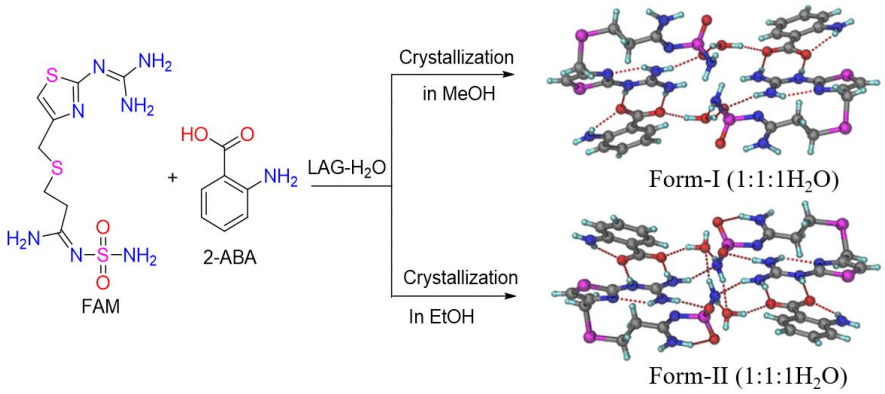
Chapter 7

Conclusion and Future Direction

This thesis reports the design and synthesis of multicomponent crystals as improved solid formulations with desired properties. Cocrystals/salts have attracted the interest of researchers to ameliorate the different properties of materials. In the process of drug development, they have been used as alternative solid forms to modify the physicochemical and pharmacokinetic properties of drug molecules [1–7]. In the formulation of pharmaceutical cocrystal/salt, a pharmaceutically acceptable compound is introduced into the crystal lattice of the drug through noncovalent interactions to change its crystal packing and material properties [8–10]. Two commercially available drug molecules, i.e., antiulcer drug famotidine and antibiotic drug trimethoprim were selected from BCS class IV (low soluble and poor permeable) and BCS class II (low soluble and high permeable) respectively. Besides that famotidine undergoes rapid degradation in acidic pH conditions. Based on the compatibility of functional groups and their ability to form strong intermolecular interactions three sets of coformers were considered to synthesize multicomponent solids. 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 phase stability, solubility, and membrane permeability were studied in simulated physiological pH media for the drug famotidine and trimethoprim. The molecular salt preparation process, structural analysis, and physiochemical properties are elaborated in this thesis. The introductory chapter, i.e., Chapter 1 brings an introduction to the background of crystal engineering. A special focus was given to multicomponent solid forms and their design principles, preparation, and applications in tailoring the physicochemical properties of different API molecules.

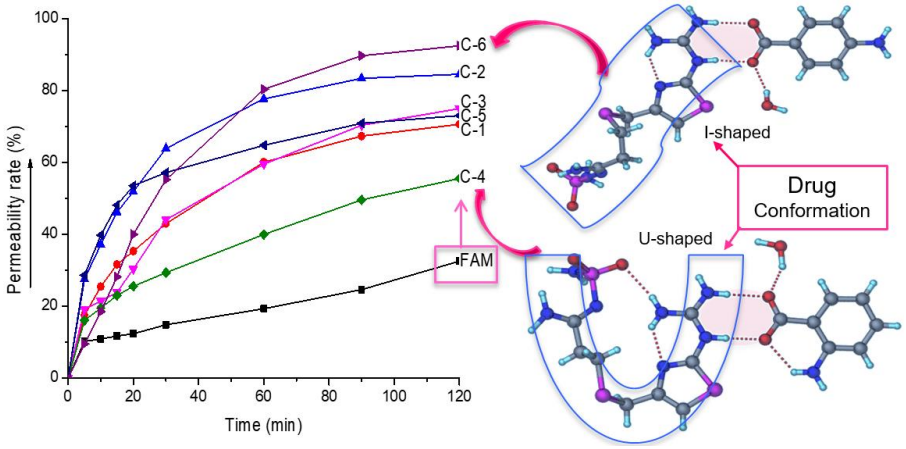
In Chapter 2, the solution crystallization method was employed to obtain dimorphic salts of famotidine with 2-aminobenzoic acid. The phase stability, solubility, and membrane permeation of the dimorphic salts were determined. The fundamental difference between the two forms is the number of hydrogen bonds accessible from the water molecule of crystallization. The better stability of Form-I is associated with the formation of stronger hydrogen bonds by water molecules of crystallization with drug and 2-ABA as compared to that of Form-II. The qualitative and quantitative contribution of weak hydrogen bond interactions established an agreeable correlation with the measured properties viz. solubility and membrane permeability of the two forms at physiological pH conditions.

This study indicates the role of the multicomponent system polymorphism in tuning drug properties.



