### 185 **2.2.7 High performance liquid chromatography (HPLC)**

186 Solution concentration of HCT and its cocrystals were analyzed by HPLC (Knauer) equipped  
187 with a UV/vis detector. A C18 Nova-Pak column 5  $\mu\text{m}$ ,  $4.6 \times 250\text{ mm}$  (Waters, USA) at  
188 ambient temperature with a flow rate of 1 mL/min was used to separate HCT, PHEN, DMAP  
189 and PICA. An isocratic method with acetonitrile and phosphate buffer (pH=2.8) mixed in a

190 ratio of 40:60 (v/v), respectively, was optimized for quantitative determination of  
191 hydrochlorothiazide (retention time 3.7 min) at an optimum wavelength of 227 nm. Sample  
192 injection volume was 20 $\mu$ L. Eurochrom software was used to collect and process the data.

### 193 3. Results and discussion

194 Three new cocrystals of HCT with heteroaromatic coformers were synthesized by the  
195 slow evaporative crystallization method (see also experimental section). Crystal  
196 structure analysis was performed to rationalize the hydrogen bonding preferences of  
197 acceptors and donors in presence of other competing functional groups.  
198 Crystallographic data is listed in the Table S2, ESI.

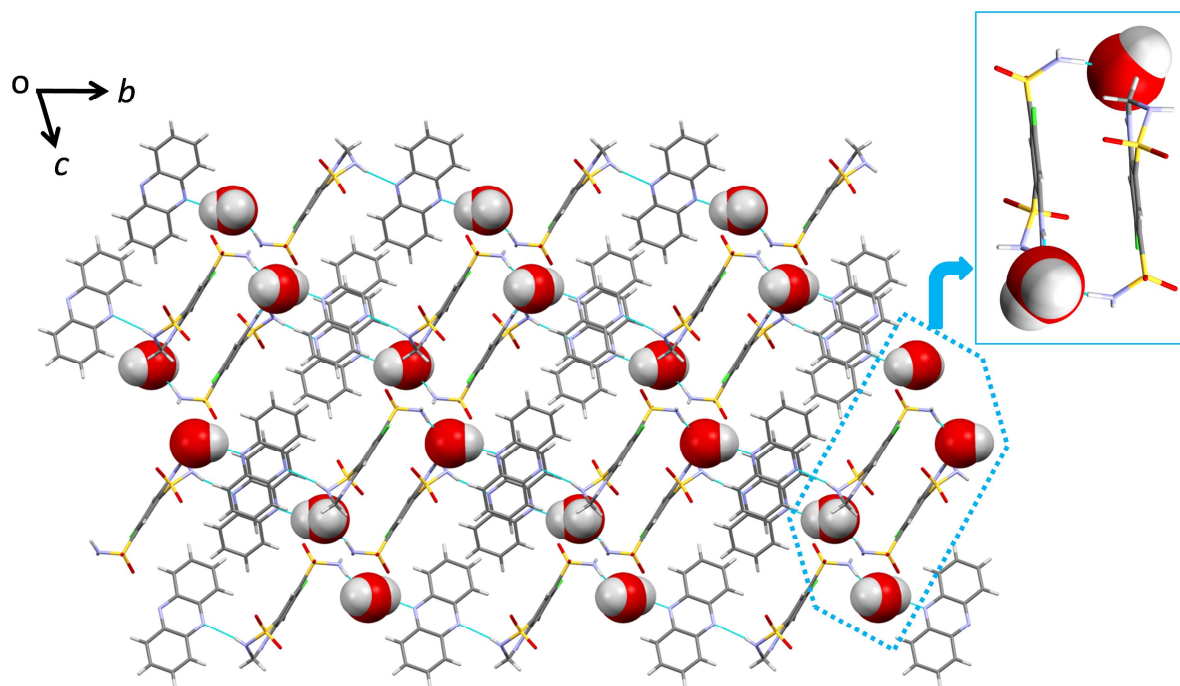
199 From the available literature on HCT cocrystals, it was found that HCT prefer to bind  
200 with a hetero atom in the coformer. Hence, strategically we chose only heteroaromatic  
201 compounds as coformers for this study. Most common synthons found in the reported  
202 HCT cocrystals are N–H $\cdots$ O and N–H $\cdots$ N by the primary and secondary sulfonamide  
203 groups of HCT with coformers. However, it was observed (in reported and present  
204 cocrystals as well) that the typical synthons, sulfonamide dimer and sulfonamide  
205 catemer that are present in polymorphs of HCT, were disrupted by the coformers to  
206 form a stable cocrystal. A common synthon in all three new cocrystals has been found  
207 as N–H $\cdots$ N between the primary sulfonamide N-H and pyridine N. Amongst the three  
208 studied compounds, only PHEN appeared as a cocrystal hydrate of HCT, which is  
209 similar to the isonicotinamide, which also exists as a cocrystal hydrate with HCT.<sup>34</sup>  
210 The detailed crystal structure analyses for all the cocrystals are discussed below and  
211 experimental details are provided in the ESI.

