The cyclodextrine (CD), a cyclic oligosaccharides finds a major application in pharmaceutical industries. The characteristic nature and structure of cyclodextrine makes it’s place in pharmaceutical exipients. Although other exipients are available cyclodextrine makes it’s own place.

**β-Cyclodextrin:**

- β-CD does not usually possess rather good complexation efficiency with drugs. However β-CD and its complexes have very limited aqueous solubility.
- It’s a NATURAL cyclodextrine.

**Cyclodextrines Derivatives of Ph’ceuticals Interest**

- RMβCD (Randomly methylated β-CD)
- HPβCD (Hydroxy propyl β-CD)*
- DMβCD (2,4- dimethyl β-CD)**
- SBEβCD (Sulfobutylether β-CD)

**Structure and characteristics of cyclodextrine:**

- Cyclodextrins are cyclic (R-1,4)-linked oligosaccharides of R-D-glucopyranose containing a relatively hydrophobic central cavity and hydrophilic outer surface. Owing to lack of free rotation about the bonds connecting the glucopyranose units, the cyclodextrins are not perfectly cylindrical molecules but are toroidal or cone shaped.
- Based on this architecture, the primary hydroxyl groups are located on the narrow side of the torus while the secondary hydroxyl groups are located on the wider edge.
- The naturally occurring cyclodextrines mainly consists of six (6), seven (7), eight (8) glucopyranose units and known as α-CD (cyclohexaamylose), β-CD(cycloheptaamylose), γ-CD (cyclooctaamylose) respectively.
- Naturally occurring cyclodextrine obtained from action of *Bacillus marcerans* amylase on starch to form homogenous cyclic α,(1→4) linkage glycoprotein.

![Figure 1](image_url) *(a) The chemical structure and (b) the toroidal shape of the β-cyclodextrin molecule.*
The aqueous solubility of the parent Cyclodextrins is much lower than that of comparable acyclic saccharides, and this could partly be due to relatively strong binding of the cyclodextrin molecules in the crystal state (i.e., relatively high crystal lattice energy).

In addition, α- and δ-cyclodextrin form intramolecular hydrogen bonds between secondary OH groups, which detracts from hydrogen bond formation with surrounding water molecules, resulting in less negative heats of hydration. Thus, intramolecular hydrogen bonding can result in relatively unfavorable enthalpies of solution and low aqueous solubilities.

### TABLE SHOWING DIFFERENT PROPERTIES:

<table>
<thead>
<tr>
<th></th>
<th>α-CD</th>
<th>β-CD</th>
<th>γ-CD</th>
<th>δ-CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular formula</td>
<td>C₃₆H₶₀O₃₀</td>
<td>C₄₂H₷₀O₃₅</td>
<td>C₴₈H₸₀O₄₀</td>
<td>-</td>
</tr>
<tr>
<td>Optical rotation[α]d</td>
<td>+150.5</td>
<td>+160.0</td>
<td>177.4</td>
<td>-</td>
</tr>
<tr>
<td>GP units</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>972</td>
<td>1135</td>
<td>1297</td>
<td>1459</td>
</tr>
<tr>
<td>Cavity diameter(A)</td>
<td>4.7-5.3</td>
<td>6-6.5</td>
<td>7.5-8.3</td>
<td>10.3-11.2</td>
</tr>
<tr>
<td>Solubility(g/100 ml)25°C</td>
<td>14.5</td>
<td>18.5</td>
<td>23.2</td>
<td>-</td>
</tr>
</tbody>
</table>

- The cyclodextrine mainly used for solubilization, stabilization and to increase bioavailability of pharmaceutical agent. Also used to prevent drug-drug, drug-addative interaction or to minimize the GIT and ocular irritation.
- The major drawback of naturally occurring cyclodextrine is it's limited aqueous solubility (limited intrinsic activity).
- β-cyclodextrine finds major application in pharmaceutical industry than other cyclodextrine. Because, α- cyclodextrine has a small cavity so it can incorporated with a small molecules only while γ- cyclodextrine has a high cost.
- β- Cyclodextrine has sufficient cavity size for incorporation of most pharmaceuticals.

