Pharmacophore

(An International Research Journal)

Available online at http://www.pharmacophorejournal.com/

Review Article

CYCLODEXTRINS IN PHARMACY- AN OVERVIEW

N.Kanaka Durga Devi1[1]*, A.Prameela Rani[2], Muneer Javed.M[1], K.Sai Kumar[3], J.Kaushik[3], V.Sowjanya[3]

[1]* KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada-520010, Andhra Pradesh, India

[2] University College of Pharmaceutical Sciences, ANU, Nagarjuna Nagar-522510, India

[3] Manipal College of Pharmaceutical Sciences, Manipal-576104, India

ABSTRACT

Cyclodextrins are a group of compounds that enhances permeability through biological membrane, by which they act as permeation enhancers. In this present review article, the history, chemical structure, synthesis, physicochemical properties, uses, complexation phenomenon, approaches for making inclusion complexes, and its characterisation, advantages of inclusion complexes, mechanism of drug release, regulatory status and applications of cyclodextrins have been explained neatly and legibly. The future prospects of Cyclodextrins (CDs) 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. Cyclodextrins (CDs) can serve as useful tools in the hands of pharmaceutical scientists for optimizing the drug delivery.

Keywords: Inclusion complex, Host-Guest interaction, Complexation, Hydrophobic.

INTRODUCTION

Cyclodextrins (sometimes called cycloamyloses) are a family of compounds made up of sugar molecules bound together in a ring (cyclic oligodissacharides). Cyclodextrins are composed of five or more alpha-D-glucopyranoside units linked by 1, 4 as in amylase (A fragment of starch).Typical cyclodextrins contain a number of glucose monomers ranging from six to eight units in a ring, creating a cone shape.Thus denoting:

I. α –Cyclodextrin: Six membered sugar ring molecule.

II. β –Cyclodextrin: Seven sugar ring molecule (Shown in Fig.1).

III. γ –Cyclodextrin: Eight sugar ring molecule.

Cyclodextrins are produced from starch by means of enzymatic conversion. Over the last few years they have found a wide range of applications in food, pharmaceutical[1] and chemical industries.

HISTORY OF CYCLODEXTRINS

Cyclodextrins (CDs) are belongs to the category of carbohydrates and are cyclic oligosaccharides discovered just over 100 years ago. They are called "Cellulosine", when first discovered by A.Villiers in1891.After that F.Schardinger identified the three naturally occurring Cyclodextrins α, β and γ. And these were referred to as "Schardinger Sugars". For 25 years, between 1911 and 1935, Pringsheim in Germany was the leading researcher in this area, demonstrated that CDs formed stable aqueous complexes with many other chemicals (drugs). In the mid 1970 each of the natural cyclodextrins had been structurally and chemically characterized and many more complexes had been studied. In the 1953, first patent on cyclodextrin and there complexes was registered. Till 1970 only small amount of relatively pure cyclodextrin was generated and high production cost prevented their industrial use.[1]

CHEMICAL STRUCTURE

γ-CD Toroid structure showing spatial arrangement (Shown in Fig.2).

Typical cyclodextrins are constituted by 6-8 glucopyranoside units, can be topologically represented as toroids with the larger and the smaller openings of the toroid exposing to the solvent secondary and primary hydroxyl groups respectively. Because of this arrangement, the interior of the toroids is not hydrophobic, but considerably less hydrophilic than the aqueous environment and thus able to host other hydrophobic molecules. In contrast, the exterior is sufficiently hydrophilic to impart cyclodextrins (or their complexes) water solubility. The formation of the inclusion compounds greatly modifies the physical and chemical properties of the guest molecule, mostly in terms of water solubility. This is the reason why cyclodextrins have attracted much interest in many fields, especially pharmaceutical applications, because inclusion compounds of cyclodextrins with hydrophobic molecules are able to penetrate body tissues, these can be used to release biologically active compounds under specific conditions.[2] In most cases the mechanism of controlled degradation of such complexes is based on pH change of water solutions, leading to the cleavage of hydrogen or ionic bonds between the host and the guest molecules. Alternative means for the disruption of the complexes take advantage of heating or action of enzymes able to cleave α-1, 4 linkages between glucose monomers.

