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## Potentials of Inclusion Complex with special Reference to Cyclodextrin

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### ABSTRACT

Cyclodextrins, the unique cyclic carbohydrates are successfully utilized as the potential complexing agents which form inclusion complex with insoluble drugs. "Inclusion complex", this term refers to the dispersion of one or more actives ingredients in an inert carrier or matrix at molecular state. Now a day several drugs molecules are being introduced and many newer techniques have been developed for the formulation of dosage forms but when these drug molecules become more and more complex, sophistication has to find its way in the area of excipients, which are needed to formulate these drug substances optimally. One such versatile adjuvant, tailored with the help of advances in biotechnology and enzyme technology is cyclodextrin. Cyclodextrin are cyclic oligosaccharides which have been recognized as useful pharmaceutical excipients. The molecular structure of these glucose derivatives generates a hydrophilic exterior surface and a non polar cavity interior. Such cyclodextrin can interact with appropriate size drug molecules which lead to the formation of inclusion complexes. A comprehensive literature survey was made collect the rightful utilization of cyclodextrins as complexing, solubility enhancing agents and permeation enhancers.

**Key words:** Inclusion complexes, Cyclodextrins, Excipients, Complexing agent, Hydrophilic exterior surface

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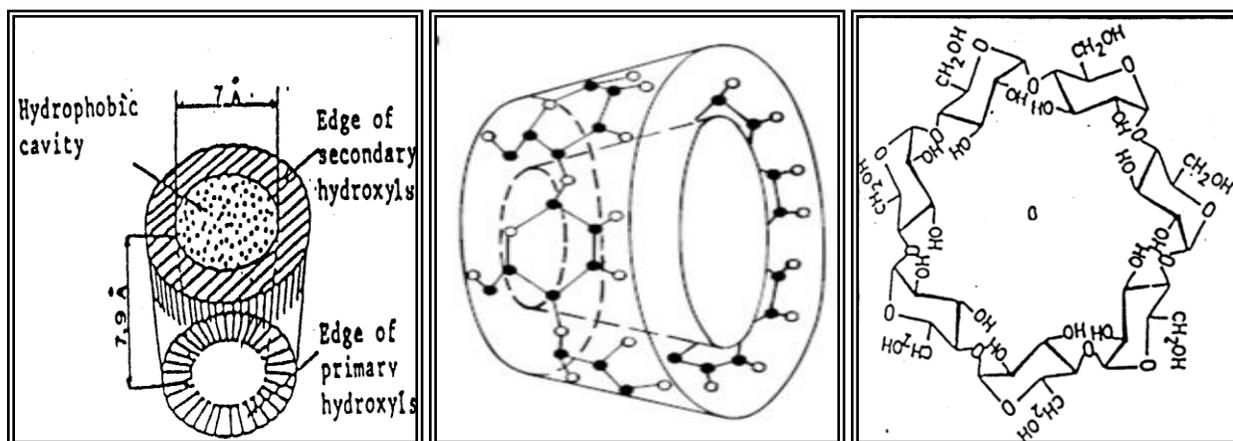
## INTRODUCTION

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. DDS make a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly<sup>1</sup>. Orally administered drugs completely absorb only when they show fair solubility in gastric medium and such drugs shows good bioavailability. Oral drug delivery remains the most popular route of administration. However, limitations in the physical–chemical properties of the drug sometimes prevent a successful therapeutic outcome<sup>2</sup>. Problem of solubility is a major challenge for formulation scientist which can be solved by different technological approaches during the pharmaceutical product development work<sup>3</sup>. Several difficulties are faced in designing formulations for better absorption and enhanced bioavailability<sup>4</sup>. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. use of surfactants, use of salt forms, alteration of pH of the drug microenvironment, use of meta stable polymorphs, solute - solvent complexation, selective adsorption on insoluble carriers, solid solutions, eutectic mixtures, molecular encapsulation with cyclodextrin, Solid dispersion, solvent deposition, micronization are some vital approaches routinely employed to enhance the solubility of poorly water soluble drugs<sup>5-8</sup>. Each approach suffers with some limitations and advantages. Among all, complexation technique has been employed more precisely to improve the aqueous solubility, dissolution rate, and bioavailability of poorly water soluble drugs<sup>9-14</sup>.

Nearly one-third of drugs in development are water insoluble and one-half in trials because of under privileged pharmacokinetics<sup>15</sup>. These poorly water soluble drugs are allied with slow drug absorption leading to inadequate and variable bioavailability and gastrointestinal mucosal toxicity<sup>16</sup>. Therefore, most of new chemical entities under development these days are intended to be used are solid dosage form that originate an effective and reproducible *in-vivo* plasma concentration after oral administration<sup>17, 18</sup>.