212

#### 213 3.1 Hydrochlorothiazide:Phenazine:H<sub>2</sub>O (1:1:1), (HCT-PHEN.H<sub>2</sub>O)

214 The crystal structure of HCT-PHEN.H<sub>2</sub>O revealed that it is a monohydrate of the 1:1  
215 cocrystal of HCT and PHEN. The cocrystal crystallized in monoclinic  $P2_1/n$  space  
216 group with one molecules of each HCT, PHEN and H<sub>2</sub>O in the asymmetric unit (Fig.  
217 S1, ESI). In the crystal packing, two molecules of each HCT and H<sub>2</sub>O formed a  
218 tetrameric motif as shown in Fig. 1. The alternative tetrameric motifs were connected  
219 by PHEN molecules *via* strong N–H $\cdots$ N ( $d/\text{\AA}$ ,  $\theta^\circ$ ; 0.77  $\text{\AA}$ , 171 $^\circ$ ) and moderately  
220 strong O–H $\cdots$ N (0.92  $\text{\AA}$ , 146 $^\circ$ ) interactions to form 1D sheets along *b*-axis. The  
221 interlinked PHEN molecules in the 1D tape are stacked by  $\pi$  -  $\pi$  interactions

222 perpendicular to HCT molecular plane. The overall crystal packing from the top view  
223 of *a*-axis is shown in Fig. 1.

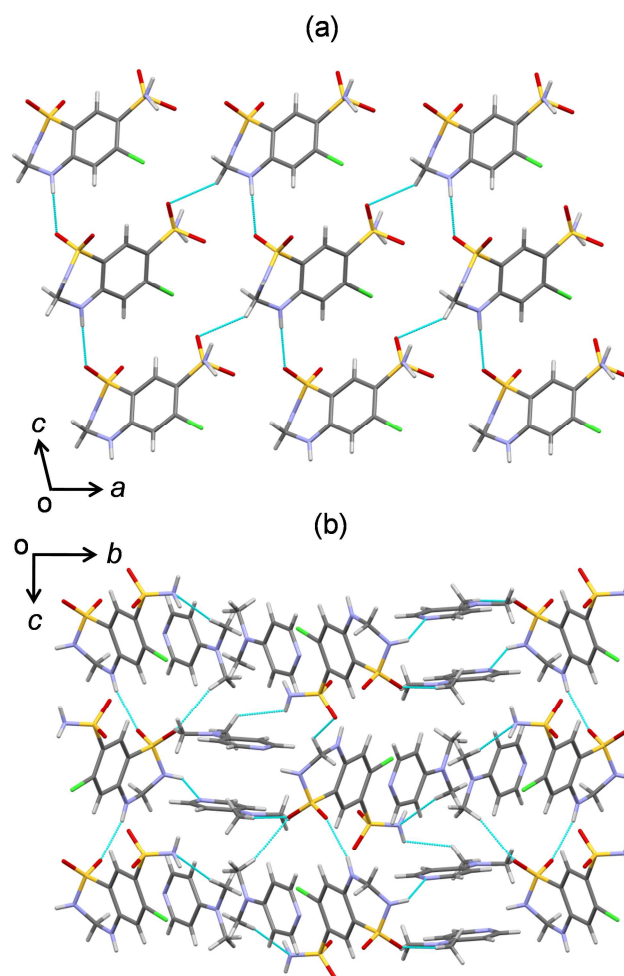


224  
225 **Fig. 1.** HCT-PHEN.H<sub>2</sub>O crystal packing view along *a*-axis, where the water molecule  
226 incorporated in the crystal structure is represented with a space fill model. The inset  
227 highlights the tetrameric motif in the crystal packing.