SYNTHESIS AND PRODUCTION

The production of cyclodextrins involves treatment of starch with *cyclodextrin glycosyltransferase (CGTase)* and *α-amylase.*[3] Starch is liquefied by two processes by heat treatment or using α-amylase then, for enzymatic conversion CG Tase is added. This conversion product gives three main types of cyclic molecules mixture, α, β and γ cyclic molecule, which depend on CGTase enzyme used. Each CGTase has its own characteristic α, β, and γ synthesis ratio. For purification of the three types of cyclodextrin, techniques used like chromatography, crystallization, and use of organic solvents like toluene, ethanol etc. as a complex forming agent with cyclodextrin formingprecipitate.

This results in formation of precipitated cyclodextrins from the starch, which is collected by centrifugation.

PHYSICAL AND CHEMICAL PROPERTIES[4]

Some physical properties of natural cyclodextrins (Shown in Table.1).

Chemical properties

- ***Chemical reactivity***

Cyclodextrin has no reducing end groups. No formic acid or formaldehyde is formed in the periodate oxidation of α, β and γ-cyclodextrin, providing that these molecules do not contain free end groups.

USES OF CYCLODEXTRINS

About 30 different pharmaceutical products containing cyclodextrins are now on the market worldwide and numerous food products, cosmetics and other commercial products contain cyclodextrins. In these products cyclodextrins are mainly used as solubilising agents to increase water solubility of lipophilic compounds. However, cyclodextrins can also be used to increase both chemical and physical stability of various compounds, including proteins. To enhance availability of compounds, for example; to enhance taste or to enhance bioavailability of drugs. Cyclodextrins can be used to convert liquids to solid powders, to reduce local irritation, to prevent skin absorption of topically applied compounds (e.g. Sunscreen agents), and to obtain sustained release of, for example drugs or fragrances.

CYCLODEXTRINS AND COMPLEXATION PHENOMENA

Inclusion complexation with cyclodextrin is like a "Host-Guest Interaction" (see Fig.2).In this interaction cyclodextrin act as host molecule and the drug molecule to be entrapped in host cavity act as guest molecule. Comparing to other encapsulation methods, which involve entrapment of more than one guest,

- ***Radiolysis***

On γ-Irradiation, cleavage of β and γ-cyclodextrin occurs mainly at the 1-4 glycosidic bonds. The mechanism is different from that of acid hydrolysis. No glucose is formed.The main products being malto-hexose, malondialdehyde and gluconic acid, also hydrogen, carbon monoxide and carbon dioxide.

- ***Acid hydrolysis***

Acid hydrolysis yields glucose and series of acyclic maltosaccharides. In the hydrolysis of oligopolysaccharides, the glycosidic bond of terminal glucose unit is cleaved faster than bond between non-terminal members

cyclodextrin complexation involve entrapment of one molecule of guest in cyclodextrin cavity. For formation of complex with cyclodextrin, variety of non-covalent forces like Vander wall forces, hydrophobic interaction, and dipole movement are responsible. In majority of cases only a single guest molecules is entrapped in the cavity. For High molecular weight molecules, more than one molecule of cyclodextrins can bind to the guest.

For the preparation of complex, many solvents are used, but generally water is preferred as a solvent for complexation. The cavity of cyclodextrin in non-polar and it favours non-polar area of guest molecule. Water gives driving force for formation of complexation. Not all guests are sufficiently soluble in water. It is not necessary that complete solubilization of guest should be done. Small amount of guest must be soluble to form a complex. Some times water miscible solvents in small quantities are helpful for dissolution of guest, which enhances complexation reaction. After addition of the dissolved guest to the solution of cyclodextrin, either guest may be dissolved or suspended in the form of high precipitate. Excess quantity of solvent if added, results in decrease in driving force for complexation reaction by reducing the difference in polarity between the bulk solution

and cyclodextrin cavity which ultimately leads to little or no complexation but good solubilization of guest. Heat can destabilize the inclusion complex. Complexation stability

