Chapter-1

Introduction
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### 1.1 Inclusion Compounds

Inclusion compounds are defined as compounds formed by inclusion of one kind of molecules, called **guest molecules** into cavities of a crystalline framework composed of molecules of another kind (or into cavity of one large molecule), called **host molecules** without forming any specific chemical bond between guest and host; the essential criterion is simply that the enclosed molecule or "guest" be of a suitable size and shape to fit into a cavity within a solid structure formed by "host" molecules (Sinko, 2005). Unlike the case of traditional chemical compounds, **favorable spatial complementarity** of guest and host subsystem, not chemical reactivity, plays the important role in formation of these compounds from the components. This principle of formation allows molecules that are coordinated saturated and do not interact chemically with each other to be brought together so that they form supramolecule or supramolecular crystalline phases that are thermodynamically more stable than a mixture of initial components (Dyadin and Terekhova, 2004).

Inclusion compounds are representative of class of chemistry called supramolecular chemistry, which is defined as the 'chemistry of molecular assemblies and of the intermolecular bond' (Lehn, 2002) or as 'chemistry beyond the molecule'. Other definitions include phrases such as 'the chemistry of the noncovalent bond' and 'nonmolecular chemistry'. Fig. 1.1 illustrates the relationship between molecular and supramolecular chemistry in terms of both structures and function.

In this context, the host is defined as the molecular entity possessing **convergent** binding sites (e.g. Lewis basic donor atoms, hydrogen bond donors etc.). The guest possesses **divergent** binding sites (e.g. a spherical, Lewis acidic metal cation or hydrogen bond acceptor halide anion). The relationship with the resulting host-guest complex has been defined as follows:

> Complexes are composed of two or more molecules or ions held together in unique structural relationships by electrostatic forces other than those of full covalent bonds.............. molecular complexes are usually held together by hydrogen bonding, by ion pairing, by metal-to- ligand binding, by van der Waals attractive forces, by solvent reorganizing, and by partially made and broken covalent bonds (transition states).................. (Donald J.Cram, 1986)

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The host-guest binding event may be likened to catching a ball in the hand. The hand, acting as the host, envelops the ball providing a physical (steric) barrier to dropping it (disassociation). This analogy falls down at the electronic level, however, since there is no real attractive force between hand and ball. The analogy does serve to introduce the term 'inclusion chemistry', however (the ball is included in the hand), hence the inclusion of one molecular in another (Steed and Atwood, 2000).

The stereochemistry and possibly the polarity of both the host and the guest molecules determine whether inclusion can occur. The resulting close fit of the two components produces a combination of significant strength due to the total dispersion forces between the interacting components. This type of spatial complex formation does not occur by means of ionic, covalent or coordinate covalent bonds but rather is dependent upon dispersion forces and highly oriented dipoles for stability, contrasting markedly with the usual concept of chemical complexation. The presence of the guest component in
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Inclusion compound could not be detected by odor; however, when inclusion compound was heated or dissolved in water, the guest molecule was released (Frank, 1975).

1.2 Brief History

J Priestly (1778) is believed to be the first to have observed formation of a compound that today we call as clathrate. He described anomalous ice formed at positive temperature which sank in the aqueous solution of sulfur dioxide. Since then for nearly 170 years, outstanding chemists of the world, H. Davy, M. Faraday, F. Wohler and B. Rooseboom often encountered these compounds (Wohler, 1849). In some cases they approached the understanding of their nature, however, for a long time, these compounds were mainly considered as laboratory curiosity (Dyadin and Terekhova, 2004). Inclusion compounds were also observed by Mylius in 1886 as unusual complexation occurring between hydroquinone and several volatile compounds (Mylius, 1886; Hagan, 1962). He proposed the interaction of two compounds without chemical bonding and suggested that the one molecule was enclosed within another. The crucial role of van der Waals forces in the formation of these compounds was highlighted for the first time by Russian chemist B.A. Nikitin in 1936-1938, during investigations of molecular compounds of noble gases (Nitikin, 1936). These observations were confirmed many years later by X-ray analysis and it was determined that that one molecule of gas or liquid formed an insoluble inclusion compound with three molecules of hydroquinone, the host component, which formed cage-like structure around the guest molecule (Palin and Powell, 1947). Independently, but somewhat later, the same conclusion was made by M. von Stackelberg on the basis of X-ray analysis of the hydrate of sulphur dioxide (von Stackelberg, 1949) and by W. Schlenk, who investigated channel inclusion compounds of urea (Schlenk, 1949a). In 1956, a statistical-thermo dynamical ideal model of clathrate formation was constructed (van der Waals and Platteeuw, 1959). The presence of the guest component in inclusion compound could not be detected by odor; however, when inclusion compound was heated or dissolved in water, the guest molecule was released (Frank, 1975).
1.3 Terms and classifications

The term clathrate (originating from Latin word “clathratus”, which means closed or surrounded from all sides) was introduced by H.M. Powell for inclusion compounds of β-hydroquinone (Powell, 1948). In 1949, W. Schlenk introduced the term “inclusion compounds” for channel compounds of urea and thiourea (Schlenk, 1949b). At first, the term clathrate was used to include only cage inclusion compounds. At present, along with the term inclusion compounds, it is used independently of the shape of cavity, provided there is no specific chemical interaction between the guest and host. Other terms that have been used to describe these complexes are “occlusion compounds”, “adducts”, “host-guest complexes”, “addition compounds” and “supramolecular assemblies”.

There are several different types of inclusion compounds, and these are categorized into following types according to the structure of the host lattice (Figure 1.2) (Dyadin and Terekhova, 2004):

a) Cryptoclathrates: (cryptov in Greek is secrecy) Compounds having cage structure, wherein the guest molecules are included within closed cavities formed by the host molecules e.g. β-hydroquinone clathrates, Dianin’s compounds, gas hydrates and cyclodextrins. Latest entry into this category includes Fullerenes.

b) Tubulatoclathrates: (tubus in latin tubes) May be divided further into two types:

One dimensional non-intersecting channel inclusion compounds in which the host forms non-intersecting channels or tunnels which include the guest molecules. e.g. urea, thiourea, choleic acids.

