

## Review Article

# A REVIEW ON SUPRAMOLECULAR CHEMISTRY IN DRUG DESIGN AND FORMULATION RESEARCH

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## ABSTRACT

Supramolecular chemistry, other way called as intermolecular chemistry disclose the relationship of molecules with environment. It exploits while exposing the physicochemical phenomena that happens when two like or unlike molecules/ions/systems contact each other. Drug action involve the target recognition process and response triggered by the intermolecular complex of drug and target. Drug design therefore require in depth study of intermolecular forces that exist between drug and target. Formulation of the drug or Active Pharmaceutical Ingredient (API) is also regulated by these forces. Compatibility and incompatibility in formulations are nothing but of the effect of the intermolecular forces on physical behavior of systems. Therefore review of intermolecular chemistry in general and its role particularly in pharmaceutical research is presented here for the benefit of the students and research scholars who aspire to work on interdisciplinary projects in the field of pharmacy.

**Key words:** intermolecular forces, hydrogen bond, drug design, active pharmaceutical ingredient (API), crystal.

## SUPRAMOLECULAR CHEMISTRY

Molecules are social. They mutually interact and speak to one other in the language of electrostatics. The force that was generated by the differences in electrostatic potentials brings the molecules close to associate. The association can be among the like molecules or different molecules. While functional groups acting as charged points, the complementarily mediates the association process. The forces of association are described as non covalent and the resulted associations are categorized as complexes/aggregates/systems/assemblies. Overall the discipline is termed as supramolecular chemistry.

Supramolecular Chemistry has the philosophical roots developed from the postulates of Johannes Diderik van der Waals and Nobel laureate Hermann Emil Fischer. However, the importance of supramolecular chemistry was established by Donald J. Cram, Jean-Marie Lehn, and Charles J. Pedersen to whom in 1987 the Nobel Prize for Chemistry was awarded in recognition

of their work in this area (Nobel Prize, 1987). The development of selective "host-guest" complexes in particular, in which a host molecule recognizes and selectively binds a certain guest, was cited as an important contribution. Lehn defined supramolecular chemistry as 'chemistry beyond the molecule', i.e. the chemistry of molecular aggregates assembled via non-covalent interactions (Lehn, 1978). IUPAC defines it as a field of chemistry related to species of greater complexity than molecules that are held together and organized by means of intermolecular interactions. The objects of supramolecular chemistry are supermolecules and other polymolecular entities that result from the spontaneous association of a large number of components into a specific phase (membranes, vesicles, micelles, solid state structures *etc.*) (McNaught *et al.*, 1997). With the understanding of intermolecular interactions in more detail the subject has now become interdisciplinary with wide range of applications in basic and applied sciences.

Supramolecular chemistry designed the nature in three basic forms namely solid, liquid and gas. These forms are due to intermolecular forces and whose strength varies from strong, medium to very weak in the said forms respectively. The force that holds the molecules to give them a form is affected by the force of surrounding environment. The environment force could be in any form that supplies energy to break or weaken the intermolecular bonds. The assemble disassociates as the environmental force become stronger. A well known example to explain this is existence of three forms of water. The stronger intermolecular force among water molecules (hydrogen bond) in ice form is weakened to liquify due to increase kinetic energy by heat supply. Further they broke down and the water vaporizes. Another well known example for supramolecular assemble in life maintenance is DNA double helix. The double helical structure of DNA is stabilized primarily by two forces: hydrogen bonds between nucleotides and base-stacking interactions among the aromatic nucleobases (Yakovchuk *et al.*, 2006). In the aqueous environment of the cell, the conjugated  $\pi$  bonds of nucleotide bases align perpendicular to the axis of the DNA molecule, minimizing their interaction with the solvation shell and therefore, the Gibbs free energy.

Way back from about 45 years supramolecular concept has been established in various theoretical and application discoveries that include protein folding (Rossmann *et al.*, 2006), enzyme/receptor/carrier/membrane functions (Sisson *et al.*, 2006; Ludden *et al.*, 2006; Rudkevich, 2004; Chen B *et al.*, 2002; Hof F *et al.*, 2002; Ikkala *et al.*, 2002; Lehn, 1985), cell signaling (Leyton *et al.*, 2002), biodevices (Saha *et al.*, 2007; Liu *et al.*, 2002), biosensors (Pinalli *et al.*, 1999; Beer *et al.*, 1997), opticalchemo sensors (Bell *et al.*, 2002), biomaterials (Salditt *et al.*, 2002), host-guest/inclusion complexes (Zhang *et al.*, 2011; Seidel *et al.*, 2002), dendrimers (Diederich *et al.*, 2002) cyclodextrins (Jing *et al.*, 2007), fullerenes (Nierengarten *et al.*, 2001; Nakamura *et al.*,

2003) porphyrins (Shi *et al.*, 2001), photoactive complexes (Yagai *et al.*, 2005), polymers (De Greef *et al.*, 2009; Serpe *et al.*, 2007), electrooptic materials (Okamoto *et al.*, 2009), catenanes (Frišćić, 2012), rotaxanes (Dalrymple *et al.*, 2002), molecular capsules (Atwood *et al.*, 2002; Gracia-Garibay, 2005), molecular machines (Balzani *et al.*, 2002), crystals, polymorphs (Moulton *et al.*, 2001; Desiraju, 1995), cocrystals (Trask *et al.*, 2005), liquid crystals (Kato *et al.*, 2005), chirality (Arnal-Hérault *et al.*, 2007; Barberá *et al.*, 2005), Sustained gas delivery therapeutic molecular devices (Alberto *et al.*, 2007), metallosupramolecular assemblies (Steed, 2009; Steel, 2005) catalysis (Sakai *et al.*, 2004), and nanostructures (Fenske *et al.*, 2012; Atmaja *et al.*, 2009; Hirst *et al.*, 2008) etc. In synthetic chemistry the transition state of a reaction is supramolecular complex. It is therefore hard to imagine life existence without intermolecular chemistry. A more detailed view of intermolecular forces is given below.