As the oral drug delivery is the simplest and easiest way of drug administration, because of the greater stability, lesser bulk, accurate dosage, cheaper cost of production and easy process, solid oral dosage forms have advantages over other dosage forms<sup>19,20</sup>. Infact, all the poorly water soluble drugs after oral administrations are not well absorbed<sup>21</sup>. And thus leads to decreased inherent efficiency of drugs<sup>22-25</sup>. Therefore, the improvement of drug solubility thereby its oral bio-availability remains one of most challenging aspects of drug development process especially for oral drug delivery system.

Cyclodextrins (CDs) are cyclic oligosaccharides containing six ( $\alpha$ -CD), seven ( $\beta$ -CD) or eight ( $\gamma$ -CD)  $\alpha$ -1,4-linked glucopyranose units, with a hydrophilic hydroxyl group on their outer surface and a hydrophobic cavity in the center. 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 the 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 (Figure 1).



**Figure 1(a): The chemical structure and (b) the toroidal shape of the  $\beta$ -cyclodextrin molecule.**

### (c) Planner representation and the molecular shape of $\beta$ -CDs

The most common cyclodextrins are  $\alpha$ -cyclodextrin ( $\alpha$ CD),  $\beta$ -cyclodextrin ( $\beta$ CD) and  $\gamma$ -cyclodextrin ( $\gamma$ CD) which consist of six, seven and eight glucopyranose units respectively. But due to steric factors, cyclodextrins having fewer than six glucopyranose units cannot exist, cyclodextrins containing nine, ten, eleven, twelve and thirteen glucopyranose units, which are designated  $\delta$ -,  $\epsilon$ -,  $\zeta$ -,  $\eta$ - and  $\theta$ -cyclodextrin, respectively have been reported. The chemical and physical properties of the four most common cyclodextrins are given in Table 1. CDs are capable of forming inclusion complexes with many drugs by taking up a whole drug molecule, or some part of it, into the cavity. Such molecular encapsulation will affect many of the physicochemical Properties of drugs, such as their aqueous solubility and rate of dissolution<sup>26-28</sup>.

**Table 1: Chemical and physical properties of  $\alpha$ ,  $\beta$ ,  $\gamma$  and  $\delta$  cyclodextrin<sup>31</sup>**

Physicochemical properties	$\alpha$	$\beta$	$\gamma$	$\Delta$
No. of glucopyranose units	6	7	8	9
Molecular weight	972	1135	1297	1459
Central cavity diameter ( $\text{Å}$ )	4.7-5.3	6.0-6.5	7.5-8.3	10.3-11.2
Water solubility at 25°C (g/100 mL)	14.5	1.85	23.2	8.19

Many poorly water soluble drugs have been formulated as liquid systems showing enhanced drug release<sup>29</sup>, also Cyclodextrin complexation has been extensively applied to enhance the solubility, dissolution rate and bioavailability of slightly water-soluble drugs<sup>30</sup>.

### Properties of Cyclodextrin

$\alpha$ -CD with 6 Glucose units has the smallest cavity diameter, which in most cases is too small for a pharmaceutical molecule.  $\beta$ -CDs with 7 glucose units is more convenient due to size of a polar cavity being optimum for a large number of molecules.  $\Gamma$ -CDs, with 8 glucose units should obviously be the best one. But it is not intensively produced because of the requirement of advanced technology for its production. Hence it remains impossible to use on an industrial scale. However, it is too expensive. Thus among the three types of CDs  $\beta$ -Cyclodextrin is known to be more suitable for practical use because of the following three reasons<sup>32-34</sup>.

- a) Its cavity diameter is the best one for guest molecules.
- b) Its production procedure does not require sophisticated technologies.
- c) It is cheaper.