Intersecting channel type inclusion compounds, wherein the host forms intersecting channels which accommodate the guest molecules e.g. zeolites,

c) Intercalatoclathrates: Layered inclusion compounds in which the guest molecules are sandwiched between sheets of the host matrix e.g. clays.

Another classification is based upon the organization of inclusion compounds by their structure and properties (Frank, 1975):

Polymolecular inclusion compounds: consist of a host structure composed of several molecules orienting in a loosely arranged lattice. The host framework is completely constructed using covalent bonds; the inclusion cavity with specific dimensions being formed only in the presence of a guest molecule. In the absence of a guest molecule,
compounds in this category form denser crystal structure without cavities. Similar molecules belonging to same chemical class will crystallize to form cavities of different sizes and shapes, depending upon their chemical structure:

*Forming channel-like spaces* include urea, thiourea and choleic acids.

*Forming cage-like spaces* include β-hydroquinone clathrates, Dianin's compounds, gas hydrates.

*Forming either cage-like or channel-like void spaces*, depending on the size and shape of guest molecules e.g. tri-o-thymodite.

**Monomolecular inclusion compounds**: these interact generally on a 1:1 basis with the guest molecule, which is enclosed within a cavity in the host molecule. The cyclodextrins (Loftsson *et al.*, 2004), antibiotics and certain proteins are included in this category.

**Products of blue-iodine reactions**: polymerization of iodine within unique channels formed by starch, cyclodextrins, flavons, coumarin, benzophenone, cellulose and barbaturic acid gives blue addition compounds (Rundle and Baldwin, 1943; Schoch and Williams, 1944).

**Macromolecular inclusion compounds**: The host framework in macromolecular clathrate is completely constructed using covalent bonds; it is impossible to distinguish an individual host molecule and the framework is a macromolecule as a whole. Examples of this category include zeolites, which act as molecular sieves. These compounds have been investigated extensively and have wide use in industrial and laboratory processes (Flanigen and Sand, 1971). The basic structure of the zeolite is a crystalline framework of a silicon-oxygen or aluminium—oxygen tetrahedral which forms a three dimensional array with many cavities and interconnecting channels (Grosse-Kunstleve *et al.*, 1999). Depending upon the size and shape of these void spaces, various guest molecules can enter and be enclosed within the network.

Inclusion compounds can be also be **subdivided into two subtypes on the basis of the relative topological relationship between host and guest** (Steed and Atwood, 2000):

1. **Cavitands** may be described as hosts possessing intramolecular cavities. Thus the cavity available for guest binding is an intrinsic molecular property of the host and exists both in solution and in the solid state. This is a typical feature of
Fig. 1.2 Different types of host lattices which form inclusion compounds.

a) clathrate inclusion compounds (gas hydrates)  
b) non-intersecting channel inclusion compounds (urea)  
c) layered inclusion compounds (clays)  
d) Intersecting channel inclusion host structure (zeolites) (Dyadin and Terekhova, 2004).
monomolecular clathrates and examples of these hosts include crown ethers, cyclodextrins, cryptands, rotaxanes and catenanes.

2. Clathrands are host with extramolecular cavities, guest molecules are located within the architecture of a solid host material, and in these cases the association of host and guest components is *strictly a solid phenomena* exhibiting disassociate on dissolution in a solvent. Gas hydrates, urea clathrates and a wide variety of crystalline solvates fall into this category.

1.4 Significance and Applications of inclusion compounds

Inclusion phenomena are wide spread throughout chemistry. Inclusion chemistry is no more curious thing in the chemical laboratory as it was often understood (Davies *et al*, 1983). On the contrary, there is a broad actual field of practical and research applications using clathrate compounds and a great many of the future applicabilities wait for exploration. Some of the important aspects are as follows:

➢ One important field of applications, industrial objectives included, is directed to *chemical analysis* and *molecular separation processes*. Corresponding to size, the shape and the chemical nature of the holes generated in an inclusion lattice, guest molecules may be included selectively. Out of a mixture of compounds the one which matches the conditions of the lattice holes most suitably is preferably accommodated (Mandelcorn, 1966; Arad-Yellin *et al* 1984). Chemically different species are separated (e.g. hydrocarbons and ketones) as well as constitutional isomers, *positional* isomers, *regioisomers*, *stereoisomers* and even *isotopic* isomers.

*Fig. 1.3 Principle of molecular separation by host-guest complexation (Arad-Yellin *et al* 1984).*
Size selectivity, which has been recognized as a characteristic feature of the host lattices is an object most promising in industry. Compounds having closed melting points may be separated by inclusion crystallization at a lower cost, compared to costly distillation process (Findlay, 1962). On the analytical scale, clathrate compounds were successfully applied in chromatography (Smolkova et al, 1978).

The characteristic of crystal lattices is a strict periodic succession of structurally identical molecular units, in the sense of an inclusion lattice also of holes, channels, layers etc. which may include guest molecules in an oriented fashion. This organizing principle makes topochemistry possible (Gavezzotti and Simonetta, 1982). One of the studies in this area was inclusion polymerization of dienes in the channels of urea leading to stereoregular polymers (White, 1960).

The chemical reactivity of a substrate molecule, e.g. at photo- or thermal isomerization may also be altered on lattice enclosure since conformations different to the substrate free of constraint of the lattice environment are likely (Dewar and Nahlovsky, 1974). This will lead to modified reaction pathways and thus cause different products or if the reactivity of an included molecule is drastically reduced, the host lattice offers a protective function.

Another objective which is of benefit to chemical synthesis is derived from host-guest reactivity under oriented conditions. The intercalates e.g. of graphite and of sheet silicates are representative examples (Thomas, 1982). Some inclusion compounds impose relatively confining steric conditions on the guest molecules, and so some types of reactions, such as photochemical reactions, can have very different results when carried out in an inclusion compound matrix as compared to the reaction in solution (Casal et al, 1983).

Resembling the use of the matrix isolation technique, inclusion compounds have been recognized as source and reservoir of unstable species, mainly of free radical-type (Birell et al, 1971).