Intermolecular forces have four major contributions: a repulsive component resulting from the Pauli exclusion principle that prevents the collapse of molecules;

Attractive or repulsive electrostatic interactions between permanent charges (in the case of molecular ions), dipoles (in the case of molecules without inversion center), quadrupoles (all molecules with symmetry lower than cubic), and in general between permanent multipoles. The electrostatic interaction is sometimes called the Keesom interaction or Keesom force after Willem Hendrik Keesom;

Induction (also known as polarization), which is the attractive interaction between a permanent multipole on one molecule with an induced multipole on another. This interaction is sometimes called Debye force after Peter J.W. Debye;

Dispersion (usually named after Fritz London), which is the attractive interaction between any pair of molecules, including non-polar atoms, arising from the interactions of instantaneous multipoles.

### Van Der Waals interactions

Johannes Diderik van der Waals, a Dutch theoretical physicist and thermodynamicist whose name is primarily associated with van der Waals forces (forces between stable molecules) was the first to describe intermolecular force. Van der Waals forces are the attractive or repulsive forces between molecular entities (or between groups within the same molecular entity) other than those due to bond formation or to the electrostatic interaction of ions or of ionic groups with one another or with neutral molecules.

The term includes: force between two permanent dipoles (Keesom force); force between a permanent dipole and a corresponding induced dipole (Debye force); force between two instantaneously induced dipoles (London dispersion force).

The term is sometimes used loosely for the totality of nonspecific attractive or repulsive intermolecular forces

### Dipole-dipole interactions

Dipole-dipole forces are attractive forces between the positive end of one polar molecule and the negative end of another polar molecule. Dipole-dipole interactions result when two polar molecules approach each other in space. The nature of dipole bonding begins when atoms differ in their electro negativity, which quantifies an individual atom's ability to attract electrons to it. When a covalent bond forms between two atoms, the electrons will be distributed between the two atoms unequally; the more electronegative atoms will have the larger electron density. This unequal sharing of electrons creates a charge separation, and the molecule under inspection will develop partial charges where the electronegative atom will develop a partial negative charge and its adjacent atom will develop a partial positive charge. The molecule is then said to be polarized due to this charge separation. When molecules exhibit this charge separation, there is a pseudo-electrostatic force between the partial charges of molecules. When this occurs, the partially negative portion of one of the polar molecules is attracted to the partially positive portion of the second polar molecule.

The key to dipole bonding is charge separation within a molecule. Dipole-dipole forces have strengths that range from 5 kJ to 20 kJ per mole. They are much weaker than ionic or covalent bonds and have a significant effect only when the molecules involved are close together.

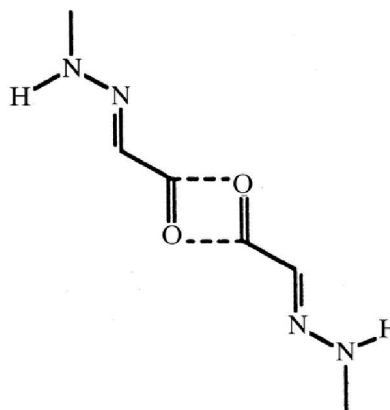


Figure 1. Dipole-dipole attractions in solid state structure of anti- $\beta$ -ketoarylhydrazone molecules (Bertolasi *et al.*, 1999).

In the molecule (Figure 1) the more electronegative oxygen atom bears the partial negative charge; the less electronegative carbon atom bears the partial positive charge. The partially positive carbon end of one molecule is attracted to the partially negative oxygen end of another molecule. A dashed line is used to represent an intermolecular attraction between molecules. Dipole-dipole forces are characteristically weaker than ion-dipole forces. Dipole-dipole forces increase with an increase in the polarity of the molecule.

### Ion-Dipole Interactions:

An ion-dipole force is an attractive force that results from the electrostatic attraction between an ion and a neutral molecule that has a dipole. These interactions are most commonly found in solutions. These are especially important for solutions of ionic compounds in polar liquids. A positive ion (cation) attracts the partially negative end of a neutral polar molecule. A negative ion (anion) attracts the partially positive end of a neutral polar molecule.

Ion-dipole attractions become stronger as either the charge on the ion increases, or as the magnitude of the dipole of the polar molecule increases.

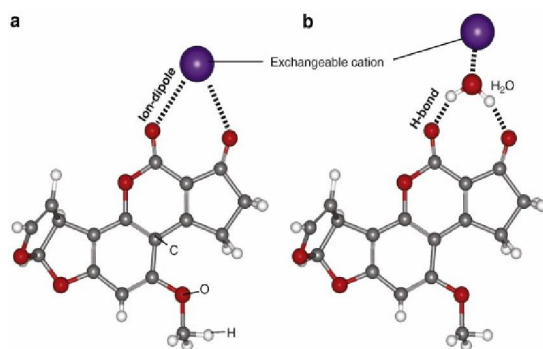


Figure 2. Ion-dipole interaction in the binding mechanism of aflatoxin molecule with exchangeable cation (Deng *et al.*, 2010).

### Dipole-induced dipole interactions

A dipole-induced dipole attraction is a weak attraction that results when a polar molecule induces a dipole in an atom or in a non-polar molecule by disturbing the arrangement of electrons in the non-polar species. In the dipole-induced dipole interactions, the presence of partial charges of the polar molecule causes a polarization, or distortion, of the electron distribution of the other molecule. As a result of this distortion, the second molecule acquires regions of partial positive and negative charge and thus it becomes polar. The partial charges thus formed behave just like those of permanently polar molecule and interact favourably with their counter parts in the polar molecule that originally induced them. Hence, the two molecules cohere. Dipole-induced dipole interactions were explained for molecular recognition in base pairing of novel nucleosides (Ferguson *et al.*, 2004).