### MECHANISM OF COMPLEXATION

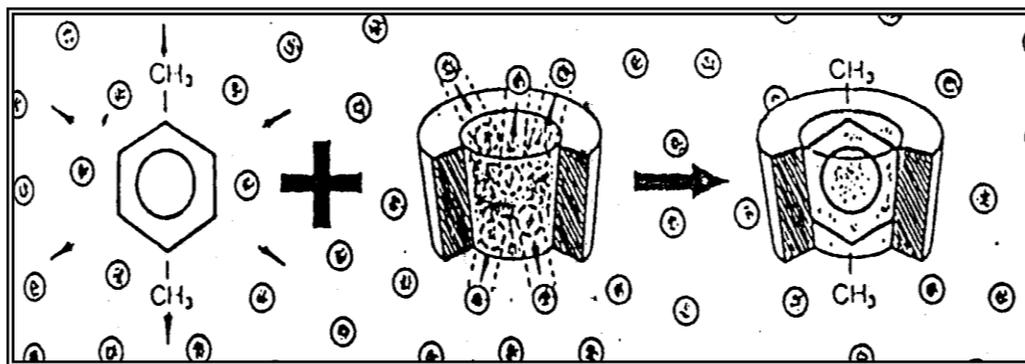
CDs can be regarded as cylinders with hydrophilic outside and hydrophobic inside. The hydrophobic cavity forms an ideal harbor in which poorly water soluble molecules or molecules to be protected from the surrounding atmosphere shelter their most hydrophobic parts or whole molecules. These hydrophobic molecules which can fit in the CD cavity are included in it in the presence of water. In aqueous solution the polar CD cavity is occupied by water molecules that are in an energetically unfavoured state (Polar – a polar repulsion) and are therefore, readily replaced by an appropriate guest molecules that is less polar than water and forms an inclusion complex<sup>33,34</sup>.

The degree of complexation with CD depends upon the dimensions and lipophilicity of the guest molecule. The guest molecule or as part of it must fit into the CD cavity. For many drugs  $\beta$ -CD offers the most interesting cavity size. Its dimensions are comparable to those of the substituted phenyl groups. Such groups are often most hydrophobic parts of drug and are therefore responsible for their poor solubility in water. Hiding these groups in CDs will markedly increase their overall aqueous solubility.

There are four energetically favorable interaction that helps shift the equilibrium towards complex formation.

- 1) Displacement of polar water molecule from the polar cyclodextrin cavity.

- 2) The increase number of hydrogen bond formed as the displaced water returns to the larger pool.
- 3) A reduction of the repulsive interaction between hydrophobic guest and the aqueous environment.
- 4) An increase in hydrophobic interaction as the guest insert itself into the polar cyclodextrin cavity<sup>35</sup>.



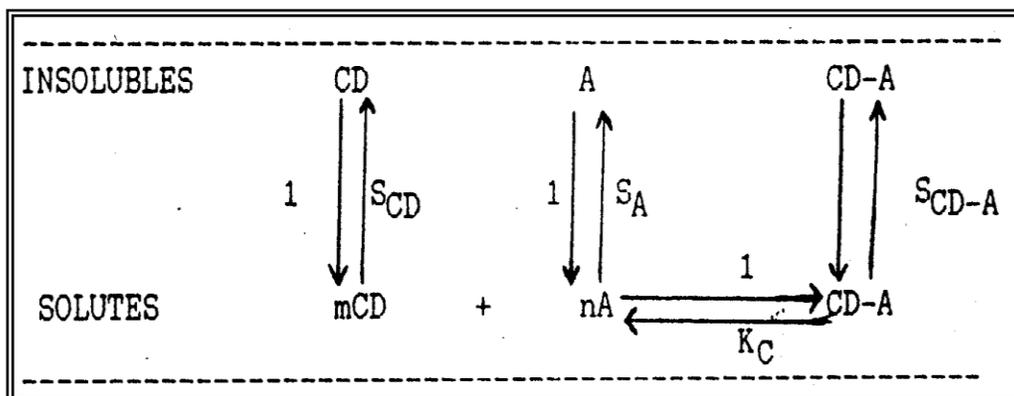
**Figure 2: Schematic Illustration of the Complexation**

Reactional mechanism concerned with the production of Cyclodextrins inclusion compounds<sup>33</sup>. The diffusion of reagent in contact with Cyclodextrin needs at least one solvent (water, alcohol). In a stirred medium, several kinetic reactions may occur; they lead to the formation of inclusion compounds; in the direction I. At the end of reaction, equilibrium is reached; it can be modified by variation of temp., pressure or solvent quantity.

- ✓ CD: Cyclodextrin molecules
- ✓ A: Guest molecules
- ✓ CD-A: Molecules inclusion compound
- ✓ n: Number of CD molecules in the inclusion compound (usually 1)
- ✓ m: Number of A molecule in the inclusion compound (usually 1)
- ✓ The equilibrium between A and CD-A is characterized by the equilibrium constant KC.

$$K = \frac{[\text{CD-A}]}{[\text{CD}]^m \times [\text{A}]^n}$$

- ✓ The equilibrium between the solute and insoluble forms are governed by the solubility constant S, depending on the used solvent:
  - ✓  $S_{\text{CD}}$  : Solubility of CD
  - ✓  $S_{\text{A}}$  : Solubility of guest molecule
  - ✓  $S_{\text{CD-A}}$  : Solubility of inclusion compound CD-A.



