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INCLUSION COMPLEX WITH CYCLODEXTRIN: A BOON TO PHARMACEUTICAL WORLD

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ABSTRACT

Microbial resistance to existing drugs and their increasing side effects are causing serious concern for synthesizing new drugs or modifying the existing drugs for better pharmacological activities. One of the ways for increasing drug efficiency is to form inclusion complex with cyclodextrins, the well known non toxic cyclic oligosaccharide. Due to lipophillic inner cavity and hydrophilic outer surface, the cyclodextrins encapsulate the drug molecules thereby increasing their solubility and bioaccessibility. In addition, the inclusion complex with cyclodextrins has application in drug formulation with minimum side effects. An attempt has been made to discuss structure, synthesis and pharmacological applications of cyclodextrins and their inclusion complexes.

Keywords: Cyclodextrins, Bioavailability, Bioaccessibility

INTRODUCTION

Cyclodextrins are cyclic oligosaccharides consisting of six (in case of α-cyclodextrin), seven (in case of β-cyclodextrin) and eight (in case of γ-cyclodextrin),1,4-linked glycopyranose units. They are also known as cycloamyloses,cyclomaltoses and schardinger dextrins **[1, 2]**. The cyclodextrins have hydrophillic outer surface and hydrophobic cavity at the centre. Due to lack of free rotation about the bonds connecting to glycopyranose units, the cyclodextrins are not perfectly cylindrical molecules but are toroidal or cone shaped. Based on the architecture, orally administered drugs are completely absorbed only when they show fair solubility in gastric medium and such

drugs show good bioavailability. In the process of formulation development, the two properties of drugs such as solubility and dissolution play an important role **[3]**. The problem of solubility of the drugs can be solved by different approaches. Some of the approaches include use of surfactants, use of salt forms, alteration of pH at the microenvironment of the drugs, use of metastable polymorph, solute-solvent complexation, selective adsorption on insoluble carriers, solid solution, eutectic mixtures, molecular encapsulation with cyclodextrin, solid dispersion, solvent deposition etc. **[5-8]**. Each process has its advantages and limitations. However, all complexation techniques have been employed more precisely to improve the aqueous solubility, dissolution rate and bioavailability of poorly water soluble drug **[9-10]**. Cyclodextrins are capable of forming inclusion complexes with many drugs by taking up entire drug molecule or some part of it into its cavity. Such molecular encapsulation will affect many of the physicochemical properties of drugs, such as changes in melting point, spectral characteristics (UV, IR, NMR, and XRD etc), aqueous solubility and rate of dissolution **[11-12]**.

Structure

Cyclodextrins are a group of structurally related natural products formed during bacterial digestion of cellulose. These cyclic oligosaccharides consist of [α-1, 4]-linked α -D-glucopyranose units and contains a somewhat lipophilic central cavity and a hydrophilic outer surface. Due to the chair conformations of glucopyranose units, the cyclodextrin are shaped like a truncated cone rather than perfect cylinders. The hydroxyl functional groups are oriented to the cone exterior with primary hydroxyl groups at the wider edge. The central cavity is lined with the skeletal carbons and ethereal oxygen of glucose residues which gives it lipophilic character **[13]**. The arrangement of different atoms and groups in cyclodextrins is shown in **Figure 1** and general properties of different cyclodextrins are given in **Table 1**.

Synthesis of Cyclodextrins

The synthesis of cyclodextrins involves treatment of ordinary starch with a set of easily available enzymes. Commonly used enzyme is cyclodextrin glycosyltransferase (CGT) which is employed along with α-amylase. First starch is liquefied either by heat treatment or using α-amylase and then CGTase is added for the enzymatic conversion. All forms of cyclodextrins can be synthesized form CGTases thus the product of the conversion results in a mixture of the

three main types of cyclic molecules, in ratios that are strictly dependent on the enzyme used because each CGTase has its own characteristic. The purification of the three types of cyclodextrins takes the advantage of their differential water solubility. β-CD which is very poorly water soluble can be easily retrieved through crystallization while the more soluble α- and γ-CDs (145 and 232 g/l respectively) are usually purified by means of expensive and time consuming chromatography techniques. As an alternative a "complexing agent" can be added during the enzymatic conversion step. Such agents (usually organic solvents like toluene, acetone or ethanol) form a complex with the desired cyclodextrin which subsequently precipitates. Usually, 1-Decanol is the complexing agent for α-cyclodextrin while the toluene is used for the complexation of β-cyclodextrin . The cyclodextrin with highest number of glucose units, γ-cyclodextrin is separated to solid mass in presence of cyclohexadec-8-en-1-one. The complex formation drives the conversion of starch towards the synthesis of the precipitated cyclodextrin, thus enriching its content in the final mixture of the products **[14, 15]**.

