Cycloexdrins (CDs), homologous cyclic oligosaccharides have long been known to increase the apparent solubility of many lipophilic drugs through non-covalent inclusion complexation\textsuperscript{1,2}. Cyclodextrins and their derivatives play an important role in the formulation development due to their effect on solubility, dissolution rate, chemical stability and absorption of a drug\textsuperscript{3,4}.

The $\alpha$-, $\beta$- and $\gamma$-cyclodextrins are cyclic oligosaccharides consisting of six, seven and eight glucose units respectively. While it is thought that, due to steric factors, cyclodextrins having fewer than six glucopyranose units cannot exist. Chemical and physical properties of the four most common cyclodextrins are given in Table 2.1. The melting points of $\alpha$-, $\beta$- and $\gamma$-cyclodextrins are between 240° and 265°C, consistent with their stable crystal lattice structure\textsuperscript{5}.

\textbf{Table 2.1}

\textbf{Some Characteristics of $\alpha$-, $\beta$-, $\gamma$- and $\delta$-Cyclodextrins}

<table>
<thead>
<tr>
<th></th>
<th>$\alpha$</th>
<th>$\beta$</th>
<th>$\gamma$</th>
<th>$\delta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of glucopyranose 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>Central cavity diameter (Å)</td>
<td>4.7-5.3</td>
<td>6.0-6.5</td>
<td>7.5-8.3</td>
<td>10.3-11.2</td>
</tr>
<tr>
<td>Water solubility at 25°C (g/100 ml)</td>
<td>14.5</td>
<td>1.85</td>
<td>23.2</td>
<td>8.19</td>
</tr>
</tbody>
</table>
They are enzymatic conversion products of starch. The enzyme cyclodextrin-glucosyl transferase produced by B. macerans acts on partially hydrolysed starch (a mixture of linear dextrins) and produces a mixture of cyclic and acyclic dextrins, from which pure cyclodextrins (CDs) are isolated. The structure of the most important CD, β-cyclodextrin is shown in Fig. 2.1.

**Fig.2.1: The Structure of β-cyclodextrin**

The ‘torus' shaped macro-ring is built of α-1,4-D-glucose units. As a consequence of conformation of glucopyranose units, all secondary OH-groups are located on one edge (wider edge) of the ‘torus’ like CD molecule while all primary OH-groups are on the other side (narrow side of torus). The lining of the internal cavity is formed by OH-atoms and glucosidic oxygen-bridge atoms, therefore, the inner surface is hydrophobic, but outer surface is hydrophilic.
Pharmacokinetics of Cyclodextrins:

- The parent CDs are poorly absorbed from the g.i. tract
- Oral absorption studies have shown ≤ 2%, 0.1-0.3% and ≤ 0.1% absorption respectively with α-, β-, and γ - CDs.
- Intravenously administered CDs disappear rapidly from systemic circulation; excreted mainly through kidney. The $t_{1/2}$ of β-CD 23.9 – 50.2 min in rat.
- The $t_{1/2}$ of HP-β-CD is 24 min in rat, 48 min in dog and 72-108 min in human.
- α- and β-CDs are excreted almost completely in their intact form
- Little or no distribution of most CDs into other tissues or storage compartments is observed.

Safety of Cyclodextrins:

- Parent CDs are reported to be non-toxic and safe even at high oral doses.
- The LD$_{50}$ in rats is reported to be greater than 12.5, 18.8 and 8.0 g/kg body weight for α-, β-, and γ-CD respectively.
- α- and β-CDs produced no toxic effects when fed to rats for 30-90 days at 1%, of the diet or at 1 and 2 g/kg daily doses.

