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Research Article

Crystal Engineering: A Powerful Tool towards Designing Pharmaceutical Solids with Desirable Physicochemical Properties

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Abstract

Nowadays various techniques have been applied for the improvement of physicochemical properties such as solubility, bioavailability, stability and hygroscopic nature of pharmaceutical solids without effecting the biochemical composition of the active pharmaceutical ingredients (API). Supramolecular approach specially the crystal engineering technique is one of the best techniques which play an important role to improve the physico-chemical, thermal and mechanical properties of drug molecules. Crystal engineering approach offers a number of routes such as co-crystallization, polymorphism, hydrate and salt formation with the help of which drug molecules with good physico-chemical behavior can be prepared. This article covers the concept of supramolecular chemistry and crystal engineering approach for the preparation of co-crystals and their application in pharmaceutical industries.

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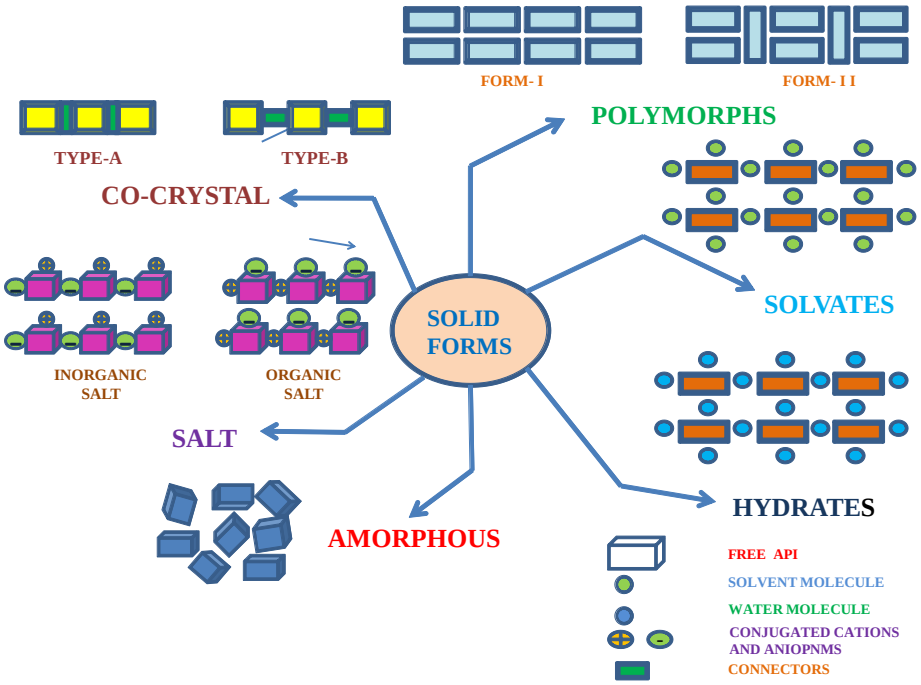
Introduction

Molecules generally exist either in solid, liquid or gaseous forms and also some meta-stable stages such as semi-solid or semi–liquid under a certain set of conditions. Solid organic or inorganic compounds are found to be existed either in crystalline or amorphous form. Many solid organic or inorganic compounds, organo-metallic complexes exhibit themselves as biologically active molecules and few of them can be treated as drug molecules for particular diseases after long investigation. These solids are then considered as pharmaceutical solids. A finished pharmaceutical product (FPP) has direct effect in the diagnosis, mitigation, treatment and prevention of disease. A pharmaceutical product will be considered as a active pharmaceutical ingredient (API) [1] if they will not destroy the physiological functions in human being during application or functioning. Active pharmaceutical ingredients of a drug molecule are generally delivered to the patient in the stable solid format either in the form of a tablet or capsule. In these capsules or tablets the solid APIs are kept in several distinct forms such as co-crystals, polymorphs, solvates, hydrates, salts and amorphous solids according to requirement in order to increase the physicochemical properties such as bioavailability, purity, stability and also good performing ability of the drug molecule [2]. The design and synthesis of active pharmaceutical solids by understanding and controlling the solid-state chemistry without effecting the functional properties of pure drug substances in the formulated products, is therefore a challenging job in the drug development process. The concept of supramolecular chemistry and crystal engineering can provide valuable idea for designing and synthesizing such active pharmaceutical solids in approved dosage form.

