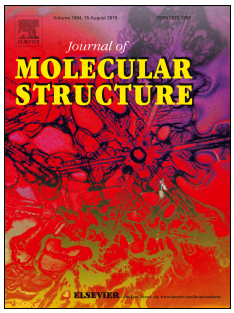
Accepted Manuscript



Three new hydrochlorothiazide cocrystals: Structural analyses and solubility studies

Subham Ranjan, Ramesh Devarapalli, Sudeshna Kundu, Venu R. Vangala, Animesh Ghosh, C. Malla Reddy

PII: S0022-2860(16)31309-6

DOI: 10.1016/j.molstruc.2016.12.019

Reference: MOLSTR 23217

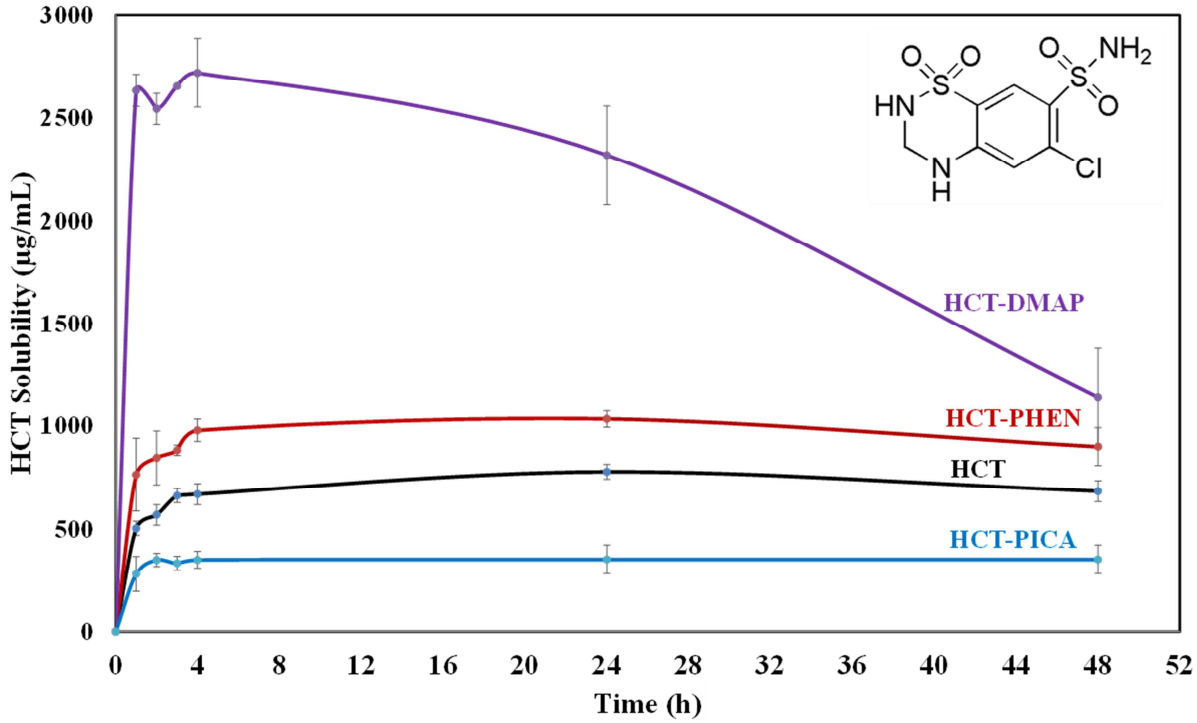
To appear in: *Journal of Molecular Structure*

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.



