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Review Article

AN UPDATED REVIEW OF CYCLODEXTRINS –AN ENABLING TECHNOLOGY FOR CHALLENGING PHARMACEUTICAL FORMULATIONS

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ABSTRACT

Cyclodextrins (CDS) due to their complexation ability and other versatile characteristics, widely used in the field of pharmaceutical industry and in different areas of drug delivery system. Cyclodextrin molecules are relatively large molecules with number of hydrogen donors and acceptors, thus in general they do not permeate lipophilic membrane. CDS widely used to enhance the solubility, bioavailability, stability and safety of drug molecules. A number of cyclodextrin based product are now available in market, due to their ability to camouflage undesirable physiochemical properties of drugs. The aim of this review is to discuss about types of cyclodextrins, their use in delivery system, complexation techniques, also focus its use in novel drug delivery system and expected to solve many problems associated with the delivery of different novel drugs through different delivery routes. Studies in both human and animals have shown that cyclodextrins can be used to improve drug delivery from almost any type of drug formulations. However addition of cyclodextrin to any existing formulations without further optimisation will seldom result in acceptable outcome. The objective of this review article is to explain the use of natural and derivatized cyclodextrins in the different routes of administration.

Keywords: Cyclodextrin, Types of cyclodextrins, Complexation techniques, Complex formation, Solubility, Novel drug delivery system

INTRODUCTION

A drug is said to be pharmacologically active if it possess some degree of aqueous solubility, which are lipophilic in nature are able to permeate the biological membrane by a process called passive diffusion. The simplest and the most preferred route of drug administration is through oral route due to its advantages like versatility, patient compliance, non-invasiness, greater stability and ease of ingestion. The 40% of the marketed drugs have solubility problem and this is one of the major challenge for formulators and to overcome this problem many techniques have been developed[1].Some available techniques are Micronization, Salt formation, Particle size reduction, Solid dispersion, Adsorption, Melt extrusion, and Cyclodextrin complexation. Among this, complexation with Cyclodextrins is the most commonly used method because cyclodextrin system (CDS) has the property to change the physical, chemical, and biological properties of guest drug molecules by the formation of Inclusion Complex. Complexation can be defined as the process of formation of reversible interaction between the substrate and ligand molecule to form a new compound. Co-valent bond, Vander Waals force, Ion dipole, Dipole-dipole, Hydrogen bonding are some of the intermolecular forces involved in the formation of complexes.

Various uses of complexation are given below:[2, 3& 4]

- Increase in Dissolution Rate.
- Increase in stability.
- Bioavailability can be increased.
- Enhancement of solubility of poorly soluble drugs.
- Taste of bitter drugs can be masked.
- Unpleasant or obnoxious odour can be masked.
- Volatility of the drugs can be prevented.
- Antidote for metal poisoning.
- Manufacturing technique is very simple.
- Cost is very low.

This review article provides detailed information of Cyclodextrin as a complexing agent, different methods used for complex formation, its uses in the drug delivery field, and the effect of Cyclodextrins on various properties of drug.

CYCLODEXTRINS (CDS)

Cyclodextrins are structurally related natural products, they belong to the family of cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic central cavity which are formed by the bacterial digestion of celloulose.CDS also known as Schardinger dextrin's and this CDS contain (1, 4)-linked D-glucopyranose units. This D-glucopyranose have chair conformation because of which this CDS are cone shaped (Figure 1)

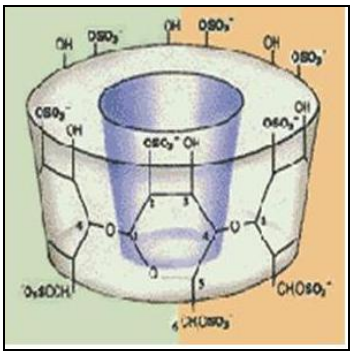

Fig. 1: Chemical structure of cyclodextrin [5]

