Chapter 7

Conclusion and Future Direction

7.1 Conclusion

The prime objective of the research work undertaken and presented in this thesis is to engineer a few crystalline API's for new drug formulation with desired properties and process development. The solid forms diversity of drug offers remarkable prospects for amending its material properties [1–4]. Pharmaceutical cocrystals are recently emerging as attractive viable alternative solid forms with the potential to fine-tune the physiochemical and biopharmaceutical properties of a drug molecule [5–8]. There are, however, lacks understanding of cocrystal screening, scale-up and formulation in drug product development. Combination of knowledge-based design for coformer selection along with appropriate experimental methods is essential for cocrystal formation. Encouraged by the rapid development of pharmaceutical cocrystal, the primary objective of this thesis is to draw up an outline how cocrystals as an emerging class of pharmaceutical materials, can be utilized to enhance the specific properties of pharmaceutical solids. It includes poor aqueous solubility and membrane permeability of APIs like ethenzamide, propofol, sulfathiazole and physical stability improvement of drug theophylline and famotidine. The essential insight into the mechanism of formation, structural and physiochemical properties of pharmaceutical cocrystals are discussed in this thesis.

Chapter 1 reflects the background of different pharmaceutical solid forms. Special emphasis has been given to pharmaceutical cocrystal. The synthetic techniques, classification and potential applications of cocrystals in modulating different properties of drug molecules have been discussed.

In Chapter **2** part **A**, a tactical approach for coformer selection to stabilize theophylline cocrystal has been demonstrated [9]. Seven new cocrystals of bronchodilator drug theophylline were synthesized. The hydration stability and aqueous solubility of the cocrystals were determined. It has been observed that theophylline cocrystal with phenol coformers facilitate water assimilation in the crystalline lattice. The water assimilation is

attributed to the weaker O−H···$N_{(imidazole)}$ synthon present in the cocrystals of phenolic coformer. On the contrary, due to stronger COOH···N $_{(imidazole)}$ H-bond synthon offered by the –COOH group inhibits water incorporation and provides additional physical stability to the cocrystal at high humid condition. The effects of solvents, coformer selection on cocrystal stability have been examined. This study of deliberate coformer selection signifies the practicability of cocrystal design of an API to tailor physiochemical properties relied on hydrogen bond synthons.

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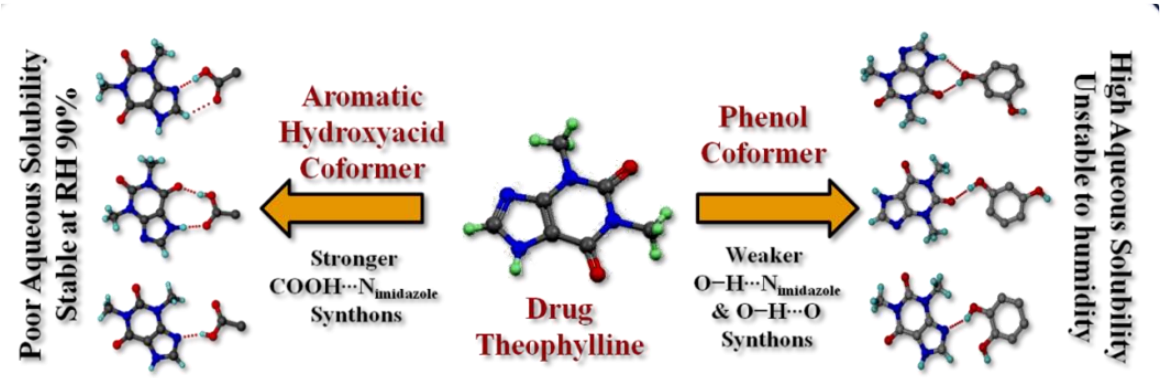
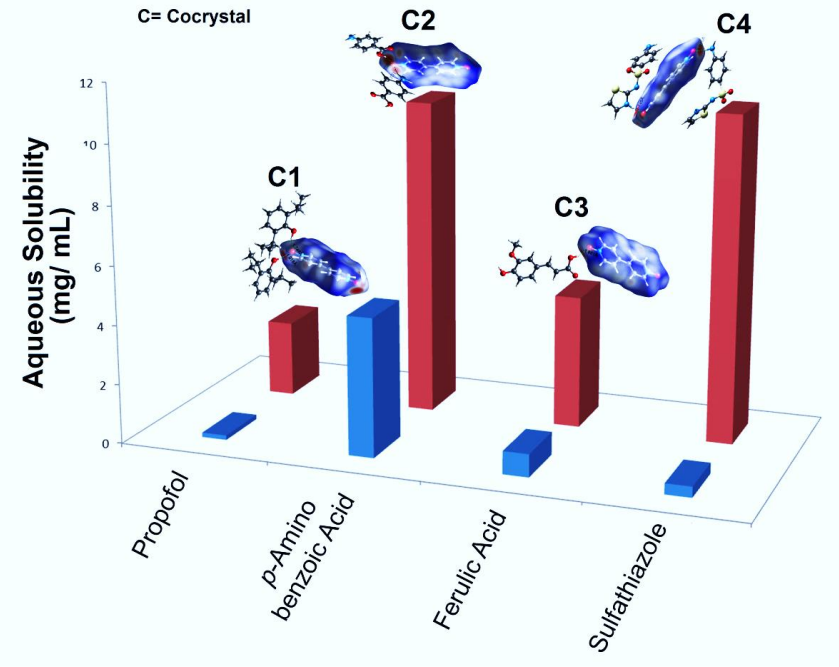