### Dispersion forces or London forces

This type of interaction acts between all types of molecule, polar or non-polar. When two non-polar molecules are near each other, the electron density will be fluctuating, even though there are no permanent partial charges on either molecule. As a result of these

fluctuations, regions of equal and opposite partial charge arise in one of the molecule and gives rise to a transient dipole. This transient dipole can induce a dipole in the neighboring molecule, which then interacts with the original transient dipole. Although the latter continuously flickers from one direction to another, the induced dipole follows it and the two correlated dipoles interact favourably with one another and cohere. This force of attraction was first proposed by the German physicist Fritz London, and for this reason force of attraction between two temporary dipoles is known as London force. Another name for this force is dispersion force. These forces are always attractive and interaction energy is inversely proportional to the sixth power of the distance between two interacting particles (i.e.,  $1/r^6$  where  $r$  is the distance between two particles). These forces are important only at short distances ( $\sim 500$  pm) and their magnitude depends on the polarisability of the particle. London dispersive forces were well demonstrated in base crystalline magnesium nitrate hexahydrate (Ewelina *et al.*, 2012).

### Hydrogen bonding

Hydrogen bond is the most important of all directional intermolecular interactions. It is crucial in determining conformation of molecule, molecular aggregation, and the function of a large number of chemical systems ranging from inorganic to biological. The dissociation energy is around 3 to 5 kcal/mol (Steiner, 2002). A large part of the terminology concerning hydrogen bonds was not uniformly used in the literature, therefore hydrogen bond was redefined in 2011. The criteria for defining the hydrogen bond as discussed below has been taken from the IUPAC recommendations on hydrogen bond (Arunkashi *et al.*, 2010). The hydrogen bond is an attractive interaction between a hydrogen atom from one molecular fragment X-H in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule, in which there is evidence of bond formation.

A typical hydrogen bond may be depicted as  $X-H\cdots Y-Z$ , where the three dots denote the bond.  $X-H$  represents the hydrogen bond donor. The acceptor may be an atom or an anion  $Y$ , or a fragment or a molecule  $Y-Z$ , where  $Y$  is bonded to  $Z$ . In some cases,  $X$  and  $Y$  are the same. In more specific cases,  $X$  and  $Y$  are the same and  $X-H$  and  $Y-H$  distances are the same as well leading to symmetric hydrogen bonds. In any event, the acceptor is an electron rich region such as, but not limited to, a lone pair of  $Y$  or  $\pi$ -bonded pair of  $Y-Z$ .

The evidence for hydrogen for bond formation may be experimental or theoretical, or ideally, a combination of both. Some criteria useful as evidence is listed below. The greater the number of criteria satisfied, the more reliable is the characterization as a hydrogen bond. List of criteria (Elangannan *et al.*, 2011): For a hydrogen bond  $X-H\cdots Y-Z$ :

The forces involved in the formation of a hydrogen bond include those of an electrstatic origin, those arising from charge transfer between the donor and acceptor leading to partial covalent bond formation between  $H$  and  $Y$ , and those originating from dispersion.;

The atoms  $X$  and  $H$  are covalently bonded to one another and the  $X-H$  bond is polarized, the  $H\cdots Y$  bond strength increasing with the increase in electronegativity of  $X$ .

The  $X-H\cdots Y$  angle is usually linear ( $180^\circ$ ) and the closer the angle is to  $180^\circ$ , the stronger is the hydrogen bond and the shorter is the  $H\cdots Y$  distance;

The length of the  $X-H$  bond usually increases on hydrogen bond formation leading to a red shift in the infrared  $X-H$  stretching frequency and an increase in the infrared absorption cross-section for the  $X-H$  stretching vibration. The greater the lengthening of the  $X-H$  bond in  $X-H\cdots Y$ , the stronger is the  $H\cdots Y$  bond are generated;

The  $X-H\cdots Y-Z$  hydrogen bond leads to characteristic NMR signatures that typically include pronounced proton deshielding for  $H$  in  $X-H$ , through hydrogen bond spin-spin couplings between  $X$  and  $Y$ , and nuclear Overhauser enhancements;

The Gibbs energy of formation for the hydrogen bond should be greater than the thermal energy of the system for the hydrogen bond to be detected experimentally.

### Types of hydrogen bonds

Hydrogen bonds can occur within one single molecule, between two like molecules, or between two unlike molecules.

#### Intramolecular hydrogen bonds

Intramolecular hydrogen bonds are those which occur *within* one single molecule. This occurs when two functional groups of a molecule can form hydrogen bonds with each other. In order for this to happen, both a hydrogen donor an acceptor must be present within one molecule, and they must be within close proximity of each other in the molecule. For example, The intramolecular hydrogen bond is found to play a significant role in controlling the configuration of cyclic compounds (Arunkashi *et al.*, 2010).

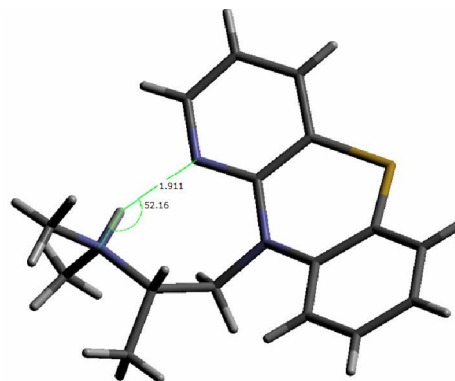


Figure 3. Intramolecular hydrogen bond observed in crystal structure of thiopendyl complex (Arunkashi *et al.*, 2010).

#### Intermolecular hydrogen bonds

Intermolecular hydrogen bonds occur between separate molecules in a substance. They can occur between any number of like or unlike molecules as long as hydrogen donors and acceptors are present an in positions in which they can interact. For example, the crystal packing of hydrated organic substances is majorly due to intermolecular hydrogen bonding (Metrangolo *et al.*, 2008).

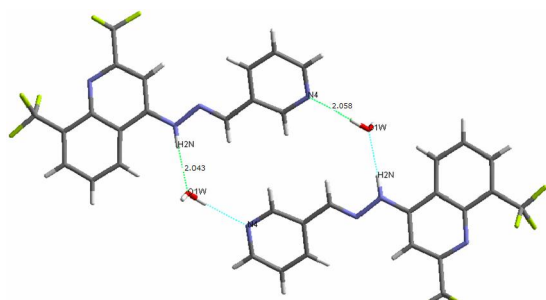


Figure 4. Intermolecular hydrogen bond observed with cocrystalized water in crystal packing of quinoline hydrazone derivative (Devarajegowda *et al.*, 2010).