Three new hydrochlorothiazide cocrystals: Structural analyses and solubility studies

Subham Ranjan,[a] Ramesh Devarapalli,[a] Sudeshna Kundu,[a,b] Venu R. Vangala,[c,*] Animesh Ghosh[b,*] and C. Malla Reddy[a,*]

[a]*Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Kolkata, Mohanpur Campus, Mohanpur 741 246, India*

[b]*Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Mesra Ranchi 835 215, India*

[c]*Centre for Pharmaceutical Engineering Science and School of Pharmacy, University of Bradford, Richmond Road, Bradford BD7 1DP, United Kingdom*

* Corresponding author:

1. C. Malla Reddy
   Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Kolkata, Mohanpur Campus, Mohanpur 741 246, India
   E-mail: cmallareddy@rediffmail.com, cmallareddy@gmail.com

2. Animesh Ghosh
   Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Mesra Ranchi 835 215, India.
   E-mail: aghosh@bitmesra.ac.in, anim_1607@yahoo.co.in

3. Venu R. Vangala
   Centre for Pharmaceutical Engineering Science and School of Pharmacy, University of Bradford, Richmond Road, Bradford BD7 1DP, United Kingdom.
   E-mail: V.G.R.Vangala@bradford.ac.uk

Abstract

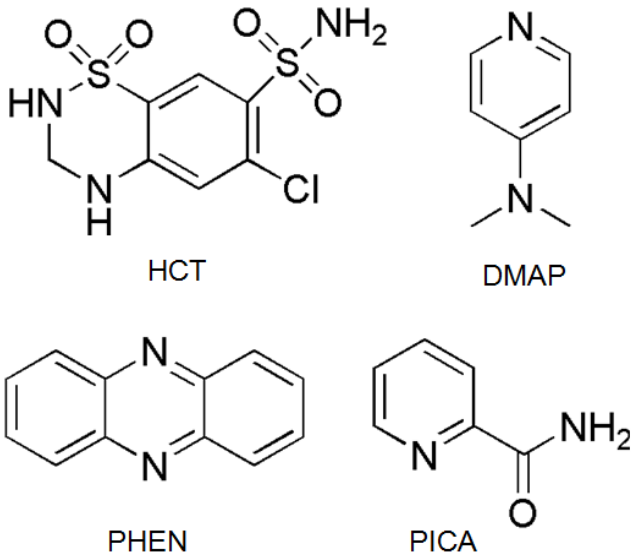
Hydrochlorothiazide (HCT) is a diuretic BCS class IV drug with poor aqueous solubility and low permeability leading to poor oral absorption. The present work explores the cocrystallization technique to enhance the aqueous solubility of HCT. Three new cocrystals of HCT with water soluble coformers phenazine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

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

1. Introduction

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

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



Scheme 1. Chemical structures of hydrochlorothiazide (HCT) and the coformers used in this study.

Several researchers have attempted to improve the solubility of HCT by complexation with cyclodextrins,[20] soliddispersions,[21] liquid−solid compacts,[22] lecithin/chitosan nanoparticles,[23] pluronic® nanoaggregates,[24] etc. It reveals that these formulations could favorably impact an aqueous solubility of HCT. Recently, HCT has also been investigated for its cocrystallization tendencies where there is a potential for solubility enhancement at the molecular level. HCT cocrystals involving some coformers were reported and they exhibited improved aqueous solubility and dissolution than the drug itself.[19,25]

Hydrochlorothiazide moiety, the principal functional unit i.e. two sulfonamide and one aromatic amine group is expected to form S=O···H and N–H···O hetero-synthons. On this basis several coformers including aromatic acids and amides were attempted for cocrystallization with HCT (see Table S1, Electronic Supplementary Information, ESI for complete list of coformers tested). However, the cocrystals were identified with only three coformers, phenazine (PHEN), 4-dimethylaminopyridine (DMAP) and picolinamide (PICA) and are reported herein. From the literature it has been found that the coformers phenazine (PHEN),[26] picolinamide (PICA)[28] could form cocrystals or a coformer, 4-dimethylaminopyridine (DMAP),[29] forms salt with APIs and have altered the physicochemical properties of the API. Thus in this study,we undertaken these coformers and investigated the solubility of all three HCT cocrystals.

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.[30] 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-Kα radiation (λ = 0.71073 Å). 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[2],[31] with Superflip[32] structure solution program using Charge Flipping solution method and refined with the ShelXL[33] 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-Kα radiation (1.540 Å). The tube voltage and amperage were set at 20 kV and 35 mA, respectively. Each sample was scanned between 5 and 50° 2θ 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)

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

Differential scanning calorimetry (DSC)

DSC was conducted on a Mettler-Toledo DSI1 STAR^e instrument. Accurately weighed samples (4–5 mg) were placed in hermetically sealed 40 µL aluminium crucibles and scanned from 50 to 300 °C at a heating rate of 10 °C/min under a dry nitrogen atmosphere (flow rate 60 ml/min). The data was managed by STAR^e software.