The most common type of Cyclodextrins is alpha, beta and gamma formed by 6, 7 & 8 glucose units, [4, 6] (Figure 2)

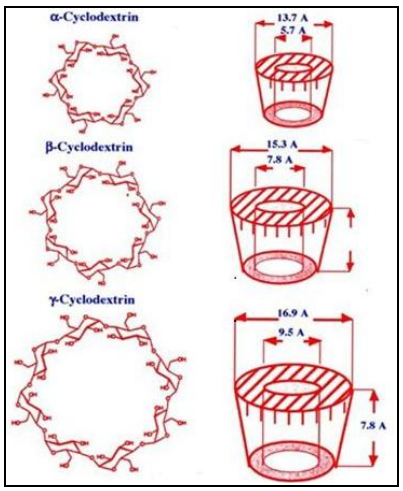

Fig. 2: Structure of alpha, beta & gamma cyclodextrins [5]

But these alpha, beta and gamma Cyclodextrins have limited solubility therefore various derivatives are mainly used in pharmaceutical field as mentioned below: [5, 7]

- Natural Cyclodextrins
- Hydroxy alkylated CDS-hydroxy propyl beta CD &hydroxyl propyl gamma CDS
- Methylated CDS-RAMEB(randomly methylated beta CDS
- Acetylated CDS-acetyl gamma CDS
- SBE CDS-(sulfo butyl ether beta CDS)
- Branched CDS-maltosyl &glucosyl beta CDS
- Reactive CDS-chlorotriazinyl beta CDS.

The properties of alpha, beta and gamma CDS are given in (Table 1)[8].

Table 1: Types of cyclodextrins [8]

Types	Internal Diameter Å	External Diameter Å	Molecular weight (g.mol-1)	Solubility (g/100ml)
α-CD	4.9	14.6	972	14.5
β-CD	6.2	15.4	1135	1.85
δ-CD	7.9	17.5	1297	23.2

Types of cyclodextrins

Hydrophilic CDS: These types of cyclodextrins help to modify the release of poorly water soluble drugs and there by enhance the drug absorption. Beta cyclodextrins have been widely used because of its ready availability, but this have some limitations like low solubility and nephrotoxicity[8].Hydroxypropyl beta cyclodextrins are highly water soluble, are mainly used in parental preparations, they are amorphous in nature and have lower haemolytic activity[9].

Hydrophobic CDS: These types of cyclodextrins are formed when ethyl, acetyl or longer acyl groups are substituted on hydroxyl groups of CDS.The FDA Bio pharmaceutics classification system categorizes drugs according to their aqueous solubility and ability to permeate the intestinal mucosa. Bioavailability of class1drugs are not possible to improve with the help of hydrophilic cyclodextrins, but they are used to reduce the drug irritation and to increase the rate of drug absorption.Class II drugs have limited solubility resulting in dissolution rate limited oral absorption, but with the help of water soluble cyclodextrins complexes of these drugs will enhance diffusion to the mucosal surface leading to increased bioavailability[8, 10].

In pharmaceutical field CDS are mainly preferred because;[11]

1. Using environmental friendly technique tons of cyclodextrin can be produced per year.
2. By choosing appropriate CD derivatives or cyclodextrin type, toxic effect can be eliminated,
3. By simple enzymatic conversion of starch these naturally occurring CDS can be made.

Cyclodextrins can be also used to

- Prevent skin irritation.
- Prevent unwanted body odour.
- Stabilize emulsions and suspensions.
- Absorption of various compounds into skin can be increased or decreased.
- Interactions between various formulation ingredients can be prevented.

Advantages of cyclodextrins:[4, 6, 12].

- CDS have high aqueous solubility.
- Toxicity is very low.
- CDS do not have pharmacological activity.
- Drugs can be protected from biodegradation.
- Shelf life of the product can be increased.
- Therapeutically inert.
- Complex formation can be easily made.
- Up to 300 degree CDS have thermal stability.
- Non-irritating.
- Different molecular size drugs can be entrapped due to different cavity diameter of CDS.