### Halogen bonding

Halogen bonding is the non-covalent interaction between a halogen atom in one molecule, such as one of the bromine atoms in  $\text{Br}_2$ , and an electronegative atom in another molecule, such as the nitrogen in  $\text{NH}_3$ . The halogen bond is represented by general scheme  $\text{D} \cdots \text{X} \cdots \text{Y}$  wherein X is the halogen (Lewis acid, halogen bond-donor), D is any electron-donor (Lewis base, hydrogen bond-acceptor), and Y is carbon, halogen, nitrogen, etc.) (Metrangolo *et al.*, 2008; Metrangolo *et al.*, 2008).

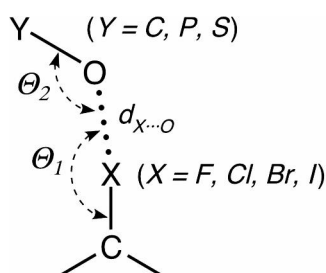


Figure 5. Schematic of short halogen (X) interactions to various oxygen-containing functional groups (where  $\text{O} \cdots \text{Y}$  can be a carbonyl, hydroxyl, or carboxylate when Y is a carbon; a phosphate when Y is a phosphorus; or a sulfate when Y is a sulfur) (Auffinger *et al.*, 2004).

Halogens participating in halogen bonding include: iodine (I), bromine (Br), chlorine (Cl), and sometimes fluorine (F). All four halogens are capable of acting as XB donors and follow the general trend:  $\text{F} < \text{Cl} < \text{Br} < \text{I}$ , with iodine normally forming the

strongest interactions (Politzer *et al.*, 2007). Dihalogens ( $\text{I}_2$ ,  $\text{Br}_2$ , etc.) tend to form strong halogen bonds. The strength and effectiveness of chlorine and fluorine in hydrogen bond formation depend on the nature of the hydrogen bond donor. If the halogen is bonded to an electronegative (electron withdrawing) moiety, it is more likely to form stronger halogen bonds (Metrangolo *et al.*, 2008). Halogen bonds are strong, specific, and directional interactions that give rise to well-defined structures. Halogen bond strengths range from 5–180 kJ/mol. The strength of halogen bond allows it to compete with hydrogen bonds, which are a little bit weaker in strength. Another contributing factor to halogen bond strength comes from the short distance between the halogen (Lewis acid, halogen bond donor) and Lewis base (halogen bond acceptor). The attractive nature of halogen bonds result in the distance between the donor and acceptor to be shorter than the sum of vander Waals radii. The halogen bond interaction becomes stronger as the distance decreases between the halogen and Lewis base.

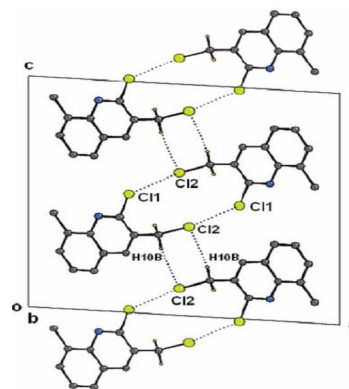


Figure 6. Crystal packing of 2-chloroquinoline derivatives an example for halogen bond (Venkatesha *et al.*, 2010).

### $\pi$ -Interactions

$\pi$  systems involving non covalent interactions are called as  $\pi$ -effects or  $\pi$ -interactions. Just like in an electrostatic interaction, the electron-rich  $\pi$  system can interact with a metal (cationic or neutral), an anion, another molecule and even another  $\pi$  system (Anslyn *et al.*, 2005).



The most common types of  $\pi$ -interactions involve: Aromatic-aromatic interactions ( $\pi$  stacking): involves interactions of aromatic molecules with each other; Cation- $\pi$  interactions: involves interaction of a metal and the face of a  $\pi$  system, the metal can be a cation (known as cation- $\pi$  interactions) or neutral; anion- $\pi$  interactions: interaction of anion with  $\pi$  system

#### Aromatic-aromatic interactions ( $\pi$ Stacking)

The conventional understanding of  $\pi$  stacking involves quadrupole interactions between delocalized electrons in p-orbitals (Hunter *et al.*, 1990). In other words, aromaticity should be required for this interaction to occur. The key feature of these interactions is that an aromatic ring is not non-polar: it has a quadrupole moment which gives rise to a fixed non uniform charge distribution on its surface. Crystal structure of a fullerene bound in a buck catcher is a beautiful example for aromatic stacking interactions (Sygula *et al.*, 2007).

#### Cation- $\pi$ interactions

The most studied cation- $\pi$  interactions involve binding between an aromatic  $\pi$  system and an alkali metal or nitrogenous cation. Cation- $\pi$  interaction is a noncovalent molecular interaction between the face of an electron-rich  $\pi$  system (e.g. benzene, ethylene, acetylene) and an adjacent cation (e.g.  $\text{Li}^+$ ,  $\text{Na}^+$ ). This interaction is an example of noncovalent bonding between a monopole (cation) and a quadrupole ( $\pi$  system).

Cation- $\pi$  interactions have an approximate distance dependence of  $1/r^n$  where  $n < 2$ . The interaction is less sensitive to distance than a simple ion-quadrupole interaction which has  $1/r^3$  dependence (Dougherty *et al.*, 1996).

Nature's building blocks contain aromatic moieties in high abundance. Recently, it has become clear that many structural features that were once thought to be purely hydrophobic in nature are in fact engaging in cation- $\pi$  interactions. The amino acid side chains of phenylalanine, tryptophan, tyrosine, histidine, are capable of binding to

cationic species such as charged amino acid side chains, metal ions, small-molecule neurotransmitters and pharmaceutical agents.

An example of cation- $\pi$  interactions in molecular recognition is seen in the nicotinic acetylcholine receptor (nAChR) which binds its endogenous ligand, acetylcholine (a positively charged molecule), via a cation- $\pi$  interaction to the quaternary ammonium (Beene *et al.*, 2002).