In general inclusion will cause altered physical properties of any guest molecule (Parsonage and Staveley, 1984). This may manifest itself

\[ \rightarrow \] In a reduced volatility and therefore lower possible storage and handing problems of a compound when included (Weber, 1989).
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→ Toxic and hazardous substances becoming safer (Cross et al, 1973).
→ Altered the redox properties of a compound, its color and other physical dimensions (Davies et al, 1983).

There is considerable interest in the altered physical properties of the inclusion compounds for the use in battery systems, room temperature superconductors and further aims of future technology (Weber, 1989).

➢ Some inclusion compounds provide systems in which the guest molecules are fairly isolated, so studies of these systems can reveal differences in guest-host interactions when compared to interactions in the guest in bulk (Powell, 1948).

Some of the present important applications of clathrates are short-listed as follows (Vaidya, 2004):

➢ Medical applications such as in magnetic resonance imaging.
➢ Used to study the photo-behavior of organic and inorganic molecules by introducing them as probes (guests) into clathrate cages.
➢ Resolution of racemic mixtures.
➢ Zeolites can remove atmospheric pollutants, ozone-depleting CFC's and harmful organics from water.
➢ Since clathrate compound formation is based on molecular size rather than on chemical similarity, it can be used practically in the separation of chemically similar but physically different molecules. These compounds are now emerging on the chemical scene to take a place of increasing importance.
➢ They are used as materials for superconductivity (Ba-Na-Si46 series).

Some of the promising future prospects of clathrate chemistry are as follow (Vaidya, 2004):

➢ Pharmaceutical preparation by clathration separation appears promising.
➢ Clathrates provide a convenient means of storing radioactive isotopes of Kr and Xe produced in nuclear reactors and also toxic fluids found in nature.
➢ Useful for studies of air pollution, process control and meteorology.
➢ They display intriguing lattice and electronic properties pointing at future potential applications.
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➢ Potential candidates for thermoelectric applications due to their thermal conductivity. Inorganic clathrates can be used as superhard materials.

Studying the nature of inclusion compounds requires special determination techniques which work in the solid state. Those have been developed in the range of

➢ Infra-red spectroscopy.
➢ Raman spectroscopy.
➢ Magic angle spinning spectroscopy.
➢ High resolution electron spectroscopy.
➢ X-ray crystallography.
➢ Electronic spin resonance.
➢ Differential thermal analysis/ differential scanning calorimetry.
➢ Quasi-electron neutron scattering.
➢ Molecular dynamic simulation.

These have been successfully applied on clathrates. The clathrate phenomena, thus, acted as stimulus to develop physical measuring systems to a high standard.

1.5 Various adductors

Inclusion phenomena are quite widespread in chemistry and inclusion compounds have become one of the significant components of chemical structure and behavior (Powell, 1984). After the initial discovery of hydroquinone as host moiety, the number and type of inclusion compounds have grown tremendously. Although the type of space in an inclusion compound cannot strictly be described without consideration of the included component, it is common place to speak of hosts as having closed cavities, channels or interlayer spaces (Powell, 1984). Some of the more important and extensively studied host molecules along with the organization and topology of the cavity formed by these are listed in Table 1.1.
### Table 1.1 Various adductors along with their most widely occurring shape and size of the cavities.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Name of the adductor</th>
<th>Organization of host molecules</th>
<th>Shape of the cavity</th>
<th>Size of the cavity (Å)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Urea</td>
<td>Polymolecular</td>
<td>Hexagonal channels</td>
<td>5.25</td>
<td>George and Harris, 1995</td>
</tr>
<tr>
<td>2.</td>
<td>Thiourea</td>
<td>Polymolecular</td>
<td>Hexagonal channels</td>
<td>7.0</td>
<td>Harris, 1997</td>
</tr>
<tr>
<td>3.</td>
<td>Deoxy-choleic acids</td>
<td>Polymolecular</td>
<td>Channel like</td>
<td>4</td>
<td>Bishop and Dance, 1989</td>
</tr>
<tr>
<td>4.</td>
<td>4-4’-dinitrobiphenyl</td>
<td>Polymolecular</td>
<td>Face-centered channels</td>
<td>4</td>
<td>Rapson et al, 1946</td>
</tr>
<tr>
<td>6.</td>
<td>Water (liquid or gas hydrates)</td>
<td>Two types a) 46 water molecules with 8 guest moieties.</td>
<td>Eight cage-like cavities 2 dodecahedrons 6 tetradecahedrons</td>
<td>5 6</td>
<td>Frank, 1975</td>
</tr>
<tr>
<td>7.</td>
<td>Phenol</td>
<td>12 phenol molecules</td>
<td>Rhombohedral cage</td>
<td>-</td>
<td>Lahr and Williams, 1959</td>
</tr>
<tr>
<td>8.</td>
<td>Dianin’s compound</td>
<td>Hexamolecular</td>
<td>Hourglass shaped cage</td>
<td>11 Å long 6.2 Å wide</td>
<td>Flippen and Karle, 1971</td>
</tr>
<tr>
<td>9.</td>
<td>Tri-othymodite</td>
<td>Polymolecular</td>
<td>Elongated cage for of guest molecules (length &lt; 9.5 ) Channel for guest molecules longer than 9.5.</td>
<td>-</td>
<td>Williams and Lawton, 1975</td>
</tr>
<tr>
<td>12.</td>
<td>Amylose</td>
<td>Polymolecular</td>
<td>Helical coils</td>
<td>8.0</td>
<td>Rundle and Balwin, 1943</td>
</tr>
</tbody>
</table>
Harris proposed that within the broad range of solid inclusion compounds, host molecules can be further subdivided depending upon stability of host structure (Harris, 1997). Thus two categories of host molecules were proposed \textit{i.e.}

**Hard hosts**: the host compounds which remain stable when the guest component is removed, \textit{e.g.} cyclodextrins.

**Soft hosts**: those for which the host structure undergoes substantial reorganization when the guest component is removed. In this case, the structure organization generally involves collapse of the low-density \textit{empty} host structure, with recrystallization to a more compact structure of higher density. Thus, for inclusion compounds of soft hosts, the guest component generally acts as an essential template for the formation of the host structure as well as for maintaining the stability of the host structure. Urea and thiourea inclusion compounds are representative examples of this class.

