1. INTRODUCTION

Diabetes mellitus can be conceived as “the perfect global epidemic” afflicting millions of people (Hu, 2011). As the human race is switching from infectious diseases to chronic diseases predominantly, type II diabetes mellitus has become one of the leading diseases for putting the world to distress. This unceasing disease demands long-lasting pharmacological and non-pharmacological supervision to avert complications (Figure 1.1) such as stroke, retinopathy, neuropathy and nephropathy (Qaseem et al., 2012).

![Figure 1.1: Pictorial representation of long term side effects of diabetes mellitus](image)

A number of oral antidiabetic agents have been found effectual in type II diabetes management and are FDA approved (Ibrahim, 2010). Unfortunately, many among them have a setback of low solubility and bioavailability which consequently affects safety and efficacy of these orally administered drugs (Stegemann et al., 2007).

The paucity of the favorable physicochemical properties as well as the hurdles during formulation of these antidiabetic agents, demand either for the synthesis of new molecules or modification of these existing ones. Generally, two types of approaches, *i.e.*, a covalent approach involving lead optimization and non-covalent approach employing supramolecular chemistry can be exploited to alter the physicochemical properties on a molecular level. The synthesis and preclinical/clinical trial of a new molecule is comprised of high investment of money and yet don’t guarantee the fruitful output (DiMasi et al., 2003). Therefore, it is not a
wonder to optimize the existing antidiabetic agents and rule out the shortage of new molecules. In this context, supramolecular chemistry is a good alternative for optimizing the performance of oral antidiabetics in a solid state as the physicochemical properties of the crystalline solids are the puppets in the hands of supramolecular interactions. Besides this, these reversible non-covalent interactions do not alter the pharmacological properties. Therefore, this thesis is based on the improvement of solubility, bioavailability and thus biopharmaceutical performance of some selected oral antidiabetics using supramolecular chemistry approach.

Supramolecular chemistry takes into account the weak non-covalent intermolecular interactions such as hydrogen bond, pi-pi interaction and van der Waals forces etc. (Maitland et al., 1983; Dunitz, 1991; Aakeröy and Seddon, 1993; Lehn, 1995; Steed and Atwood, 2000; Desiraju, 2001; Metrangolo, 2001; Sinnokrot and Sherrill, 2006) and has premised upon the concept of molecular recognition (Desiraju, 1995). The curiosity to understand the mysterious functioning of biological systems has given birth to this important realm of chemistry. The theory of supramolecular chemistry could be understood easily by the analogy given by Lehn (Figure 1.2) that the molecules are formed by the units of atoms, connected through covalent bonds; in a similar way, supermolecules are constructed by the molecules which are linked through non-covalent bonds (Lehn, 1973; Lehn, 1978; Lehn, 1985; Lehn, 1988; Lehn, 1995; Steed et al., 2007).

![Figure 1.2: The concept and the principle of the molecular chemistry and supramolecular chemistry](image)

In the recent era, supramolecular chemistry has emerged as an interdisciplinary field and has found its applications in the biological, chemical and pharmaceutical sciences (Desiraju, 1995; Desiraju, 2008). The modulation of the physicochemical, biopharmaceutical and formulation aspects of an API by the designing of supramolecular therapeutics has gained popularity in pharmaceutical industries (Rodríguez-Spong et al., 2004).
It consists of two distinct branches: synthesis of supermolecules in solution (molecular recognition) and in solid state (crystal engineering). However the underlying principle and nature of interactions for both is similar and directional in nature (Balzani and Cola, 1992). The characteristic of directional nature of molecular recognition events has cater the opportunities to design and synthesize the new chemical entities in solid state (Nangia, 2010). Furthermore the properties of supermolecules are superior to its constituents.

Supramolecular chemistry that is used for tailoring the physicochemical and biopharmaceutical properties in solid state includes different non-covalent derivatives such as cyclodextrin complexes, polymorphs, salts, hydrates, solvates, cocrystals and eutectics (Figure 1.3). However, in the present work, the emphasis will be laid on the formation of cocrystals and polymorphs using this viable and fruitful approach.

Cocrystals are the crystalline complexes of multiple solid constituents which are neutral and adhered through non-covalent interactions, in a well-defined stoichiometry. The multiple matching of different functional groups, present on the individual components give rise to a variety of crystal lattices (supermolecules) having different physicochemical properties (Desiraju, 2008). In the current scenario, cocrystals are considered a lucrative choice to tune the properties of pharmaceutical products. They not only ameliorate the performance of the drugs but also offer regulatory advantages (Desiraju and Parshall, 1989; Desiraju, 2010; Trask, 2007).
Polymorphism is a phenomenon where a molecule can attain different conformations and various packing arrangement that leads to the generation of numerous crystalline forms (Moulton and Zaworotko, 2001). The ability of crystal forms to influence the physicochemical, biopharmaceutical and technological properties of solids urge for exploring the various polymorphs of the pharmaceutical relevant compounds (Rustichelli *et al*., 2000). Polymorphs can be considered a type of supramolecular isomers (vice-versa is not true) as the same type of molecules are connected via non-covalent interactions and give rise to different supramolecular network (Moulton and Zaworotko, 2001; Delori *et al*., 2012). The compounds which contain multiple functional groups and posses conformational flexibility are prone to exhibit polymorphism. The importance of polymorphs in the pharmaceutical field is marked by the failure of Norvir® capsule in 1998 (Bauer *et al*., 2001). The knowledge of polymorphism and crystallization is crucial for the development of pharmaceutical products.

The present work is focused on the design, synthesis and evaluation of supermolecules (cocrystals and polymorphs) of some selected oral antidiabetic agents (gliclazide, glipizide and repaglinide) to improve their biopharmaceutical performance (Figure 1.4).

**Figure 1.4: The outline of the present work**