Cation- $\pi$  interactions have been observed in the crystals of synthetic molecules as well. For example, Aoki and coworkers compared the solid state structures of Indole-3-acetic acid choline ester and an uncharged analogue. In the charged species, an intramolecular cation- $\pi$  interaction with the indole is observed, as well as an interaction with the indole moiety of the neighboring molecule in the lattice. In the crystal of the isosteric neutral compound the same folding is not observed and there are no interactions between the *tert*-butyl group and neighboring indoles (Aoki *et al.*, 1995).

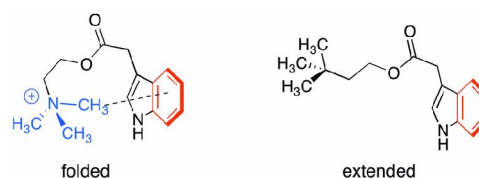


Figure 73. Folding observed in crystal structure of Indole-3-acetic acid choline ester was due to cation- $\pi$  interactions between the *tert*-butyl group and neighboring indoles (Aoki *et al.*, 1995).

#### Anion- $\pi$ interactions

In many respects, anion- $\pi$  interaction is the opposite of cation- $\pi$  interaction. Significantly fewer examples are known to date. In order to attract a negative charge, the charge distribution of the  $\pi$  system has to be reversed. This is achieved by placing several strong electron withdrawing substituents along the  $\pi$  system (e.g. hexafluorobenzene) (Quiñonero *et al.*, 2002). The existence of anion- $\pi$  interactions in compounds that facilitate the transport of anions across phospholipid membranes was exploited (Davis *et al.*, 2010).

## **SUPRAMOLECULAR CHEMISTRY IN PHARMACEUTICALS RESEARCH**

Supramolecular interactions of pharmaceutical substances that have been fascinating the pharmaceutical scientists are: drug-macromolecule interactions; drug-metal interactions; drug-excipient interactions.

Non covalent interactions of drug substance with biological macromolecule and metal are found to be useful in drug discovery process, where as the interactions with excipients or other small molecules were found to be useful in modulating the physical properties of the drug substance during formulation development. Therefore the above interactions can be discussed under two broad headings

## **SUPRAMOLECULAR CHEMISTRY IN DRUG DESIGN**

### **Drug-macromolecule interactions**

Molecular recognition is one of the central processes in drug action. Comparison and detection of binding sites is a key step in the prediction of potential interactions. Various biological macromolecules that interact with the drug molecule are enzymes, receptors, nucleic acids, membranes, carriers and proteins etc. These are all the targets for the drug action and the structure of these targets is used to model and display the interactions with drug structure. These interactions are crucial and must be understood before the design of new molecule for better interactions. The intricate process of using the information contained in the three-dimensional structure of a macromolecular target and of related ligand-target complexes to design novel drugs is alternately called as structure based drug design.

Prerequisite for tight ligand binding are specific interactions formed with protein atoms in the binding site. These are usually non-covalent in nature (e.g. ionic interactions, hydrogen bonds, van der Waals forces) and should in sum exceed unfavorable contributions such as desolvation or conformational restraints. A detailed analysis of the receptor site should, therefore, identify 'hot spots' of binding, i.e. those regions where most favorable non-covalent interactions are formed.

Several approaches directed toward this task are available. Most of them try to determine favorable binding locations by placing atom probes, molecular fragments, or small molecules at various points in the binding site and evaluating their interactions. Such methods have been classified as 'fragment location', 'fragment placement', and 'site-point connection' methods (Murcko *et al.*, 1997). The simple display of the results (hot spots) together with the receptor structure can already be used as valuable guide for the design of new ligands. Some methods also allow to use these results directly for subsequent ligand construction or docking to the binding site (Murcko *et al.*, 1997).

A further, completely different class of methods is given by rule-based or knowledge-based approaches, the essence of which is to make use of the information stored in the vast amount of experimental (crystallographic) data through the derivation of rules for preferred protein-ligand interaction patterns. This idea has been followed in the so-called composite crystal-field approach (Klebe *et al.*, 1994; Murray-Rust *et al.*, 1984). Here, the Cambridge Structural Database (CSD) of small molecule crystal structures (Allen *et al.*, 1991) was statistically analyzed for intermolecular contact geometries of various functional groups, as found in the crystal packing of organic molecules. The composite picture of possible interaction geometries indicates orientational preferences and can thus be used to guide the placement of ligand functional groups in the protein binding site.

The idea of analyzing small molecule crystal structures for intermolecular contacts has also resulted in the generation of an entire database of nonbonded interaction geometries, called ISOSTAR (Bruno *et al.*, 1997). This database presents non-bonded interactions in terms of scatterplots, which show the distribution of contacting groups around a central group. These distributions can be transformed into density maps, which can then be displayed as contoured surfaces. The library contains more than 22161 scatterplots based on nonbonded contacts observed in the CSD



compiled from about 300 central groups surrounded by up to 48 types of different contact groups.

### Drug-metal interactions

Transition metals have an important place within medicinal biochemistry. Research has shown significant progress in utilisation of transition metal complexes as drugs to treat several human diseases like carcinomas, lymphomas, infection control, anti-inflammatory diabetes and neurological disorders. The transition metal complexes feature coordination bonds between a metal and organic ligands. The organic ligands often bind the metal through a heteroatom such as oxygen or nitrogen.

Transition metals exhibit different oxidation states and can interact with a number of negatively charged molecules. This activity of transition metals has started the development of metal based drugs with promising pharmacological application and may offer unique therapeutic opportunities.

Some of them are as follows: Transition metal complexes as anticancer drugs: Platinum complexes like cisplatin, carboplatin, oxaliplatin, found major antitumour activity. Non platinum complexes like titanium complexes called titanocene, gold complexes with aromatic bipyridyl ligands. Ruthenium complexes act as anti proliferative agents; transition metals have also been used as anti inflammatory and anti arthritic agents: several injectable transition gold complexes like sodium aurothiomalate, aurothioglucose and sodiumaurothiopropanol used clinically in the treatment of rheumatoid arthritis; as anti diabetic agents: vanadium complexes with organic ligands have been shown to have insulin mimetic properties; Zinc (II) complexes have found applications in treatment of neurological disorders; used as delivery probes and diagnostic tools.

