6. SUMMARY AND CONCLUSIONS

Supramolecular chemistry is one of the escalating domains which encompass rational design and fabrication of the supermolecules. Supramolecular interactions in the solid state of a crystalline form play a vital role in controlling its physicochemical properties. The work in this thesis demonstrates the implementation of the supramolecular chemistry approach in improving the biopharmaceutical performance of antidiabetic drugs gliclazide (GL), glipizide (GPZ) and repaglinide (RPG) by adopting cocrystallization technique. Besides this, the current work also includes the exploration of various polymorphic forms of RPG.

Cocrystallization is a supramolecular phenomenon that comprises of the collection of more than two dissimilar solid entities in a crystalline lattice via non-covalent interactions. It has been used widely to ameliorate the physicochemical profile of the pharmaceutical ingredients. The antidiabetic drug molecules, chosen for the study have the setback of dissolution limited bioavailability. To overcome this drawback, cocrystallization was adopted as this approach has never been explored for these selected molecules. The availability of numerous hydrogen bond donors and acceptors in GL, GPZ and RPG make them promising molecule for cocrystallization. Moreover, the ability of the cocrystals to customize the physicochemical properties at root level without forming or breaking the covalent bonds make the cocrystals a better alternative to improve the clinical performance of these drugs. The systematic experimental protocols lead to the synthesis of cocrystals of GL, GPZ and RPG with GRAS (Generally Recognized as Safe) status coformers. The cocrystals of all the drug molecules were synthesized using the solvent drop grinding method. The use of GRAS coformers and acceptable solvents in nominal amount in the preparation of the cocrystals of GL, GPZ and RPG has made their synthesis as a part of sustainable green process. Besides this, the catalytic amount of solvent, used in the preparation of cocrystals helped in enhancing the molecular mobility and in accelerating the reaction rate. The addition of solvent has also lead to the generation of more crystalline products with control over polymorphic behavior. Various analytical techniques such as DSC, PXRD, FTIR and SSNMR have been employed to characterize the new crystal forms systematically. The sharp endothermic peaks different from the individual molecular entities in DSC and appearance of new peaks along with disappearance of characteristic peaks of parent components in PXRD pattern revealed the existence of new crystalline phase upon grinding. Furthermore, the DSC of physical mixture of all the crystalline phases in stoichiometric ratio showed the two broad peaks, representative of individual components which negated the formation of eutectics and supported the cocrystals. FTIR spectral analysis
assisted in imparting the information regarding the formation of hydrogen bonds among the complementary functional groups. The stored information in the PXRD patterns, regarding the positions of atoms in the crystal lattice were used to determine the crystal structures of the cocrystals. The crystal structure illustrated the formation of heterosynthons (drug-coformer interactions) in preference to homosynthons (drug-drug interactions) in the cocrystals. The supramolecular network of the cocrystals as determined by PXRD was further supported by changes in the chemical shifts shown by SSNMR. The successfully cocrystallized forms have shown better equilibrium solubility, intrinsic dissolution rate, antidiabetic activity and pharmacokinetic parameters in comparison to respective drug molecules.

From the studies, it has been concluded that the supramolecular chemistry is a viable approach for customizing the properties of drug molecules by synthesizing the cocrystals. The solubility of the coformers and the arrangement of molecules in the crystal lattice are the main factors that determine the properties of the cocrystals. Besides this, the reduction in dose of drug upon cocrystallization also aids in improving the therapeutic effectiveness. The study unfolded in this thesis i.e., cocrystals of GL, GPZ and RPG exemplify the green and economical route of improving the profile of poorly soluble drugs via cocrystallization which can potentially be developed into the formulation.

Polymorphism is another supramolecular phenomenon that leads to the multiple crystalline forms of a molecule due to the conformational flexibility and different crystal packing arrangements. For pharmaceuticals, the exploration of the plausible polymorphic form is of utmost importance but in some cases, stable polymorph takes years to nucleate. In this scenario, an alternative computational strategy, CSP (Crystal Structure Prediction) has emerged as a useful tool for determining the crystal structure, for accounting the probable conformations and for predicting a range of thermodynamically favored crystal packing. The computational findings along with experimental screening give a way to rational polymorph screening. In the present work, a synergistic experimental and computational approach has been used to screen the various polymorphic forms of RPG. The polymorphs of RPG were isolated experimentally using solvent evaporation method. The obtained products were characterized by DSC and PXRD which confirmed the isolation of three different crystal forms. The collected PXRD pattern was used to determine the crystal structures of the polymorphs. To complement these studies, crystal structure prediction (CSP) has employed to account for the conformational flexibility and to obtain the information about the crystal packing pattern of RPG polymorphs. For gaining the insight about the polymorphic behavior
shown by RPG, the lattice energy landscape which depicted the relationship between lattice energy and density of the polymorphs was plotted for various possible polymorphs. The experimentally isolated polymorphs have successfully fitted into lattice energy landscape. The presence of a large number of structures near the global minima also anticipates the likelihood of existence of more metastable crystal forms. However, they have not been isolated and are under consideration.

From this study, it has been established that the conformational analysis and polymorph prediction in conjunction are helpful to anticipate the plausible polymorphs of a drug molecule. The polymorphs of RPG and its crystal energy landscape, provided in the present study would be fruitful in mapping of more metastable potential polymorphs of RPG.