Regulatory Status of Cyclodextrins:

- Accepted as new pharmaceutical excipients by USFDA

**Formation of Complexes:**

One of the most important characteristics of CDs are their ability to form inclusion complexes. Inclusion complexation involves entrapment of a guest molecule totally or partially in the cavity of host molecule without formation of any covalent bonds. CDs are typical host molecules and can entrap a wide variety of drug molecules resulting in the formation of monomolecular inclusion complexes. Usually 1 : 1 complexes are formed, but when a guest molecule is too long to find complete accommodation in one cavity, its other end is also amenable to complex formation leading to 2 : 1 (CD : drug) or sometimes 3 : 1 or 4 : 1 complexes. It may also be possible to form 1: 2 and 1: 3 (CD: drug) complexes. The central cavity of the cyclodextrin molecule is linked 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 Measurements of stability or equilibrium constants (K_c) of the drug-cyclodextrin complexes are important properties of a compound upon inclusion.
Detection of inclusion complexation in the solution state:

Phase solubility technique is the one of the widely used methods to detect the inclusion complexation in solution state. The general experimental operation in studying molecular interactions by means of phase solubility method entails the addition of an equal weight (inconsiderable excess of its normal solubility) of a slightly soluble compound, S (substrate or guest) into each of several vials containing increasing concentrations of a relatively soluble compound, L (ligand or host or complex agent), which are closed and brought to solubility equilibrium at constant temperature. The solution phases are then analyzed, by any suitable means, for their total concentration of compound S (guest), no matter what its molecular state may be.

A phase diagram is constructed by plotting, on the vertical axis, total molar concentration of S found in the solution phase against the molar concentration of L.

Fig. 2.2. Phase solubility diagram
The phase diagrams are observed to fall into two main classes, type A and type B with some variation within the classes (Fig 2.2).

The type A can be further classified in subtypes $A_L$, $A_P$ and $A_N$, where the guest solubility of first type increases linearly with cyclodextrin concentration while those of the second and third types deviate positively and negatively, respectively from the straight line. The complex formation with a 1:1 stoichiometry gives the $A_L$ type diagram, where as the higher order complex formation in which more than one cyclodextrin molecules are involved in the complexation gives the $A_P$-type. The interaction mechanism for the $A_N$-type is complicated, because of a significant contribution of solute-solvent interaction to the complexation. In the case of the $B_s$ type, the initial ascending portion of the solubility change is followed by a plateau region and then a decrease in the solubility at higher cyclodextrin concentrations accompanying a microcrystalline precipitation of the complex. The $B_l$-type diagram is indicative of the formation of insoluble complexes in water.

The stability constant ($K_s$) and stoichiometry of complexes are determined by analyzing quantitatively the phase solubility diagram.
Detection of inclusion complexation in the solid state:

Detection of the inclusion complexation in solid state can be done by Powder X-ray diffractometry, Single crystal X-ray structure analysis, Thermo analytical, Thin layer chromatography, Paper chromatography, Infrared spectroscopy, Scanning electron microscopy and Dissolution study methods.

Methods of Preparation of CD Complexes:

Many techniques are known to form complexes with cyclodextrins, these are briefly described below.

1. Physical blending / Grinding method: Inclusion complexes can be prepared by simply grinding/ triturating the drug with cyclodextrin in mortar, on small scale. Whereas on large scale, the preparation of complexes is based on extensive blending of the drug with cyclodextrin in a rapid mass granulator usually for 30 minutes.

2. Kneading method: Paste of cyclodextrin is prepared with small amount of water to which the drug is added without a solvent or in a small amount of ethanol. After grinding paste, solvent get evaporated and powder like complex is formed. On laboratory scale kneading can be achieved by using a mortar and pestle. On large scale the kneading can be done by utilizing the extruders and other machines. Parikh reported the dissolution enhancement of Nimesulide using complexation method.
3. **Co-precipitation:** Cyclodextrin is dissolved in water and the guest is added while stirring the cyclodextrin solution. By heating, more cyclodextrin can be dissolved (20%) if the guest can tolerate the higher temperature. The cyclodextrin and guest solution must be cooled under stirring before a precipitate is formed. The precipitate can be collected by decanting, centrifugation or filtration and washed. Moyano\textsuperscript{15} had studied the solid-state characterization and dissolution characteristics of Gliclazide-Beta-cyclodextrin inclusion complexes.

