ABSTRACT

This thesis entitled “Multicomponent Crystals of Famotidine and Trimethoprim as Improved Pharmaceutical Materials: Design, Characterization, and Properties” consists of seven chapters.

The introductory chapter, i.e., Chapter 1 brings an introduction and the background of crystal engineering with a special emphasis on multicomponent solid forms and their design principles, preparation, and applications in the modulation of physicochemical properties. Then follow on five successive chapters cover experimental work, results, and discussion. Chapter 2 reports the isolation of dimorphic molecular salts of the antiulcer drug famotidine from different solution crystallization. The application of multicomponent polymorphic systems in the modulation of drug properties is discussed. In Chapter 3, molecular salts of the drug famotidine with isomeric aminobenzoic acids and hydroxybenzoic acids are synthesized and their physicochemical properties are measured. The variation in the physicochemical properties due to the conformational adjustment of the drug in the salts guided by the isomeric position functional groups of the coformers is demonstrated. The improvement of stability via the conformational adjustment of the drug famotidine in the molecular salts and the change in lipophilicity of the drug by the inclusion of coformer and the water molecules of crystallization which is linked with the enhancement of the solubility and permeability is covered in Chapter 4. The difference in the number of the water molecules of crystallization depends on the isomeric positions of OH groups of coformers, its impact in stabilizing the multicomponent systems, and related to the observed difference in the physicochemical properties of molecular salts of drug trimethoprim discussed in Chapter 5. The solubility and permeability improvement of the antibiotic drug trimethoprim via the formation of molecular salts with isomeric mono-substituted benzoic acids is demonstrated in Chapter 6. Chapter 7 presents a summary of the key research findings in the thesis with a future perspective.

Chapter 1

Introduction

Crystal engineering has become a versatile technique to fine-tune the solid-state properties of pharmaceutical compounds. Physicochemical properties such as solubility, permeability, bioavailability, stability, etc. are major hurdles in the drug development process. Different multicomponent solid forms such as cocrystals, salts, eutectics, solid

solutions, and polymorphs can be engineered by inserting pharmaceutical-acceptable compounds into the crystal lattice of the drug via noncovalent interactions such as hydrogen bonds, π-stacking, halogen bonds, and van der Waals interactions. The supramolecular synthon approach is instrumental in designing new multicomponent crystals with desired properties. The formation of multicomponent crystals depends on the compatibility of the functional groups of the drug and coformer and their ability to form robust interactions between them.

Chapter 2

Regulating Drug Efficacy by Topological Distribution of N–H···O and O–H···O Interactions in Dimorphic Famotidine Molecular Salts

Dimorphic salts of the antiulcer drug famotidine with 2-aminobenzoic acid were isolated from the crystallization of ground powder in methanol and ethanol respectively. The obtained two polymorphs were characterized by thermally, spectroscopy, powder X-ray diffraction, and single crystal X-ray diffraction. Both forms are found to be monohydrated salts with noticeable differences in the orientation of the water molecules of crystallization leading to variations in intermolecular interactions. The stability of the structures is related to the estimated hydrogen bond energy by DFT calculation and total energy obtained by energy framework analysis using Crystal Explorer. The qualitative and quantitative contribution of weak interactions established an agreeable correlation with the measured properties viz. solubility and membrane permeability of the two forms at physiological pH conditions. The strength and distributions of N–H···O and O–H···O along with auxiliary hydrogen bonding, and solute-solvent interactions have been identified as the key factors for the alteration of drug efficacy in the multicomponent crystal systems. Furthermore, this work demonstrates the impact of multicomponent crystal polymorphism on the physicochemical properties of drug molecules.

Chapter 3

Isomeric Coformer Responsive Conformational Adjustment to Recuperate Stability, Solubility, and In Vitro Permeation Behaviour of Drug Molecular Salts

Conformationally flexible histamine H_2-receptor inhibitor drug famotidine that shows low bioavailability and rapid degradation in an acidic environment was picked from the shelves. Six molecular salts of famotidine were synthesized with isomeric aminobenzoic acids and isomeric hydroxybenzoic acids as coformers through mechanochemical grinding. The obtained multicomponent solids were subjected to phase stability studies in

different pH media and show superior drug stability when compared to the parent drug. The solubility and membrane permeation of molecular salts were measured in three different pH conditions. The salt materials show different but improved solubility and superior membrane permeation than the pure famotidine. The primary objective of this work is to investigate the impact of change in the isomeric position and/or type of a functional group of the coformer on the drug properties. Crystal packing energy (calculated using Mercury 4.1 connected with CSD) and hydrogen bond energy (DFT calculation using Gaussian09) are correlated with the measured solubility and membrane permeation behaviour. The observed improvement in the drug properties is attributed to (i) the formation of strong and directional hydrogen bond heterosynthons between the drug and coformers and (ii) the solute···solvent interactions, and (iii) significant conformational change in the drug molecule guided by the change in the functional group and isomeric position variations leading to unique crystal packing in the solid states.