2.2.5 Thermogravimetric analysis (TGA)

TGA was carried out using a Perkin Elmer, Diamond TG/DTA analyzer, operated under nitrogen atmosphere with a heating rate of 10 °C/min and in the range of 30-300 °C.

2.2.6 Solubility studies

The solubility of HCT, HCT-PHEN, HCT-DMAP and HCT-PICA were measured in phosphate buffer, pH 7.4, at 25 °C by using shaking flask method.[19] An excess amount of the drug and cocrystals were added to 20 mL of buffer. The resulting slurry was shaken in a water bath shaker, maintained at 25 °C for 48 h. Aliquots (0.5 mL) of the slurry were withdrawn at different time intervals for a period of 48 h to confirm that the solution has achieved equilibrium. The samples were assayed after suitable dilution for drug content by HPLC at 227 nm. The amount of drug dissolved in each time interval was calculated using the standard curve (linearity range: 2-32 µg/mL) which was prepared in phosphate buffer (pH 7.4). The experiment was performed in triplicate and values were expressed as mean ± standard deviation.

2.2.7 High performance liquid chromatography (HPLC)

Solution concentration of HCT and its cocrystals were analyzed by HPLC (Knaur) equipped with a UV/vis detector. A C18 Nova-Pak column 5 µm, 4.6 × 250 mm (Waters, USA) at ambient temperature with a flow rate of 1 mL/min was used to separate HCT, PHEN, DMAP and PICA. An isocratic method with acetonitrile and phosphate buffer (pH=2.8) mixed in a

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

3. Results and discussion

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

From the available literature on HCT cocrystals, it was found that HCT prefer to bind with a hetero atom in the coformer. Hence, strategically we chose only heteroaromatic compounds as coformers for this study. Most common synthons found in the reported HCT cocrystals are N–H···O and N–H···N by the primary and secondary sulfonamide groups of HCT with coformers. However, it was observed (in reported and present cocrystals as well) that the typical synthons, sulfonamide dimer and sulfonamide catemer that are present in polymorphs of HCT, were disrupted by the coformers to form a stable cocrystal. A common synthon in all three new cocrystals has been found as N–H···N between the primary sulfonamide N-H and pyridne N. Amongst the three studied compounds, only PHEN appeared as a cocrystal hydrate of HCT, which is similar to the isonicotinamide, which also exists as a cocrystal hydrate with HCT.[34] The detailed crystal structure analyses for all the cocrystals are discussed below and experimental details are provided in the ESI.

3.1 Hydrochlorothiazide:Phenazine:H_2O (1:1:1), (HCT-PHEN.H_2O)

The crystal structure of HCT-PHEN.H_2O revealed that it is a monohydrate of the 1:1 cocrystal of HCT and PHEN. The cocrystal crystallized in monoclinic$P2_1/n$ space group with one molecules of each HCT, PHEN and H_2O in the asymmetric unit (Fig. S1, ESI). In the crystal packing, two molecules of each HCT and H_2O formed a tetrameric motif as shown in Fig. 1. The alternative tetrameric motifs were connected by PHEN molecules *via* strong N–H···N (d/Å, θ/°; 0.77 Å, 171°) and moderately strong O–H···N (0.92 Å, 146°) interactions to form 1D sheets along *b*-axis. The interlinked PHEN molecules in the 1D tape are stacked by π - π interactions