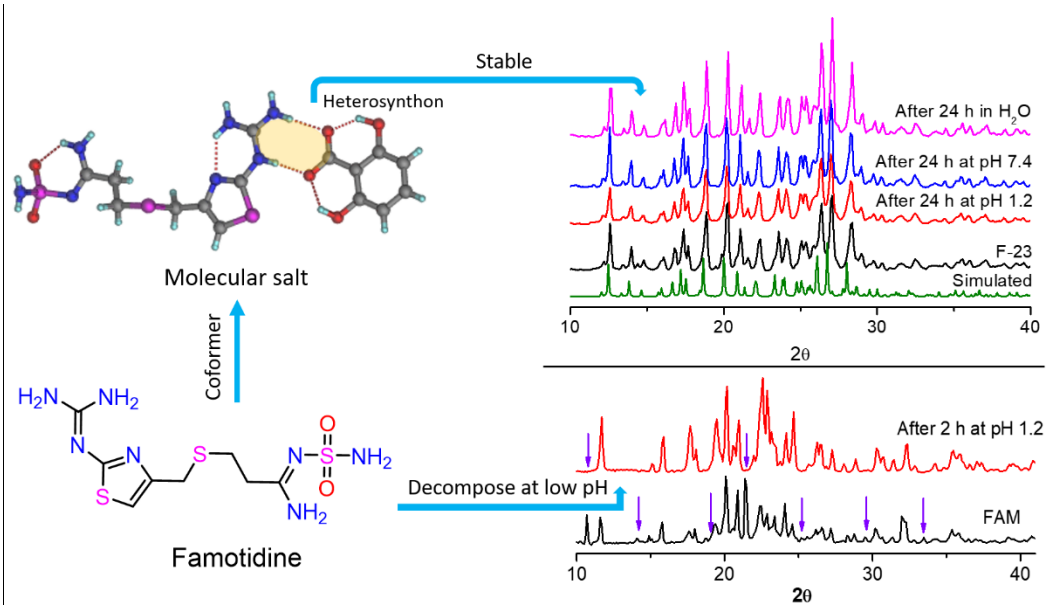
Scheme 7.1 Dimorphic salts of FAM isolated from methanol and ethanol crystallization. The orientation, as well as the number of hydrogen bonds accessible from the water molecules in the crystal structures of dimorphic salts, are different (Chapter 2).

Chapter 3 shows how the adjustment of drug conformation by altering the type and isomeric position of the functional group in the coformer enhances the stability and physicochemical properties of the drug [11]. Six molecular salts of easily degradable and BCS class IV drug FAM were synthesized by grinding with isomeric HBA and isomeric ABA. The molecular salts displayed improved phase stability as compared to pure FAM in three different pH environments. They also exhibited different but higher solubility and membrane permeation than the pure FAM. The enhancement of properties was associated with molecular packing energy, synthon energy, and solute-solvent interactions. The strength of prime synthon formed between the drug and coformers, stability of crystal packing, solute···solvent interactions and conformation change on the drug molecule have significant impacts on changing the properties of the molecular salts.



Scheme 7.2 The variation of the drug conformation in the crystal structures of molecular salts results in the difference in the permeability rate (Chapter 3).

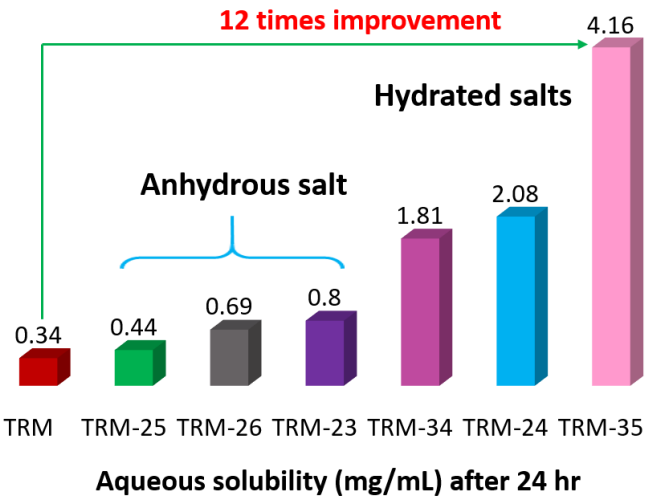
Chapter 4 demonstrated the scope of multicomponent crystal formulations as an efficient method to modify desired properties of the labile drug famotidine. Isomeric dihydroxybenzoic acids were considered as coformers to synthesize the molecular salts. 26-DHBA crystallized with the drug in an anhydrous form, whereas the remaining conformers resulted in solvated forms with different ratios of solvent inclusion. The salt products displayed better phase stability because of drug conformation adjustment resulting in better molecular geometry and assimilation of water molecules in the crystal lattice that provides stable molecular packing for the system. In addition to that factors such as lipophilicity, acidic strength of coformers, and noncovalent interactions between the drug···coformer as well as solute···solvent played a crucial role in modifying the solubility and permeability parameters of the products.



Scheme 7.3 The molecular salts of famotidine demonstrated better phase stability in different pH media when compared with the parent API (Chapter 4).