APPROACHES FOR MAKING INCLUSION COMPLEXES

Several approaches were reported for host-guest complex preparation. Some have advantageous to other.
The methods generally preferred are,

I. Kneading

The method involves the formation of paste of cyclodextrin with guest molecules by using small quantity of either water or ethanol to form kneaded mass. Kneaded mass can be dried at 45°C and pulverized.[8-10]

II. Melting

Excess quantity of guest melted, mixed with powdered cyclodextrin, after cooling excess quantity of quest is removed by washing with weak complex forming solvent. The method restricted to sublimable guest like menthol.[11]

III. Solution-enhanced dispersion by the Supercritical fluids (SEDS)

SEDS is novel, single step method, which can produce solid drug-cyclodextrin complexes. The optimization of processing conditions is essential in order to achieve the optimum complexation efficiency and to compare with drug-cyclodextrin complexation methods described earlier in the literature (e.g. kneading, freeze drying, spray drying etc). Advantages over other methods are (a) Preparation Preparation of solid-cyclodextrin complexes in single step process, (b) Achievement of high complexation efficiency (avoidance of excess cyclodextrin in powder). (c) Possibility to minimize the contact of drug with cyclodextrin during the process. (d) Achievement of enhanced dissolution rate of the drug (which is comparable to the dissolution behavior of micronized drug-cyclodextrin complex).[12]

depends on the temperature of guest and it must be optimized for every guest.[4,5,6,7] (Shown in Fig.3).

IV. Co-evaporation / Solvent evaporation method

To the alcoholic solution of guest, aqueous solution of host is added and stirred for sometimes and evaporated at room temp until dried mass obtained, pulverized and sieved and fraction is collected.[13-15]

V. Microwave Irradiation

This method is developed for rapid organic synthesis and reactions, which require shorter reaction time and higher aim product.[16]

VI. Freeze Drying / Lyophilisation technique

The required stoichiometric quantity of host and guest were added to aqueous solution of cyclodextrin and this suspension stirred magnetically for 24 hours, and resulting mixture is freeze dried at 60°C for 24 hours.[17]

VII. Spray drying / Atomisation

In this method, host solution prepared generally in ethanol: water 50% v/v. To this guest is added and resulting mixture is stirred for 24 hr. at room temperature and solution is spray dried by observing following conditions-air flow rate, atomizing air pressure, inlet temperature, outlet temperature, flow rate of solution etc. Product obtained by passing through 63-160 micrometer granulometric sieve.[18]

CHARACTERIZATION OF INCLUSION COMPLEXES

a. Differential Scanning Calorimetry
b. Powder X-RAY Diffraction
c. Fourier Transform Infrared Spectroscopy
d. Scanning Electron Microscopy

ADVANTAGES OF CYCLODEXTRIN INCLUSION COMPLEXATION[19]

CDs have mainly been used as complexing agents to increase the aqueous solubility of poorly water-soluble drugs and to increase their bioavailability and stability. In addition, CDs have been used to reduce or prevent gastrointestinal or ocular irritation, reduce or eliminate unpleasant smells or tastes, prevent drug-drug or drug-additive interactions, or even to convert oils and liquid drugs into microcrystalline or amorphous powders.

I. Enhancement of Solubility [20]

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.

II. Enhancement of Bioavailability [20]

When poor bioavailability is due to low solubility, CDs are of extreme value. Preconditions for the absorption of an orally administered drug are 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.

III. 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.

IV. 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.

V. 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.

VI. 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.

VII. 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.

MECHANISM OF DRUG RELEASE FROM THE COMPLEXES [4, 20]

(Shown In Fig.4)

a. Drug, CDs complexation is a reversible process.

b. In aqueous solutions Drug–CD complexes are continually forming and dissociating with life times in the range of milliseconds and the rates are fast and instantaneous.

c. After administration, the drug is released from the complex upon dilution & in some cases by competitive displacement with endogenous lipophiles

REGULATORY STATUS OF CYCLODEXTRINS

α- CD, β -CD and γ -CD are listed in the generelly regarded as safe (GRAS) list of the FDA for use as food additive and HP-β-CD is cited in the FDA's list of Inactive Pharmaceutical Ingredients. SBE-β-CD is also available in various pharmaceutical dosage forms and is also listed in the FDA's compilation of Inactive Pharmaceutical Ingredients.