Examples of some of the marketed formulations containing Cyclodextrins are given in (Table 2)

Table 2: Marketed pharmaceutical formulation containing cyclodextrins [13].

Drug	Cyclodextrin	Trade name	Formulation	Company(Country)
Alprostadil	α CD	Caverject Dual	IV Solution	Pfizer(Europe)
Benexate	β CD	Ulgut	Capsule	Terkoku(Japan)
Cetrizine	β CD	Cetrizin	Chewing tablet	Losan Pharma
Meloxicam	β CD	Mobitil	Tablet and Suppository	Medical Union Pharmaceuticals'(Egypt)
Nicotine	β CD	Nicorette	Sublingual tablet	Pfizer(Europe)
Itraconazole	HPβCD	Sporanox	Oral&IV Solutions	Jannssen(Europe, USA)
Mitomycin	HPβCD	MitoExtra	IV Infusion	Novartis(Europe)

Complex formation

The thermodynamic interaction between the different components of the cyclodextrin and the drug is called complexation. The most stable three dimensional structure of cyclodextrin is a toroid with the larger and smaller openings presenting hydroxyl groups to the external environment and mostly hydrophobic functionality lining the interior cavity. This configuration creates a thermodynamic driving force, which is required to form complex of active drug with polar molecules and functional group.[2, 4]There are four possible interactions between cyclodextrin and active drug which shift the equilibrium towards complex formation(Figure3) [5].

Fig. 3: Schematic illustration of the association of free CD and drug to form drug-CD complexes [5].

During complex formation, no co-valent bonds are formed or broken. During this process drug molecules in the complex are in rapid equilibrium with free molecules in the solution. The phase solubility studies described by the Higuchi and Connors, is the most widely used method to study complexation[12, 14].

Complexation techniques:[4, 8, 15]

Complexation of the cyclodextrin with drug can be done using different techniques; some of the methods are explained here

1. Physical blending/milling/co-grinding: By using high level of mechanical energy, the drug and the cyclodextrin are blended, milled or co-grinded.
2. Kneading Method: In this method Cyclodextrin is first taken in mortar then drug is slowly added into it and using small portion of water it is triturated using pestle to get a paste like consistency. The above paste is kneaded for sufficient time then this mixture is dried and is passed through suitable sieve.

3. Co-precipitation method: The Cyclodextrin and the drug are added to water or alcohol and a saturated solution is formed at 40-60 and after that it is cooled to precipitate the complex and it is filtered or centrifuged.
4. Freeze drying method: In this method, water and co-solvent mixture is used to dissolve drug and Cyclodextrin, and by freeze drying the solution complexes can be isolated.
5. Spray drying: Using suitable solvent amonophasic solution of drug and CD is prepared then it is stirred to attain equilibrium and then solvent is removed by spray drying.

For the characterization of inclusion complexes, several analytically techniques are available, and are listed in (Table 3) & (Table 4)[4, 15, 16].

Table 3: Techniques used to characterize drug- cyclodextrins complex in solid [5]

Techniques	Approaches
Scanning Electron Microscopy(SEM)	Crystalline or amorphous state of active drug and complex can be characterized.
X-ray diffractiometry(XRD)	Diffraction pattern of active drug and complex can be characterized.
Infra-Red(IR)Spectroscopy	Characterize the shift of absorbance band to the lower frequency, increases the intensity and widens the band caused by the stretching vibration of the group involved in the formation of hydrogen bonds with cyclodextrin-active drug complex.
Thin Layer Chromatography(TLC)	Characterise the Rf value of an active drug diminishes to considerable extent and this help in identifying the completion of complex formation.
Thermo-analytical methods	Broadening, shifting, and appearance of new peaks or disappearance of certain peaks in thermo gram can be characterized with the help of Differential Scanning Colorimetric (DSC) and Differential Thermal Analysis (DTA).