Supramolecular chemistry

The concept of bond formation between atoms by sharing the electron pair between themselves and the concept of hybridization created enormous interest among the chemists for synthesizing new molecules with useful properties. The development of synthetic organic chemistry or covalent synthesis started with the synthesis of urea by Friedrich Wöhler in 1828 [3].Thereafter many efficient and important methodologies have been evolved in a galloping manner for synthesizing novel and complex molecules by making and breaking bonds in a controlled and precise fashion. Beyond molecular chemistry, there lies another field of chemistry based on non-covalent interactions which is popularly known as supramolecular chemistry. The concept and the term of supramolecular chemistry were first introduced by Jean Marie Lehn in 1978. J. M. Lehn defined it as, “Just as there is a field of molecular chemistry based on covalent bond, there is a field of supramolecular chemistry, the chemistry of molecular assemblies and of the intermolecular bond” [4].The field of supramolecular chemistry was started with the discovery of chlorine hydrate by Sir Humphry Davy in 1810. After the discovery of “lock and key” principle [5] by Sir Emil Fischer in 1894 and the concept of receptor introduced by Paul Ehrlich in 1906, supramolecular chemistry started expanding fast and within a short period it had emerged as a major area of research due to its multidisciplinary nature and applicative aspects ranging from biology to material science. Donald J. Cram [6], Jean-Marie Lehn [7], and Charles J. Pedersen [8] were awarded the Nobel Prize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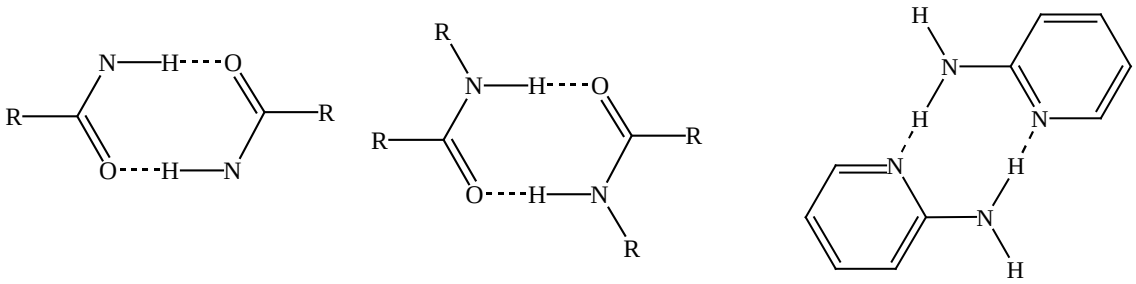
molecules. The "Crystal Engineering" is defined by G. R. Desiraju [12] as "the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design of new solids with desired physical and chemical properties". The process of crystallization deals with the aggregation of millions of molecules through non-covalent interactions. Therefore, Dunitz [13] defined crystals as "*supermolecules par excellence*." The fundamental concepts of supramolecular chemistry and crystal engineering are same as both deals with the precise and controlled aggregation of molecules via non-covalent interactions [14]. One of the important features of crystal engineering is to generate or recognize proper synthon which ensures the predictability one, two, three- dimensional networks during aggregation of molecules through non-covalent interaction.

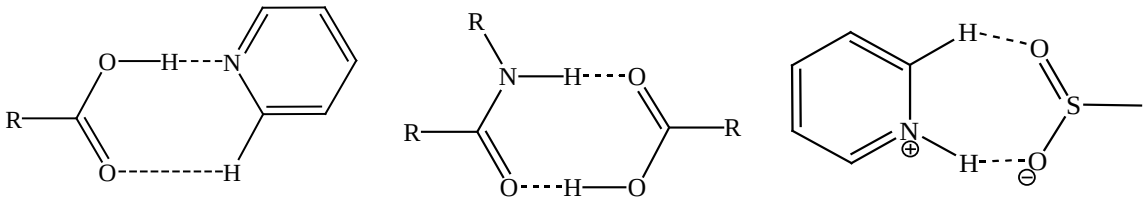
Smaller building units are the fundamental and essential tools for synthesizing both covalently bonded complex organic molecules and non-covalently bonded supramolecular architectures. In 1967, E. J. Corey introduced concept of "synthon" which is the root for the synthesis of targeted organic molecule [15]. Corey defined synthons as "*structural units within molecules which can be formed and/or assembled by known or conceivable synthetic operations"*. Similarly, for designing predictable supramolecular architectures *via* crystal engineering technique, identification of proper synthon is essential. Therefore, the term "Supramolecular Synthon" was introduced by G. R. Desiraju in 1995 in the context of supramolecular synthesis [16]. He defined supramolecular synthons as "*structural units within supermolecules which can be formed and/or assembled by known or conceivable synthetic operations involving intermolecular interactions"*. Supramolecular synthons *via* conventional hydrogen bonds are the most popular and commonly used but supramolecular synthons involving weak interactions such as π···π interactions, halogen-halogen interactions, cation···π and anion···π interactions also play a major role in assembling the molecules in the solid state.

