Abstract

This thesis entitled "*Hydrogen Bonds in Molecular Crystals to Alter Properties and Controlling Drug Polymorph Nucleation*" consists of seven chapters.

Chapter 1

Hydrogen Bonds in Molecular Crystals: An Introduction

In the realm of crystal engineering, the idea of pharmaceutical cocrystal has become an emerging and reliable approach to alter the physiochemical properties of active compounds especially pharmaceutical drugs. In the context of drug development, properties such as bioavailability, dissolution, solubility, stability etc. are major apprehensions. A pharmaceutical cocrystal incorporates active pharmaceutical ingredient (API) with a pharmaceutically acceptable molecule (coformer) in their crystal lattice without any structural modification of the parent drug. They are formed using different intermolecular interactions including hydrogen bond, π-stacking, and van der Waals forces. The supramolecular synthon approach is the key in designing new cocrystal. Design of cocrystal relies on competition and cooperation of hydrogen bonding among various functionalities of the drug molecule and the coformer component. Furthermore, understanding of intermolecular interactions in particular hydrogen bond synthon approach that aids in orienting the desired drug polymorph nucleation by designed organogels is a promising area of research in pharmaceutical crystallization. This thesis encompasses seven chapters and Chapter 1 summarizes a brief background of cocrystal materials, their design, synthesis, and physiochemical applications with few recent examples. Pharmaceutical crystallization using organogels as crystallization media is also discussed. Chapter 2 reports on the synthon based design and synthesis of pharmaceutical cocrystals of bronchodilator drug theophylline. It also briefly discusses the salt cocrystal continuum and potential factors that lead to solvate formation. Synthon based stabilization of cocrystal towards relative humidity was examined based on coformer selection and highlighted. Pyridine N-oxides as efficient coformers in the development of drug cocrystals is also demonstrated. Variable stoichiometry cocrystals of the drug theophylline with isomeric aminobenzoic acids are prepared and their physiochemical properties are evaluated as well as structure-activity relationship is discussed in Chapter 3. A trade-off between solubility/permeability of cocrystal is established and correlated with different solute….solvent and weak intermolecular

interactions. The change in lipophilic nature manifested by conformational adjustment of non-steroidal anti-inflammatory drugs (NSAIDs) ethenzamide in cocrystals has established and linked for the attributed enhanced properties of cocrystals which cover in Chapter 4. A cocrystallization strategy is used as a tactical technique to improve the chemical stability of drug famotidine in acidic condition and depicts in Chapter 5. An important aspect of pharmaceutical crystallization, i.e. gel phase crystallization is described in Chapter 6. Use of designed drug mimetic organogels in controlling crystallization of imide drugs barbital and thalidomide based on supramolecular synthon approach is demonstrated. The concluding chapter, i.e. Chapter 7 briefs the summary of the work covered in the thesis with a future perspective.

Chapter 2

PART-A: Hydrogen Bond Synthon Competition in the Stabilization of Theophylline Cocrystals

Bronchodilator drug theophylline is considered as a model drug to synthesize cocrystals considering hydroxybenzoic acids and phenolic compounds as coformers. Solvent assisted mechanochemical grinding is employed to impede the synthesis of six new cocrystals. All new cocrystals are characterized thermally, spectroscopy, powder X-ray diffraction and single crystal X-ray diffraction. Hydrogen bond synthons are analysed in the crystal structures and their energies are calculated by DFT calculation which predicts the hydroxybenzoic acid coformers provide stable cocrystal as they contain COOH···$N_{imidazole}$ stronger hydrogen bond synthon. The aqueous solubility of these cocrystals is determined and correlated the trend with hydrogen bond energies. Relative humidity (RH) test is also performed and confirms the higher stability of cocrystal with hydroxybenzoic acid conformers.

PART-B: Pyridine *N*-oxides as Coformers in the Development of Drug Cocrystals

A crystal engineering strategy is accounted for cocrystal synthesis of various drugs having different functional group considering heterocyclic *N*-oxide as coformer. In this study, 4,4′-bipyridine-*N*,*N*′-dioxide is employed as the coformer. The types of heterosynthons exhibited by the cocrystal systems are analyzed and compared with the structural database (CSD). The formation of hydrogen bond synthons such as COOH···pyridine *N*-oxide, OH or N–H···pyridine *N*-oxide is found to be robust and followed the trend observed in the CSD. These synthons are further correlated with the

ameliorated properties of the drugs, which is supported by experiments, DFT studies and Hirshfeld surface analysis. Moreover, this work demonstrates the solid formulation of liquid drug propofol through cocrystallization approach.

Chapter 3

Hydrogen Bond Synthons in the Interplay of Solubility and Membrane Permeability/Diffusion in Variable Stoichiometry Drug Cocrystals

Theophylline (THP) is considered as a representative compound to prepare variable stoichiometry cocrystals with isomeric aminobenzoic acids (*o*-ABA, *m*-ABA, and *p*-ABA) as coformers. Solvent assisted mechanochemical grinding afforded four different stoichiometry cocrystals for *o*-aminobenzoic acid [CC-I (2:3), CC-II (2:2:2-isoBuOH), CC-III (3:2:4H_2O), CC-IV (2:1:4H_2O), whereas *m*-ABA and *p*-ABA afforded only guest free 1:1 cocrystals [CC-V and CC-VI]. The unmatched ratio of hydrogen bond donors/acceptors in the starting components results in different stoichiometry, and solvent inclusion. All cocrystal materials are characterized by spectroscopy, thermal analysis, powder and single crystal X-ray diffraction. The aqueous solubility of cocrystal materials is determined and the trend is correlated with hydrogen bond energy calculated by DFT computation using Gaussian 03. Diffusion/membrane permeability and thereby flux of the drug is calculated using 'dialysis membrane-135'. Cocrystal materials showed different and improved solubility and high diffusion/membrane permeability compared to the parent drug THP. Different energy supramolecular synthon and solute···solvent interactions are further correlated to understand the interplay of solubility and drug bioavailability. The prime objective of this work is to establish the relationship between permeability and solubility with drug-coformer and solute···solvent interactions in different stoichiometry cocrystals.