Table 4: Techniques used to characterize drug- cyclodextrins complex in solution state [5]

Techniques	Approaches
Solubility	• Characterize by enhancement of solubility of active drug.
Electrochemistry	• Polarimetry-This study was conducted as supporting tool for the complex formation. • Conductivity-conductivities are affected by inclusion complex formation with cyclodextrins.
Spectroscopy	• Nuclear Magnetic Resonance (NMR)-direct evidence for the inclusion of a drug into a cyclodextrin cavity in solution. • Ultraviolet/Visible-characterize by change in the absorption spectrum of a drug. • Fluorescence spectroscopy-characterize by change of excitation and emission wavelength of drug. • Circular Dichroism-characterize by change in circular dichroism spectra of drug and complex. • Electron Spin Resonance (ESR)-technique used to investigate inclusion complexation with radicals in aqueous solutions.

Advantages of cyclodextrin in novel drug delivery

Cyclodextrin can act as potential candidates for the efficient delivery of precise amount of drug to the targeted site for necessary period of time because of its ability to form complex with the drug

Role of cyclodextin in liposomal drug delivery:[11]

The main purpose is to combine the advantages of cyclodextrin such as increased drug solubility with the advantages of liposome such as drug targeting. Some of the problems associated with cyclodextrin can be avoided by incorporating it in liposome and complexation with CDS can also improve the stability of liposome. Selection of CD has a significant effect on the amount of drug associated with vesicles example-Hydroxy propyl beta cyclodextrin. This result in high aqueous solubility and can incorporated high amount of drugs in vesicles than beta cyclodextrin[8, 17].

Role of cyclodextrin in microspheres

The role ofcyclodextrin in microsphere formulation was first studied by DR.Loftsson[18]. Hydroxyl propyl beta cyclodextrin used as a promising agent for stabilizing lysozyme and bovine serum albumin during primary emulsification of PLGA or poly(lactic-co-glycolic acid) microsphere preparation[8].

Role of cyclodextrin in osmotic pump tablet

Based on the principle of osmosis, osmotically controlled oral drug delivery systems are designed. By using osmotic tablets many advantages like zero order delivery, patient compliance can be improved, simple to operate and high level of in-vitro in-vivo correlation can be obtained. This osmotic pump tablet consists of a core which includes the active ingredient, an osmogent and other excipients coated with a semipermeable membrane. An orifice is present and through this drug is released by hydrostatic pressure. The drug release from this osmotic pump depends on the drug solubility and the osmotic pressure of the core. The push- pull osmotic tablets were developed in the 1980s and used to deliver drugs having low to high water solubility[19].

Role of cyclodextrin in nanoparticles

When compare to Liposomal delivery system, Nano particles are more stable. However a major disadvantage associated with drug loading efficiency of nano particles. Therefore cyclodextrins are used to improve water solubility and stability of drugs for better loading capacity. Progesterone complexed with hydroxyl propyl beta cyclodextrin and loaded into bovine serum albumin nanospheres, dissolution rate of progesterone were increased by complexation with CDS with respect to free drug [20].

Cyclodextrin in drug delivery system

This section mainly deals with the application of cyclodextrin in oral, rectal, sublingual, ocular, nasal, pulmonary, and in dermaldelivery system.

Oral drug delivery

After oral administration, the drug release time profile can be divided into two types, rate controlled and time controlled types. Rate controlled type can be further divided into immediate release, prolonged release, and modified release types.

Immediate release

The rate and extent of oral bioavailability of the drugs manly depends on the dissolution rate. Oral bioavailability of steroids, non steroidal anti inflammatory drugs, antiepileptic, anti diabetics, vasodilators can be enhanced by using hydrophilic cyclodextrins[21, 22]. This is mainly due to the enhanced solubility and wet ability of the drugs through the formation of inclusion complexes.

Prolonged release

Alkylated and acylated derivatives of Cyclodextrins which are hydrophobic in nature are used as slow release carriers for water soluble drugs[8].

