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PHARMACEUTICAL APPROACH TO SUPRAMOLECULAR CHEMISTRY – A COMPREHENSIVE REVIEW

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ABSTRACT

Supramolecular chemistry refers to the area of chemistry beyond the molecules and focuses on the chemical systems made up of a discrete number of assembled molecular sub-units or components. A Super molecule is an organized, complex entity that is created from the association of two or more chemical species held together by intermolecular forces. There is a wide scope for supramolecular chemistry in improving the characteristics of chemical entities. The technique is pharmaceutically used to increase the bioavailability, solubility and stability of the active pharmaceutical ingredients by formation of complexes, inclusion complexes and co crystals. This article highlights the role of supramolecular chemistry in design and synthesis of novel pharmaceutical multiple component crystalline phases.

Keywords: Supramolecular chemistry, Complexes, Chemical entities.

INTRODUCTION

Supramolecular chemistry is an emerging and interdisciplinary branch of chemistry and science. Supramolecular chemistry is defined as "chemistry beyond the molecule" i.e. the chemistry [1] of molecular aggregates assembled via non covalent interactions. Physico-chemical properties of the active pharmaceutical ingredients depend on orderly internal spatial arrangement of the molecules present in it. Components can be broadly classified into amorphous and crystalline forms. Crystalline for solids implies an ideal crystal in which the structural units, termed unit cells, are repeated indefinitely and regularly in three dimensions in space. The unit cell, containing at least one molecule, has a definite orientation and shape defined by the translational vectors, a, b, and c. The unit cell therefore has a definite volume that contains the atoms and molecules necessary for generating the crystal. Amorphous solids lack the long-range order present in crystals. Crystalline forms for APIs are strongly preferred because they tend to be more stable, reproducible and amenable to purification than other types of solids.

Molecular Crystals

Molecular crystals can be classified into single-component and multi component crystals. Multi component crystals further constitutes salts, solvates, hydrates and co-crystals [2]. Most drugs are developed in their crystalline form as they are more thermodynamically stable and have advantages in their mechanical properties such as milling, tablet compressing etc. However, the stable crystal form of the parent compound may exhibit inadequate solubility or dissolution rate resulting in poor oral absorption, particularly for water insoluble compounds. When this is the case, alternative solid forms with adequate solubility and dissolution rate need to be investigated [3]. Crystalline materials obtain their fundamental physical properties from the molecular arrangement within the solid, and altering the placement and/or interactions between these molecules can have a direct impact on the properties of the particular solid. Currently, solid-state chemists call upon a variety of different strategies when attempting to alter the chemical and physical solid-state properties of APIs, namely, the formation of salts, polymorphs, hydrates, solvates and recently co-crystals [4]. The formation of molecular complexes (co-crystals) and co- crystals is becoming increasingly important as an alternative to salt formation, particularly for neutral compounds or those having weakly ionizable groups.

The forces responsible for the spatial organization for crystal formation may vary from weak (intermolecular forces, electrostatic or hydrogen bonding) to strong (covalent bonding), provided that the degree of electronic coupling between the molecular component remains small

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with respect to relevant energy parameters of the component while traditional chemistry focuses on the covalent bond supramolecular chemistry examines the weaker and reversible non-covalent interactions between molecules. These forces include hydrogen bonding, metal coordination, hydrophobic forces, interactions and electrostatic effects. Important concepts that have been demonstrated by supramolecular chemistry include molecular self assembly, folding, molecular recognition, host-guest chemistry, molecular architectures and dynamic covalent chemistry.

The study of non covalent interactions is crucial to understanding many biological processes from cell structure to vision that rely on these forces for structure and function. Biological systems are often the inspiration for supra molecular research.

Supermolecules

A Supermolecule is an organized, complex entity that is created from the association of two or more chemical species held together by intermolecular forces.

