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Supramolecular Chemistry: An Alternative Approach to Improve Potential Active Pharmaceutical Ingredient's (APIs)

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Research Article

ABSTRACT

Supramolecular interactions in the solid state of a crystalline from plays a vital role in controlling of its physicochemical properties. The tailoring of these non-covalent interactions, in already established APIs can be utilized to design a new chemical entity with improved biopharmaceutical properties. This review article throws the light on the supramolecular chemistry in different crystalline forms (polymorphs, cyclodextrin complexes, salts and co-crystals) and how the supramolecular architecture has contributed for the betterment of the potential APIs.

Keywords: Supramolecular chemistry, Polymorphs, Cyclodextrin complexes, Salts, Co-crystals

INTRODUCTION

Most of the pharmaceutical products are developed and marketed in the solid dosage forms and comprise of an API, preferably in crystalline form due to thermal stability and purity [1]. Despite having therapeutic potency, most of the molecules exhibit unfavorable bioavailability, because of poor solubility, which consequently affects safety and efficacy of the administered drugs [2]. The lack of the desired physicochemical properties and challenges during formulation of APIs, created a demand to explore economical alternative methods to improve the existing molecules. The application of the concept of supramolecular chemistry is an excelling choice for the betterment of potential APIs in a solid state as the crystalline solids are the proof of self-assembly and the diversity of solid state forms is influenced by collective non-covalent interactions in a crystal.

The aim of the present review is to highlight the fundamentals of supramolecular chemistry in solid state and events of molecular recognition and self-assembly along with its significance and application in pharmaceutical industries for the betterment of APIs.

Supramolecular chemistry is the chemistry beyond the molecule, exploring new domains of chemistry that chiefly targets the noncovalent weak and reversible molecular contacts such as hydrogen bond, metal coordination, pi-pi interaction, van der Waals forces. It has grown around Lehn's analogy that "super molecules are to molecules and the intermolecular bond what molecules are to atoms and covalent bond". In the past, the deep desire to understand and unveil the mysterious biological systems and their functions at the molecular level, opened the new door for chemistry to a world of super molecules. But, nowadays, supramolecular chemistry has turned out to be an interdisciplinary field with a broad array of applications in the biological, chemical and pharmaceutical sciences [3,4]. The pharmaceutical industries are witnessing the era of supramolecular therapeutics and the designing of super molecules with fine tunable pharmacological activity [5].

The building of supramolecular assembly relies on the concept of molecular recognition, which is 'the strategy by which a molecule bears supramolecular functions'. The complementary functionalities in the molecules interact via intermolecular forces, in an explicit way and assemble spontaneously. Supramolecular architecture is also characterized by self-assembly i.e., the spontaneous assembling of the molecules, which are attached through non-covalent interactions. The theory and principles of recognition and the nature of the interaction that intervene supramolecular assembly are almost the same in solution and in the solid state [6]. However, supramolecular synthesis in solution is known as molecular recognition and in solid state as crystal engineering. The directional molecular recognition events in solid state can be used as the design elements to produce new chemical entity by using crystal engineering approach [7].

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The process of generation of different type of super molecules is a stepwise process, which can be represented in Figure 1.

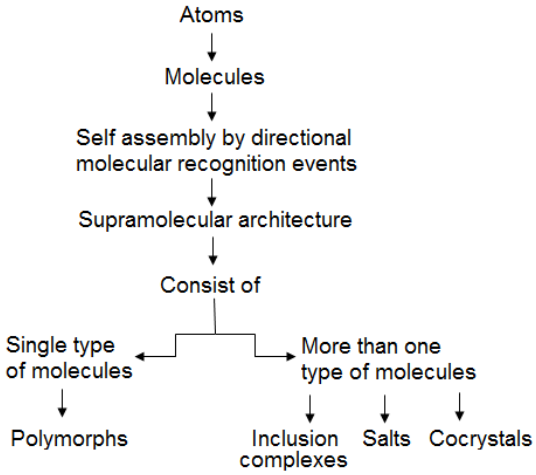

Figure 1. Generation of different type of super molecules.

The structure and characteristic properties of super molecules are not additive, but far superior and distinct than the constituent molecular species. Along this, super molecules utilize noncovalent interactions of reversible nature and don't alter the pharmacological activity of APIs3. These are the supreme reasons why supramolecular chemistry has become substantial strategy for the modification of physicochemical properties of APIs in the pharmaceutical industry.