Generally the synthons that are formed between same functional group of one chemical component are termed as homomeric synthons. The hydrogen bonded homosynthon of –COOH group is found in the crystal structure of the dimmers of different carboxylic acid compounds. Some example of homomeric synthons are shown in the scheme 1.



Scheme1 Hydrogen bonded homomeric synthons.

Heteromeric synthons are formed between same or different functional groups of two or more chemical components. The well known examples are acid-pyridine, acid-amide, amide-pyridine and pyridine-hydroxyl etc (Scheme 2).



Scheme 2 Hydrogen bonded heteromeric synthons.

The rational design and prediction of structures in solid state with the help of proper synthons formation are the main objectives of crystal engineering. There are several crystal engineering techniques for designing predictable single crystals such as slow evaporation after dissolving the functional materials in proper solvent system, bi-layer technique, seeding technique and vapor diffusion technique. All these techniques are very important for the synthesis of co-crystals in order to increase the physico-chemical properties of APIs.

Co-crystal

Aakeröy defined co-crystals as the aggregation of two molecules in the crystalline form at ambient conditions [17]. In 2007, G.P Stahly modified the definition of co-crystals as, "Co-crystals consist of two or more components that form a unique crystalline structure having unique properties" [18]. Zaworotko defined co-crystal as 'A co-crystal is a multiple component crystal in which all components are solid under ambient conditions when in their pure form. These components co-exist as a stoichiomeric ratio of a target molecule or ion and a neutral molecular co-crystal former(s)' [19]. Co-crystals are designed based on the principles of the supramolecular synthesis; it provides a powerful approach for proactive discovery of novel pharmaceutical solid phases. Co-crystals consist of multiple components at defined stoichiometric ratios, where different molecular species interact by hydrogen bonding and other non-covalent interactions. Co-crystals can have different properties than the crystals of individual components. A very early example of a co-crystal is the 1:1 molecular complex between benzoquinone and hydroquinone, named quinhydrone, reported by Wöhler in 1844. It is the first crystal structure of a co-crystal in the Cambridge Structural Database (CSD) [20] with reported coordinates for two polymorphic forms, a monoclinic form (*P*21/c, QUIDON02) and a triclinic form (*P*-1, QUIDON). The use of hydrogen bonding rules, synthons and graph sets may assist in the design and analysis of co-crystal systems. Etter and co-workers proposed the guidelines to facilitate the deliberate design of hydrogen-bonded solids [21]. According to Etters rule, (i) all good proton donors and acceptors are used in hydrogen bonding, (ii) six-membered ring intramolecular hydrogen bonds form in preference to intermolecular hydrogen bonds and (iii) the best proton donor and acceptor remaining after intramolecular hydrogen bond formation will form intermolecular hydrogen bonds to one another (but not all acceptors will necessarily interact with donors).

Pharmaceutical co-crystals

In 2011, Qiao defined pharmaceutical co-crystals as a multiple component crystals in which one of the co-crystal components act as an API and the rest components are called conformers. The multi-component molecular assemblies by employing the supramolecular and crystal engineering concept opens a new arena in the field of pharmaceutical industries for developing targeted drug molecules with desired physical and chemical properties (Table 1). In 2007, Trask mentioned that co-crystals may enhance a large number of essential parameters including chemical stability, hygroscopicity, compressibility and flow ability in addition to potential improvements in solubility, bioavailability, and physical stability of pharmaceutical solids. So co-crystals can be recognized as an attractive alternative for solid forms of drug products.