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

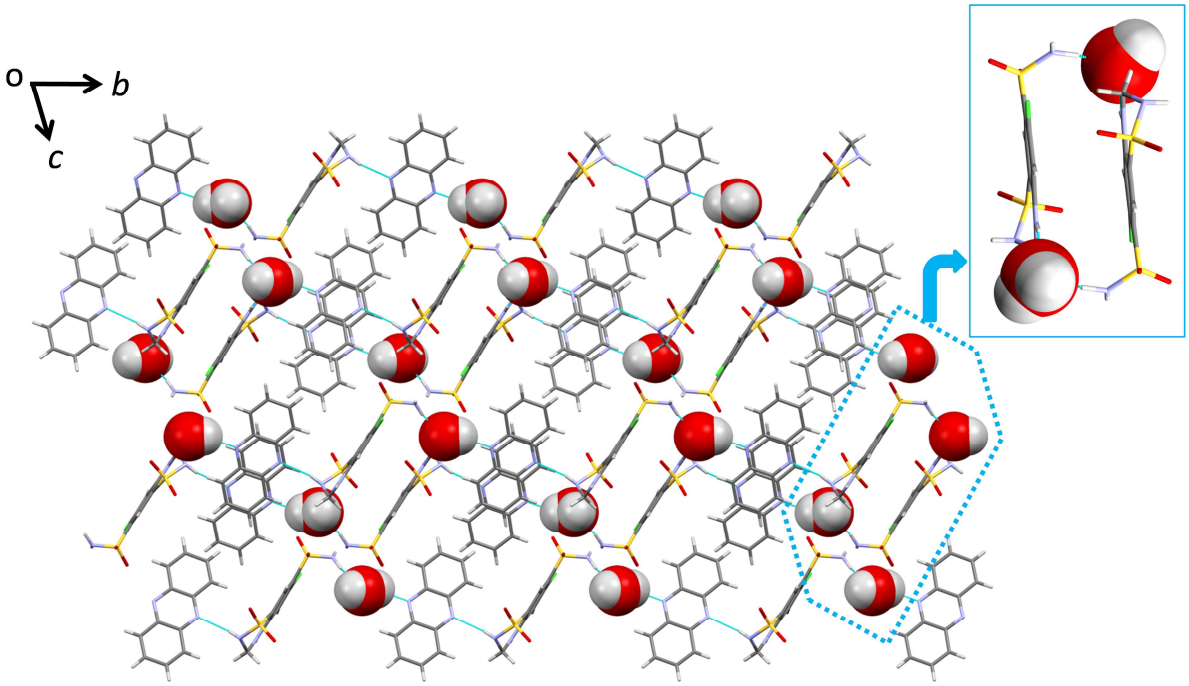


Fig. 1. HCT-PHEN.H_2O crystal packing view along *a*-axis, where the water molecule incorporated in the crystal structure is represented with a space fill model. The inset highlights the tetrameric motif in the crystal packing.

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

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

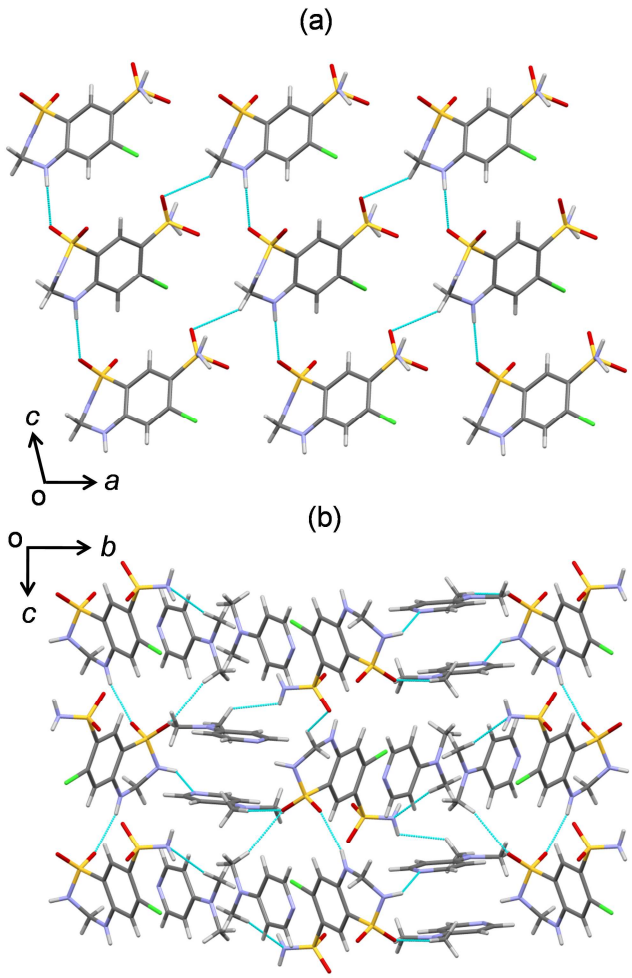


Fig. 2. Crystal packing of HCT-DMAP where (a) 2d sheet in *ac* plane and (b) crystal packing, when viewed down *a*-axis.