The purpose of using supramolecular synthesis in the solid state is the design-driven fabrication of 'super molecules' that are assembled by a series of molecular recognition events that involve intermolecular interactions between the constituent components. The beauty of supramolecular chemistry lies in its rapid and effective synthesis of new chemical entities as compared too covalent means [8].

The physicochemical properties of the APIs can be improved either by modification in the supramolecular arrays (screening of new polymorphs), existing in the molecules of same type or by altering the non-covalent interactions by incorporating new components (inclusion complexes, salts and co-crystals) [9].

Polymorphs

Polymorphism is a phenomenon of the existence of a molecule in more than one crystalline form, which occurs due to either various conformations of a molecule or different crystal packing in space [10,11]. The exploration of the various polymorphs in the pharmaceutical industry is of utmost importance as they have a significant impact on solid-state properties that consequently influence biopharmaceutical and technological behavior of APIs [12].

In the polymorphs, the molecules are linked to each other via non covalent interactions and thus, polymorphism may be called as a type of supramolecular isomerism if elucidated in the terms of supramolecular interactions. In simple way, polymorphs are the supramolecular isomers (although vice-versa is not true) that are built from same molecules using same supramolecular synthons, but give rise too different supramolecular architecture [10,13].

In the crystal lattice, the molecules of APIs get assembled via non-covalent interactions and form self-complementary functionalities [14]. Different polymorphs have a small free energy difference among them and under various conditions transform from metastable to stable form or rather say undergo isomerization reaction in supramolecular terminology. In solid state phase transformation, a small change in the crystal lattice is transmitted to distant molecules through supramolecular interactions, which results in different conformations and packing arrangements of molecules, and thus affects the physicochemical properties of the solids [15].

A profound knowledge of the polymorphism and crystallization is critical to pharmaceutical product development and screening of the polymorphic forms under various experimental conditions may help in finding the better form with improved properties.

Inclusion complexes

The molecular assemblies i.e., super molecules involving macrocyclic host has been a fascinating approach to improve the physicochemical properties of the pharmaceutical products. Among the all macrocyclic host, cyclodextrin (CDs) have been used widely because of their high-water solubility, easy availability, cost effectiveness and ability to form reversible inclusion complexes [16-18]. CDs are the truncated cone shaped cyclic oligosaccharides with hydrophobic inner cavity and

hydrophilic outer face and this inner hydrophobic cavity provides the opportunity to form non-covalent host-guest inclusion complexes [19,20]. CDs complexes serve a simple and good example to understand the supramolecular self-assembly process and molecular recognition [21].

During the formation of inclusion complexes, indirect measures like heat changes or changes in photo physical properties etc., at molecular level are used as an evidence of the molecular recognition event. A successful attempt to demonstrate these recognition events by self-assembly process at macroscopic level was made by Harada et al. They demonstrated the specificity of the molecular recognition and reversible nature of the self-assembly formed by the host i.e., cyclodextrin and guest i.e., acrylamide based gels, by dying with different colors [22].

Inclusion of a drug molecule in the CDs improves the potential APIs in several ways. It enhances the apparent solubility and bioavailability of a drug and thus helps in improving the BCS class II and IV drug molecules, which consequently results in increase in pharmacological effects and thus dose reduction [23-26]. Besides this, CD complexes also have been prepared to achieve other goals like to control the rate and time of drug release to minimize ocular and gastrointestinal irritation, to mask smells or tastes of the drugs, to lower volatility, and to convert oily substances into microcrystalline or amorphous powders [19,24,27-29]. Numerous products are marketed in the CD complexes form e.g. piroxicam-β CD complex (Brexin, Cicladol), alprostadil (PGE1)-α CD complex (Prostavasin/Edex/Caverject) and itraconazole-2-β CD (Sporanox) etc. [30].

Cocrystals/Salts

Marketing of a drug in a salt form is a popular trend and it has influenced the pharmaceutical industries to a great extent. For the drugs, which are ionizable and have suitable functional moieties, formulating a salt is an easy and effective approach to improve physicochemical properties. Along with it, salt formation also affects purity and technological properties of APIs [31-33].

On the other hand, pharmaceutical research world is booming with co-crystals, now a day. Co-crystals are the crystalline complexes of two or more neutral molecular constituents bound through noncovalent interactions in the crystal lattice in specific stoichiometry. Co-crystals, not only widen the alternatives to modify the physicochemical properties of ionizable drugs, but also offer an attractive approach to alter the solid-state properties of non ionizable drugs. Pharmaceutical co-crystals are attractive to the pharmaceutical industry because they offer multiple opportunities to modify and control the physicochemical properties of an API without making or breaking covalent bonds [34,35].