Mechanism of Inclusion Complex Formation

The most remarkable feature of cyclodextrins is their ability to form solid inclusion complexes (host–guest complexes) with a very wide range of solid, liquid and gaseous compounds by a molecular complexation **[1]**. In these complexes **(Figure 2)**, a guest molecule is encapsulated within the cavity of the cyclodextrin host molecule. Complex formation occurs when there is compatibility in between host cavity and guest molecule **[16]**. The lipophilic cavity of cyclodextrin molecule provides a microenvironment into which appropriately sized non-polar moieties can enter to form inclusion complexes **[17]**. No covalent bonds are broken or formed during formation of the inclusion complex **[18]**. The main driving force of complex formation is the release of enthalpy-rich water molecules from the cavity. Water molecules are displaced by more hydrophobic guest molecules present in the solution to attain an apolar–apolar association and decrease of cyclodextrin ring strain resulting in a more stable lower energy state **[19]**.

The ability of a cyclodextrin to form an inclusion complex with a guest molecule depends on the following two key factors.

- The first is steric factor which depends on the relative size of the cyclodextrin to the size of the guest molecule or certain key functional groups within

the guest. If the guest is of wrong size, it will not fit properly into the cyclodextrin cavity.

- The second critical factor is the thermodynamic interactions between the different components of the system (cyclodextrin, guest, solvent). For a complex to form, there must be a favorable net energetic driving force that pulls the guest into the cyclodextrin cavity.

All the three basic cyclodextrins (α,β,γ) are having equal heights. Therefore the internal diameter of the cavity and its volume depends on the number of glucose units. Based on these dimensions,

- α -cyclodextrin can typically complex with low molecular weight molecules or compounds with aliphatic side chains
- β-cyclodextrin will complex aromatics and heterocycles
- γ -cyclodextrin can accommodate larger molecules such as macrocycles and steroids.

Generally there are four energetically favorable interactions that help to form the inclusion complex:

i. The displacement of polar water molecules from the apolar cyclodextrin cavity.

ii. The increased number of hydrogen bonds formed as the displaced water returns to the larger pool.

iii. A reduction of the repulsive interactions between the hydrophobic guest and the aqueous environment.

iv. An increase in the hydrophobic interactions as the guest inserts itself into the apolar cyclodextrin cavity **[20]**.

Techniques of Complexation

There are several techniques for the cyclodextrin inclusion complexation **[3, 21, 22]**

a) **Grinding**: Inclusion complexes can be prepared by simply grinding the guest with CD.

b) **Solid dispersion / co- evaporated dispersion**: The drug & CD are dissolved in ethanol and in water separately. Then both the solution are mixed and stirred to attain equilibrium. The resulting solution is evaporated to dryness preferably under vacuum.

c) **Neutralization method**: Drug and CD are separately dissolved in 0.1 N NaOH mixed and stirred for about half an hour. The pH is recorded and 0.1 N HCl is added drop wise with stirring until pH reaches 7.5, where upon

complexes precipitate. The residue is filtered and washed until free from chlorine. It is dried at 250^0C for 24 hrs. and stored in a desiccators.

d) **Kneading method**: Paste of CD is prepared with small amount of water to which the guest component has been added without a solvent or in a small amount of ethanol. After grinding paste solvent get evaporated and powder like complex formed.

e) **Precipitation method**: Drug and CD are dispersed in water and solution is heated to obtain concentrate, viscous and translucent liquid. The solution is left to give precipitate of inclusion complex. The precipitate is filtered and dried to get solid inclusion complex.

f) **Spray drying**: In this first monophasic solution of drug and CD is prepared using a suitable solvent. The solution is then stirred to attain equilibrium following which the solvent is removed by spray drying.

g) **Freeze-drying**: Similar to spray drying except that in this after attaining equilibrium, the solvent is removed by freeze drying.

h) **Melting**: Complexes can be prepared by simply melting the guest, mixed with finely powdered CD. In such cases there should be a large excess of guest, and after cooling this excess is remove by careful washing with a weak complex, forming solvent or by vacuum sublimation.

i) **Extrusion:** Extrusion is a variation of the heating and mixing method and is a continuous system. Cyclodextrin, guest and water can be premixed or mixed as added to the extruder. Degree of mixing, amount of heating and time can be controlled in the barrel of the extruder. Depending upon the amount of water, the extruded complex may dry as it cools or the complex may be placed in an oven to dry.