The research and development of metal supramolecular complexes as anticancer supramolecular drugs, which are aggregates

mainly formed by one or more inorganic metal compounds with one or more either inorganic or organic molecules in general via coordination bonds, has been a quite rapidly developing, increasingly active and newly rising highlight interdisciplinary field. Numerous efforts have been directed toward metal supramolecular complexes as potential anticancer agents and the unprecedented progress has been made. This has opened up a wholly new and infinite space to create novel metal-based bioactive supermolecules.

The pursuit of novel metallodrug candidates that selectively target enzymes is now the subject of intense investigation in medicinal bioinorganic chemistry and chemical biology. In the field of drug design, it is recognised by many that exploiting the structural and chemical diversity of metal ions for the identification of potential hit and lead candidates can dramatically increase the number of possible drug candidates that may be added to the already abundant armoury of chemotherapeutic agents. The enormous clinical success of classical platinum drugs, amongst others, coupled with the wealth of knowledge accumulated in recent years on enzyme structure and function, has undoubtedly been the impetus behind the development of new metallodrug candidates with enzyme inhibitory properties.

Strategy for designing inhibitors of metalloenzymes is to attach an metal-binding moiety to a substrate backbone. This approach utilizes favorable contacts with the substrate binding pocket to fix the inhibitor in the active site, thereby positioning the potential metal-binding functionality within reach of the enzyme cofactor. This strategy has been applied to generate numerous inhibitors of metalloenzymes. For example Iron-sulfur ligand interactions have been widely studied in heme-based enzymes because of their effect on reduction potential (Tezcan *et al.*, 1998), involvement in O-O bond cleavage (Voegtli *et al.*, 2003) and mediation of a fluxional process (Zhong *et al.*, 2004).

## SUPRAMOLECULAR CHEMISTRY IN FORMULATION RESEARCH

Physical interaction between API and excipient in a formulation is determinant for its performance and stability. The study of Supramolecular interaction among the formulation constituents can also be termed as formulation chemistry. The non covalent interactions between drug & excipient result in formation of various physical systems. that include : eutectic mixtures; deep eutectic solvents; ionic liquids; co-crystals; liquid co-crystals; salts

### Eutectic mixtures

According to Goldberg, a simple eutectic mixture consists of two compounds (A&B) that are completely miscible in the liquid state but have only a very limited distribution in the solid state. It has a melting point lower than any of the pure components (A&B) (Goldberg *et al.*, 1966). It is a useful technique to change the solubility and dissolution rate of an API. The phase diagram (Ermias, 2010) as shown below, demonstrates a binary phase eutectic mixture of A&B. the relative concentration of the two components A&B are plotted along X-axis and temperature along Y-axis. The lower part of the phase diagram represents the binary mixture (A&B) that exist as solid and top of the diagram illustrates that the two components are melted. The left corner of the phase diagram which is in between the solid and liquid state shows that component A exists as solid and component B as liquid. Similarly in the right corner of the phase diagram, component B exists as solid and component A as liquid. The eutectic point, e is the point at which both components A&B exist as liquids. The temperature that corresponds to this point is known as eutectic temperature. The composition of the two components at e varies depending upon the types of two components in the mixture. At the eutectic composition, when the eutectic mixture is cooled, A&B crystallize out simultaneously where as when other compositions are cooled, one of the components crystallize out before the other (Juppo *et al.*, 2003; Leuner *et al.*, 2000).

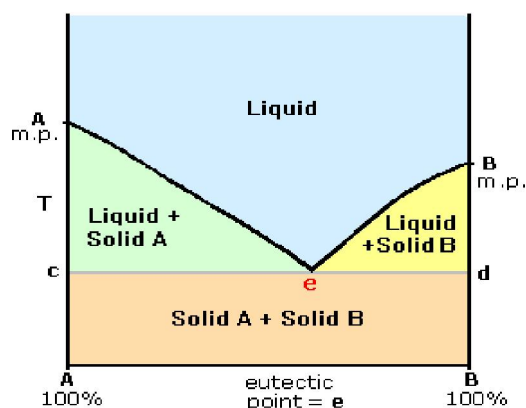


Figure 8. Phase diagram for eutectic mixtures

Eutectic mixtures can also be formed with more than two constituents i.e. ternary (3 components) and quaternary (4 components) eutectic mixtures. Example: quaternary eutectic mixture of prilocaine/lidocaine /bupivacaine/ tetracaine in the weight ratio of 10-40% /5-35% /2-28% / 30-70% respectively (Pacheco *et al.*, 2010). The formation of eutectic mixture depend on the proper concentration of its constituents which must promote the formation of intermolecular forces such as vander waal forces, hydrogen bonds.

Eutectic mixtures can be prepared by using fusion method, solvent method, fusion-solvent method and physical mixture method (Ermias, 2010). Eutectic mixtures can increase the solubility and dissolution rate of poorly aqueous soluble API's. This can be achieved by preparing eutectic mixture of the desired API (hydrophobic) with suitable polymer (hydrophilic carrier) such as PEG etc. Examples: Eutectic mixture of Tolbutamide : PEG 8000 (7:3), tolbutamide : nicotinamide (8:2), haloperidol : aminophyllin (11:9), tolbutamide:niacin (8:2) (Ermias, 2010) itraconazole : poloxamer (188.5 : 95) (Dan *et al.*, 2006).

Eutectic mixtures have various applications due to their peculiar properties. They are mainly used in topical drug delivery. Some of the successful topical eutectic mixtures include ibuprofen : methyl nicotinate, ibuprofen: methanol 4 : 96, ibuprofen : thymol

(40:60), lidocaine : prilocain ( Peter, 2007). Eutectic mixtures can also be used in transdermal drug delivery. As eutectic mixtures lowers the melting point of a drug it helps in faster passage of drug through the stratum corneum. e.g: Ibuprofen:thymol (40:6) (Stott *et al.*, 1998).