Most of the classical clathrate hosts have been discovered by accident and not via directed synthesis (Davies, 1981). Efforts have also been made to create new host compounds simply by altering an individual section of a known host constitution (Weber, 1989). Typical examples are Dianin’s compounds and its structural modifications, \textit{e.g.} it is possible to vary the cavity size being formed in the crystal lattice of Dianin’s compound via modification of molecular segments (MacNicol \textit{et al}, 1978). Further, with regards to many applications of clathrate compounds, easy construction of new clathrate compounds \textit{i.e.} Directed Host Design is also being investigated (MacNicol and Wilson, 1976; Weber \textit{et al}, 1984; Jacobs \textit{et al} 2005). Directed host design of a host compound is the synthesis of a new clathrate host unrelated to any known lattice but would be expected to act as a host lattice (Weber, 1989).

Among different adductors and different types of cavities available, the present work deals with urea inclusion compounds which form helical inclusion compounds in the presence of suitable guest moiety.


1.6 Helical inclusion compounds (tubulatoclathrates)

Helix (or helices) is twisted shape like a spring, screw or spiral (correctly termed as helical) staircase. Helix in chemical biology terminology is defined as a spiral structure in a macromolecule that contains a repeating pattern. Helices are important in biology as some biological aggregates of macromolecules involve canal topology and incorporate helicity. DNA is helical and many protein molecules have spiral substructures (Fig. 1.4). The helical proteins are stabilized by hydrogen bonds between e.g., =C=O and HN= groups of different peptide bonds (Emberly et al, 2002). In addition to the above, the helical topology is important in the formation of transmembrane ion channels through ionophores, which facilitate ion transport. The majority of ionophores are natural antibiotics and their synthetic analogues e.g. nystatin, amphotericin B, gramicidin, bacteriorhodopsin to name a few.

As pertaining to inclusion phenomena, for a relatively long period there were known only few chemical systems, where helical canal inclusion compounds could be generally prepared and utilized, namely urea, thiourea and deoxycholeic acids systems. However, new helical inclusion networks have been discovered and characterized lately. Different terms like ‘canal’, ‘channel’, ‘tube’ and ‘tunnel’ have been used to describe host cavities extended in one dimension without restriction on cross-sectional shape. The canal inclusion complexes may of unimolecular type, where the host is a single molecule or multimolecular type which require many host molecules for constriction of the canal. Thus in the former type, long host molecules
wind around the canal. Generally this host molecule is a polymer and helical canal conformation is expected to be result of specific attractive interaction, along the pitch of the helix, between non-sequential monomeric residues. A multimolecular helical canal contains corresponding series of distinct host molecules maintained in similar topology by inter-host attractions around and along the helix (Bishop and Dance, 1989). Following are the different host molecules which crystallize as helical inclusion compounds;

1.6.1 Urea, thiourea and selenourea inclusion compounds
The fortuitous discovery that urea forms inclusion compounds with many unbranched organic molecules was first reported by Bengen in 1940. Structural studies determined the now familiar canal structure of these materials. Similarly, both thiourea and selenourea have been found to form canal inclusion compounds. The selenourea compounds, reported very briefly, appear to form rhombohedral canals, the dimensions of which are susceptible to the size of guest moieties (Bekkum, 1967). While urea forms hexagonal helices with diameter of ~ 5.5 Å enclosing mostly long chain unbranched organic compounds, thiourea canal inclusion compounds have a larger cross-sectional area (5.8-6.8 Å). As a consequence, thiourea forms tunnel inclusion compounds with cyclohexane, several derivatives of cyclohexane, ferrocene, other organometallics, and certain compound containing a benzene ring (Schiessler and Flitter, 1952). While the host tunnel in conventional urea inclusion compounds is fairly cylindrical (with only small fluctuations in tunnel diameter on moving along the tunnel), the thiourea tunnels have rhombohedral structure, with prominent bulges (diameter ~ 7.1 Å) and constrictions (diameter ~ 5.8 Å) at different positions along the tunnel. Hence thiourea inclusion compounds have host structure more closely resembling to ‘cage’ type rather than ‘tunnel’ type (Harris, 1997).
1.6.2 Deoxycholeic acid and derivatives

Deoxycholic acid and apocholeic acid are the typical examples of the bile acid family of materials, but with the unique property of forming inclusion compounds with a wide variety of guest molecules including carboxylic acids, esters, alcohols, ethers, phenols, and hydrocarbons. DCA forms canal inclusion compounds, known as choleic acids, which most frequently have orthorhombic cavity (Giglio, 1984). In such crystals the DCA molecules hydrogen bond to each other to form an extended bilayer structure, thereby creating a hydrophobic canal between adjacent bilayers (Ciro et al, 1985).

1.6.3 Tri-o-thymodite (TOT) inclusion compounds

Unsolvated TOT crystallizes in the orthorhombic space group, but forms inclusion compounds with an extremely wide range of organic materials of different arrangements. Both cage and canal structures are commonly produced, with structure adopted almost depending entirely on the size of the guest molecules. Guests less than 9.5Å in length, generally lead to the formation of cage inclusion compounds with trigonal structure, e.g.
inclusion compounds with 2-bromobutane, chlorocyclohexane, ethyl methyl sulfoxide (Williams and Lawton, 1975; Allemand and Geradil, 1982). However, guests over 9.5 Å in length, e.g. n-alkyl bromide and iodide for C₆ to C₁₈ give rise to canal structures. In common with the situation for DCA, the helical canal inclusion compounds of TOT have so far received little attention compared to the research activity on urea.

### 1.6.4 Amylose inclusion compounds

The reaction between starch and iodine to form an inclusion compound was first reported in 1814 and has since become familiar to all chemists through its application in analytical chemistry. Its deep blue color (λ_max 620 nm) has been known for years to result from a linear arrangement of ‘polyiodide’ within a canal formed by helical coil of amylose (Fig. 1.6) (Schoch, and Williams, 1944). The helical structure has an outer diameter of 13.0 Å, an inner diameter of 5 Å, and a pitch of 8.0 Å with six glucose units per turn (Rundle and Baldwin, 1943; Saenger, 1984).