j) **Paste complexation** : This is a variation of the slurry method. Only a small amount of water is added to form a paste, which is mixed with the cyclodextrin using a mortar and pestle, or on a large scale using a kneader. The amount of time required is dependent on the guest.

k) **Co-precipitation method** : The solution of the compound in required concentration is added drop by drop to β –cyclodextrin solution of the required concentration. The mixture is

stirred for a period of 48 hours and filtered.The filtrate is cooled for 24 hours in refrigerator. The precipitate obtained is filtered through G-4 crucible, washed with water and dried in air for 24 hours

Advantages of Inclusion Complex Formation

In the inclusion complex, the guest molecule is surrounded the host (cyclodextrin). This can lead to advantageous changes in the chemical and physical properties of the guest molecules. The advantages of inclusion complex are

- Increases the stability of light- or oxygen-sensitive substances.
- Modification of the chemical reactivity of guest molecules.
- Fixation of very volatile substances.
- Improvement of the solubility of desired substances.
- Modification of liquid substances to powders.
- Protection against degradation of substances by microorganisms.
- Masking of ill smell and taste.
- Masking pigments or the colour of substances.
- Catalytic activity of cyclodextrins with guest molecules

Applications to Drug Delivery System

Oral Drug Delivery

Applications of cyclodextrins in oral drug delivery include improvement of drug bioavailability due to increased drug solubility, improvement of rate and extent of dissolution, and/or stability of the drug at the absorption site, eg, the gastrointestinal tract (GIT) or in formulation, reduction of drug induced irritation, and taste masking. Cyclodextrin complexation was found to decrease local drug irritation and also modify the time of drug release during GI transit **[23]**. An itraconazole oral preparation containing 40% (wt/vol) of HP-β-CD (with reduced drug irritation) has been commercialized in the United States and Europe.

Rectal Drug Delivery

Since rectum is capable of absorbing unused drugs causing side effect, the rectal absorption of drugs can be avoided through inclusion complex formation. The hydrophilic surface of inclusion complex does not develop any interaction with vehicles in rectum **[24]**.

Sublingual Drug Delivery

Sublingual drug delivery is one of the most efficient ways to bypass hepatic first-pass metabolism **[25]**. In this method the drug enters the systemic circulation by dissolving in the mucosa. In the sublingual formulations the complexation of poorly water soluble drugs with cyclodextrin has been shown to

increase the bioavailability of various lipophilic drugs. For example, 2-hydroxypropyl-β-cyclodextrin has been shown to increase the bioavailability of 17β-oestradiol **[26]**.

Pulmonary drug delivery

The pulmonary drug delivery can be improved by increasing aqueous solubility and drug dissolution, though inclusion complex formation **[27]**.

Dermal drug delivery

Cyclodextrins have a significant safety margin in dermal application and can be used to optimize the transdermal delivery of drugs intended local or systemic use. They also enhance the transdermal absorption of drugs, sustains the drug release from the vehicle and avoids undesirable side effects associated with dermally applied drugs **[28]**.

Nasal drug delivery

In nasal formulations, cyclodextrins are normally used to increase the aqueous solubility of lipophilic drugs so as to increase permeability properties for systemic drug delivery **[29]**.

Ophthalmic drug delivery

The inclusion complexes with cyclodextrins enhance drug permeability through biological membranes such as eye cornea and skin by disrupting the membrane, either by permeating into the membrane or by extracting or complexing with some lipophilic components such as cholesterol and phospholipids from the membrane. Cyclodextrins have also been used to reduce ophthalmic drug irritation and to increase chemical stability of drugs in aqueous ophthalmic formulations **[30]**.

Colon Specific Drug Delivery

Cyclodextrins are barely hydrolysed and only slightly absorbed in stomach and small intestine but are absorbed in large intestine after fermentation into small saccharides by colonic microbial flora. The peculiar hydrolyzing property of CDs makes them useful for colon drug targeting. Biphenyl acetic acid (BPAA) prodrugs for colon specific delivery have been developed by conjugation of the drug onto one of the primary hydroxyl groups of α-, β-, and γ- CDs through an ester or amide linkage **[31]**.

Peptide and Protein Delivery

In the peptide and protein delivery, P-glycoprotein (P-gp) is an efflux transporter present in the epithelial cells of the brain, kidney, liver and GI tract. P-gp opposes the movement of the protein and peptide drugs in the epithelial cells. DM- β-CD not only inhibits the efflux function of P-glycoprotein but also decrease the level of P-gp by allowing its release from the apical membranes into the transport buffer **[32]**.