The only remarkable difference between a salt and a co-crystal is whether a proton has been transferred or not. Along with it, salts are characterized by electrostatic interaction and co-crystals possess hydrogen bonds preferably [5,31,36].

Crystal engineering of multicomponent systems and molecular recognition are twin facets of supramolecular chemistry that depend on multiple matching of functionalities among molecular components to optimize several intermolecular interactions, which may have varying strengths, directionalities and distance-dependent properties [3]. The complementary matched functionalities that are repetitive and involve noncovalent interactions are known as supramolecular synthons. As synthons contain all geometrical and chemical information inherent to recognition phenomenon and are of repetitive and well defined nature, they can be relied upon to generate supramolecular functional material. Among all the types of noncovalent interactions, hydrogen bonding is considered most significant because of its directional nature. The design of supramolecular synthon demands a correct assessment of the energetic and spatial attributes of the noncovalent, intermolecular forces which will result from the assembly of a given molecular structure or structures [37].

Multicomponent systems witness the dominance of supramolecular heterosynthon (a synthon formed by different but complementary functional group) over the supramolecular homosynthons, already established in drug molecules.

The commonly occurring synthons that can be explored in the preparation of co-crystals are given in **Figure 2.**

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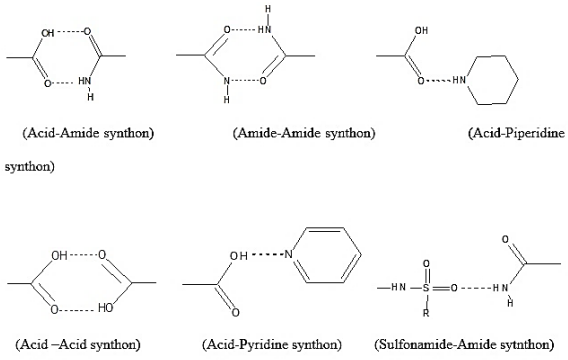

Figure 2. Commonly occurring synthons.

The search of complementary functional group by Cambridge structural database (CSD), quantifies the likelihood of occurrence (propensity) of all the possible hydrogen bonds in the formation of homo and hetero synthons and Etter's empirical rules for hydrogen bonding also helps in predicting the hydrogen bonding pattern in synthons [38,39].

The differences in pKa of the reactants (ΔpKa) also act as a guide in predicting the likelihood of proton transfer during co-crystallization. The ΔpKa region 0-3 is now widely regarded as a region of uncertainty in which either a salt or co-crystal may form. In general, a larger ΔpKa (greater than 3) will result in salt formation while a smaller ΔpKa will almost exclusively result in co-crystals formation [40-43].

By formulating the salts/co-crystals solubility, bioavailability and stability properties can be fine-tuned very well by the precise control over the supramolecular assembly [34,35]. Along with it, salt formation also has been used to improve hygroscopic (Thiamine with diacetyl sulfate), thermal stability (Theophylline with Isobutanolamine), organoleptic properties (e.g. Vincamine with dioctyl sulfosuccinate), compressibility, toxological profile (e.g. Kanamycin with pamoic acid), to reduces pain on injection (Cephalosporin's with N-Methylglucamine) and for prolonging the action of drugs (Ampicillin with dibenzyl ethylenediamine) [32].

Dapaglifazone propylene glycol monohydrate, recently approved by USFDA was the first API to be marketed as a co-crystal in Europe.

CONCLUSIONS

Prevailing of drugs with undesirable properties has forced pharmaceutical industries to explore the various approaches to optimize the solid form. In the last few decades, supramolecular chemistry has opened new avenues for addressing the several issues in the development of APIs. Supramolecular chemistry in solid state helped not only to widen the scope of chemistry beyond covalent bond but also to understand the fundamentals in solid state. By seeing the recent scenario of pharmaceutical products and the demand of pharmaceutical industries, this article has summarized the concept of supramolecular chemistry in different solid forms like polymorphs, inclusion complexes, salts and co-crystals. Although, supramolecular synthesis in solid state has become popular yet it has not achieved the same level of sophistication as in solution chemistry. Thus, supramolecular synthesis in solids poses many challenges for the academic and industrial researchers, to be solved soon.

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