**Figure 3: Reaction mechanism of production of CD inclusion**

**The quality of CD-A (X) depend on:**

1. The quality of cyclodextrin and guest molecules introduced in the blend.
2. The equilibrium constant  $K_C$ .
3. The quantity of solvent (Q)
4. The solubility  $S_{CD-A}$  of molecular inclusion compounds.

### CYCLODEXTRINS AS PERMEATION ENHANCERS

In spite, the solubility enhancement application, CDs can also be used as membrane permeability enhancer and stabilizing agents<sup>36,37</sup>. The permeability through biological membrane is enhanced by the presence of cyclodextrins. Masson<sup>38</sup> reported about the permeation enhancement property of poorly water soluble drugs in presence of the CDs. These acts as permeation enhancers by carrying the drug through the aqueous barrier which exists before the lipophilic surface of biological membranes<sup>39</sup>. This can also be achieved through the double characteristics of the CDs, thus present character much lipophilic as hydrophilic. CDs can also be used as nasal permeation enhancers acting by interaction with nasal epithelium by modifying tight junction & lipid and protein content of the membrane, which enhances the permeation of the membrane<sup>40</sup>. CDs can also be utilized as permeation enhancer in pulmonary drug delivery systems. Rifampicin is a so-called concentration-dependent antibiotic, the rate and extent of bacterial kill is related to the attainment of high maximum concentration relative to the minimal inhibitory concentration. The rifampicin-CD inclusion compound can improve the lung transport of drug when nebulized with compatible pulmonary deposition and achieve required concentration of drug in broncho-alveolar epithelium lining-fluid when administered as aerosolized solution<sup>41-45</sup>.

### APPROACHES FOR MAKING OF INCLUSION COMPLEXES

**Physical blending method**<sup>3</sup>

A solid physical mixture of drug and CDs are prepared simply by mechanical trituration. In laboratory scale CDs and drug are mixed together thoroughly by trituration in a mortar and passes through appropriate sieve to get the desired particle size in the final product. In industry scale, the preparation of physical mixtures is based on extensive blending of the drug with CDs in a rapid mass granulator usually for 30 minutes. These powdered physical mixtures are then stored in the room at controlled temperatures and humidity conditions.

### **Kneading method**

This method is based on impregnating the CDs with little amount of water or hydroalcoholic solutions to converted into a paste. The drug is then added to the above paste and kneaded for a specified time. The kneaded mixture is then dried and passed through sieve if required. Parik *et al.*<sup>46</sup> have reported the dissolution enhancement of nimesulide using complexation method. In laboratory scale kneading can be achieved by using a mortar and pestle<sup>47-49</sup>. In large scale the kneading can be done by utilizing the extruders and other machines. This is the most common and simple method used to prepare the inclusion complexes and it presents very low cost of production.

### **Co-precipitation technique**

This method involves the co-precipitation of drug and CDs in a complex. In this method, required amount of drug is added to the solution of CDs. The system is kept under magnetic agitation with controlled process parameters and the content is protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex. Moyano *et al.*<sup>50</sup> have studied the solid-state characterization and dissolution characteristics of gliclazide-bete-cyclodextrin inclusion complexes. This technique leaves a drug-CD solution in very close conditions to the saturation and through abrupt changes of temperature with addition of organic solvents. It is obtained to the precipitation of the material forming inclusion complex. The powders are obtained by rotation or filtration with heat while stirring the solution<sup>51</sup>. However, due to low yield, risk of using organic solvents, and longer time required for the preparation in larger scale, this method is attaining little attraction in the industrial scale<sup>52</sup>.

### **Solution/solvent evaporation method**

This method involves dissolving of the drug and CDs separately in to two mutually miscible solvents, mixing of both solutions to get molecular dispersion of drug and complexing agents and finally evaporating the solvent under vacuum to obtain solid powdered inclusion compound. Generally, the aqueous solution of CDs is simply added to the alcoholic solution of drugs. The

resulting mixture is stirred for 24 hours and evaporated under vacuum at 45 °c. The dried mass was pulverized and passed through a 60-mess sieve. This method is quite simple and economic both on laboratory and large scale production and is considered alternative to the spray drying technique.

### **Neutralization precipitation method**

This method is based on the precipitation of inclusion compounds by neutralization technique and consists of dissolving the drug in alkaline solutions like sodium/ammonium hydroxide and mixing with an aqueous solution of CDs. The resultant clear solution is then neutralized under agitation using hydrochloric acid solution till reaching the equivalence point. A white precipitate is being formed at this moment, corresponding to the formation of the inclusion compound. This precipitate is filtered and dried. Doijad et al.<sup>53</sup> have studied the enhancement of solubility of piroxicam by complexation with beta-cyclodextrin. Acid and alkaline susceptible drugs can undergo degradation during this process is the limitation associated with this method.