Scheme 7.1 Stronger COOH···N synthon stabilizes the cocrystals of theophylline with aromatic hydroxy acid at high humid condition whereas weaker OH···$N_{imidazole}$ and OH···O synthon destabilize cocrystals of theophylline with phenolic coformer.

In Chapter **2** part **B**, several pyridine *N*-oxides were synthesized via a convenient method and used in the preparation of drug cocrystals [10]. Drugs accompanied by aqueous solubility issues like propofol, ferulic acid, sulfathiazole, p-aminobenzoic acid etc. were used as the representative active ingredients to manufacture pharmaceutical solids with desired properties. In this study, 4,4′-bipyridine-*N*,*N*′-dioxide was picked as the cocrystal former. The types of supramolecular heterosynthons exhibited by the cocrystals of *N*-oxide and drugs were analyzed. The formation of hydrogen bond synthons such as COOH···pyridine *N*-oxide, OH or NH–pyridine *N*-oxide was found to be robust and followed the trend observed in the CSD. These synthons were further correlated with the ameliorated properties of the drugs, which was supported by experiments, DFT studies and Hirshfeld surface analysis. Overall, in this work the recurring COOH···pyridine *N*-oxide, O–H or N–H···pyridine *N*-oxide synthons in cocrystals of heterocyclic *N*-oxides are examined, their strength and predictability are evaluated, and their reliability is

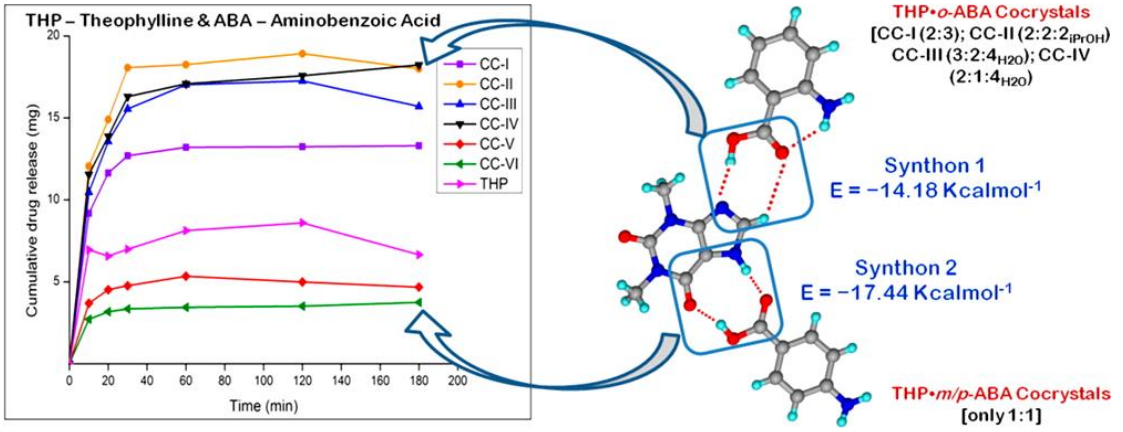
explored. The solid formulation of liquid drug propofol through cocrystallization is also emphasized



Scheme 7.2 Pictorial representation depicting the aqueous solubility improvement of pharmaceutical cocrystal of various drugs with 4,4′-bipyridine-*N*,*N*′-dioxide as coformer.