Chapter 4

Solubility and in Vitro Drug Permeation Behaviour of Ethenzamide Cocrystals Regulated in Physiological pH Environments

This chapter reports the synthesis of four different cocrystals of Ethenzamide (ZMD), a non-steroidal anti-inflammatory drugs (NSAIDs) considering 2,5-dihydroxybenzoic acid (2,5-DHBA), 2,6-dihydroxybenzoic acid (2,6-DHBA), 3,4-dihydroxybenzoic acid (3,4-DHBA) and 3,5-dihydroxybenzoic acid (3,5-DHBA) as coformers. The cocrystals were characterized by FT-IR, DSC, TGA, powder X-ray diffraction and single crystal X-ray data. The solubility and diffusion kinetics of these cocrystals are examined in different pH buffers. The present

study emphasizes the correlation that exists between non-covalent interactions and effective bioavailability. Essentially, different supramolecular synthons played crucial roles in modifying the lipophilicity in these multicomponent drug formulations, which is a critical property for predicting final doses. The trade-off nature between the solubility and diffusivity of these cocrystal systems is also discussed. The conformational twist of the drug during the packing of molecules in the lattice with the coformers can lead to molecular planarity or can improve the molecular symmetry, which might lead to better solubility and permeation behaviour and thereby better efficacy.

Chapter 5

Cocrystal Technology to Control the Degradation of Histamine H2-receptor Antagonist Drug Famotidine

This chapter demonstrates the cocrystal technology as an efficient way to prevent the degradation of drug famotidine in acidic condition. Famotidine is a histamine H2 receptor antagonist and readily degrades in acidic condition. Cocrystal technology is used to alter the molecular conformation of the drug molecule through different hydrogen bonding interactions with coformer, and consequently prevent the degradation of famotidine in acidic condition. The cocrystals of famotidine with different xanthine derivatives are prepared and thoroughly characterized. The prepared cocrystals are further subjected to stability studies and compared with famotidine. Kinetics of degradation has been evaluated. The cocrystals demonstrate incredibly high stability in acidic condition. Structure activity relationship is inspected and correlates with the stability of cocrystals.

Chapter 6

Role of Drug Mimetic Organogels in Nucleating Pure Polymorphic Phases of Drug

In this chapter, a design and synthesis strategy of three new drug mimetic organogels and their applications as crystallization media to control crystallization outcome of imide functionalized drugs is reported. The prepared organogels are characterized by using FT-IR, PXRD, SEM, elemental analysis, NMR, Mass spectrometry. The characterized compounds are further subjected to gel screening. Gel screening is carried out in a range of solvents and gelation behaviour is confirmed by vial inversion test and rheological analysis. Imide functionalized drug thalidomide and barbital have been chosen as model drugs for crystallization using the prepared drug mimetic gelators. The gel induced

crystallization outcome is further compared to solution crystallization outcome to understand the interplay of solvent effect and gelator functionality on crystallization. The crystals obtained from both solution crystallization and gel phase crystallization is analysed by microscopy, FT-IR, PXRD and/or unit cell determination etc. The gelators are found to prevent concomitant crystallization of drug barbital and thalidomide.

Chapter 7

Conclusion and Future Direction

This chapter contains the perspective of overall research work carried out during the PhD program under the domain of crystal engineering and its potent applications in the field of pharmaceutical crystallization. It contains the general outcome of each previously discussed chapter. Chapter 1 discusses the background of crystal engineering with special emphasis on pharmaceutical cocrystal that includes its synthetic techniques, classification and potential applications of cocrystals in tuning the physiochemical properties of drug molecules. Chapter 2 demonstrates a synthon based design of cocrystal considering different functionalized coformers. Cocrystals properties are further correlated with the stability of the synthon observed in the cocrystals. Variation of solubility/ permeability of drug with different stoichiometry cocrystals is presented in Chapter 3. Conformational variation of ethenzamide molecule upon cocrystallization is studied and the role of different non-covalent interactions in modulating the physiochemical properties at physiological pH environment is demonstrated in Chapter 4. An approach to stabilizing the drug famotidine in acidic condition through cocrystal technology is demonstrated in Chapter 5. Famotidine can endure low pH condition on cocrystallizing with xanthine derivatives as coformer. Drug mimetic organogels is applied as a crystallization media to prevent concomitant crystallization of drug thalidomide and barbital, which is demonstrated in Chapter 6.

Overall, this thesis conveys the potential applications of cocrystals in modulating physiochemical properties of drug molecules. In addition, the role of different intermolecular interactions on alteration of the properties of cocrystal is discussed. The cocrystal synthesized has the potential of being a viable alternative to a conventional drug. The application of designed organogel as nucleation surface based on hydrogen bond synthon approach, to prevent concomitant crystallization of imide functionalized drug molecules, has promising application in scaling up the manufacturing process.