An electropositive hydrogen bond donor moves towards an electronegative acceptor, cation-anion electrostatic interaction in metal complexes and salts, and strikes in one part of the molecule fit into hollows of another portion (hydrophobic interactions). While the fundamental recognition processes that guide aggregation of supramolecular are administrated by the same principles and forces.The chemical systems studied were generally classified into two major classes, in general molecular recognition in solution is referred to as supramolecular chemistry, and periodic arrangement of supermolecules in the solid state as crystal engineering

Supramolecular structures are the result of not only additive but also cooperative interactions. The properties are different (often better) than the sum of the properties of each individual component

Mechanisms involved in Supramolecular Chemistry

I) Self- assembly

II) Host- guest chemistry

Selectivity

The binding of one guest, or family of guests, significantly more strongly than others, by a host molecule. Selectivity is measured in terms of the ratio between equilibrium constants.

i. Lock-and-key principle

The substrate (guest) has a complementary size and shape to the enzyme (host) binding site.

ii. Induced-fit model

An induced fit has occurred and as a consequence the protein backbone or the substrate binding site itself changes shape such that the enzyme and the substrate fit more precisely i.e. are more mutually complementary.

Complementarity

Both the host and guest must have mutual spatially and electronically complementary binding sites to form a supermolecule. The binding site of the host must not only be complementary to the guest in terms of size and shape (cf. the lock and key and induced-fit models) but the binding sites on both partners must also be chemically complementary [2].

e.g. Hard/soft acid-base interactions

Supramolecular Synthons

A supramolecular synthon (as shown in fig.no.9) is a consistent and well-defined linear association between molecular building blocks. Synthons are formed by the gathering of two molecules through molecular functionalities that interact with each other in a predictable fashion by non-covalent interactions. Self-complementary functional groups, such as alcohols, amides, and carboxylic acids contain both a hydrogen bond donor and acceptor and are therefore capable of forming supramolecular homosynthons. Functionalities of other functional groups, which contain only hydrogen bond donors or acceptors, do not have this ability. Though, all functionalities are capable of forming supramolecular heterosynthons with other complementary functional groups.

Functionalities that are capable of forming supramolecular synthons [5] include, but are not restricted to; alcohol, acids (carboxylic, sulfonic, phosphonic, and boronic), amino-pyridine, ketone, aldehyde, ether, ester, primary and secondary amine, aromatic nitrogen, primary and secondary amide, sulfoxide, sulfonamide, cyano, imine, nitro, sulfonyl, water, and ions such as Cl^- and Br^-. Also, competition between intramolecular interactions can happen within a structure that contains a multiple number of Functionalities capable of forming hydrogen bond.

Supramolecular chemistry – a pharmaceutical approach

Complexation

Complexation [6] is the association between two or more molecules to form a nonbonded entity with a well-defined stoichiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions. Staching complexes are formed by the overlap of the planar regions of aromatic molecules. Nonpolar moieties tend to be squeezed out of water by the strong hydrogen bonding interactions of water. This causes some molecules to minimize the contact with water by aggregation of their hydrocarbon moieties. This aggregation is favored by large planar nonpolar regions in the molecule. Stacked complexes can be homogeneous or mixed. The former is known as self-association and later as complexation.

Inclusion complexation

Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another

molecule or group of molecules (known as host). The major structural requirement for inclusion complexation is a snug fit of the guest into the cavity of host molecule. The cavity of host must be large enough to accommodate the guest and small enough to eliminate water, so that the total contact between the water and the nonpolar regions of the host and the guest is reduced.

The most commonly used host molecules are cyclodextrins. The enzymatic degradation of starch by cyclodextrin-glycosyltransferase (CGT) produces cyclic oligomers, Cyclodextrins. Cyclodextrins are non-reducing, crystalline, water soluble, cyclic, oligosaccharides. Cyclodextrins consist of glucose monomers arranged in a donut shape ring. Three naturally occurring CDs are α-Cyclodextrin, β-Cyclodextrin, and γ- Cyclodextrin. The complexation with cyclodextrins is used for enhancement of solubility. Cyclodextrin inclusion is a molecular phenomenon in which usually only one guest molecule interacts with the cavity of a cyclodextrin molecule to become entrapped and form a stable association. The internal surface of cavity is hydrophobic and external is hydrophilic, this is due to the arrangement of hydroxyl group within the molecule.

Molecules or functional groups of molecules those are less hydrophilic than water, can be included in the cyclodextrin cavity in the presence of water. In order to become complex, the "guest molecules" should fit into the cyclodextrin cavity. The cavity sizes as well as possible chemical modifications determine the affinity of cyclodextrins to the various molecules.