**Fig. 1.6 Amylose inclusion compounds with iodine (Saenger, 1984).**

The amylose helix forms a blue charge-transfer complex with molecular iodine (starch-iodide test).

### 1.7 Applications of inclusion compounds in drug formulation

The use of high through put screening and similar techniques in drug discovery has put a number of evolutionary pressures on drug candidates such that over time there is a tendency for them to increase in molecular weight, increase in log k_(octanol/water) and decrease in water solubility. Thus, approximately 40% of the drugs being discovered are
known to possess poor solubility and therefore their bioavailability upon oral administration is incomplete or irregular because of low dissolution rate. Even in case of complete absorption, the time for orally administered drug to reach the effective blood level is too long, so that reduction of the pharmacological time lag is desired. Some of the drugs are chemically unstable and because of their autodecomposition, polymerization or degradation by atmospheric oxygen, absorbed humidity, light, etc., a dosage form with satisfactory shelf life can not be formulated. Some drugs possess physical instability, which may be demonstrated by volatilization or sublimation of contents or by hygroscopicity. On the other hand, some of the good drug candidates have unpleasant odor or have bitter or irritating taste. Dose of some of the drug candidates is extremely low, therefore content uniformity is problematic. Moreover, because of extremely high biological activity of these potent drugs, working with powders of such drugs is rather hazardous.

The complexation of a drug molecule with an appropriate host can be considered in all the above listed problems of drug formulation. An important tool in this regard has been the use of cyclodextrins as the host molecule. These starch derivatives interact via dynamic complex formation and other mechanisms in a way that camouflages undesirable physicochemical properties including low aqueous solubility, poor dissolution rate and limited drug stability. Thus cyclodextrins have become popular modalities for increasing oral bioavailability and absorption rate. The database on cyclodextrins-drug complexes is increasing tremendously as evidenced by large number of research papers/ patents being reported during past 25 years. Some of the applications of cyclodextrins in pharmaceutical sciences have been exemplified in Table 1.2.
Table 1.2 Applications of cyclodextrins in pharmaceutical sciences.

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Application</th>
<th>Cyclodextrin</th>
<th>Drug</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Enhanced solubility and dissolution</td>
<td>β-CD</td>
<td>Nimuslide</td>
<td>Chowdary and Nalluri, 2000</td>
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<td></td>
<td></td>
<td></td>
<td>Piroxicam</td>
<td>Cavallari and Abertini, 2002</td>
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<td></td>
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<td>Ketoprofen</td>
<td>Ahn \textit{et al}, 1997</td>
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<td>Griseofulvin</td>
<td>Dhanaraju \textit{et al}, 1998</td>
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<td></td>
<td></td>
<td>γ-CD</td>
<td>Lorazepam</td>
<td>Sanghavi \textit{et al}, 1993</td>
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<td></td>
<td>Glibenclamide</td>
<td>Jayachandra and Pundit, 1995</td>
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<td>HP- β- CD</td>
<td>Omeprazole</td>
<td>Arias \textit{et al}, 2000</td>
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<td>Digitoxin</td>
<td>Uekama \textit{et al}, 1983</td>
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<td>DM- β- CD</td>
<td>Albendazole</td>
<td>Castillo \textit{et al}, 1999</td>
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<td>Levernopamil</td>
<td>McCandless and Yalkowsky, 1998</td>
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<td>Ketoprofen</td>
<td>Ahn \textit{et al}, 1997</td>
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<td></td>
<td>Carbamazepine</td>
<td>Londhe and Nagarsenker, 1999; Brewster \textit{et al}, 1997;</td>
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<td></td>
<td>Phenytoin</td>
<td>Latrofa \textit{et al}, 2000</td>
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<td>Gliclazide</td>
<td>Aggrawal \textit{et al}, 2002</td>
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<td>Gliquidone</td>
<td>Sridevi \textit{et al}, 2003</td>
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<td>Uekama \textit{et al}, 1992</td>
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<td>Nitrendipine</td>
<td>Choi \textit{et al}, 2003</td>
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<td>SBE- β- CD</td>
<td>Danazol</td>
<td>Jain and Adeyeye, 2001</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Fluasterone</td>
<td>Zhao \textit{et al}, 1999</td>
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<td></td>
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<td></td>
<td>Spiranolactone</td>
<td>Kaukonen \textit{et al}, 1998</td>
</tr>
<tr>
<td>2.</td>
<td>Increased photostability of drug</td>
<td>HP- β- CD</td>
<td>Promethazine</td>
<td>Loftsson and Peterson, 1998</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SBE- β- CD</td>
<td>DY-9760e</td>
<td>Nagase \textit{et al}, 2001</td>
</tr>
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<td>3.</td>
<td>Increased thermal stability in solid state</td>
<td>β- CD</td>
<td>Diclofenac sodium</td>
<td>Cwiertnia \textit{et al}, 1999</td>
</tr>
<tr>
<td>4.</td>
<td>Stability against intramolecular cyclization in solid state</td>
<td>β- CD</td>
<td>Quinaril</td>
<td>Li \textit{et al}, 2002</td>
</tr>
<tr>
<td>5.</td>
<td>Stability against hydrolysis</td>
<td>γ- CD, HP- γ- CD</td>
<td>Digoxin</td>
<td>Uekama \textit{et al}, 1983</td>
</tr>
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<td></td>
<td></td>
<td>Paclitaxel</td>
<td>Singhla \textit{et al}, 2002</td>
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### Introduction