- **Examples of drugs whose solubility is increased by CDs**
  - sulphonamides, tetracyclines, morphine, aspirin, 
  - benzocaine, ephedrine, reserpine and testosterone
  - Sulphonylureas like glipizide, glicazide, glidebclamide, tobutamide, &acetohexamine.
  - Ziprasidone HCl, Itraconazole, Valdecoxib, Ketoprofen, piroxicam.
Solubility enhancement by the use of 0.1 M SBE – β – CD

<table>
<thead>
<tr>
<th>Solute</th>
<th>Solubility enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>2020</td>
</tr>
<tr>
<td>Prednisolone acetate</td>
<td>426</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>189</td>
</tr>
<tr>
<td>Dapsone</td>
<td>106</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>89</td>
</tr>
</tbody>
</table>

- Whereby solubility enhancement is the ratio of solubility in solubilizer solution and solubility in water.

Solubility enhancement by the use of high concentrations of Hp – β – CD

<table>
<thead>
<tr>
<th>Solute</th>
<th>%Hp - β – CD</th>
<th>Solubility Enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estriol</td>
<td>50</td>
<td>13,666</td>
</tr>
<tr>
<td>Estradiol</td>
<td>40</td>
<td>7000</td>
</tr>
<tr>
<td>Progesterone</td>
<td>40</td>
<td>2266</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>40</td>
<td>1400</td>
</tr>
<tr>
<td>Testosterone</td>
<td>40</td>
<td>1461</td>
</tr>
<tr>
<td>50 % Digoxin</td>
<td>50</td>
<td>971</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>50</td>
<td>240</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>50</td>
<td>88</td>
</tr>
<tr>
<td>Diphenyl hydantoin</td>
<td>50</td>
<td>57</td>
</tr>
</tbody>
</table>

- Chemical modification of cyclodextrine:
  - Theoratically the cyclodextrine can have up to 3(n) substitution where n is the number of glycoprotein unit which comprise the cyclodextrine molecules. This called dreege of substitution (DS).
  - The DS refer to substitution other than hydrogen (substitution on hydroxy group)

CYCLODEXTRIN COMPLEXES

- The central cavity of the cyclodextrin molecule is lined with skeletal carbons and ethereal oxygens of the glucose residues. It is therefore lipophilic. The polarity of the cavity has been estimated to be similar to that of aqueous ethanolic solution. It provides a lipophilic microenvironment into which suitably sized drug molecules may enter and be included.

- No covalent bonds are formed or broken during drug-cyclodextrin complex formation, and in aqueous solutions, the complexes are readily dissociated. Free drug molecules are in equilibrium with the molecules bound within the cyclodextrin cavity.
Method for preparation of cyclodextrine complex:

- The important interplay of atomic (van der walls), thermodynamic (hydrogen bond), solvent (hydrophobic) that account for the stable complex that may be formed with chemical substance while in apolar environment of cyclodextrine cavity.

- The complex exists in equilibrium depend on concentration of cyclodextrine, guest chemical and water amount.

For solution phase:

- Excess amount of drug is added to an aqueous cyclodextrine solution, suspension and agitated up to one week at desired temperature.

- The suspension then filtered or centrifuged to form clear drug- cyclodextrine solution.

For solid phase:

- Water is removed from aqueous drug cyclodextrine complex solution by evaporation and/or sublimation.

- Also by super saturation solution through sonication followed by precipitation at desired temperature.

To get highest drug solubilization:

(a) Use unionized drug because it form a more stable complex than ionized drug.

(b) Lower the aqueous solubility of pure drug the greater relative solubility enhancement obtained through cyclodextrine complexation.

(c) Cyclodextrine derivative of lower molecular weight substance are better solubilizer than same type of derivative of higher molar substitution.