Co-crystals

Co-crystals are defined as multiple component structures whose components interact by non-covalent interactions such as hydrogen bonding or other weak intermolecular interactions rather than by ion pairing. An important approach to understanding and designing co-crystals is to employ supramolecular synthesis, in particular exploitation of supramolecular heterosynthons [7]. In the framework of co-crystals, supramolecular synthesis is a relatively low-risk strategy, as the approach employs theories of molecular recognition and self-assembly rather than creating covalent bonds.

Functionalities present in a given molecule is the first step in designing a co- crystal since it facilitates choice of molecules that contain the appropriate complementary Functionalities. Herein, these complementary molecules will be referred to as co-crystal formers [8].

Whereas co-crystals can be easily achieved under the proper conditions, this does not mean that their synthesis and isolation is nonetheless practice. Solvent selection can be vital in obtaining a particular co-crystal; though the role of solvent in the nucleation of crystals and co-crystals remains inadequately understood [9]. As well, undesired products such as polymorphs, solvates, hydrates, or pure substances can often result from co-crystallization experiments.

Pharmaceutical Co-crystals

An alternative approach available for the enhancement of drug solubility, dissolution and bioavailability, is through the application of crystal engineering to co-crystals, historically referred to as molecular complexes. The physicochemical properties and the bulk material properties of the API can be modified, at the same time as maintaining the intrinsic activity of the drug molecule. Pharmaceutical co-crystallization is emerging as an attractive alternative to polymorphs, salts and solvates in the modification of an active pharmaceutical ingredient (API) during dosage form design. The intellectual property implications of creating co-crystals are also highly relevant.

This approach ofco-crystal involves the expansion ofa supramolecular library of co-crystallizing agents. A hierarchy of guest functional groups is classified within the library according to a specific role to a crystal packing arrangement, which is dependent on the host molecule functionalities. These are obtained from investigation of structure property relationships present in the CSD which contains classes of known crystal structures [9,10]. Generally in the pharmaceutical industry, Chemists and engineers try to deliver crystalline forms of their active compounds, principally due to the inherent stability of crystalline materials and the well-established impact of crystallization processes on isolation and purification of chemical substances[11]. Increasing interest is now receiving on the impact of properties of material on drug discovery and development [10-14].

The task of pharmaceutical industry is to quick advance development programs through good confidence with the intention that formulation problems are unlikely to occur and to maximize a compounds potential as a therapeutic. The solid form which is preferred usually is the thermodynamically most stable crystalline form of the compound [15]. On the other hand, the stable crystal form of the parent compound may show insufficient solubility and/or dissolution rate which resulting in poor oral absorption, mainly for poorly aqueous soluble compounds. In this case, alternative solid forms may be explored.

A major tool which is accountable for the majority of directed intermolecular interactions in molecular complex pharmaceuticals is the hydrogen bond. Co-crystal are multi-component crystals depend on hydrogen bonding interactions lacking the transfer of hydrogen ions to form salts. Pharmaceutical co-crystals can be defined as multi-component crystalline materials comprised of an API and one or more unique co-crystal formers, which are solids under ambient conditions.

For nonionizable compounds, co-crystals enhance pharmaceutical properties by modification of solubility, dissolution rate, chemical stability, mechanical behavior,

moisture uptake and bioavailability [16-19]. Recently, Pharmaceutical co-crystallization has only gained widespread attention as a tool of changing the physicochemical properties of drugs, for the reason that co-crystal formation may probably be employed with all drugs, including acidic, basic and non ionizable molecules and a large number of probable 'counter molecules' which possibly considered to be nontoxic possibly rising the scope of the pharmaceutical co crystallization over the salt forms. To salt selection, a correlation can be drawn in which pKa point of view is used to select acid-base pairs that can be converted to salt compounds.

The key remunerations associated with approach of co-crystallization to alter the properties of pharmaceutical solids are the theoretical ability of all types of drug molecules to form co-crystals including weakly ionizable and non-ionizable, and the existence of numerous, potential counter- molecules, including preservatives, food additives, pharmaceutical excipients as well as other drugs, for co-crystal synthesis. Major advantage for the pharmaceutical industry is co-crystal synthesis which may offer is an opportunity to address intellectual property (IP) issues by extending the life cycles of old APIs2 [20-22].