Consensus seems to be building among regulators that cyclodextrins are pharmaceutical excipients and not part of the drug substance although various opinion have given and interpretation related to this point can be division and product-specific.

Regulatory status of natural cyclodextrins and HP-β –CD [5] (shown in Table.2)

APPLICATIONS OF CYCLODEXTRINS [20]

I. Oral Drug Delivery

CD helps in improvement of drug bioavailability by increasing drug solubility. Helps to increase the rate of dissolution and stability of drug at the absorption site eg. GIT. In formulation, CD helps in taste masking and reduction of drug induced irritation eg. An itraconazole oral preparation containing 40% w/v of HP-β-CD. (which reduces drug irritation)

II. Parentral Drug Delivery

CD derivatives such as Amorphous HP-β-CD and SBE-β-CDs are widely used for parenteral use because of high aqueous solubility and minimum toxicity. Increase in solubility of drug, reduces drug irritation at the site of administration. Helps in maintaining stability but it is unstable in aqueous solution. Eg. Itraconazole parentral injection.

III. Ocular Drug Delivery

Helps to increase solubility and chemical stability of drug, reduces the drug (ocular) irritant and enhancement of drug permeability. Hydrophilic CDs especially HP- β-CD and SBE-β-CDs are used mainly in this delivery.

IV. Nasal Drug Delivery

CDs improve nasal drug absorption either by increasing aqueous drug solubility or by enhancing nasal drug permeability. Helps to improve nasal bioavailability of drug especially in peptides. Reduces the nasal toxicity. DM-β-

CD improves the nasal bioavailability of estradiol in rabbits and rats.[19]

V. Rectal Drug Delivery

Enhancement the drug absorption from suppository base either by enhancing drug release from the base or by increasing drug mucosal permeability. Increase in drug stability, provide sustained release and also reduces drug induced irritation. Hydrophilic CDs specially methylated and hydroxypropyl CDs are most considerably used.

VIII. Controlled Drug Delivery

Since the CDs have ability of complex formation it is used for delivery of required amounts of drug to the targeted site for necessary period of time. β-CDs derivatives have been classified as:

- Hydrophilic derivatives.
- Hydrophobic derivatives.
- Ionisable derivatives.

Use:

Hydrophilic and hydrophobic CD derivative are used in immediate and prolong release type of formulation. While, ionisable derivative are use to improve the inclusion.

IX. Colon Specific Drug Delivery

CDs are partially hydrolyzed and slightly absorbed in stomach and small intestine but in large intestine after fermentation process it get converted into small saccharine by colonic microbial flora. Peculiarly, hydrolyzing property of CDs make them useful for colon drug targeting.

X. Peptide and Protein Delivery

Problems related with practical use of therapeutic peptides and proteins are:

- Chemical enzymatic and instability.
- Poor absorption through biological membrane.
- Rapid plasma clearance.
- Peculiar dose response curves.
- Immunogenicity.

CDs due to the property of bioadaptability has an ability to interact with cellular membranes can act as potentials carriers for the delivery of proteins, peptides and oligonucleolide drugs.

XI. Gene and Oligonucleotide Delivery

CDs can solve many problems related with *in vivo* delivery of oligonuceotide (ONs).It can improve cellular uptake of ONs and delay their degradation time, by increasing their stability against endonucleases. ON admantane conjugated with the help of HP-β-CD increases cellular up take of ONs.

XII. Dermal and Transdermal Delivery

Enhances the drug release and permeation, increases the stability in formulation at absorption site, reduces the drug induced drug irritation, releases the drug from vehicles and also alters the drug bioconversion in viable skin. Nitroglycerin complexation with DE- β-CDs accelerates the drug release rate from ointment but the same time β-CDs retards the drug release, hence a combination of drug complexes with DE-β-CDs and β-CDs was suggested to obtain sustain release of percutaneous preparations of drug.