(d) Charged cyclodextrine can be powerful solubilizer but their effect appears to depend on the relative proximity of the charge to cyclodextrine cavity.

(e) Use water soluble polymer in aqueous solution which increase the solubilising effect of cyclodextrine on various hydrophilic drug by increase the apparent stability constant of drug- cyclodextrine complex.

>e.g.-Enhanced solubility & dissolution rate of **LAMOTRIGINE** by inclusion Complexation with β-CD.

The inclusion complex of Lamotrigine with β-CD was prepared In equimolar ratios by a KNEADING method.

- Cyclodextrins may increase or decrease the reactivity of guest molecule depending on the nature of of the reaction and the molecule within the CD cavity.
- Thus , α-CD tends to favor pH-dependent hydrolysis of indomethacin in aqueous solution, whereas β-CD inhibits it.
- *e.g.* - The aqueous solubility of RETINOIC ACID (0.5 mg/litre), a drug used topically in the treatment of acne, is increased to 160mg/litre by complexation with BETA cyclodextrine.

- In addition to hydrophilic derivatives, hydrophobic forms of BETA-CD have been found useful as sustained release drug carriers.

- Thus, the release rate of the water-soluble calcium antagonist DILTIAZEM was significantly decreased by complexation with ethylated BETA-CD.

- Ethylated BETA-CD has also been used to retard the delivery of isosorbide dinitrate.

  *e.g.* - Amorphous derivatives of β-CD and γ-CD are more effective as solubilizing agents for sex hormones than the parent cyclodextrines.

- Complexes of testosterone with amorphous hydroxypropyl β-CD allow an efficient transport of hormone into the circulation when given SUBLINGUALLY.

  - The bitter taste of suspension of FEMOXETINE, an antidepressant, is greatly suppressed by complexation of the drug with BETA-CD.

  *e.g.* - Solubility enhancement of NITROBENZAMIDE in aqueous solution by Beta-Cyclodextrine.....

- To increase aqueous solubility of Drugs.

- To increase chemical stability of drugs.

**Drug stability in cyclodextrine complex:**

----Cyclodextrine can insulate a labile compound from a potentially corrosive environment and in this way reduce or even prevent drug hydrolysis, oxidation, polymerization etc.

----Cyclodextrine have not any effect on reactivity and can’t accelerate drug degradation.

- The fundamental property that describes the strength of interaction between a drug and a cyclodextrine is binding constant (stability constant) $k$ that is related to thermodynamic property $\Delta G$, a standard free energy change during complexation.

**CALCULATION OF $U_{cd}$ FOR UNIONISABLE DRUG**

\[
D + C \overset{K}{\leftrightarrow} DC
\]

\[
K = \frac{[DC]}{[D][C]}
\]

Where,

$K$ = Binding Constant

$[D]$ = Concentration of Free Drug
\[ [C] = \text{Concentration of Free Cyclodextrin} \]
\[ [DC] = \text{Concentration of Complex} \]
\[ So = \text{Intrinsic Solubility of Drug} \]
\[ [Ct] = \text{Total Concentration of Cyclodextrin} \]

\[
K = \frac{[DC]}{So \{ [Ct] - [DC] \}}
\]

\[
KSo\{[Ct]\} / KSo\{[DC]\} = [DC]
\]

\[
KSo\{[Ct]\} = [DC] \times [1 + KSo]
\]

\[
[DC] = \frac{KSo}{1 + KSo} \times [Ct]
\]

Total Solubility = Intrinsic Solubility + Drug in Complex

\[
S_T = So + [DC]
\]

\[
S_T = So + \frac{KSo}{1 + KSo} \times [Ct]
\]  

(1)

If \( Dt \) = Dose of Drug

\( CDt \) = Total amount of Cyclodextrin

\( V \) = Volume available for dissolution

Therefore,

\[
\text{Total Concentration of Cyclodextrin} \ [Ct] = \frac{CDt}{V} \rightarrow \quad \text{(2)}
\]