Modified release

Nifedipine, a calcium-channel antagonist must be dosed either twice or three times daily because of short elimination half life in the case

of conventional formulation [23]. This drug having problems like low oral bioavailability and during storage crystal growth occurs and which will lead to decrease in the dissolution rate. Therefore the release rate of nifedipine must be modified in order to obtain better oral bioavailability with prolonged effect.

Sublingual drug delivery

Hepatic first pass metabolism can be eliminated by sublingual drug delivery system. Complexation of poorly water soluble drugs with cyclodextrin has shown to increase bioavailability of various lipophilic drugs in the case of sublingual formulations. For example the bioavailability of 17-beta-oestradiol has increased in the presence of hydroxyl –propyl beta cyclodextrin[24]. Increased bioavailability is due increase in the aqueous solubility due to the presence of cyclodextrins.

Ocular drug delivery

Ophthalmic preparations should be non irritant to the ocular surface, because irritation will result in reflex tearing and blinking. Advantage of using cyclodextrin is that solubility, stability can be increased and discomfort, irritation can be avoided. Among various derivatives of cyclodextrins, hydroxyl-propyl-beta cyclodextrins and sulfo-butyl beta cyclodextrin have no toxic effect to the eye[25, 26]. Hydrophilic cyclodextrins are not able to penetrate bilogical barriers of the eye but enhance the bioavailability by keeping the drug in solution. Econazole nitrate loaded chitosan nanoparticles developed using sulfobutylether-β-cyclodextrin sodium as polyanionic cross-linker to achieve sustained therapeutic effect for ocular drug delivery systems [27].

Nasal drug delivery

First pass metabolism can be eliminated by using nasal route. First drugs should be dissolved in the aqueous nasal fluids then will enter into systemic circulation. Aqueous solubility of lipophilic drugs can be increased by using cyclodextrins. Bioavailability can be increased by using methylated cyclodextrins .For example, the nasal bioavailabilty of insulin in rats was increased from 0-100% by including methylated cyclodextrins in formulation[28].Promising results from nasal delivery of dihydroergotamine[28], midazolam[29], heparins[30]and ondansetron[31] have also been reported.

Pulmonary drug delivery

First pass metabolism and drug degradation in gastrointestinal tract can be eliminated by choosing pulmonary drug delivery system. Because of the large surface area, good blood supply and low enzymatic activity, absorption of drug in the lungs is very effective. However the pulmonary drug delivery can be limited by low aqueous solubility and slow dissolution. Solubility, stability, dissolution rate of water insoluble and chemical unstable drugs can be improved with the help of cyclodextrins, thereby leading to decreased clearance, increased drug absorption and faster onset of action. By complexing the drug with cyclodextrin, a liquid drug can be converted into solid form, two incompatible drugs can be mixed in dry powder formulation, bad smell and taste can be reduced, local irritation in lungs can be reduced. Among various derivatives of cyclodextrins, 2-hydroxy propyl beta cyclodextrins and sulfo- butyl ether beta cyclodextrins are safer for parental administration. In inhalation powder cyclodextrins can be used without lowering the pulmonary deposition of the drugs.

Dermal drug delivery

Stratum cornea is the major barrier for drug absorption through the skin, this can be overcome by using penetration enhancers. Cyclodextrins also have safety margin in transdermal drug delivery of drugs intended for local or systemic effect. They enhance the drug delivery through aqueous diffusion layers, but suitable vehicle must be selected so that cyclodextrins can exert their functions. Release rate of lipophilic drug from hydrophilic aqueous can be increased by using hydroxyl propyl beta cyclodextrin (HPβCD). Hydroxy propyl beta Cyclodextrin increases drug bioavailability in dermal formulations. Physical and chemical changes of the skin will not take place by using HPβCD. Complexation with cyclodextrin has been variously reported to increase in skin penetration[32].