XIII. Brain Drug Delivery

The concept of chemical drug delivery (CDs) was applied for targeting drugs such as steroids, antitumor agents and calcium channel antagonists to brain. HP-β-CD due to its property of chemical stability and solubility helps dihydronicotinic acid (in aqueous solution) to solve the problems of solubility.

XIV. In Design of Novel Drug Delivery System

- ***Liposome***

In drug delivery the entrapment of CD drug complexes into liposomes increases the advantage of both of them. Most stable liposomal formulation is: Eg, Metronidazole and verapamil were obtained by direct spray drying of lipid drug and HP-β-CDs mixture.

- ***Microcapsules***

Cross linked β-CD Microcapsules, due to their ability to retard the release of water soluble drugs through semi permeable membrane, which will act as release modulator. Double microcapsules, prepared by encapsulating methylene blue with different amount of β-CD microcapsules inside a cross linked human serum albumin (HAS) shows decrease release rate of methylene blue with increase amount of β-CD microcapsules.

- ***Nanoparticles***

Nanoparticles are stable system which provide targeted drug delivery enhances the efficacy and bioavailability of poorly soluble drug. CDs increases loading capacity of nanoparticles as well as spontaneous formation of either nanocapsule or nanosphere. Addition of steroidal drugs, hydrocortisone and progesterone in β-CD or HP-β-CD the resultant complex will maintain the size of solid lipid nanoparticles below 100 nm with the steroids dispersed amorphous state.

XV. As an excipient

β-CD, due to its excellent compatibility and minimal lubrication requirement, used as filler binder in tablet manufacturing, was also found to be useful as solubility enhancer in tablets.

Taste Masking

CDs can be used to mask the taste of drugs in solution. Masking of bitter taste by CDs was reported to be in order of α-CD < β-CD < Y-CD reflecting the stability constant of the complexes**.**

Pelletization

It is a novel drug delivery system. In formulation it helps in drug polymer interaction. Solvent evaporation method is use to prepare pellets.

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.[19]

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.

CONCLUSION

The present article explores various applications of cyclodextrins in pharmaceutical formulations. Cyclodextrins are able to form inclusion complexes with drugs, which can improve solubility and bioavailability. Poor dissolution is a major problem of almost all BCS (Biopharnaceutics Classification System) class II drugs, which leads to poor bioavailability. Cyclodextrins can be used extensively as a polymer in novel drug delivery systems like liposomes, nanoparticles and microspheres that can be expected to improve the therapeutic efficacy of drug and patient compliance.

ACKNOWLEDGEMENT

The authors are very much thankful to Management of KVSR Siddhartha College of pharmaceutical sciences, Vijayawada for their support and constant encouragement.

Table1: Some physical properties of natural cyclodextrins

Characteristic	α	β	γ
No. Glucose unit	6	7	8
Molecular weight	972	1135	1297
Solubility in water (gm/100ml)	14.5	1.85	23.2
Cavity diameter A°	4.7-5.3	6-6.5	7.5-8.5
Volume of cavity (approx) A°	174	262	472
Crystal forms (from water)	Hexagonal plates	Monoclonic parallelogram	Quadratic prism
Crystal water %	10.2	13.2-14.5	8.13-17.7
pKa (by potentiometric) at 25° C	12.3312	12.202	12.081

Table2: Regulatory status of natural Cyclodextrins and HP- β- CD

Cyclodextrin	Food Approval			Pharmacopoeia Monographs		
	US	Europe	Japan	USP/NF	Ph.Eur.	JPC
α-CD	"GRAS"	Planned	Yes	Yes	Yes	Yes
β-CD	"GRAS"	Food Additive	Yes	Yes	Yes	Yes
γ-CD	"GRAS"	Pending	Yes	In Progress	In Progress	Yes
HP-β-CD	-	-	-	In Progress	Yes	-

GRAS = Generally regarded as safe list of the Food and Drug administration in the U.S
USP/NF = United States Pharmacopoeia
Ph.Eur = European Pharnacopoeia
JPC = Japanese Pharmaceutical Codex

