Control Crystallization on Self-Assembled Organic Monolayer and Non-covalent Interactions Guided Multi-component Crystals

Chapter 1: Crystallization is an important separation and purification process in industries like pharmaceuticals, food industry, agrochemicals etc. Numerous approaches are available for the crystallization of various solid phase products, such as solution evaporation, anti-solvent technique, gel phase crystallization, laser technology, high temperature methods, etc. Understanding the role of different intermolecular interactions, solvent for crystallization, stoichiometric ratio, functional surfaces and various environmental variables such as temperature, relative humidity etc. during solution crystallization process is the prime objective of the thesis work. Solution crystallization primarily proceeds through two steps, i.e., nucleation and growth. The nucleation step plays a decisive role in determining various properties like crystal structure, size distribution and thereby affects materials properties. Therefore, understanding the process of nucleation is very important to have control over these properties. Nucleation can result in different crystalline phases, essentially different polymorphs from the same initial component, multi-component cocrystals, salts, solvates, eutectics, solid solutions, etc. All these materials can have significant importance in different fields such as pharmaceuticals, optoelectronics, and agrochemicals and so on. Thus, the work embodied in this thesis mainly focuses on controlling the nucleation event to form desired end product that has pharmaceutical importance and examined the role of intermolecular interactions, stoichiometry, solvent, humidity and temperature in the nucleation of different crystalline systems that have modulated physiochemical and solid state properties.

Concomitant polymorphism is one of the challenging issues associated with many flexible drug molecules that can affect the performance of the drug and needs serious attention during drug formulation stage. Therefore, polymorph screening/control to crystallize only single form is one of the prime concerns of the pharmaceutical industries. Use of 2D functional surfaces, such as self-assembled monolayers (SAMs) to control nucleation of single phase crystals is a recent approach with very limited studies available. For instance, Myerson et al. studied the heterogeneous template-directed nucleation of L-alanine, glycine, ROY, mefenamic acid etc. to generate desired polymorphic forms. Even though the mechanisms of interaction between SAMs and the induced crystals are not fully understood. Therefore, we have chosen a conformationally flexible sulfonamide drug, i.e., sulfathiazole as a representative system to control its concomitant crystallization behavior and to understand different intermolecular interaction probabilities which could transmit the information via interface to nucleate single polymorphic phases. The designed SAM surfaces are successful in the nucleation of pure phases of the drug sulfathiazole along with a new polymorphic form and discussed in chapter 2. Polymorphism in multi-component crystalline materials is equally important especially in pharmaceutical industry as they are considered to be new drug formulations. In continuing this aspect, ethenzamide, a BCS class II drug showing extremely low solubility is subjected for cocrystallization with β-resorcylic acid by varying starting stoichiometry and solvent for crystallization to understand the nucleation of different polymorphic forms. Three polymorphs of the cocrystal are successfully isolated by tuning these

parameters. Further, the properties of these forms are also examined and incorporated in chapter 3. Similar to polymorphic phases, various multi-component solid phases including solvates and hydrates from same starting materials are also significant as their property is concern. Role of different factors that affect the formations of such phases is essential considering the reproducibility and stability of the forms. Environmental variables such as temperature, humidity, seasonal variation, solvent of crystallization etc. could impact the nucleation process to produce different multi-component phases. Understanding these parameters in crystallization conducted at ambient environmental conditions throughout the year is focused and discussed in chapter 4 (part A). Again, organic cocrystal materials can also be designed as promising materials in the molecular optoelectronic devices. Incorporation of a second molecule in the multicomponent system changes the overall electronic behavior and intermolecular interactions of the parent system which finally impacts the emissive property and is discussed in chapter 4 (Part B). Intermolecular interactions including hydrogen bonding, π-stacking, van der Waals forces are important intermolecular forces that can regulate the molecular aggregation in solution and property modulation. The role of intermolecular interactions such as π···π stacking in addition to directional hydrogen bonding to modulate the solubility and bioavailability of different multicomponent phases is discussed in chapter 5. The concluding chapter, i.e., Chapter 6 briefs the work embodied in the thesis with a focused continuation of the understanding and a future perspective.