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<th>Drug</th>
<th>Reference</th>
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<td>Increased degradation</td>
<td>SBE-β-CD, HP-β-CD</td>
<td>Spiranolactone</td>
<td>Jarho <em>et al.</em>, 2000</td>
</tr>
<tr>
<td>7</td>
<td>Increased shelf life</td>
<td>β-CD</td>
<td>Glibenclamide</td>
<td>Babu and Pundit, 1999</td>
</tr>
<tr>
<td>8</td>
<td>Colon-specific delivery</td>
<td>α-CD</td>
<td>Prednisolone</td>
<td>Yano <em>et al.</em>, 2002</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Nicardipine</td>
<td>Fernandes <em>et al.</em>, 2003</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Salbutamol</td>
<td>Lemesle –Lamache <em>et al.</em>, 1996</td>
</tr>
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<td>Improvement in drug safety/ Reduced drug toxicity</td>
<td>β-CD SBE-β-CD</td>
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<td>Nicolazzi <em>et al.</em>, 2002</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td>Kim <em>et al.</em>, 2004</td>
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<td>11</td>
<td>Reduced irritation</td>
<td>β-CD HP-β-CD</td>
<td>Piroxicam</td>
<td>Serni, 1993</td>
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<td></td>
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<td>β-CD</td>
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<td>Funasaki <em>et al.</em>, 1999</td>
</tr>
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<td>Teixeira <em>et al.</em>, 2006.</td>
</tr>
</tbody>
</table>

Note: HP- β-CD - hydroxypropyl β-CD; HP-γCD hydroxypropyl γCD; m- βCD-methylated β-CD; SBE-7-β-CD sulfobutyl ether β-CD; E-β-CD ethylated β-CD.

Considering the lengthy development and the strict requirement for approval of a new chemical entity (a cyclodextrin complex of a well known drug molecule is always considered to be a new chemical entity) it must be considered a significant achievement that more than 30 drugs have already been approved and marketed in complexed form with cyclodextrins (Table 1.3).
Table 1.3 Examples of marketed drug formulations in complexed form with cyclodextrins.

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Trade name</th>
<th>Drug</th>
<th>Cyclodextrin</th>
<th>Formulation</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sporanox</td>
<td>Itraconazole</td>
<td>3-HP-β-CD</td>
<td>Oral/IV</td>
<td>Janssen</td>
</tr>
<tr>
<td>2</td>
<td>Prepulsid</td>
<td>Cisapride</td>
<td>3-HP-β-CD</td>
<td>Suppository</td>
<td>Janssen</td>
</tr>
<tr>
<td>3</td>
<td>Prostavasin</td>
<td>PGE₁</td>
<td>α-CD</td>
<td>Intraarterial</td>
<td>Ono, J.,</td>
</tr>
<tr>
<td>4</td>
<td>Prostarmon E</td>
<td>PGE₁</td>
<td>β-CD</td>
<td>Sublingual tablet</td>
<td>Ono, J.,</td>
</tr>
<tr>
<td>5</td>
<td>Geodon</td>
<td>Ziprasidone</td>
<td>SBE-7-β-CD</td>
<td>IM</td>
<td>Zoldex</td>
</tr>
<tr>
<td>6</td>
<td>Vfend</td>
<td>Voriconazole</td>
<td>SBE-7-β-CD</td>
<td>IV</td>
<td>Pfizer</td>
</tr>
<tr>
<td>7</td>
<td>Mitozytrex</td>
<td>Mitomycin</td>
<td>3-HP-β-CD</td>
<td>IV Infusion</td>
<td>Genzyme</td>
</tr>
<tr>
<td>8</td>
<td>Dexacort</td>
<td>Hydrocortisone</td>
<td>3-HP-β-CD</td>
<td>Liquid</td>
<td>Island</td>
</tr>
<tr>
<td>9</td>
<td>Cardiotecc</td>
<td>Teboroxime</td>
<td>HP-γCD</td>
<td>I.V. Infusion</td>
<td>Bracco, USA</td>
</tr>
<tr>
<td>10</td>
<td>Voltaren ophta</td>
<td>Hydrocortisone</td>
<td>HP-γCD</td>
<td>Eye Drops</td>
<td>Novartis,</td>
</tr>
<tr>
<td>11</td>
<td>Clorocil</td>
<td>Chloramphenicol</td>
<td>m-βCD</td>
<td>Eye Drop</td>
<td>Oftalder,</td>
</tr>
<tr>
<td>12</td>
<td>Brexin</td>
<td>Piroxicam</td>
<td>β-CD</td>
<td>Tablets/Suppository</td>
<td>Chiesi,</td>
</tr>
<tr>
<td>13</td>
<td>Glymesason</td>
<td>Dexamethsone</td>
<td>β-CD</td>
<td>Ointment</td>
<td>Fujinaga</td>
</tr>
<tr>
<td>14</td>
<td>Nitopen</td>
<td>Nitroglycerin</td>
<td>β-CD</td>
<td>Sublingual tablets</td>
<td>Nippon</td>
</tr>
<tr>
<td>15</td>
<td>Tranillium</td>
<td>Chlordiazepoxide</td>
<td>β-CD</td>
<td>Tablet</td>
<td>Gador, Ar.</td>
</tr>
<tr>
<td>16</td>
<td>Surgamyl</td>
<td>Thyaprofenic acid</td>
<td>β-CD</td>
<td>Tablet</td>
<td>Roussel-</td>
</tr>
<tr>
<td>17</td>
<td>Aerodiol</td>
<td>17-estradiol</td>
<td>m-βCD</td>
<td>Nasal Spray</td>
<td>Servier,</td>
</tr>
<tr>
<td>18</td>
<td>Mena-Gargle</td>
<td>Iodine</td>
<td>β-CD</td>
<td>Gargling</td>
<td>Kyushin</td>
</tr>
<tr>
<td>19</td>
<td>Xund, Tegra</td>
<td>Garlic oil</td>
<td>β-CD</td>
<td>Dragees</td>
<td>Bipharm</td>
</tr>
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<td>20</td>
<td>Ulgut</td>
<td>Benexate</td>
<td>β-CD</td>
<td>Capsules</td>
<td>Teikoku</td>
</tr>
</tbody>
</table>

Note: HP-β-CD - hydroxypropyl β-CD; HP-γCD hydroxypropyl γCD; m-βCD-methylated β-CD; SBE-7-β-CD sulfobutyl ether β-CD.