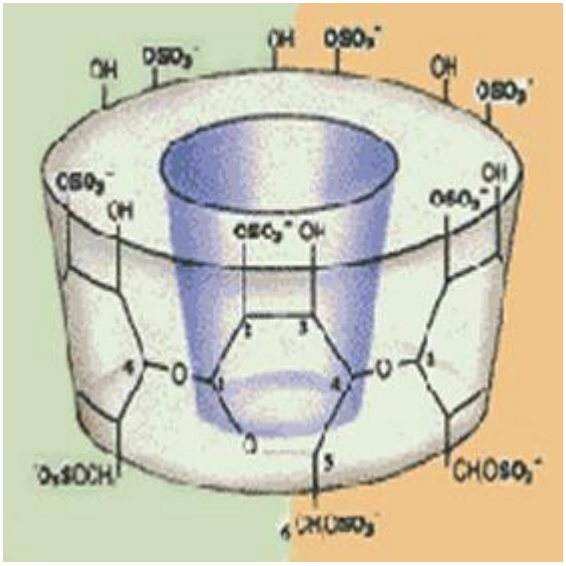

Figure 1: Chemical structure of β-Cyclodextrin

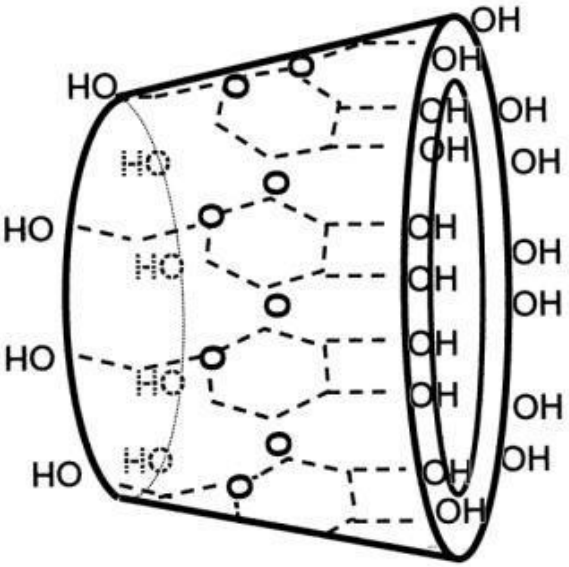

Figure 2: Toroid structure of γ –cyclodextrin

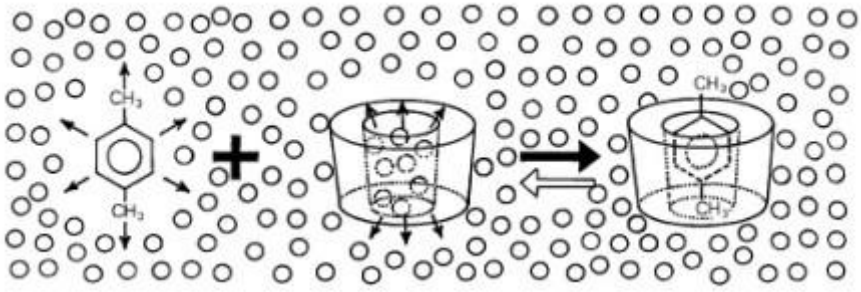

Figure 3: Schematic representation of host-guest interaction

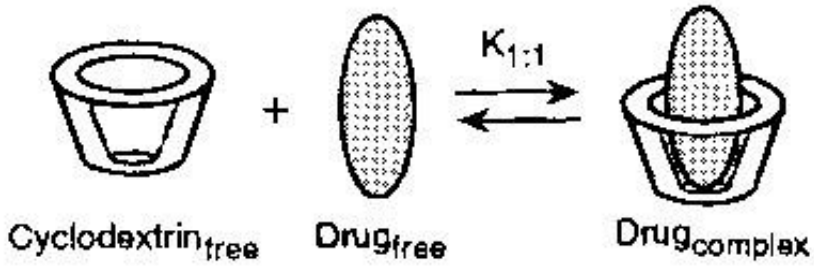

Figure 4: Drug-cyclodextrin complex formation

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