Chapter 2: Oriented crystallization on organic monolayers to control concomitant polymorphism

Sulfathiazole is a short-acting antimicrobial sulfa drug known for its concomitant polymorphism with five existing forms. The nucleation events and crystals growth can be guided by different intermolecular interactions at the interface. Control concomitant crystallization of drug is of vital necessity in pharmaceutical industries from drug efficacy and formulation perspective. Functional self-assembled monolayer of organic thiol on gold surface has been identified as an efficient approach to control nucleation of a desired polymorph and highlighted. Crystallization on functionalized SAM surfaces is a kinetically driven process which nucleated a new metastable form (i.e. sixth form) and is supported by spectroscopy, thermal analysis and X-ray diffraction studies.

Chapter 3: Trimorphic cocrystals of ethenzamide and 2,4-dihydroxybenzoic acid

Multi-component polymorphism has vital significance in pharmaceutical industry and already exists in the market as new drug formulations. In this regard, three cocrystal polymorphs of the analgesic and anti-inflammatory drug ethenzamide with β-resorcylic acid (i.e., 2,4-dihydroxybenzoic acid) are isolated. The possibility of conformational variation in the amide group of ethenzamide and hydroxyl group of 2,4-dihydroxybenzoic acid, variation in crystallization media and stoichiometric ratio played an important role in the nucleation of these cocrystal polymorphic phases and is emphasized. Further, the polymorphic forms are also subjected for solubility and in vitro cell membrane permeation studies at various physiological pH ranges (i.e., pH = 1.2 SAL and 7.4 PBS) and is discussed.

<u>Chapter 4 Part A:</u> Role of solvent and environmental variables in controlling different cocrystal phases of Phenazine and 3,4-dihydroxybenzoic acid

Six different multi-component phases of phenazine and protocatechuic acid (i.e. 3,4-dihydroxybenzoic acid) were isolated varying stoichiometry and solvent for crystallization having same starting materials. Being located in the geographical region like Tezpur shows four different seasons with varied relative humidity and temperature throughout a year. Thus, the role of these environmental variables alongside solvent and starting ratios in the nucleation of these multi-component phases are investigated and discussed. We further investigated the thermodynamic relationships and phase transition behavior of these phases and emphasized.

<u>Part-B</u>: Study emission properties of cocrystals of phenazine and isomeric dihydroxybenzoic acids

Phenazine seems to show fluorescence behavior due to its planar structure with a heterocyclic pyrazine core and π-conjugated system supported by C–H···π interactions. Incorporation of a coformer in the crystal lattice can disturb the planarity and π-conjugation of phenazine molecule inducing polarity to the overall system. Accordingly five new multi-component systems of phenazine and isomeric dihydroxybenzoic acids are synthesized and characterized. Incorporation of polar coformers having the same functionality at different positions influences the π-stacking behavior of the system. Changing the π···π stacking interaction changes the electronic behavior of the cocrystal system which affects the emissive properties and discussed.

Chapter 5: Regulation of π···π stacking interactions in small molecule cocrystals and/or salts for physiochemical property modulation

Cocrystals/salts of acridine and isomeric dihydroxybenzoic acids were synthesized based on weak intermolecular interactions. Acridine was employed as a representative cocrystal partner with isomeric dihydroxybenzoic acids to study the role of *π···π* stacking interactions in presence of hydrogen bonding to regulate certain physiochemical properties. Experiments were performed in various pH range (pH = 1.2 SAL and 7.4 PBS) in order to imitate human physiological conditions. Molecular packing and interaction energies suggest a significant contribution of π···π interactions in the modulation of property. In fact, coformers conformational energy, lipophilicity, and log P values were found to be valued contributors. Therefore, the present study anticipates the contribution towards understanding the impact of π···π and C−H···π interactions supported by hydrogen bonds on modulating physiochemical properties, essentially improving the efficacy of a drug.

Chapter 6:

Conclusion: The work embodied in this thesis is an attempt to cult a clear understanding of nucleation and crystal growth. Heterogeneous 2D functionalized surfaces are utilized to control concomitant nucleation of drug and are emphasized. Various factors affecting the nucleation process such as intermolecular interactions, relative humidity, temperature,

solvent, stoichiometry etc. in isolating different multi-component solid phases are another prime objective of the thesis. The role of intermolecular interactions such as hydrogen bonding and $\pi\cdots\pi$ interactions in modifying the physicochemical and solid state properties of multi-component systems is also studied. With these understandings, this thesis looks forward to nucleate desired solid phases and scale up for market purpose.