### **Milling/Co-grinding technique**

A solid binary inclusion compounds can be prepared by grinding and milling of the drug and CDs with the help of mechanical devices. Drug and CDs are mixed intimately and the physical mixture is introduced in an oscillatory mill and grinded for suitable time. Alternatively, the ball milling process can also be utilized for preparation of the drug-CD binary system. The ball mill containing balls of varied size is operated at a specified speed for a predetermined time, and then it is unloaded, sieved through a 60-mesh sieve. This technique is superior to other approaches from economic as well as environmental stand point in that unlike similar methods it does not require any toxic organic solvents<sup>54</sup>. This method differs from the physical mixture method where simple blending is sufficient and in co-grinding it requires to achieve extensive combined attrition and impact effect on powder blend.

### **Atomization/Spray drying method**

Spray-drying is a common technique used in pharmaceuticals to produce a dry powder from a liquid phase. Another application is its use as a preservation method, increasing the storage stability due to the water elimination<sup>55</sup>. This method represents one of the most employed methods to produce the inclusion complex starting from a solution. The mixture passes to a fast elimination system propitiate solvent and shows a high efficiency in forming complex. Besides, the product obtained by this method yield the particles in the controlled manner which in turn improves the dissolution rate of drug in complex form. Vozone et al.<sup>56</sup> have developed complexation of budesonide in cyclodextrins and particle aerodynamic characterization of the

complex solid form for dry powder Inhalation. The sufficient and efficient interaction between drug and CDs to form a perfect complex is the added advantage of atomization/spray drying method where as thermal stress and low yield of the final product are the limitations associated with this technique.

### **Lyophilization/ Freeze drying technique**

In order to get a porous, amorphous powder with high degree of interaction between drug & CD, Lyophilization/ freeze drying technique is considered as a suitable<sup>57, 58</sup>. In this technique, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug & CD at reduced pressure. Thermo labile substances can be successfully made into complex form by this method. The limitations of this technique are long time process and yield poor flowing powdered product. Lyophilization/ freeze drying technique is considered as an alternative to solvent evaporation and involve molecular mixing of drug and carrier in a common solvent<sup>59,60</sup>.

### **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. Deshmukh *et al.*<sup>61</sup> have developed inclusion complexes of ziprasidone hydrochloride with beta-cyclodextrin and hydroxypropyl beta-cyclodextrin to design the fast dissolving formulation using various superdisintegrants. Microwave irradiation method is a novel method for industrial scale preparation due to its major advantage of shorter reaction time and higher yield of the product<sup>62,64</sup>.

### **Supercritical antisolvent technique**

This method has been introduced in the late 1980s. 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<sup>65,66</sup>.

## APPLICATIONS OF CYCLODEXTRINS IN DRUG DELIVERY

### Oral Drug Delivery<sup>67</sup>

- a. Immediate Release<sup>68</sup>
- b. Delayed Release<sup>69</sup>
- c. Prolonged Release
- d. Modified Release
- e. Taste masking<sup>70</sup>

### Parenteral Drug Delivery<sup>71</sup>

#### Ophthalmic Drug Delivery<sup>72-73</sup>

#### Nasal Drug Delivery<sup>74</sup>

#### Rectal Drug Delivery<sup>75</sup>

#### Colon Specific Drug Delivery<sup>76</sup>

#### Peptide and Protein Delivery<sup>77</sup>

#### Gene and Oligonucleotide Delivery<sup>78</sup>

#### Topical Drug Delivery<sup>79</sup>

#### Brain Drug Delivery or Brain Targeting<sup>78</sup>

#### Preparation of Liposomes<sup>80</sup>

#### Preparation of Microspheres<sup>81</sup>

#### Preparation of Nanoparticles<sup>82</sup>

## CONCLUSION

Cyclodextrin and their derivatives have been of widespread attention in the pharmaceutical field because of their potential to form complexes with a variety of drug molecules. Cyclodextrin are used to increase the solubility of water insoluble drug through inclusion complexes formulation. The hydrophobic cavity of Cyclodextrin is capable of trapping a variety of molecules within to produce inclusion complexes. Many advantages of drugs complexed with Cyclodextrin have been reported which includes-increased solubility, enhance bioavailability, improved stability, the masking of bad taste or odor, reduced volatility, transformation of liquid or gas into solid form, reduced side effect, and the possibility of a drug release system, thus it shows that inclusion complex with cyclodextrin play important role to solve various problem associated with drug delivery through the complexation.

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