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

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

In the crystal structure of HCT–NIC co-crystal, NIC molecules form 1D chains through amide···pyridine (N–H···N) synthons and HCT molecules are sandwiched between these alternate 1D chains. But, the INIC molecules in the crystal structure of HCT–INIC–H_2O form amide-amide supramolecular homosynthons and are linked to HCT molecules by water molecules. Here, the water molecules act as both H-bond donor (to pyridyl moieties of INIC) and acceptor (to sulfonamide groups of HCT). The crystal packing in the present case HCT-PICA is completely different compared to above two. Here, a two molecules of each HCT and PICA form a tetrameric motif (Fig. 3a) *via* N–H···O (0.86 Å, 160°; 0.96 Å, 150°) interactions. Inthe overall crystal packing the tetramers were propagated along the *b* and *c*-axes directions *via* N–H···N and N–H···O interactions, respectively (Fig. 3b).

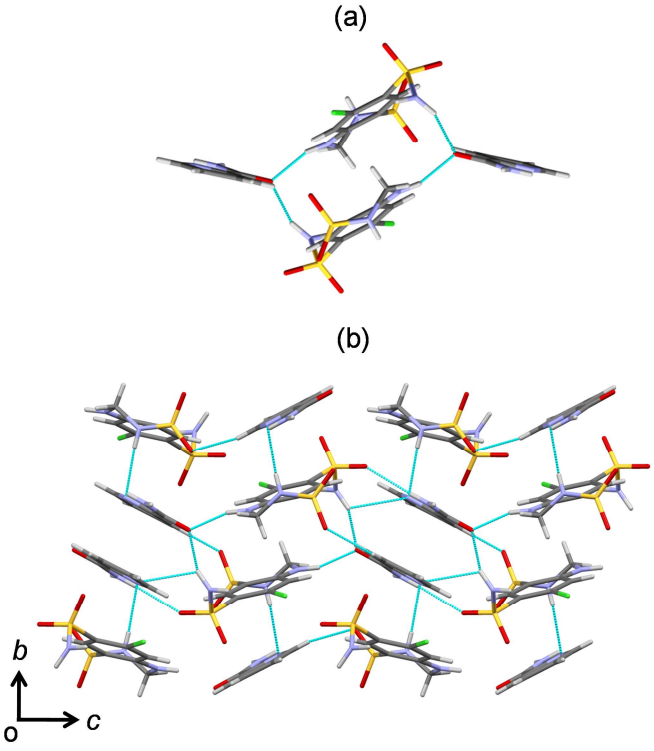


Fig. 3. Crystal packing diagram of HCT-PICA. (a) Tetrameric motif in the crystal packing formed by two molecules of HCT and two molecules of PICA. (b) Crystal packing, when viewed down *a*-axis.

3.4 Powder X-ray diffraction (PXRD)

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

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

3.5 FT-IR analysis

The cocrystals were further characterized by FT-IR spectroscopy, which is a cogent tool to make sure the cocrystal formation. The comparison of the stretching frequency shifts as shown in Fig. S6, ESI corroborated the formation of hydrogen bonds between the functional groups in cocrystals. At first instance, the SO_2 asymmetric region (1320–1380 cm^{-1}) was found to be very broad in the FT-IR spectra of HCT than when compared to the same region in the spectra of cocrystals. Furthermore, The NH and NH_2 stretching frequencies in free HCT observed at 3267 and 3361 cm^{-1} respectively. But, in the cocrystals the NH frequency merged with NH_2 and appeared as a broad peak compared to free HCT.