Besides the above applications of CDs towards the drug delivery systems, they can be used for the followings

Agricultural and Chemical Industries

Cyclodextrins form complexes with a wide variety of agricultural chemicals including herbicides, insecticides, fungicides repellants, pheromones and growth regulators. Cyclodextrins can be applied to delay germination of seed.

In chemical industry, cyclodextrins are used to catalyse reactions, to separate isomers and enantiomers, to remove or to detoxify waste materials. In electrochemical industry cyclodextrins can be used to mask contaminating compounds.

Cyclodextrin can play a major role in environmental pollution control. These are used to remove organic pollutants, heavy metals from soil, water and atmosphere. Cyclodextrins are also applied in water treatment to increase stabilizing action, encapsulation and adsorption of contaminants **[33]**.

Food Processing Industries

Cyclodextrins are used in food industries for flavour protection. The flavours on complexation with cyclodextrins can protect their characteristics. They are also useful to remove cholesterol from dary products **[34]**.

Cosmetic Industries

The number of applications dealing with cyclodextrins in cosmetic industries is enormous. Complexation with cyclodextrins protects the guest molecule from light and oxidation. The formation of undesired compounds is prevented. The cyclodextrin complex has an improved stability against colouring in the lapse of time. A large number of cosmetic components are nearly insoluble in water. These chemical substances are able to form inclusion complexes with cyclodextrins. As a result, these complexes are more soluble compared to the pure compounds. This effect can be generally used for the formulation of cosmetics **[35]**.

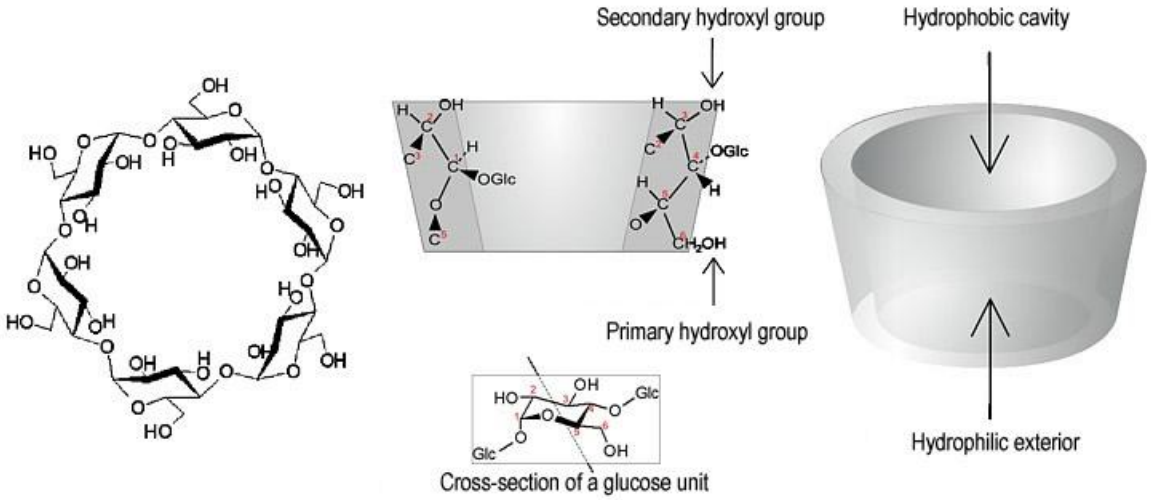

Figure 1: Structural Arrangements in Cyclodextrins

Figure 2: Mechanism of Inclusion Complex Formation

Table 1: General Properties of α-cyclodextrin, β- cyclodextrin, γ- cyclodextrins

Properties	α-CD	β-CD	γ-CD
Glucose units	6	7	8
Molecular mass	972	1135	1297
Solubility in water mg/ml at 25^0C	145	18.5	232
pK_a	12.33	12.2	12.08
Inner diameter (nm)	0.57	0.78	0.95
Outer diameter (nm)	1.46	1.54	1.75
Height (nm)	0.79	0.79	0.79
Cavity vol. (m mol^{-1})	174	262	427

CONCLUSION

Due to easier method of preparation of inclusion complexes with cyclodextrins and their vast applications in increasing drug efficiency and reducing side effects of existing drugs, inclusion complexes with cyclodextrins is definitely a boon for the pharmaceutical world.

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