Table 1 Recent case studies of Pharmaceutical co-crystals

API	CONFORMER	PREPARATION METHOD	IMPROVED PROPERTY	REFERENCE
Theophylline	Nicotinamide	Solvent evaporation	Solubility	Lu *et al* 2009
Sulphamethazine	Theophylline	Solvent evaporation	Thermal stability, Spectroscopic and X-ray diffraction properties	Lu *et al* 2011
Sulphamethazine	Aspirin, Benzoic acid, Trimethoprim, 4-Amino salicylic acid	Solvent evaporation	Physical stability	Caira *et al* 2007
Piroxicam	Saccharin	Solvent evaporation	Physical stability	Childs *et al* 2007
Carbamazepine	Nicotinamide, Saccharin	Cooling crystallization	Physical stability Dissolution rate and Oral Bio-availability	Hickey *et al* 2007
Aspirin	4,4'-bipyridine	Slurry Conversion	Physical stability	Walsh *et al* 2003
Indomethacin	Saccharin	Solvent evaporation or solvent assisted grinding	Physical stability and dissolution rate	Basavoju *et al* 2008

Norfloxacin	Isonicotinamide Succinic acid Malonic acid Maleic acid	Solvent evaporation	Solubility	Basavoju *et al* 2006
Ibuprofen	4,4'-dipyridyl-nicotinamide	Solvent evaporation	Solubility	Walsh *et al* 2003
Paracetamol	4,4'-bipyridine	Solvent evaporation	Physical stability and dissolution rate	Walsh *et al* 2003
Flubiprofen	4,4'-bipyridine	Solvent evaporation	Physical stability	Oberoi *et al* 2005
Acetaminophen	Pyridine-2,4-dicarboxylic acid	Solution mediated phase transfer technique	Physical stability	Sander *et al* 2010
Itraconazole	Malic acid Tartaric acid Succinic acid	Solvent evaporation	Improved dissolution rate	Remenar *et al* 2003
Caffeine	Maleic acid Gluteric acid	Solution mediated phase transfer technique	Physical stability	Guo *et al* 2010 Yu *et al* 2010
Fluoxetine hydrochloride	Benzoic acid Fumaric acid Succinic acid	Solvent evaporation	Intrinsic dissolution rate	Childs *et al* 2004

Theophylline contains hydrogen bonding donor and acceptor functionalities such as O-H and N-H sites which are also the complementary functional groups of each other play effective role for crystal formation. Theophylline itself is often used for asthma or chronic obstructive pulmonary disease treatment. The physiochemical character of Theophylline is found to be increased when Theophylline forms co-crystal with different substrates. In 2007 Caira reported that the physiochemical character of Sulfamethazine drug is also increased in the co-crystal form with different substrates such as aspirin, benzoic acid, trimethoprim, 4-aminosalicylic acid, etc. The theophylline-sulfamethazine co-crystal has unique thermal, spectroscopic and X-ray diffraction properties, but higher hygroscopic nature than individual components (Lu et al., 2011a; Lu and Rohani, 2010). In 2009 Lu and Rohani reported that the theophylline–nicotinamide co-crystal in a 1:1 molar ratio has higher solubility than theophylline itself.

Conclusion

The development of new molecular complexes in the form of a solid co-crystal and their applications as drug materials by crystal engineering approach is becoming progressively more important than the other solid forms such as salts, solvates, hydrates etc due to their large extent of purity and several valuable physico-chemical properties. Other advantages lies in the form of co-crystals are co-crystals are normally non-toxic as the active sites of the interacting molecules are involved in hydrogen bonding and other weak interactions. Co-crystals can be easily handled for various applications and even the co-crystal components can be easily isolated by applying simple techniques.

The design and synthesis of co-crystals in the form of API's depend on the basic knowledge of Supramolecular Chemistry and the identification of directionality of growth *via* proper Supramolecular synthons formation with the help of various kinds of interactions which can be determined by Crystal engineering. The knowledge of crystal engineering approach plays an important role for raising interest to produce biologically non-hazardous and non-toxic co-crystal materials in the form of API's.

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