228

### 229 3.2 Hydrochlorothiazide:4-Dimethylaminopyridine (1:2), (HCT-DMAP)

230 The cocrystal, HCT-DMAP crystallizes in the monoclinic  $P2_1/c$  space group with one  
231 molecule of HCT and two molecules of DMAP in the asymmetric unit (Fig. S2, ESI).  
232 The HCT molecules form 2D sheets *via* N–H···O (0.86 Å, 166°) interactions along *c*-  
233 axis and C–H···O (2.714 Å, 121°) interactions along *a*-axis (Fig. 2a). In the third  
234 dimension the DMAP molecules are sandwiched between the HCT 2D-sheets (Fig.  
235 2b).



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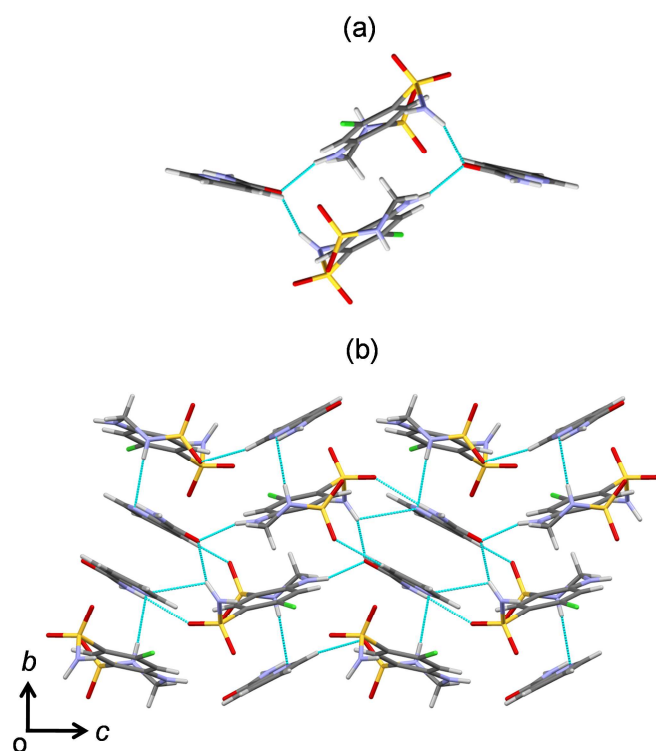
237 **Fig. 2.** Crystal packing of HCT-DMAP where (a) 2d sheet in *ac* plane and (b) crystal  
238 packing, when viewed down *a*-axis.

239

### 240 3.3 Hydrochlorothiazide:Picolinamide (1:1), (HCT-PICA)

241 The PICA is a positional isomer of nicotinamide (NIC) and isonicotinamide (INIC).  
242 NIC and INIC were reported as a cocrystal and cocrystal monohydrate of HCT,  
243 respectively.<sup>25a</sup> Here the cocrystal HCT with PICA crystallizes in the monoclinic  
244  $P2_1/n$  space group with one molecule of each HCT and PICA in the asymmetric unit  
245 (Fig. S3, ESI). Though the three coformers NIC, INIC, and PICA are isomers, they  
246 form cocrystals with HCT in three different crystal systems as orthorhombic, triclinic  
247 and monoclinic respectively. This means that the position of heteroatom of the  
248 coformer is deciding the crystal system by forming different types of intermolecular  
249 interactions with HCT.

250 In the crystal structure of HCT–NIC co-crystal, NIC molecules form 1D chains  
 251 through amide···pyridine (N–H···N) synthons and HCT molecules are sandwiched  
 252 between these alternate 1D chains. But, the INIC molecules in the crystal structure of  
 253 HCT–INIC–H<sub>2</sub>O form amide-amide supramolecular homosynthons and are linked to  
 254 HCT molecules by water molecules. Here, the water molecules act as both H-bond  
 255 donor (to pyridyl moieties of INIC) and acceptor (to sulfonamide groups of HCT). The  
 256 crystal packing in the present case HCT-PICA is completely different compared to  
 257 above two. Here, a two molecules of each HCT and PICA form a tetrameric motif  
 258 (Fig. 3a) *via* N–H···O (0.86 Å, 160°; 0.96 Å, 150°) interactions. In the overall crystal  
 259 packing the tetramers were propagated along the *b* and *c*-axes directions *via* N–H···N  
 260 and N–H···O interactions, respectively (Fig. 3b).



261

262 **Fig. 3.** Crystal packing diagram of HCT-PICA. (a) Tetrameric motif in the crystal packing  
 263 formed by two molecules of HCT and two molecules of PICA. (b) Crystal packing, when  
 264 viewed down *a*-axis.