4. **Solid dispersion / Co-evaporated dispersion:** In this method, drug and cyclodextrin are dissolved in ethanol and in water separately. Both the solutions are mixed and stirred to attain equilibrium. The resulting solution is evaporated to dryness preferably under vacuum.\textsuperscript{10}

5. **Neutralization method:** Drug and cyclodextrin are separately dissolved in 0.1 N sodium hydroxide, mixed and stirred for about half an hour, pH is recorded and 0.1 N HCl is added drop wise with stirring until pH reaches 7.5, where upon complexes precipitates. The residue is filtered and washed until free from chlorine. It is dried at 250\textdegree C for 24 h. and stored in desiccators Doijad\textsuperscript{16} had studied the enhancement of solubility of Piroxicam by complexation with beta-cyclodextrin.
6. **Spray drying:** In this method, first monophasic solution of drug and cyclodextrin is prepared using a suitable solvent. The solution is then stirred to attain equilibrium following which the solvent is removed by spray drying. Vozone\textsuperscript{17} had developed complexation of budesonide in cyclodextrins and particle aerodynamic characterization of the complex solid form for dry powder Inhalation.

7. **Lyophilization / Freeze drying technique:** To get a porous, amorphous powder with high degree of interaction between drug and cyclodextrin, lyophilization/freeze drying technique is considered as a suitable\textsuperscript{18-19}. Here, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug and cyclodextrin at reduced pressure. Thermolabile substances can be successfully made into complex form by this method.

8. **Melting:** Complexes can be prepared by simply melting the guest, mixed with finely powdered cyclodextrin. In such cases there should be a large excess of guest, and after cooling this excess is removed by careful washing with a weak complex, forming solvent or by vacuum sublimation\textsuperscript{20}.

9. **Microwave irradiation method:** This technique involves the microwave irradiation reaction between drug and complexing agent using a microwave oven. The drug and CD in definite molar ratio
are dissolved in a mixture of water and organic solvent in a specified proportion into a round bottom flask. The mixture is reacted for short time of about one to two minutes at 60 °C in the microwave oven. After the reaction completes, adequate amount of solvent mixture is added to the above reaction mixture to remove the residual, uncomplexed free drug and CD. The precipitate so obtained is separated using whatman filter paper, and dried in vacuum oven at 40 °C for 48 hrs.\textsuperscript{21}

10. **Supercritical anti-solvent technique:** In the supercritical fluid anti-solvent technique, carbon dioxide is used as anti-solvent for the solute but as a solvent with respect to the organic solvent. The use of supercritical carbon dioxide is advantageous as its low critical temperature and pressure makes it attractive for processing heat-labile pharmaceuticals. It is also non-toxic, nonflammable, inexpensive and is much easier to remove from the polymeric materials when the process is complete, even through small amount of carbon dioxide remains trapped inside the polymer, it poses no danger to the consumer. Supercritical particle generation processes are new and efficient route for improving bioavailability of pharmaceutically active compounds\textsuperscript{22}. In addition, supercritical fluid processes were recently proposed as a new alternative method for the preparation of drug cyclodextrin complexes. Supercritical carbon dioxide is suggested as a new complexation medium due to its properties of improved mass transfer and increased solvating
power\textsuperscript{23-27}. This method constitutes one of the most innovators methods to prepare the inclusion complex of drug with CD in solid state.

This is a non-toxic method as it is not utilizing any organic solvent, fast process, maintenance cost is low with promising results, but it requires a quite high initial cost. In this technique, first, drug and CD are dissolved in a good solvent then the solution is fed into a pressure vessel under supercritical conditions, through a nozzle (i.e. sprayed into supercritical fluid anti-solvent). When the solution is sprayed into supercritical fluid anti-solvent, the anti-solvent rapidly diffuses into that liquid solvent as the carrier liquid solvent counter diffuses into the anti-solvent. Because of the supercritical fluid expanded solvent has lower solvent power than the pure solvent, the mixture becomes supersaturated resulting in the precipitation of the solute and the solvent is carried away with the supercritical fluid flow\textsuperscript{28-29}

**Applications of Cyclodextrins:**

Cyclodextrins (CDs) are cyclic torus-shaped molecules with a hydrophilic outer surface and lipophilic central cavity, which can accommodate a variety of lipophilic drugs. As a consequence of inclusion process many physico-chemical properties such as solubility, dissolution rate, stability and bioavailability can be favorably affected\textsuperscript{30-41}
Recent Research Work on CD Complexation:

Several studies reported the cyclodextrin complexation of a variety of drugs for various purposes. A summary of recent research on cyclodextrin complexation for enhancing the solubility, dissolution rate and bioavailability is given in Table 2.2.