Now,

Concentration of Drug in solution \( \leq \) Total Solubility of Drug

\[
\frac{Dt}{V} \leq St \quad \text{------------------------} \quad \text{(3)}
\]
From equation (1), (2) and (3) …

\[
\frac{Dt}{V} \leq \frac{K_{So}}{1 + K_{So}} \cdot \frac{CDt}{X} \cdot \frac{1}{V}
\]

Now multiply with \( \frac{V}{Dt} \),

\[
\frac{So}{Dt} \cdot \frac{K_{So}}{1 + K_{So}} \cdot \frac{CDt}{X} \cdot \frac{1}{Dt} \geq 1
\]

\( \frac{So}{Dt} \) = Inverse of Dose No.

For poorly soluble drugs \( \frac{So}{Dt} \) value is less than 1, so that Negligible

**So, Utility Number** = \( U_{CD} = \frac{K_{So}}{1 + K_{So}} \times \frac{CDt}{Dt} \) ----- (4)

\( U_{CD} = \frac{K_{So}}{1 + K_{So}} \times \frac{M_{CD}}{MW_{CD}} \times \frac{MW_{DRUG}}{M_{DRUG}} \) ----- (5)

Where, \( M_{CD} \) = Workable amount of Cyclodextrin
\( MW_{CD} \) = Molecular weight of Cyclodextrin
\( M_{DRUG} \) = Dose of Drug
\( MW_{DRUG} \) = Molecular weight of Drug

NOTE: For calculating amount of CD to be taken, consider \( U_{CD} \) as 1.

- "K" can be determined experimentally by measuring changes in physicochemical properties (solubility, spectral etc.) of drug with changes in drug &/or Cyclodextrin’s concentration.
- We can also find K, if "IN SILICO" methods are available.
- Value of K ranges from 0 – 1,000,000 for most of drugs
- Statistical analysis of large number of drug : cyclodextrin complex shows mean binding constant \( (K) \) or \( \alpha - CD = 123 \text{ M}^{-1} \) for \( \beta - CD = 490 \text{ M}^{-1} \)
  for \( \gamma - CD = 525 \text{ M}^{-1} \)
FOR IONISABLE DRUG

\[ U_{CD} = \frac{K_{app.Sapp}}{1 + K_{app.Sapp}} \times \frac{M_{CD}}{MW_{CD}} \times \frac{MW_{DRUG}}{M_{DRUG}} \]  

\( (6) \)

for acidic drug...

\[ K_{app} = \frac{K^O}{K_{a + [H^+]}} + \frac{K}{K_{a + [H^+]}} \]

\[ S_{app} = \frac{K_{a + [H^+]}}{[H^+]} \]

for basic drug...

\[ K_{app} = \frac{K^O}{K_{a + [H^+]}} + \frac{K}{K_{a + [H^+]}} \]

\[ S_{app} = \frac{K_{a + [H^+]}}{K} \]

\( K_a = \) ionization constant

\( K^O = \) Binding constant for Neutral Drug : Cyclodextrin Complex

\( K^+ = \) Binding constant for Cationic Drug : Cyclodextrin Complex

\( K^- = \) Binding constant for Anionic Drug : Cyclodextrin Complex

Generally \( K_{app} \) lies between \( K_{neutral} \) and \( K_{charge} \)

So, value of \( K_{app} \) is checked at different pH and lowest value is selected to get \( U_{CD} \) value near to 1.

**Advantages**

1. **Enhancement of Solubility:**
   - CDs increase the aqueous solubility of many poorly soluble drugs by forming inclusion complexes with their apolar molecules or functional groups.
   - The resulting complex hides most of the hydrophobic functionality in the interior cavity of the CD while the hydrophilic hydroxyl groups on the external surface remain exposed to the environment. The net effect is that a water soluble CD-drug complex is formed.
2. Enhancement of Bioavailability:
   - When poor bioavailability is due to low solubility, CDs are of extreme value. A precondition for the absorption of an orally administered drug is its release from the formulation in dissolved form. When drug is complexed with CD, dissolution rate and consequently absorption is enhanced.
   - Reducing the hydrophobicity of drugs by CD complexation also improves their percutaneous or rectal absorption.
   - In addition to improving solubility, CDs also prevent crystallization of active ingredients by complexing individual drug molecules so that they can no longer self-assemble into a crystal lattice.