In contrast to cyclodextrins, no other adductor has been exploited in formulation development. Among the established adductors, there is some limitation on to the choice of adductors available mainly owing to their specific toxicity e.g. thiourea, hydroquinone, selenourea, hydroquinone or instability in intestinal fluids e.g. deoxycholeic acid. The new synthetic hosts which are being introduced recently are highly specific i.e. their molecular (or ionic) recognition capacity prefers a given ion or molecule. These type of hosts deliver highly specific and sensitive sensors, or entrapping agents, sequestrators, for specific ions. Thus these hosts have very restricted fields and amounts. Produced for a
very limited market, generally by complicated synthetic procedures, majority of hosts remain expensive specialty chemicals (Szejtli, 1997).

Of all the inclusion compounds forming hosts known, urea, *a biocompatible substance has been overlooked by drug formulators despite its unique characteristics like:

- Excellent solubility in water, hence can do wonders to the solubility profile of the included endocytic drug
- Offers all the advantages through which it can camouflage undesirable physicochemical properties of drugs
- Safe and non-toxic
- Highly stable
- An organic chemical extensively used in agriculture and industry for variety of applications, hence very cheap and very easily available.

While extensive use of cyclodextrins has positioned them as an important enabling and functional excipients, there lies unlimited potential to explore urea inclusion compounds as solution to problems associated with the insolubility and instability of drug substances. Although a study published in 1957 suggested that orally administered cyclodextrins were highly toxic (French, 1957), more recent animal toxicity studies in rats and dogs have shown this not to be the case, and cyclodextrins are now approved for use in orally administered formulations. β-cyclodextrins, upon parental administration, is not metabolized but accumulated in the kidneys as insoluble cholesterol complex, resulting in nephrotoxicity (Frank, 1976). However, *urea, an age old chemical, is a component of normal physiological processes of body. It can be naturally expected that the human organism is well adapted to urea within the physiological range of concentrations and even beyond. This may partly explain why urea has not been rigorously studied with toxicological tests. Nevertheless, urea appears to cause little or no toxicity to most mammalian species (ruminants are more sensitive because of microbial ammonia production) and humans at reasonable dose levels. Hence, urea is of low concern to human health (INCHEM, 1997).

Hence urea offers following distinct advantages over cyclodextrins:

- Urea is an ideal host for formulation of sparingly soluble drug into an immediate release dosage form. Owing to its excellent solubility in water (1000 mg/ml
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compared to 200mg/ml for the most soluble cyclodextrin), urea is expected to release the included endocytes instantaneously on coming in contact with water.

➢ Urea can act as an adductor for both linear aliphatic compounds and substituted cyclic compounds (through the modified technique), while cyclodextrins, owing to their large cage-like cavity, can include only substituted cyclic compounds.

➢ Owing to larger cavity of cyclodextrin cages, there are chances of isomerization of guest molecules even when included within the cage. Hence, cyclodextrins are known to fasten photo-degradation of some of the drugs. In contrast, the guest molecules constrained within the narrow hexagonal tunnels formed by urea molecules are unlikely to isomerize owing to spatial limitations.

➢ Urea being a part of normal physiological processes has always been considered to be GRAS and was never subjected to rigorous toxicological investigations. With some of the derivatized cyclodextrins, issues need to be resolved regarding their toxicological potential.

➢ Though pharmaceuticals is a cost insensitive industry, but the fact that urea is very cheap compared to cyclodextrins can not be overlooked.

➢ Last but not the least, cyclodextrins are the most exploited formulation modifiers investigated so far while urea inclusion compounds have not been exploited by the pharmaceutical industry for the formulation development of problematic drugs.

Thus, amongst various adductors, urea being highly soluble, stable, inexpensive, biodegradable and very easily available was selected as adductor for the present studies.

1.8 Urea as an adductor

Urea is quite versatile and is widely used in agriculture and industry. In addition, urea is a biologically important molecule in that it is produced by the body and excreted by the kidneys as a component of urine, and a significant amount of biological research has been carried out on urea. However, urea is not only of biological interest, and over the past 60 years a large amount of chemical research involving urea has been undertaken due to the capacity of urea to form inclusion compounds with a large variety of organic materials.
Introduction

At room temperature and at zero pressure, urea reveals a tetragonal structure with extensive hydrogen bonding (Fig. 1.7).

Figure 1.7 Tetragonal structure of pure urea (Smith, 1952).

However, in 1940, Bengen found by chance that urea can form a crystalline adduct with octyl alcohol (Bengen, 1940). Ever since that accidental discovery of urea adducts, the chemistry of urea inclusion compounds have received much attention and is a subject of continuing interest. The urea clathrates or more commonly known as urea adducts are bonded to one another by hydrogen bonds between the nitrogen and oxygen atoms. The interlinked urea molecules are arranged almost as the wax in honeycomb, leaving long tubular cavities in which the guest molecules are located (Fig. 1.8). Urea is found to form adducts with linear organic compounds with six-or more carbon atoms under ordinary conditions. It is now well established that urea crystallizes in a channel like structure permitting enclosure of unbranched paraffins, alcohols, ketones, organic acids and other compounds. In the structure of conventional urea inclusion compounds, the urea molecules form an extensively hydrogen-bonded arrangement containing linear, parallel tunnels, the guest molecules are densely packed along these tunnels. The host structure is
hexagonal at ambient temperature, with the effective channel diameter between 5.5-5.8Å (George and Harris, 1997).

Figure 1.8 A projection in the hexagonal plane of the urea-alkane molecules.

Structural compatibility between host and guest components is fundamental to most inclusion phenomena, and as a consequence, urea forms inclusion compounds with guest molecules that are based on a sufficiently long alkane chain with only a limited degree of substitution of this chain allowed. Examples of appropriate guest molecules are alkanes and derivatives such as α,ω-dihaloalkanes, diacyl peroxides, carboxylic acids, alkanones, α,ω-alkane dicarboxylic acids, (α+1),(ω-1)-alkanediones and carboxylic acids anhydrides.