Pharmaceutical Co-Crystals as Intellectual Property

Compared to other types of solid forms, co-crystals possessed particular scientific and regulatory advantages, and alongside these advantages were intellectual property issues which give co-crystals with exclusive opportunities and challenges. Researchers accounted the importance about patents on pharmaceutical co-crystals to the pharmaceutical industry [23]. The worth of co-crystals to the pharmaceutical industry should become clearer, mostly with respect to several relevant legal and regulatory issues, as products containing co-crystal technology come out from pharmaceutical development pipelines onto the market.

Fig 1. Transformation of small to super molecule

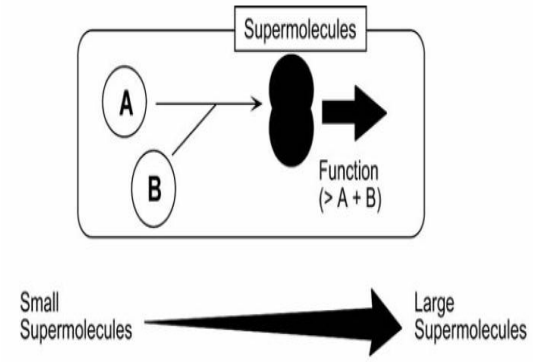


Fig 2. Host guest complexation

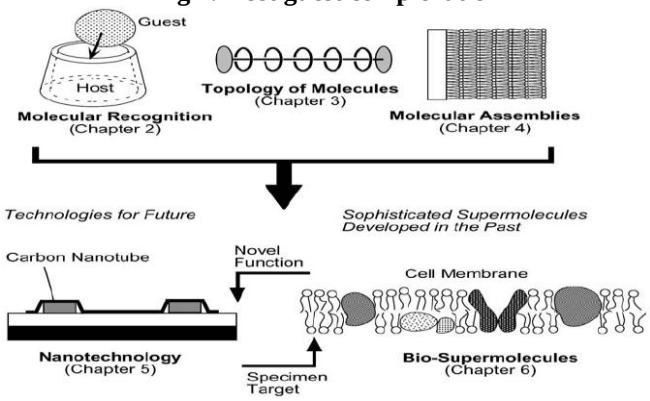


Fig 3. Supra molecular self-assembled aggregates

i. Self- assembly

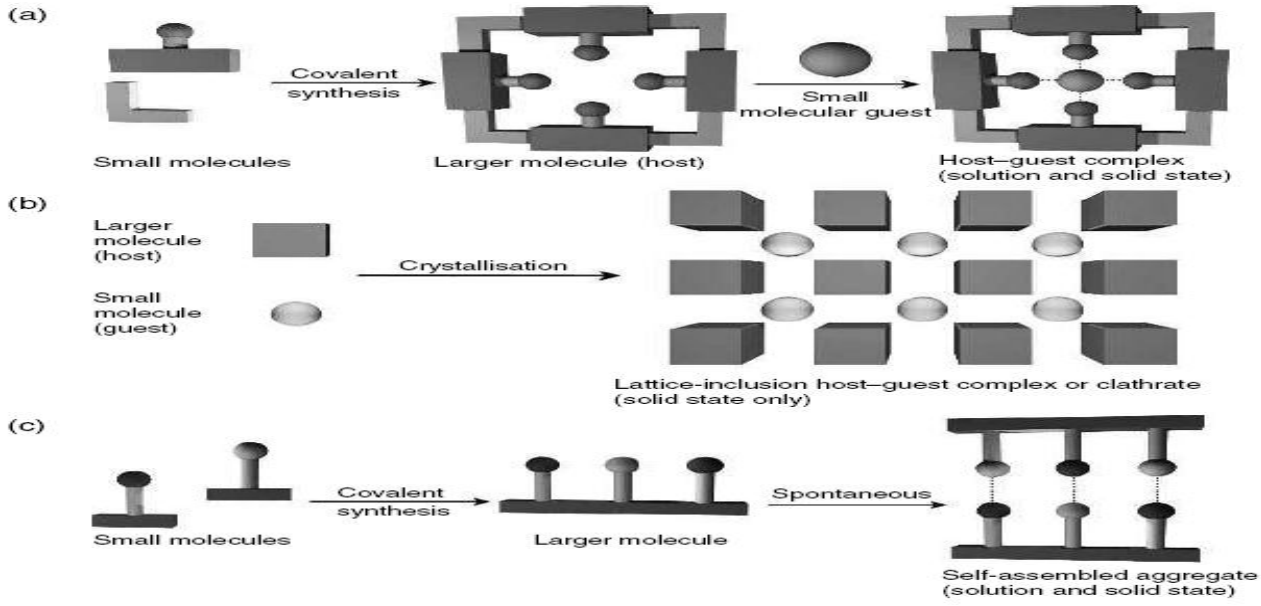


Fig 4. Host guest systems

ii. Host-Guest Systems

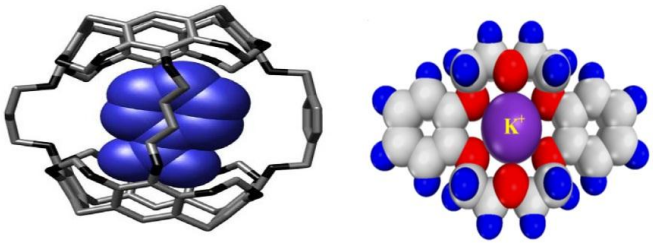


Fig 5. lock and key principle