3. Improvement of Stability:
   - CD complexation is of immense application in improving the chemical, physical and thermal stability of drugs.
   - For an active molecule to degrade upon exposure to oxygen, water, radiation or heat, chemical reactions must take place. When a molecule is entrapped within the CD cavity, it is difficult for the reactants to diffuse into the cavity and react with the protected guest.
   - In the case of thermal or radiation induced degradation, the active must undergo molecular rearrangements. Again, due to the stearic constraints on the guest molecule within the cavity, it is difficult for the entrapped molecule to fragment upon exposure to heat or light or if it does fragment, the fragments do not have the mobility needed to separate and react before a simple recombination takes place.
   - Volatile components can be stabilized against loss by reducing the volatility in case of liquids and by reducing the tendency of some solid products to sublimate.
   - The deliquescence of hygroscopic substances is also reduced by complexation with CDs. Physical changes like sedimentation and caking in suspension or recrystallization of drugs to less soluble but thermodynamically more stable polymorphic crystal forms, etc., can also be prevented or reduced by complexation with CDs.

4. Reduction of Irritation:
   - Drug substances that irritate the stomach, skin or eye can be encapsulated within a CD cavity to reduce their irritancy. Inclusion complexation with CDs reduces the local concentration of the free drug below the irritancy threshold. As the complex gradually dissociates and the free drug is released, it gets absorbed into the body and its local free concentration always remains below levels that might be irritating to the mucosa.

5. Prevention of Incompatibility:
   - Drugs are often incompatible with each other or with other inactive ingredients present in a formulation. Encapsulating one of the incompatible ingredients within a CD molecule stabilizes the formulation by physically separating the components in order to prevent drug-drug or drug-additive interaction.

6. Odor and Taste Masking:
Unpleasant Odor and bitter taste of drugs can be masked by complexation with CDs. Molecules or functional groups that cause unpleasant tastes or odors can be hidden from the sensory receptors by encapsulating them within the CD cavity. The resulting complexes have no or little taste or odor and are much more acceptable to the patient.

7. Material Handling Benefits:
- Substances that are oils/liquids at room temperature can be difficult to handle and formulate into stable solid dosage forms. Complexation with CDs may convert such substances into microcrystalline or amorphous powders which can be conveniently handled and formulated into solid dosage forms by conventional production processes and equipment.

Disadvantage
- Most important limitation is that an elementary nature, whether the drug can form any complex at all. The most important parameter that determine the formation of inclusion complex of the molecule are it's hydrophobicity and geometry in relation to those of cyclodextrine cavity.
- Another limitation related to the stochiometry of complex. CD-drug complexes usually have 1:1, 1:2, 3:2 stoichiometry. The majority drug have much lower molecular weight than CD this difference and the stochiometry of complex limit the amount of drug that can be supplied conveniently by using this method.