1.9 The proposed technique

Urea is a well known adductor for linear long chain organic compounds. In general molecules containing benzene and cyclohexane do not form inclusion compounds with urea, presumably because these structural components are too wide to fit inside the urea tunnel. However, 1-phenyl-octadecane and 1-cyclohexyleicosane, in which the ring is, located at the end of a long chain, form inclusion compounds with urea. The long chain of this compound is readily adducted and apparently the unit cell can easily withstand the distortion caused by an occasional benzene group (Findlay, 1962). Also, 3-methyl heptane (normally a non-adductible endocyte, NNAE) forms an adduct with urea only
when a more slender hydrocarbon (e.g. \(n-C_{14}H_{24}\)) -a rapidly adductible endocyte (RAE) serves as a "pathfinder" (Findlay, 1962; Schlenk, 1949). The endocytes possessing a sufficiently long \(n\)-alkane chain and hence easily adductible within urea channels are named herein rapidly adductible endocytes (RAE) while sufficiently substituted and/or cyclic endocytes which are known to be non-adductible in urea are named Normally Non-Adductible Endocytes (NNAE).

The phenomena of co-inclusion of a NNAE in presence of RAE in urea lattice was reported in literature (1949) but never investigated further. However, in 1993, the aforementioned reports were exploited, by Madan and Grover in 1993, for co-inclusion of Vitamin A palmitate in urea in the presence of a suitable RAE resulting in improved pharmaceutical characteristics of Vitamin A palmitate. Later, Bajaj and Madan patented urea inclusion formation as a process for converting liquid Vitamin E into free flowing crystalline powder having improved stability and better dissolution profile. However, there are no further reports of exploitation of aforementioned technique for improvement for pharmaceutical characteristics of drugs and till date; moreover, there is not even a single product available in the market based on the said technique.

In the present study, an attempt has been made to include normally non-adductible endocytic (NNAE) drug in urea through modified technique for the improvement of pharmaceutical characteristics such as the dissolution profile, content uniformity, safe handling characteristics apart from protection from photo- and air-degradation.

Thus, the present study relates to co-inclusion of NNA endocytic drugs in the presence of a RAE leading to formation of stable free flowing solid of urea based channel lattice complex. Due to presence of cyclic and/or substituted moieties in their molecular structure, the NNAE drugs are not known to get adducted in urea under any known conditions. However, in presence of a suitable RAE, small amount of NNAE drug co-adducts and formation of mixed crystals results. (An illustrative flow-diagram depicting method of preparation is presented in Fig. 1.9) However, presence of either cyclic and/or highly branched groups in normally non-adductible endocytic drug will result in
Fig. 1.9 Preparation of urea based co-inclusion compounds of NNAE drugs (Madan and Grover, 1993; Madan, 1994).

NNAED → UREA → RAE → METHANOL

→ Dissolution of urea and RAE in methanol

→ Solubilisation of NNAED in methanolic solution
  Of urea and RAE

→ Coinclusion

→ Allow the crystals of urea based CIC of NNAED to form and
  grow under controlled conditions of temperature and agitation

→ Separation of crystals from the magma

→ Drying

→ PRODUCT
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distortion of unit cells of hexagonal urea following co-inclusion with RAE. Any
distortion of unit cells of hexagonal urea will lead to decrease in heat of decomposition of
hexagonal urea and facilitate rapid dissolution. Since the drug is already at molecular
level, release of drug from the distorted lattice is expected to result in an almost rapid and
instantaneous release of medicament. Moreover, that when enclosed in a network of host
molecules, the guest moiety will be shielded from effect of atmospheric oxidation.
Further as the guest molecule is entrapped within the host framework, there is restricted
movement along bond axis leading to reduced possibility of photoisomerisation. Hence,
urea based inclusion complexes of drugs in presence of a suitable rapidly adductible
endocyt can be characterized by improved solubility and stability profile.
Though a number of long straight chain organic compounds such as fatty acids, alkanes,
alcohols, amino acids, monoester, diesters can be employed as RAE. Stearic acid,
palmitic acid, linoleic acid, oleic acid, n-octane and n-octanol represent some of the
rapidly adductible endocytcs. However, fatty acid-urea adducts have been shown to
exhibit improved stability as compared to those of n-aliphatic compounds mainly due to
dimerization of fatty acids in hexagonal urea lattice (McAdie, 1963). Hence, for the
present study, oleic acid was selected as the RAE for the purpose of co-inclusion of
NNAE drugs in urea.
This novel technique is naturally expected to offer following distinct advantages:

- Drug is present at molecular level. It is amorphous and does not constitute any
crystalline lattice of its own
- Improved dissolution profile of drugs caused by good solubility of urea in water
  leading to instantaneous release of the enclosed drug
- Improved photo stability due to containment of drug in lattice of host and hence
  protection from incident photons, which ultimately lead to initiation of photo-
  induced degradation reactions
- Improved air-stability due to containment of drug in host lattice and hence
  protection from atmospheric degradation
- Excellent content uniformity of the resulting product., important for low dose,
lipid (-like), barely homogenizable drugs, where content uniformity is
problematic
Introduction

- Reduced handling problems due to containment of toxic or hazardous drug in host lattice leading to prevention with direct skin contact, for obvious reasons
- Can be employed for conversion of low dose liquid medicaments into pseudosolids
- Can be utilized for adduct formation of thermolabile drugs also as it requires only moderate temperature variations (Bist and Tao, 2005)
- Can be utilized for formulation of drug where drug is incompatible with some other component of formulation
- Improved flow characteristics of resulting hexagonal urea
- The process can be incorporated into the basic drug manufacturing unit itself, where the final drug product is made available in the form of stable, free flowing powder as urea adduct and is ready to be formulated
- Low processing cost, does not require costly chemicals or machinery
- Robust process i.e. process that is reproducible and repeatable with negligible variations in results
- Easily scalable process, and can be easily upgraded from pilot plant to industrial scale
- Low energy consumption, due to non-involvement of high temperature or intense agitation
- Short processing time, runs into several minutes
- Raw materials can be recycled and reused making the process compatible with the environment

In view of the above, an attempt has been made in the present study to explore the potential of urea for inclusion of substituted cyclic drugs for improvement of pharmaceutical characteristics with main emphasis on dissolution profile, content uniformity and safe handling apart from protection from photo- and air-degradation.