### 265 3.4 Powder X-ray diffraction (PXRD)

266 PXRD is a powerful tool for preliminary characterization of new solid forms as well as  
 267 cocrystals.<sup>35</sup> In each case freshly prepared powder samples were used for the data  
 268 collection. The PXRD patterns for all the cocrystals were plotted in comparison with

269 respective individual coformers and simulated PXRD pattern (Fig. S4, ESI). The  
270 absence of characteristic peaks of starting compounds and the close superimposition of  
271 the experimental and simulated patterns confirm the cocrystal formation.

272

### 273 **3.5 FT-IR analysis**

274 The cocrystals were further characterized by FT-IR spectroscopy, which is a cogent  
275 tool to make sure the cocrystal formation. The comparison of the stretching frequency  
276 shifts as shown in Fig. S6, ESI corroborated the formation of hydrogen bonds between  
277 the functional groups in cocrystals. At first instance, the SO<sub>2</sub> asymmetric region  
278 (1320–1380 cm<sup>-1</sup>) was found to be very broad in the FT-IR spectra of HCT than when  
279 compared to the same region in the spectra of cocrystals. Furthermore, The NH and  
280 NH<sub>2</sub> stretching frequencies in free HCT observed at 3267 and 3361 cm<sup>-1</sup> respectively.  
281 But, in the cocrystals the NH frequency merged with NH<sub>2</sub> and appeared as a broad  
282 peak compared to free HCT.

283

### 284 **3.6 Thermal analysis**

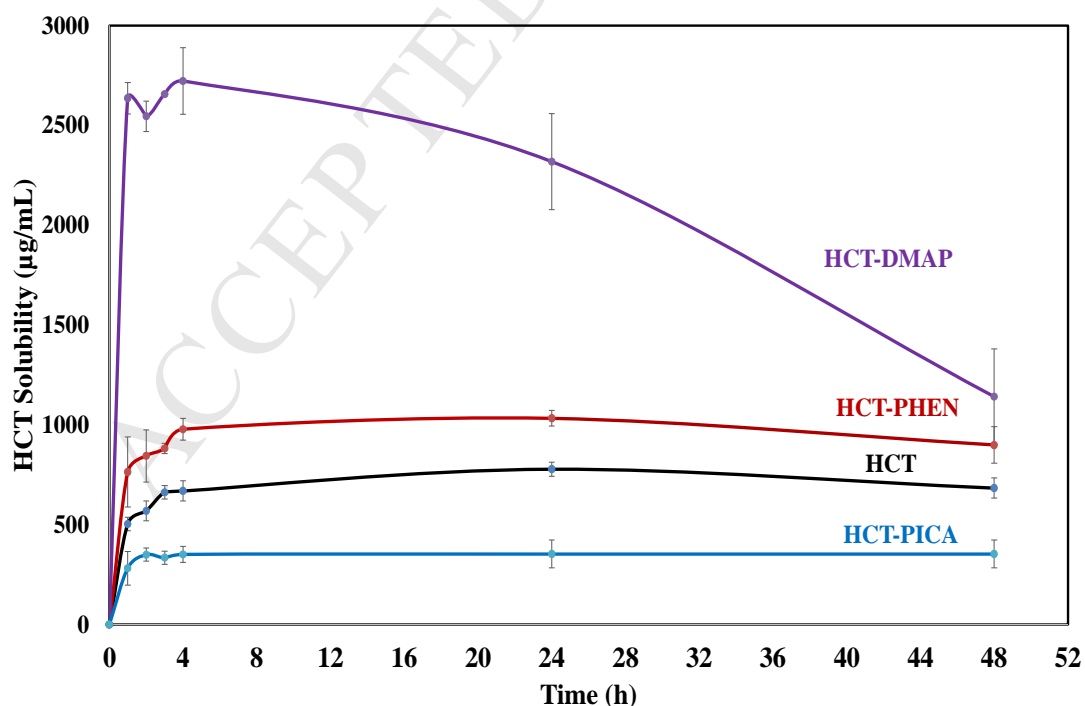
285 Thermal behavior of all the cocrystals was investigated by differential scanning  
286 calorimetry (DSC) and thermogravimetric analysis (TGA). DSC results have revealed  
287 that the melting point of all cocrystals except for the monohydrate cocrystal (HCT-  
288 PHEN) were distinct from HCT (267-269 °C) and individual coformers. In the case of  
289 HCT-PHEN, loss of crystalline water leads to dissociation of cocrystal. This confirms  
290 the formation of new crystalline phase. The melting point of HCT-DMAP and HCT-  
291 PICA cocrystals were observed as 138 °C, and 159 °C, respectively (Fig. S5, ESI).