3.6 Thermal analysis

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

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

3.7 Solubility Studies

HCT is a poorly soluble drug (0.7 g/L)[1]. 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 cocrystals 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 cocrystals 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.[19]Interestingly, our results suggest that HCT-DMAP has exhibited the highest transient solubility among the HCT cocrystals reported thus far. The parachute nature of the HCT-DMAP cocrystal 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 cocrystals.[19]Further, it reveals a selection of suitable coformer can lead to a potential modulation in the solubility of HCT in either direction.

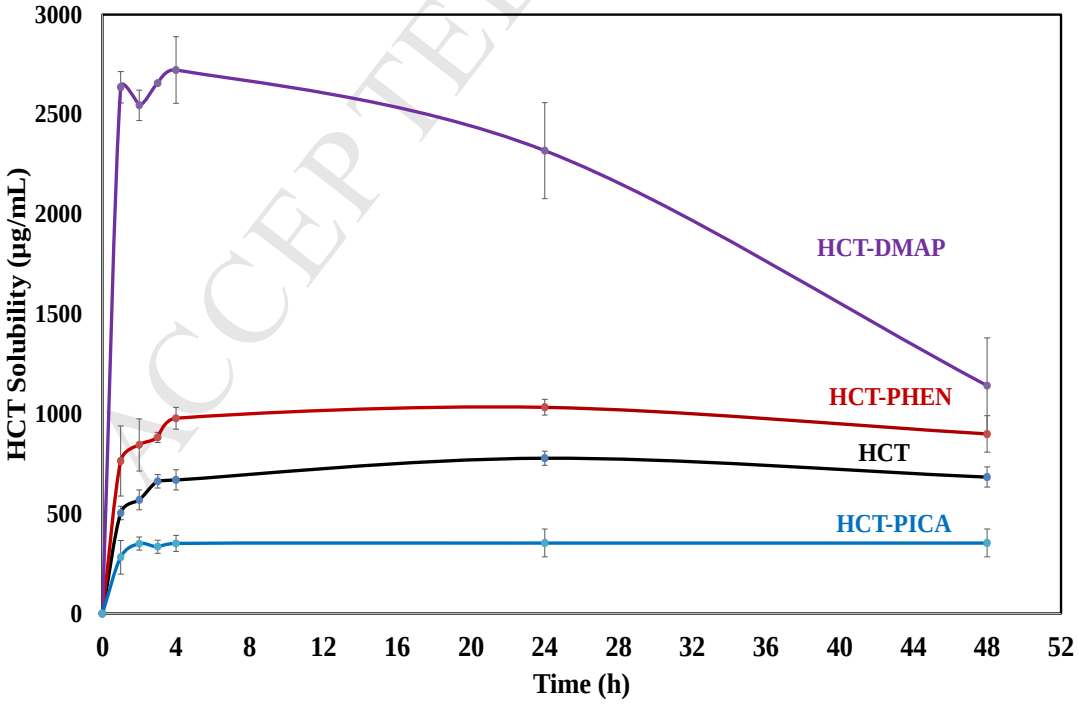


Fig. 4. Solubility profile of hydrochlorothiazide and its cocrystals (Avg. value ± SD (n=3)).

4. Conclusions

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

Acknowledgements

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

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

References

1 S. Aitipamula,A. Nangia,*Polymorphism: Fundamentals and Applications. Supramolecular Chemistry: From Molecules to Nanomaterials*, John Wiley & Sons, Ltd. 2012.

2 N. Qiao, M. Li, W. Schlindwein, N. Malek, A. Davies and G. Trappitt, *Int. J. Pharm.*, 2011, **419**, 1-11.

3 C. B. Aakeröy, S. Forbes and J.Desper, *J. Am. Chem. Soc.*, 2009, **131**, 17048-17049.

4 G. R. Desiraju, G. W. Parshall, *Crystal Engineering: The Design of Organic Solids. Materials science monographs*, Elsevier, Amsterdam, 1989.

5 B. Hancock and M.Parks, *Pharm. Res.*, 2000, **17**, 397-404.

6 C. Fandaruff, G. S. Rauber, A. M. Araya-Sibaja, R. N. Pereira, C. E. de Campos, H. C. V. Rocha, G. A. Monti, T. Malaspina, M. A. Silva and S. L.Cuffini, *Cryst. Growth Des*., 2014, **14**, 4968-4975.