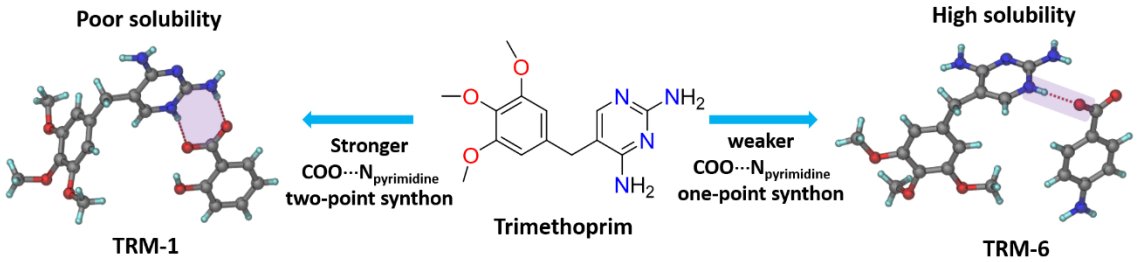
Chapter 5 covers the synthesis of six molecular salts of the BCS II drug trimethoprim with isomeric dihydroxybenzoic acids (DHBA) as coformers. The crystallization of the ground powder of the drug and coformers resulted in anhydrous salts with 23-DHBA, 25-DHBA, and 26-DHBA and hydrated salts with the rest coformers. The solubility and membrane permeation parameters of the salt materials were evaluated in the simulated stomach and intestine pH conditions. The high solubility demonstrated by hydrated salts such as TRM-24, TRM-34, and TRM-35 in comparison to anhydrous salts is attributed to an increase in polarity due to the assimilation of the water molecule(s) in their crystal lattices. A higher permeation rate and drug flux were also observed for the hydrated salts and correlated to

their solubility. This study demonstrated the contribution of the water molecules of crystallization in the improvement of drug properties.



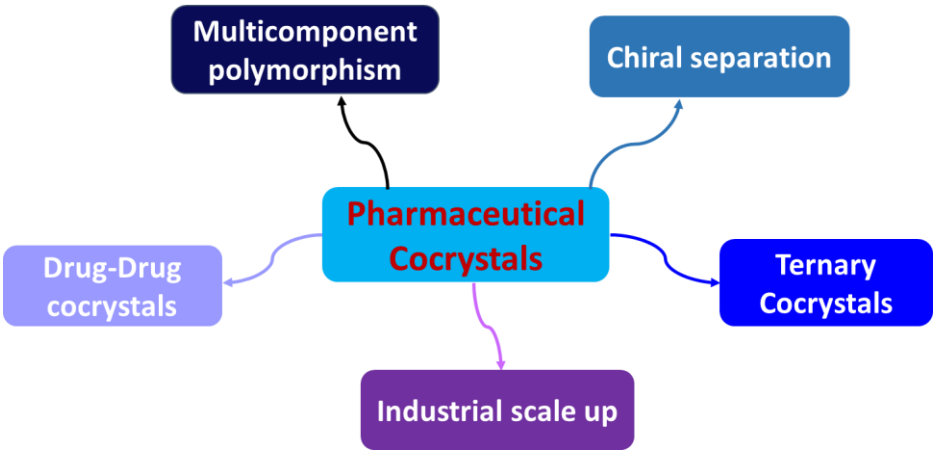
Scheme 7.4 The hydrated salts of TRM demonstrated a significant improvement in solubility as compared to the anhydrous salts (Chapter 5).

Chapter 6 reports the solubility and permeability improvement of the antibiotic drug trimethoprim via molecular salt formation with isomeric monohydroxybenzoic acids and monoaminobenzoic acids. These coformers were picked to study factors that influence the physicochemical properties of multicomponent solids when the type of functional groups or their isomeric positions are changed in the coformers. The measured solubility and permeability of the multicomponent crystals were correlated with the stability of the hydrogen-bonded synthons and crystal packing. The lipophilicity, drug conformation change, and solute···solvent interaction are factors that have significant impacts on the amendment of the drug properties. This study shows the drug properties can be tuned by changing the hydrogen bond forming function group or its isomeric positions in the coformer.



Scheme 7.5 The impact of hydrogen-bonded synthon strength on the solubility of salts of TRM. The formation of a weaker hydrogen-bonded synthon in TRM-6 resulted in higher solubility, whereas the solubility of TRM-1 is very poor among the products because of strong synthon formation (Chapter 6).

Crystal engineering has immense applications in the area of pharmaceutical crystallization. Engineering new solid forms of the drugs via cocrystallization with other pharmaceutically acceptable compounds to modify properties is one of the directions for the future. This will pave the mays for many drug candidates in the production pipelines to enter the market as well as improve the efficacy of the drugs which are already in the market. Drug-drug cocrystals are another interesting aspect of multicomponent systems that will be undertaken in the future since they improve the individual drug action by synergistic effect, minimize side effects, and can be used to design and synthesize combination therapies. Apart from that chiral separation through cocrystallization has recently attracted the attention of researchers as it is very efficient in terms of time and cost when compared with other methods. Developing method to produce cocrystal materials on a large scale is another future direction.



Scheme 7.6 Pictorial illustration of applications of pharmaceutical cocrystals and future aspects.

Reference

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