Table 2.2: Summary of Recent Research on Cyclodextrin Complexation

<table>
<thead>
<tr>
<th>Sl.No</th>
<th>Drug</th>
<th>Cyclodextrin used</th>
<th>Purpose/Result</th>
<th>Ref.No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Analgesic, Antipyretic, Anti-inflammatory Drugs</td>
<td>βCD, HP βCD, ME- βCD</td>
<td>Improved solubility and oral bioavailability</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>Nimesulide</td>
<td>βCD, HP βCD</td>
<td>Improve solubility and dissolution rate</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>Aceclofenac</td>
<td>γCD, 2-HPγCD</td>
<td>Investigated aggregation of complexes through semi-permeable membranes and transmission electron microscopy</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>Diclofenac sodium</td>
<td>γCD, 2-HPγCD</td>
<td>Drug loading capacities of CP βCD were studied and complexes were confirmed by 1H NMR and DSC</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>Indomethacin</td>
<td>Cationic βCD, CP βCD</td>
<td>Drug loading capacities of CP βCD were studied and complexes were confirmed by 1H NMR and DSC</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>Capsaicin</td>
<td>HPβCD</td>
<td>Improved percutaneous absorption</td>
<td>46</td>
</tr>
<tr>
<td>7</td>
<td>Etoricoxib</td>
<td>βCD, HP βCD, Poloxamer 407, PVP K30</td>
<td>Enhancement in solubility and dissolution rate</td>
<td>47</td>
</tr>
<tr>
<td>8</td>
<td>Ketrolac</td>
<td>HPβCD</td>
<td>Higher Transdermal Transport</td>
<td>48</td>
</tr>
</tbody>
</table>
### Paracetamol

α, β and γ cyclodextrin

γ complexes are most stable than β complexes which are more stable than α complex

<table>
<thead>
<tr>
<th>Paracetamol</th>
<th>α, β and γ cyclodextrin</th>
<th>γ complexes are most stable than β complexes which are more stable than α complex</th>
</tr>
</thead>
</table>

### Antimicrobial, Antifungal, Antiviral, Antibiotic Drugs

#### 9 Acyclovir

Fluorinated amphiphilic α cyclodextrins hexakis

To prepare aqueous suspensions of nanoparticles

<table>
<thead>
<tr>
<th>Acyclovir</th>
<th>Fluorinated amphiphilic α cyclodextrins hexakis</th>
<th>To prepare aqueous suspensions of nanoparticles</th>
</tr>
</thead>
</table>

#### 10 Rifampin

Novobiocin

Vancomycin

βCD

Affinity based antibiotic delivery mechanisms were developed

<table>
<thead>
<tr>
<th>Rifampin Novobiocin Vancomycin</th>
<th>βCD</th>
<th>Affinity based antibiotic delivery mechanisms were developed</th>
</tr>
</thead>
</table>

#### 11 Sulfamethoxazole

Hydroxypropyl-β-cyclodextrin

Increased solubility

<table>
<thead>
<tr>
<th>Sulfamethoxazole</th>
<th>Hydroxypropyl-β-cyclodextrin</th>
<th>Increased solubility</th>
</tr>
</thead>
</table>

#### 12 Trimethoprim

Sulfamethoxazole

cycloexetrins (α-, β-, and γ-CDs)

The solubility enhancement of trimethoprim is much higher than that of sulfamethoxazole in the presence of SDS micelles

<table>
<thead>
<tr>
<th>Trimethoprim Sulfamethoxazole</th>
<th>cycloexetrins (α-, β-, and γ-CDs)</th>
<th>The solubility enhancement of trimethoprim is much higher than that of sulfamethoxazole in the presence of SDS micelles</th>
</tr>
</thead>
</table>

#### 13 Vancomycin

β-cyclodextrin

modified release with improved bioavailability

<table>
<thead>
<tr>
<th>Vancomycin</th>
<th>β-cyclodextrin</th>
<th>modified release with improved bioavailability</th>
</tr>
</thead>
</table>

#### 14 Quercetin

β-cyclodextrin

Enhanced drug release

<table>
<thead>
<tr>
<th>Quercetin</th>
<th>β-cyclodextrin</th>
<th>Enhanced drug release</th>
</tr>
</thead>
</table>