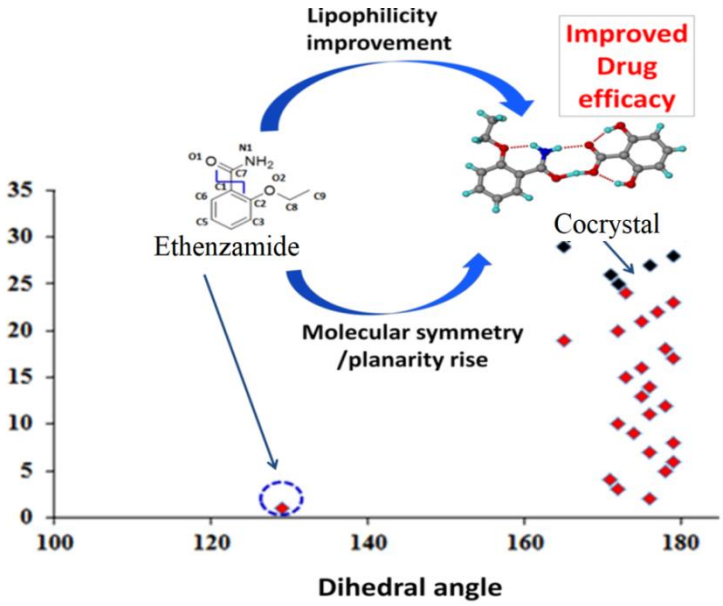
Chapter **3** demonstrated how physiochemical properties of a drug varies with different stoichiometry cocrystals [11]. The first of its kind study, the effect of variable stoichiometry cocrystal on drug physiochemical properties has been carried out. Four different stoichiometry cocrystals of drug theophylline (THP) with coformer *o*-aminobenzoic Acid (*o*-ABA) has been synthesized. The formation of different stoichiometry and solvent inclusion in the crystal lattice is attributed to the unequalled hydrogen bond donors/acceptors ratio between THP and *o*-ABA. The *o*-ABA participate in intramolecular H-bonding leading to variable no. of symmetry independent entities in the cocrystal lattice but with *m*- and *p*-isomeric aminobenzoic acid, there is no possibility of intramolecular H-bonding. As a result, only 1:1 stoichiometry cocrystal obtained. The aqueous solubility and membrane permeability of the cocrystals materials were evaluated. The cocrystals showed different and enhanced solubility and high membrane permeability compared to the drug THP. Almost 12 times higher solubility is observed for non-solvated cocrystal CC-I of THP and *o*-ABA. The improvement of properties is correlated with different supramolecular synthons observed in the crystal structures and

the propensity of solute-solvent interactions. The different intermolecular interactions present in the crystal lattice are found to have a profound influence on altering the physiochemical properties of different stoichiometry cocrystal. A trade-off nature among the solubility and permeability of the cocrystals has also been observed and correlated with drug−coformer and solute···solvent interactions. This study explains the importance of control over stoichiometry of cocrystals for better efficacy of drug molecules.



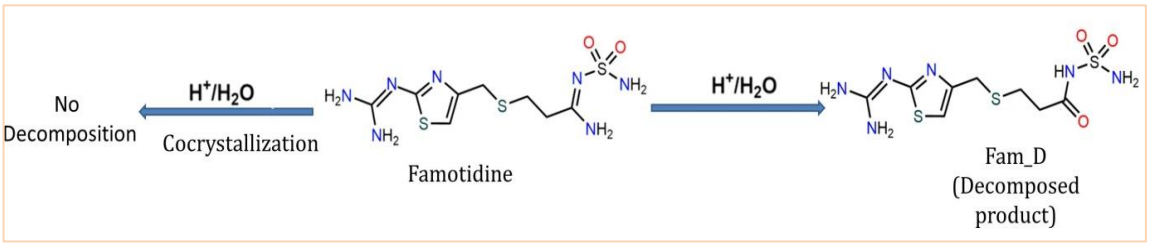
Scheme 7.3 Variable stoichiometry cocrystals of theophylline exhibiting different drug release behaviour controlled by intermolecular interactions.

Chapter **4**, reports the synthesis of four pharmaceutical cocrystals of BCS class-II analgesic drug ethenzamide with gentisic acid; *γ*-resorcylic acid; protocatechuic acid; *α*-resorcylic acid [12]. The solubility and membrane diffusion behaviour through a cellulose membrane were determined in different physiological pH buffers. The cocrystals showed improved drug absorption, release and distribution *in vitro*. This study has investigated several extremely important parameters that can significantly influence drug efficacy. Based on cocrystal technology, this study has addressed how alteration of lipophilic behaviour by tuning weak intermolecular interactions between solute···solute and solute···solvent, supramolecular synthons, and conformational adjustment of the drug contribute towards the modification of drug bioavailability.