**METHODS TO ENHANCE COMPLEXATION EFFICIENCY**

<table>
<thead>
<tr>
<th>EFFECT</th>
<th>CONSEQUENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Ionization</td>
<td>Unionized drugs do usually form more stable complexes than their ionic counterparts. However, ionization of a drug increases its apparent intrinsic solubility resulting in enhanced complexation.</td>
</tr>
<tr>
<td>Salt formation</td>
<td>It is sometimes possible to enhance the apparent intrinsic solubility of a drug through salt formation, i.e. forming a more water-soluble salt of the drug without significantly reducing its ability to form cyclodextrin complexes.</td>
</tr>
<tr>
<td>The Acid/Base Ternary complexes</td>
<td>It has been shown that certain organic hydroxy acids (such as citric acid) and certain organic bases are able to enhance the complexation efficiency by formation of ternary drug/cyclodextrin/acid or base complexes.</td>
</tr>
<tr>
<td>Polymer complexes</td>
<td>Water-soluble polymers form a ternary complex with drug/cyclodextrin complexes increasing the observed stability constant of the drug/cyclodextrin complex. This observed increase in the value of the constant increases the complexation efficiency.</td>
</tr>
<tr>
<td>Metal complexes</td>
<td>Many drugs are able to form somewhat water-soluble metal complexes without decreasing the drugs ability to form complexes with cyclodextrins. Thus, the complexation efficiency can be enhanced by formation of drug: metal ion: cyclodextrin complexes.</td>
</tr>
<tr>
<td>Cosolvents</td>
<td>Addition of cosolvents to the complexation media can increase the apparent intrinsic solubility of the drug that can lead to enhanced complexation efficiency.</td>
</tr>
<tr>
<td>Ion pairing</td>
<td>Ion pairing of positively charged compounds with negatively charged cyclodextrins enhances the complexation efficiency.</td>
</tr>
<tr>
<td>Combination of 2 or more methods</td>
<td>Frequently the complexation efficiency can be enhanced even further by combining two or more of the above mentioned methods. For example drug ionization and the polymer method, or solubilization of the cyclodextrin aggregates by adding both polymers and cations or anions to the aqueous complexation medium.</td>
</tr>
</tbody>
</table>

**DRUG AVAILABILITY FROM CYCLODEXTRIN - CONTAINING PRODUCTS**
- It has been widely believed that drug availability in cyclodextrin-containing formulations will be hampered by the slow release of drug molecules from the cyclodextrin cavities.
- However, it has been shown that the rates for formation and dissociation of drug/cyclodextrin complexes are very close to diffusion controlled limits with complexes being continually formed and broken down.
- Consequently, presence of water-soluble drug/cyclodextrin complexes right at the hydrated epithelial surface will frequently increase the availability of dissolved drug molecules, especially of lipophilic drugs with poor aqueous solubility.
- Studies have shown that cyclodextrin enhance oral bioavailability of FDA’s Class II (poor aqueous solubility, high permeability) drugs but they can hamper bioavailability of Class I (high solubility, high permeability) and Class III (high solubility, poor permeability) drugs.

**APPLICATIONS OF CYCLODEXTRINE IN DRUG DELIVERY SYSTEMS**

1. **Oral Drug Delivery System:**
   - CDs have been used as an excipient to transport the drugs through an aqueous medium to the lipophilic absorption surface in the gastro-intestinal tract, i.e., complexation with CDs has been used to enhance the dissolution rate of poorly water-soluble drugs. Hydrophilic CDs have been particularly useful in this regard.
   - Rapid dissolving complexes with CDs have also been formulated for buccal and sublingual administration. In this type of drug delivery system, a rapid increase in the systemic drug concentration takes place along with the avoidance of systemic and hepatic first pass metabolism.

2. **Rectal Drug Delivery System:**
   CDs, to be used as excipient in rectal drug delivery system should have the following characteristics:
   - They should be non-irritating to the rectal mucosa.
   - They should inhibit the reverse diffusion of drugs into the vehicle.
   - They should have a low affinity for the suppository base.
   - Complexations of hydrophobic drugs with CDs have resulted in a significant increase in the rectal absorption of the drugs. The reason for the enhanced release has been
attributed to the formation of a hydrophilic complex, which has a low affinity for the
base and rapidly dissolves in the rectal fluids.

CDs have also been studied as rectal permeation enhancers. They have been found to
increase the permeation of drugs through rectal epithelium cells.

It has been reported that complexation of morphine HCl with α and β-CD resulted in
an increase in the bioavailability of morphine when it was formulated as a suppository.
The complexation increased only the bioavailability and did not alter the release rate
of morphine from the vehicle.