7 S. Aitipamula, A. B.Wong, P. S. Chow and R. B.H. Tan, *Cryst. Growth Des.*, 2014, **14**, 2542-2556.

8 U. B. Rao Khandavilli, S. Gangavaram, N. Rajesh Goud, Cherukuvada, S. Raghavender, A. Nangia, S. G. Manjunatha, S. Nambiar and S. Pal, *CrystEngComm*, 2014, **16**, 4842-4852.

9 R. Chadha,A. Kuhad, P. Arora and S.Kishore, *Chem. Cent. J*., 2012, **6**, 114.

10 (a) A. T.Serajuddin, *Adv. Drug Deliver.Rev.*, 2007, **59**, 603-616; (b) H.S. Gwak, J. S. Choi andH. K.Choi, *Int. J. Pharm.*, 2005, **297**, 156-161.

11 N. Rasenack and B. W.Müller, *Pharm. Res.*, 2002, **19**, 1894-1900.

12 L. M. Gonçalves, F. Maestrelli, L. Di Cesare Manelli, C. Ghelardini, A. J. Almeida and P. Mura, *Eur. J. Pharm. Biopharm*., 2016, **102**, 41-50.

13 (a) C. Leuner and J.Dressman, *Eur. J. Pharm. Biopharm.*, 2000, **50**, 47-60; (b) T.Vasconcelos, B. Sarmento and P.Costa, *Drug discov. Today,* 2007,**12**, 1068-1075; (c) P. A. A. Borba,M. Pinotti, C. E. M. de Campos, B. R. Pezzini and H. K.Stulzer, *Carbohyd. Polym.*, 2016, **137**, 350-359.

14 N. Ni, T. Sanghvi and S. H.Yalkowsky, *Int. J. Pharm.*, 2002, **249**, 257-264.

15 (a) R. A. Rajewski and V. J.Stella, *J. Pharm. Sci.*, 1996, **85**, 1142-1169; (b) A.Vyas, S. Saraf and S. Saraf,*J. Incl. Phenom. Macro.*, 2008, **62**, 23-42

16 S. Aitipamula, R. Banerjee, A. K. Bansal, K. Biradha, M. L. Cheney, A. R. Choudhury, G. R. Desiraju, A. G. Dikundwar, R. Dubey, N. Duggirala, P. P. Ghogale, S. Ghosh, P. K. Goswami, N. R. Goud, R. R. K. R. Jetti, P. Karpinski, P. Kaushik, D. Kumar, V. Kumar, B. Moulton, A. Mukherjee, G. Mukherjee, A. S. Myerson, V. Puri, A. Ramanan, T. Rajamannar, C. M. Reddy, N. Rodriguez-Hornedo, R. D. Rogers, T. N. G. Row, P. Sanphui, N. Shan, G. Shete, A. Singh, C. Q. C. Sun,J. A. Swift, R. Thaimattam, T. S. Thakur, R. K. Thaper, S. P. Thomas, S. Tothadi, V. R. Vangala, N. Variankaval, P. Vishweshwar,D. R. Weyna and M. J. Zaworotko, *Cryst. Growth Des.*, 2012,**12**, 2147−2152.

17 (a) S. Ghosh, P. P. Bag and C. M.Reddy, *Cryst. Growth Des*., 2011, **11**, 3489–3503; (b) B. K.Saha, A. Nangia andM.Jaskólski, *CrystEngComm*, 2005, **7**, 355–358.