### Deep eutectic solvents (Des)

A deep eutectic solvent (DES) is a type of ionic solvent, composed of a mixture which forms a eutectic with a melting point much lower than either of the individual components. The deep eutectic phenomenon was first described in 2003 for a mixture of choline chloride and urea in a ratio of 1:2 respectively. The melting points of choline chloride and urea were 302°C and 133°C. The eutectic mixture melted at 12°C. Deep eutectic solvents are generally formed by mixing of quaternary ammonium salts with hydrogen bond donors. The decrease in melting points of the individual components is due to the charge delocalization occurring through hydrogen bonding between the hydrogen bond acceptor with the hydrogen bond donor moiety.

Recently DES's are being described as a new class of ionic liquids as they share many characteristics of ionic liquids. Most of DES's are non-reactive with water, biodegradable, non-volatile, non-flammable, and conductive (Seshadri, 2007). Their low cost and ease of manufacture makes them particularly desirable than conventional ionic liquids, for large scale synthetic applications. The difference between ionic liquid and DES is that, ionic liquid contains only ions where as DES contains both ions and neutral molecules. They are prepared by simple mixing of the two components with gentle heating until they completely melt.

Deep eutectic solvents can be used to enhance the solubility of poorly soluble compounds. These solubilization systems have more solubilization potential than aqueous systems. Some drugs showed greater solubility in DES than in water. For example poorly water soluble drugs like griseofulvin, danazol, itraconazole showed greater solubility in urea: choline chloride and malonic acid:choline

chloride DES systems than in aqueous system (Morrison *et al.*, 2009). The solubility of benzoic acid was improved from 3mg/ml in pure water to 229 mg/ml in urea: choline chloride and 35mg/mL in malonic acid:choline chloride (Morrison *et al.*, 2009). There are some other similar examples in which poor aqueous soluble drugs showed greater solubility in DES than in aqueous systems. Hence these systems can be used as vehicles for the delivery of poorly aqueous soluble drugs to the site of action by using pharmaceutically acceptable components for preparing DES. They also increase the exposure of poorly soluble drugs in preclinical studies. Other applications of DES include: as solvent of choice for many enzyme based biotransformation, some biocatalytic processes can be carried out in DES as they have benefits like extended enzyme stability, potential for product selectivity, high substrate solubility (Morrison *et al.*, 2009).

### Ionic liquids (IL)

Ionic (IL) liquids are salts in liquid state with a melting point below 100°C. Ionic liquids are made of ions and short lived ion pairs (Bhupinder *et al.*, 2011). These ionic liquids have attractive physical and chemical properties. The unique properties that differentiated ionic liquids from other liquids include the following (Matthias, 2008):

Existing as molten salts, in many cases even below room temperature: Highly polar; Non flammable; Electrically conducting; No vapour pressure; Remarkable dissolution properties

Due to these unique properties they provide an alternative to certain solvent to carry out some reactions to synthesize intermediates and API's. They make a unique platform on which the properties of both anion and cation can be independently modified, enabling tunability in the design of new functional materials, while retaining the desired features of an ionic liquid (Wasserscheid *et al.*, 2000).

At present day almost 50% of pharmaceutically active compounds are administered as salts which are combination of an active ion with simple and inert counter ion. But the troublesome issue of salt form is

polymorphic transformation (Stoimenovski *et al.*, 2010). This can be avoided by liquid salt forms of API which is an alternative versatile tool in the pharmaceutical industry. These ionic liquids have many advantages such as enhancement of solubility, bioavailability, stability, elimination of polymorphism and new delivery options by the adjustment of the counter ion.

The general method for preparation of IL consists of separately dissolving the salt of cation and anion in a solvent and then combining these solutions and stirring them with heating if necessary or at room temperature. The products are then extracted from the aqueous phase with chloroform and the chloroform phase washed with water to remove any inorganic salt. A rotary evaporator can be used to remove the solvent and the resulting IL may be placed in vacuum to remove any residual solvent.

In some cases, an active cation and an active anion can be combined to produce a liquid possessing dual functionality (Vineet *et al.*, 2010). Such drug combination, upon dissolution, will dissociate in the body fluids, where upon will dissociate in the body fluids, where upon the cationic and anionic components follow their independent kinetic and metabolic pathways. The counter ion can be chosen in such a way so that it can either synergistically enhance the desired effects or to neutralize unwanted side effects of the active entity (Vineet *et al.*, 2010). The solubility of poorly aqueous soluble drug can also be enhanced by altering the counter ion. For example Lidocaine docusate ionic liquid exhibited modified solubility, increased thermal stability and significant enhancement in the efficacy of topical analgesia in mouse when compared to lidocaine hydrochloride (salt form) (Whitney *et al.*, 2007; Whitney *et al.*, 2007). The important factor in preparing API-IL's is the proper selection of ions. This approach requires knowledge of specific biological function possessed by each ion and what ion combinations will produce IL's (Whitney *et al.*, 2007). The other applications of ionic liquids include organic synthesis, electro

chemistry, chromatography, transition metal catalysis, biocatalytic transformations, asymmetric synthesis, polymers, biomaterials etc.

### Co-crystals

Co crystals are an emerging class of pharmaceutical materials which can enhance the physico-chemical properties of an API. The first reported co-crystal is quinine in 1844. It is composed of two organic components – quinine and hydroquinone (Stahly, 2009). A co-crystal can be defined as a multi-component crystal of two or more neutral molecules bound together in the crystal lattice through non-covalent interactions primarily hydrogen bonding. Generally the formation of pharmaceutical co-crystals involves API as one of the component along with another pharmaceutically acceptable molecule, known as co-crystal former in the crystal lattice (Sabiruddin *et al.*, 2008). The selection of co-crystal former is important because it is the co-crystal former which plays an important role in altering the physico-chemical properties of an API. Co-crystal former can be an excipient or another drug. Several phase diagrams have been constructed in order to predict the stable phase for cocrystal formation. Phase diagrams determined from the contact method of thermal microscopy is found to be helpful in the discovery of new co-crystals (Ainouz *et al.*, 2009).