Fig 6. Induced fit model

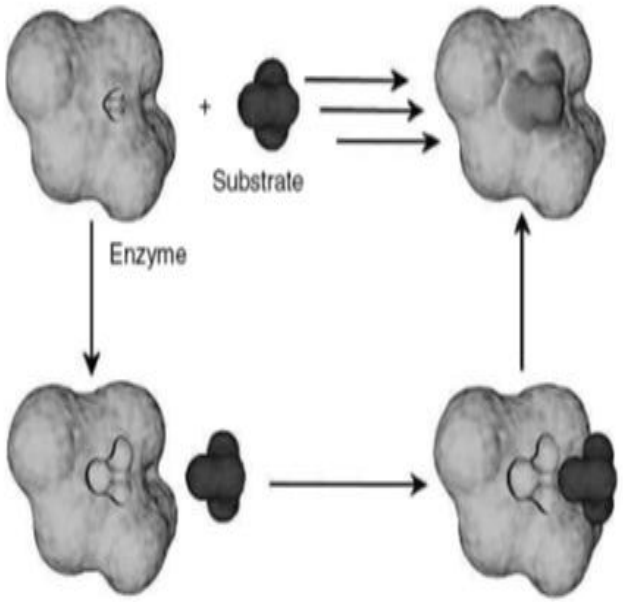
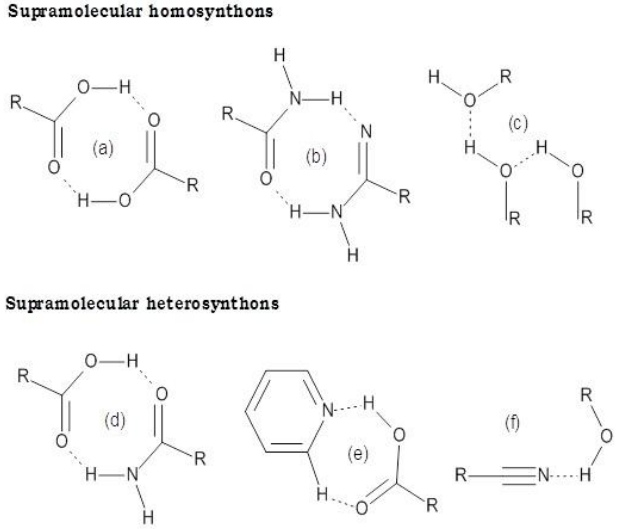


Fig 7. Examples for supramolecular homosynthons (a) Carboxylic acid dimer (b) primary amide dimer (c) alcohol homosynthon chain; supramolecular heterosynthons (d) Carboxylic acid---primary amide (e) Carboxylic acid---pyridine (f) Cyno---Alcohol.



CONCLUSION

Supramolecular chemistry, the area of chemistry beyond the molecules focuses on the chemical systems made up of a discrete number of assembled molecular sub-units or components. Pharmaceutical applicability of supramolecular chemistry remains untapped. Supra molecular chemistry plays a key role in altering the physicochemical properties that can strongly influence the bioavailability, manufacturability, purification, stability and other performance characteristics of the API by adopting methods like complexation and cocrystal formation. Hence it is inevitable to apply supramolecular chemistry pharmaceutically in design and development of novel multicomponent cocrystals.

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