18 (a) J. Li, L. Wang, Y. Q.Ye,X. Fu,Q.Ren, H. Zhang and Z.Deng, *Eur. J. Pharm. Sci.*, 2016, **8**, 47-52; (b) S.Aitipamula, P. S. Chow and R. B.H. Tan, *Cryst. Growth Des.*, 2014, **14**, 6557-6569; (c) M.Mureşan-Pop, L.Chiriac,F. Martin and S. Simon, *Compos. PART B-Eng.*, 2016, **89**, 60-66; (d) K.Vasisht, M.Karan, R.Chadha, Y. Bhalla and A. Jena, *CrystEngComm*, 2016, **18**, 1403–1415; (e) B.Swapna, D. Maddileti and A.Nangia, *Cryst. Growth Des.*, 2014, **14**, 5991-6005; (f) G. R.Krishna, L.Shi,P. P. Bag, C. C. Sun and C. M.Reddy, *Cryst. Growth Des.*, 2015, **15**, 1827-1832;(g) P. P.Bag, S. Ghosh, H. Khan , R. Devarapalli and C. M.Reddy, *CrystEngComm*, 2014, **16**,7393-7396;(h) S. Ghosh and C. M. Reddy, *CrystEngComm*,2012, **14**, 2444-2453; (i) S. Ghosh and C. M. Reddy, *Angew. Chem. Int. Ed*, 2012,**51**, 10319-10323; (j) V. R. Vangala, P. S. Chow and R. B. H. Tan, *CrystEngComm*, 2011, **13**, 759-762.

19 P.Sanphui, V. K.Devi, D.Clara,N. Malviya, S. Ganguly andG. R. Desiraju, *Mol. Pharm.*, 2015, **12**, 1615-1622.

20 M. A. S.Pires, R. A. Souza dos Santos and R. D.Sinisterra, *Molecules*, 2011, **16**, 4482-4499

21 R.Martins, M.Machado, S.Pereira, A.Nosari, L. Tacon and L. Freitas, *Dry. Technol.*, 2012, **30**, 959-967.

22 A.Khan, Z.Iqbal, Y.Shah, L.Ahmad, Z. Ullah and A. Ullah, *Saudi Pharm J.*,2015, **23**, 650-657.

23 R.Chadha, S.Bhandari, D. Kataria, S. Gupta andD. Singh Jain, *J. Microencapsulation,*2012, **29**, 805-812.

24 Y.Kadam, U.Yerramilli,A. Bahadur and P.Bahadur, *Colloids Surf B Biointerfaces*, 2011, **83**, 49-57.

25 (a) P. Sanphui and L.Rajput, *Acta. Crystallogr.B,* 2014, **70**, 81-90; (b) J.R.Wang, C. Ye and X.Mei,*CrystEngComm,* 2014, **16**, 6996-7003; (c) R. Chadha, S. Bhandari, S. Khullar, S. K. Mandal and D. V. S. Jain, *Pharm. Res.*, 2014, **31**, 2479-2489; (d) S. A. El-Gizawy, M. A.Osman, M. F. Arafa and G. M. El Maghraby, *Int. J. of pharm.,* 2015, **478**, 773-778.

26 B.Sarma,L. S. Reddy and A. Nangia, *Cryst. Growth Des.,* 2008, **8**, 4546-4552.

27 P.Sanphui, N. J.Babu and A.Nangia, *Cryst. Growth Des.,* 2013, **13**, 2208-2219.

28 H. S.Chan, G. R.Woollam, T.Wagner, M. U. Schmidt and R. A.Lewis, *CrystEngComm,* 2014, **16**, 4365-4368.

29 V. R.Vangala, P. S. Chow and R. B.H. Tan, *CrystEngComm,* 2013, **15**, 878-889.

30 D. Braga,L. Maini and F. Grepioni, *Chem. Soc. Rev.,* 2013,**42**, 7638-7648.

31 O. V.Dolomanov, L. J.Bourhis, R. J. Gildea J. A. Howard and H.Puschmann,*J. Appl. Crystallogr.,* 2009,**42**, 339-341.

32 L. Palatinus and G.Chapuis, *J. Appl. Crystallogr.,* 2007,**40**, 786-790.

33 Sheldrick, G. M. *ActaCrystallogr.* 2008**, A64**, 112-122.

34 H. D. Clarke, K. K. Arora, H. Bass, P. Kavuru, T. T. Ong, T. Pujari, L. Wojtas and M. J. Zaworotko, *Cryst. Growth Des.,* 2010, **10**, 2152−2167.

35 J. F.Remenar, M. L.Peterson, P. W.Stephens, Z.Zhang, Y.Zimekov and M. B.Hickey, *Mol. Pharmaceutics*, 2007, **4**, 386-400.

Highlights

1) Three new cocrystals of HCT with water soluble coformers 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 coformer is vital, otherwise reduced solubility can be observed as in the case of HCT-PICA.