The drawbacks for API-salt formation can be overcome by co-crystals as they can be formed with weakly ionisable and non ionisable API's and there are many potential counter ions that can be used in co-crystal synthesis (Shan *et al.*, 2008; Stanton *et al.*, 2009). The main difference between salt form and co-crystals is salt formation involves proton transfer between the API and acidic or basic substance. Such proton transfer does not take place in co-crystal formation. The components will be present as neutral entities. The components in a co-crystal will be present in a definite stoichiometric ratio and assemble by non-covalent interactions such as hydrogen bonding, ionic bonding,  $\pi$ - $\pi$  interactions, vander waal interactions. The

properties and inter-molecular packing pattern of co-crystal differ from those of the individual crystal components (Shan *et al.*, 2008)

Co-crystals can be prepared by solvent based methods and solid based methods. Solvent based methods include slurry conversion solvent evaporation, cooling crystallization and precipitation. Solid based methods include grinding, solvent assisted grinding and sonication (Trask *et al.*, 2005).

Most of the present day drugs have poor aqueous solubility and hence slow dissolution in biological fluids. Co-crystal formation is a reliable method to modify physic-chemical parameters such as solubility, dissolution rate, and stability without altering their pharmacological activity. An example demonstrating the success of co-crystal application to enhance solubility and dissolution rate is itraconazole. It is an extremely water insoluble anti-fungal agent. The co-crystals of itraconazole with various carboxylic acids showed higher solubility and faster dissolution rate than the free base (Remenar *et al.*, 2003). Other examples are fluoxetine HCl : succinic acid 2:1 co-crystal and meloxicam : aspirin co-crystal. Fluoxetine HCl : succinic acid co-crystal ( Scott *et al.*, 2004) showed two times increase in aqueous solubility than fluoxetine HCl.

Co-crystallization can also overcome the stability problems of moisture labile APIs. Example: caffeine/oxalic acid 2:1 co-crystal is more stable to humidity than caffeine anhydrate (Trask *et al.*, 2005). Characterization of co-crystals can be carried out by IR, powder-XRD, NMR. Powder-XRD is most commonly used to characterize co-crystals. Single crystal XRD may prove difficulty on some co-crystals. NMR can differentiate between chiral and racemic co-crystals of similar structure (Horst *et al.*, 2009; Friscic *et al.*, 2009). Physical properties of co-crystals are characterized by TGA and DSC. These methods are used to determine melting point, phase transitions, enthalpic factors which are compared to individual co-crystal formers.

### Liquid co-crystals

Liquid co-crystals are liquid forms of co-crystals. The driving force for the formation of liquid co-crystals is hydrogen bond formation and not salt formation which differentiates liquid co-crystals from ionic liquids. Co-crystals also have some drawbacks as that of solid drug forms like polymorphism. This can be overcome by liquid co-crystals. Liquid co-crystals can be an additional strategy to improve the API performance. Example: liquid co-crystals of lidocaine with various fatty acids (stearic acid, oleic acid, decanoic acid).

Liquid co-crystals are prepared by mixing the stoichiometric amount of both the ingredients and melting them until a clear solution is obtained. Low ionicity of liquid co-crystals provides them to penetrate easily through membranes (Kathrina *et al.*, 2011). Liquid co-crystals were not explored much. Only little information was available regarding liquid co-crystals.

### Salts

The solubility of poorly aqueous soluble drugs can be increased in their salt forms. 50% of all drug molecules used in medicinal therapy are administered as salts. This is due to the fact that a drug substance often has certain suboptimal physicochemical or biopharmaceutical properties that can be overcome by pairing a basic or acidic drug molecule with a counterion to create a salt version of the drug. The process is a simple way to modify the properties of a drug with ionizable functional groups to overcome undesirable features of the parent drug (Anderson *et al.*, 1985). Salts are formed when a compound that is ionized in solution forms a strong ionic interaction with an oppositely charged counterion, leading to crystallization of the salt form (Bhattachar *et al.*, 2006). In the aqueous or organic phase, the drug and counterion are ionized according to the dielectric constant of the liquid medium. The charged groups in the drug's structure and the counterion are attracted by an intermolecular

coulombic force. During favorable conditions, this force crystallizes the salt form (see Figure 15). All acidic and basic compounds can participate in salt formation (Bighley *et al.*, ). However, the success and stability of salt formation depends upon the relative strength of the acid or base or the acidity or basicity constants of the species involved (Florence *et al.*, 1998).

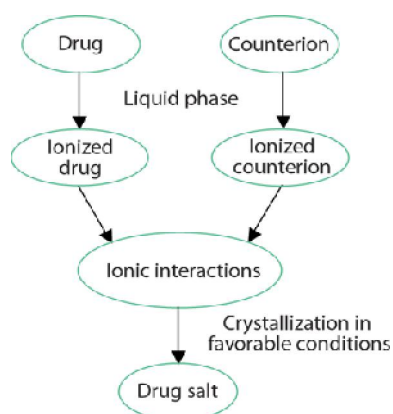


Figure 9. Schematic process of API salt formation.

The salt form is separated into individual entities (i.e., the ionized drug and the counterion) in liquid medium, and its solubility depends upon the solvation energy in the solvent. The solvent must overcome the crystal lattice energy of the solid salt and create space for the solute. Thus, the solubility of a salt depends on its polarity, lipophilicity, ionization potential, and size. A salt's solubility also depends on the properties of solvent and solid such as the crystal packing and presence of solvates (Florence *et al.*, 1998).

## CONCLUSION

Drug design and formulation development are two key components in pharmaceutical research. In this review we discussed the design of new drug like molecules taking the advantage of host-guest intermolecular chemical principles. Further, we discussed about the nature, characterization, physical properties and utility applications of various types of matter composed of API and excipient. These include eutectic mixtures, deep

eutectic solvents, ionic liquids, co-crystals and liquid co-crystals. Whereas, the range of single crystalline supramolecular forms that are possible for an API were (a) pure API (b) polymorph of pure API (c) clathrate hydrate/solvate of API (d) hydrate/solvate of API (e) salt of API (f ) pharmaceutical cocrystal. Salts and cocrystals can also form hydrates, solvates, and polymorphs. Understanding the chemistry between the API and adjuvant in terms of non covalent intermolecular forces has a great scope in development of novel materials for drug delivery and formulation development. This supramolecular chemistry knowledge shall enhance the ability of pharmaceutical chemist to anticipate the productivity of pharmaceutical product development process.

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