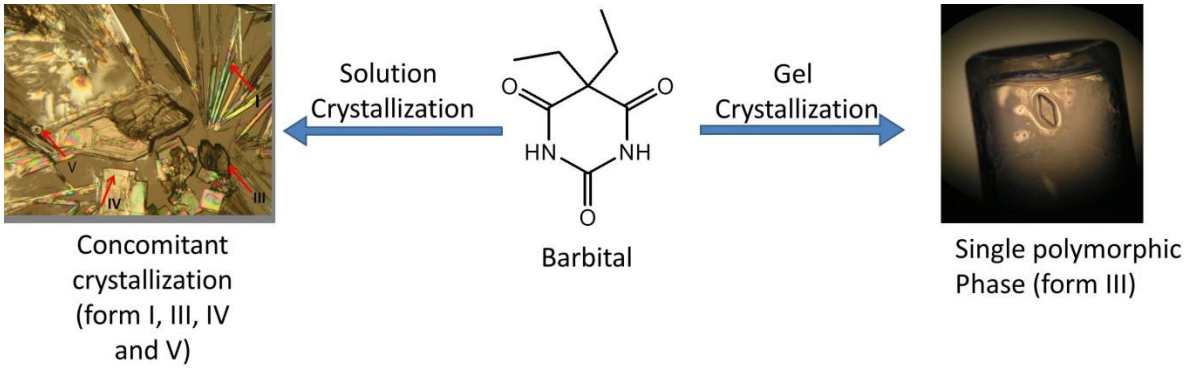
Scheme 7.4 Improving the efficacy of drug ethenzamide by changing its molecular planarity and lipophilicity via cocrystallization.

Chapter 5 demonstrated a cocrystallization strategy to prevent the degradation of histamine H2–receptor antagonist drug famotidine in acidic condition. Three cocrystals of famotidine were synthesized with theophylline, theobromine and caffeine. The cocrystals FAM.THP and FAM.THB is instrumental in preventing the degradation of famotidine and exhibit superior stability at pH 1.2 compared to the parent drug. The added stability of the cocrystals is attributed to the formation of strong intermolecular hydrogen bonding interactions of the drug with coformers. Due to the formation of these stronger synthons in cocrystals the susceptibility of acid hydrolysis at the –C=N site of the amidine group is minimized. Thus, cocrystallization can be an efficient way to address the stability of drug molecules associated with the susceptibility of acid hydrolysis.



Scheme 7.5 Pictorial representations of prevention of famotidine degradation via cocrystallization.

Chapter 6 illustrates a tactical approach to prevent concomitant polymorph nucleation of imide functionalized drug molecules by exploiting drug mimetic low molecular weight organogels as crystallization media. The crystals acquired from both solution crystallization and gel phase crystallization has been analysed by microscopy, FT-IR, PXRD and/or unit cell determination. Gel crystallization prevents the concomitant crystallization of drug barbital and reproducibly results in the crystallization of the kinetic Form III of barbital. Under same conditions, solution crystallization from alcoholic solvents result concomitant crystallization of barbital Form I, III, IV and V. Apart from the prevention of concomitant crystallization of drug barbital, the change in crystal habit inside the gel is also observed. The gelators are also found to be effective in preventing concomitant crystallization of drug (±) thalidomide as well. This work exhibits the potential of designed supramolecular gelator to be used in a targeted manner for gel phase crystallization to control the drug polymorphism.



Scheme 7.6 Controlling concomitant polymorphism of drug via drug mimetic gel phase crystallization

7.2 Future prospects

With the experience and knowledge gained during PhD program in the field of pharmaceutical crystallization, drug solid form engineering with tuned properties is aimed in the future ahead. Designing a new supramolecular system with desired properties will provide us a better understanding about non-covalent interactions between molecules within the molecular aggregates. It has the potential to transform the pharmaceutical industry and medicine by paving new ways for drug administration and new composite biocompatible materials. The idea of developing multi-component drug system including drug-drug cocrystals is interesting. Pharmaceutical cocrystals fulfil the

criteria for patent eligibility, novelty, utility, and non-obviousness for drug development. There is immense potential to explore cocrystal design of drug cocrystal to enhance solubility and bioavailability of the product. Consequently, there is a strong need to devise ways to increase the likelihood of success in generating the marketed form of drug–drug cocrystals. In this way, optimization of cocrystal screening may lead to commercialization of new cocrystal product. Scale-up of gel phase crystallization in large scale to control drug polymorphism is another future aspect.

7.3 References

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