292 In the TGA curve of HCT-PHEN, there was a weight loss of 4.19 % in the temperature  
293 range of 100-145 °C which corresponds to loss of one water molecule. This value is in  
294 accordance with the theoretical mass loss of 3.7 % for desolvation of one mole of  
295 water from the crystal lattice of HCT-PHEN. Next, there was a weight loss of 34.43 %  
296 in the temperature range of 147-197 °C. This can be attributed to the  
297 degradation/sublimation of one mole of phenazine (theoretical weight loss 36.36%).  
298 This event is followed phase transition and melting of hydrochlorothiazide. Similarly,  
299 for all other HCT cocrystals, TGA profiles corroborated well with the DSC results and  
300 their data is presented in the ESI (Fig. S5).

301

### 3.7 Solubility Studies

HCT is a poorly soluble drug (0.7 g/L)<sup>1</sup>. Poor aqueous solubility not only limits its dissolution and absorption but also challenges its pharmaceutical development. CocrySTALLIZATION was employed to modify the solubility of HCT. The solubility profile of hydrochlorothiazide and its cocrySTALLS are illustrated in Fig. 4. It was observed that cocrySTALLIZATION markedly increase the solubility of HCT. It was found that the solubility of HCT and its cocrySTALLS after four hours follows the rank order: HCT-DMAP (4 fold) > HCT-PHEN (1.4 fold) > HCT > HCT-PICA. The solubility studies conducted by Desiraju *et al.* (2015) reported improved solubility of HCT-*para*-aminobenzoic acid (2.4 times), HCT-resorcinol (1.3 times), HCT-nicotinamide (1.2 times) as compared to HCT.<sup>19</sup> Interestingly, our results suggest that HCT-DMAP has exhibited the highest transient solubility among the HCT cocrySTALLS reported thus far. The parachute nature of the HCT-DMAP cocrySTALL extended till 48 hours. On the other hand, HCT-PICA showed poor aqueous solubility as compared to HCT, which is in accordance with a literature finding of a couple of other HCT cocrySTALLS.<sup>19</sup> Further, it reveals a selection of suitable cofomer can lead to a potential modulation in the solubility of HCT in either direction.



320

321 **Fig. 4.** Solubility profile of hydrochlorothiazide and its cocrySTALLS (Avg. value  $\pm$  SD (n=3)).

#### 322 4. Conclusions

323 In this study, cocrystallization was explored to address the solubility issues of  
324 hydrochlorothiazide. The strategy to exploit the preferable binding nature of HCT with  
325 the hetero atom in the coformer has been demonstrated successfully by obtaining three  
326 new solid forms. The formation of cocrystals was confirmed by thermal, FT-IR,  
327 PXRD, and single crystal X-ray diffraction studies. The melting points of all the three  
328 cocrystals were lower than API but higher than the corresponding coformer. The  
329 solubility of the drug and cocrystal after four hours follows the order HCT-DMAP (4  
330 fold) > HCT-PHEN (1.4 fold) > HCT > HCT-PICA. HCT-DMAP solubility results  
331 suggest that a selection of an appropriate coformer would have a great potential to  
332 increase the solubility of HCT. Thus, cocrystallization approach proved to be a  
333 promising alternative in positively modifying the solubility of hydrochlorothiazide.

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#### 335 Acknowledgements

336 C. M. R. acknowledges financial support from the CSIR (02(0156)/13/EMR-II) and  
337 DST (DST/SJF/CSA-02/2014-15). A.G. acknowledges financial support from SERB,  
338 DST (EMR/000099/2014). S. R. thanks the INSPIRE fellowship from Department of  
339 Science and Technology, Govt. of India. R. D. thanks IISER-Kolkata for fellowship.  
340 S. K. thanks BIT, Mesra for providing necessary facilities. C. M. R. and V. R. V.  
341 thank Royal Society of Chemistry for Researcher Mobility Grant (2015/16).

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343 **Note:** Electronic Supplementary Information (ESI) available: ORTEP representations,  
344 PXRD patterns of all the cocrystals, DSC and TGA curves, table containing  
345 crystallographic information, ideal solubility calculations.

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**Highlights**

- 1) Three new cocrystals of HCT with water soluble cofomers were successfully prepared by solution crystallization method.
- 2) Transient Solubility of HCT was increased by 4 fold in case of HCT-DMAP cocrystal.
- 3) Selection of cofomer is vital, otherwise reduced solubility can be observed as in the case of HCT-PICA.