Chapter 4

Molecular Salts of Drug Famotidine with Isomeric Dihydroxybenzoic Acids

This chapter demonstrates the scope of multicomponent solid-state formulations as an efficient method to improve desired properties of the labile drug famotidine. The molecular salts of famotidine with isomeric dihydroxybenzoic acids were prepared via mechanochemical grinding. The product materials were characterized by spectroscopy, thermally, and X-ray diffractions. The prepared molecular salts exhibit improved stability under aqueous and various physiological pH conditions, which is attributed to the drug conformation change leading to better molecular geometry and inclusion of a water molecule(s) in the crystal lattice providing stable molecular packing to the system. The solubility and permeation behaviour of the salts were determined in three pH conditions and correlated with the noncovalent interactions. Various noncovalent interactions play important roles in modifying the lipophilic nature of these molecular salts which is instrumental for estimating the bioavailability. The relationship between solubility and permeation kinetics of molecular salts is also discussed. The change in drug conformation aided by isomeric positions of –OH groups of coformers and the inclusion of water molecules of crystallization in the molecular salts resulted in better solubility and membrane permeation.

Chapter 5

Role of Water Molecules of Crystallization in the Modulation of Solubility and Membrane Permeability of Molecular Salts of Trimethoprim

The synthesis of six molecular salts of the antibiotic drug trimethoprim considering isomeric dihydroxybenzoic acids (DHBA) as coformers is presented in this chapter. The product materials were analysed using FTIR, DSC, TGA, PXRD, and single crystal X-RD. The drug crystallized with 24-DHBA, 34-DHBA, and 35-DHBA coformers in hydrated form with different ratios of the water molecules of crystallization, whereas 23-DHBA, 25-DHBA, and 26-DHBA resulted in anhydrous forms. All products were put through solubility and membrane permeability measurements in various pH conditions. The inclusion of water molecules of crystallization in the multicomponent solids such as TRM-24, TRM-34, and TRM-35 has a colossal impact on their properties as compared to that of the anhydrous salts, i.e. TRM-23, TRM-25, and TRM-26. The modification of the intermolecular interactions in the drug through the salt formation with coformers resulted in the enhancement of solubility and membrane permeability.

Chapter 6

Molecular Salts of Antibiotic Drug Trimethoprim to Modify Its Solubility and Membrane Permeability

The antibiotic drug trimethoprim was selected as a model drug to prepare multicomponent solids with isomeric hydroxybenzoic acids and aminobenzoic acids. The drug is categorized under BCS class II. Because of its low solubility, it displays extremely poor bioavailability. Employing crystal engineering principles, six molecular salts of the drug were synthesized and characterized by FTIR, DSC, TGA, PXRD, and single crystal X-RD. The solubility of all the products was evaluated and correlated with the different hydrogen-bonded synthon energy and crystal packing energy. The permeability of the molecular salts was measured and compared with the parent drug. The new solid forms display better solubility and membrane permeability. The prime objective of this work is to evaluate the role of isomeric positions/types of functional groups of the coformers in regulating different drug properties. The improved properties of the drug are linked with the lipophilic nature of the drug manifested by the percentage contribution of noncovalent interactions, solute-solvent interactions, and hydrogen bond energies.

Chapter 7

Conclusion and Future Direction

This chapter covers the summary of all the important findings from the experimental work performed to achieve the objectives of the thesis. Pharmaceutical cocrystal/salt has been employed to improve the physicochemical properties of drug molecules. Two drug molecules, i.e., antiulcer drug famotidine and antibiotic drug trimethoprim were selected from BCS class IV and BCS class II respectively. Based on the compatibility of functional groups and their ability to form strong intermolecular interactions, three sets of isomeric coformers were selected from the GRAS list to form multicomponent solids with famotidine and trimethoprim. The coformers were selected to investigate how the isomeric positions of phenolic OH and NH_2 groups as well as the difference in these groups dictate the drug properties. The variation in the stability, solubility, and membrane permeability between dimorphic salts of the drug FAM with 2-aminobenzoic acid is presented in Chapter 2. The role of the isomeric position of functional groups of the coformers in regulating the stability, solubility, and membrane permeation of molecular salts of the drug FAM is demonstrated in Chapter 3. Physicochemical properties of molecular salts are correlated with the torsional angle change in the drug molecule, hydrogen bond energy, and molecular packing energy. Chapter 4 demonstrates the role of the water molecules of crystallization along with changes in the drug conformation in modulating the physicochemical properties of molecular salts of FAM at different physiological pH conditions. In Chapters 5 and 6, multicomponent technology is employed to enhance the solubility and membrane permeability of trimethoprim in different physiological pH conditions.

Overall, this thesis presents the potential applications of crystal engineering techniques in the design and synthesis of multicomponent solids to modulate the physicochemical properties of active pharmaceutical compounds. Apart from that the role of various intermolecular interactions strength and distribution, drug conformation, the water molecules of crystallization, the isomeric positions and types of functional groups in the coformers in modulating the properties of multicomponent solids are discussed. The synthesized new molecular salts have the potential to be alternative solid forms to the parent drug molecules.

Keywords

Crystal Engineering, Noncovalent Interactions, Multicomponent Solids, Cocrystal, Molecular Salt, Polymorphs, Active Pharmaceutical Ingredients (APIs), Famotidine, Trimethoprim, Coformers, Physiochemical Properties, Stability.