3. Nasal Drug Delivery System:
CDs, when used as excipients in nasal drug delivery system should have the following
characteristics:
1. They should not have any local or systemic effect.
2. They should not interfere with the nasal muco-ciliary functions.
3. They should not show ciliostatic effect.
4. They should be non-irritating and non-allergenic.
5. They should enhance the permeation of drugs across nasal epithelium in a reversible
manner.

The hydrophilic CDs solubilize some specific lipids from biological membrane through
the rapid and reversible formation of inclusion complexes, leading to an increase in
the membrane permeability. Of all the CDs available, HP-βCD and methylated βCDs
have been used mainly as solubilizers and absorption enhancers in nasal drug delivery
system.

The concept of pulsed estrogen therapy has recently been exploited by the
introduction of a nasal spray delivery system containing CD.

The administration of estradiol via the nasal mucosa was made possible by the use of
randomly methylated alpha-CD, which increased the solubility of estradiol.

4. Transdermal Drug Delivery System:
CDs to be used as excipients in transdermal drug delivery system should possess the
following characteristics:
1. They should be therapeutically inert.
2. They should not interfere with the normal functions of the skin such as protection from
heat, humidity, radiation and other potential insults.
3. They should not alter the pH of the skin.
4. They should not interact with any component of the skin.
5. They should not cause skin irritation.

In transdermal drug delivery system, hydrophilic, hydrophobic as well as ionizable
CDs have been used as carriers for drugs.

Hydrophilic CDs like 2,6 dimethyl-β-CD and hydroxypropyl-β-CD have been used to
improve the solubility and dissolution characteristics of insoluble drugs.

Hydrophobic CDs such as 2,6 diethyl-β-CD have been used to retard the dissolution
rate of water soluble drugs and ionizable CDs like carboxymethyl-β-CD, sulfated and
sulfobutylether-β-CD have been used to improve inclusion capacity and reduce side
effects associated with drugs.
5. Ocular Drug Delivery System:
CDs to be used as an excipient in ocular drug delivery system should possess the following characteristics:
1. They should be non-irritating to the ocular surface, as irritation can cause reflex tearing and blinking resulting in fast washout of instilled drug.
2. They should be non-toxic and well tolerated.
3. They should be inert in nature.
4. They should enhance the permeability of the drug through the corneal mucosa.
   - CDs have been used to solubilize poorly water soluble drugs and enhance ocular bioavailability of lipophilic drugs by keeping the drugs in solution and increasing their availability at the surface of the corneal barrier.
   - Hydrophilic CDs such as HP-β-CD and sulphobutyl-β-CD have been used for the purpose mainly due to their non-toxicity and hydrophilicity.

6 Controlled and Targeted Drug Delivery System:
- Various CD derivatives, hydrophobic CDs such as alkylated and acylated derivatives have been used to prolong the release rate of drugs while hydrophilic derivatives have been used to enhance the release rate.
- One of the most recent applications of CDs has been their incorporation in liposomes and neosomes. The main purpose has been to combine the advantages of CDs (such as increase solubility) with the advantages of liposomes and neosomes (such as their precision and targeting).
- Complexation with CD has also been used for brain targeting and specific cell targeting.

Future Prospects of Cyclodextrins
- The future prospects of CD and its derivatives are quite bright since they possess remarkably unique properties of forming inclusion complexes with drugs. An increasingly number of drugs being developed today have problem of poor solubility, bioavailability and permeability.
- CDs can serve as useful tools in the hands of pharmaceutical scientists for optimizing the drug delivery of such problematic drugs and also for drugs having other undesirable properties such as poor stability, objectionable taste and odor and irritation potential.
- Although, presently only conventional formulations such as tablets, capsules, solutions and ointments have been commercialized using CDs, these are extensively being studied for their utilization in novel formulations such as nanoparticles, liposomes, nasal, ophthalmic and rectal formulations, transdermal products and targeted drug delivery systems and the time is not far when such products will become commercially available.