### Anti hypertensive, Antianginal, Drugs

#### 15 Irbesartan

βCD, PEG 4000, PVP K90

Improved aqueous solubility, dissolution rate and Characterization of inclusion complexes by XRD, DSC, FTIR and SEM

<table>
<thead>
<tr>
<th>Irbesartan</th>
<th>βCD, PEG 4000, PVP K90</th>
<th>Improved aqueous solubility, dissolution rate and Characterization of inclusion complexes by XRD, DSC, FTIR and SEM</th>
</tr>
</thead>
</table>

#### 16 Carvidilol

βCD

Citric acid

Improved aqueous solubility, dissolution rate and Characterization of inclusion complexes by XRD, DSC, FTIR and SEM

<table>
<thead>
<tr>
<th>Carvidilol</th>
<th>βCD Citric acid</th>
<th>Improved aqueous solubility, dissolution rate and Characterization of inclusion complexes by XRD, DSC, FTIR and SEM</th>
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<tbody>
<tr>
<td>17</td>
<td>Felodipine</td>
<td>Cyclodextrins</td>
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<tr>
<td>18</td>
<td>Statins (Lovastatin, Simvastatin)</td>
<td>RMβCD</td>
</tr>
<tr>
<td>19</td>
<td>Valsartan</td>
<td>βCD, HP βCD, PVP K30</td>
</tr>
<tr>
<td><strong>IV</strong></td>
<td><strong>Sedatives, Antidepressant, Anti anxiety, Anticonvulsant Drugs</strong></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Lorazepam</td>
<td>HPβCD</td>
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<tr>
<td>21</td>
<td>Lamotrigine</td>
<td>βCD</td>
</tr>
<tr>
<td>22</td>
<td>Doxepin</td>
<td>βCD</td>
</tr>
<tr>
<td>23</td>
<td>Promethazine</td>
<td>monochlorotriazinyl-β-cyclodextrin</td>
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<td>24</td>
<td>Olanzapine</td>
<td>methyl- β–CD</td>
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<tr>
<td><strong>V</strong></td>
<td><strong>Anti cancer Drugs</strong></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Tacrolimus</td>
<td>Dimethyl- β-cyclodextrin</td>
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<tr>
<td>26</td>
<td>Diferuloylmethane</td>
<td>hydroxypropyl-β-cyclodextrin</td>
</tr>
<tr>
<td>27</td>
<td>Betulin</td>
<td>γ-Cyclodextrin</td>
</tr>
<tr>
<td><strong>VI</strong></td>
<td><strong>Miscellaneous</strong></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>Omeprazole (Anti Ulcer)</td>
<td>βCD, MEβCD, L- arginine</td>
</tr>
<tr>
<td>No.</td>
<td>Compound</td>
<td>Cyclodextrin Type</td>
</tr>
<tr>
<td>-----</td>
<td>-----------------------------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>29</td>
<td>Noscapine (Anti Tussive)</td>
<td>βCD</td>
</tr>
<tr>
<td>30</td>
<td>Bupivacaine HCl (Local Anaesthetic)</td>
<td>α -CD, β-CD, epichlorohydrin</td>
</tr>
<tr>
<td>31</td>
<td>Warfarin (Anti Coagulant)</td>
<td>βCD</td>
</tr>
<tr>
<td>32</td>
<td>Naringin (Antiatherogenic)</td>
<td>β-cyclodextrin</td>
</tr>
<tr>
<td>33</td>
<td>Albendazole (Anthelminthic)</td>
<td>2-hydroxypropyl-β-cyclodextrin</td>
</tr>
<tr>
<td>34</td>
<td>Meclizine (Anti Histamine)</td>
<td>2-Hydroxypropyl-β-cyclodextrins and β-cyclodextrins</td>
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<td>35</td>
<td>Thalidomide (Imunimodulator)</td>
<td>Hydroxypropyl-β-cyclodextrin</td>
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<tr>
<td>36</td>
<td>Rosuvastatin Ca (antihyperlipidemic)</td>
<td>β-CD</td>
</tr>
</tbody>
</table>
REFERENCES