Colon specific drug delivery

Cyclodextrins get absorbed in large intestine after fermentation into small saccharides by colonic microbial flora, because of this property CDS are mainly used for targeting drugs to the colon. Biphenyl acetic acid, a prodrug mainly developed for colon delivery and here drug is conjugated on to one of the primary hydroxyl group of β, α, γ CDS through an ester linkage[8, 11].

Peptide and protein delivery

Major problem associated with the therapeutic peptides and proteins are their chemical and enzymatic instability, poor absorption through biological membranes, rapid plasma clearance, immunogenicity and peculiar dose response curves. An efflux transporter that is present in the apical region of epithelial cells in the brain, kidney liver, and GI tract is P-glycoprotein. The transcellular drug movement in the epithelial cells and many peptide drugs are opposed by P-glycoprotein, but this can be inhibited by the use of Dimethyl-Beta Cyclodextrins i.e., they can decrease the level of P-glycoprotein[33].

Brain drug delivery

The blood-brain barrier which is characterized by endothelial cells of cerebral capillaries having tight continuous junctions, which restricts the passage of polar drugs to the brain and thus obstructs the delivery of neuro pharmaceuticals to the brain.One of the methods used to overcome this transport problem is to prepare prodrugs with high lipophilicity that passes through the blood-brain system. P-glycoprotein effluxes are inhibited by Dimethyl-Beta Cyclodextrins and thereby enhance the drug delivery to the brain[33, 34].

Effect of cyclodextrin on the properties of drug in formulation

- **Effect on drug solubility and dissolution**

In the formulation of poorly water soluble drugs, cyclodextrins used to improve the solubility and dissolution through the formation of inclusion complexes with the drug. Among the various CDS, methylated Cyclodextrins with a relatively low molar substitution appears to be the most powerful solubilises. CDS can able to form in-situ inclusion complexes with drug in the dissolution medium, thereby enhancing the dissolution even when there is no complexation in the solid state[35].

- **Effect on drug bioavailability**

Addition of polymers can further increase the drug permeability from aqueous cyclodextrin solutions. In the case of water soluble drugs, cyclodextrins increase the drug permeability by direct action on mucosal membranes and enhance drug absorption and bioavailability [7]. Cyclodextrins help to stabilize labile drugs and improves contact time of drug at the absorption site in nasal, ocular, rectal, and transdermal delivery[36, 37].

- **Effect on drug safety**

Cyclodextrins have been used to decrease the irritation caused by many drugs. Cyclodextrins have been used to increase the solubility there by it increases the drug efficacy and potency and reduce drug toxicity by making the drug effective at lower doses. For example Beta cyclodextrin enhanced antiviral activity of ganciclovir on human cytomegalo virus[38].

- **Effect on drug stability**

Stability of labile drugs against dehydration, hydrolysis, oxidation, photodecomposition can be enhanced with the help of cyclodextrins, and thus increase the shelf life of drugs. By providing a molecular shield, cyclodextrin complexation encapsulates labile drug molecules at the molecular level and thus insulates them against various degradation processes. Sulfobutylether-β-CD (SBE-BCD) used to enhance the stability of many chemically unstable drugs[39].The cyclodextrins have improved the photo stability of trimeprazine[40] and promethazine[41].

Future benefits of cyclodextrins

Conventional formulation such as tablets, capsules, solutions, ointment, and intravenous solutions are formulated using cyclodextrins. Now a day's Cyclodextrins have been used in novel drug delivery system such as Nanoparticles, Liposomes, and Microspheres and in targeted drug delivery system. Cyclodextrins containing polycations have unique properties that could be useful in the non-viral delivery of nucleic acid. These materials show promise for gene delivery in animals, although their utility in humans remains to be proven[2, 3].

CONCLUSION

High throughput screening, have increased the number of drug candidates, whose clinical usefulness is hampered by their insolubility in water. Cyclodextrins can alleviate many of these undesirable drug properties. Currently there are 30 different cyclodextrin containing formulations, which are available in market. Outcome of cyclodextrin formulation is highly dependent on the physicochemical properties of the drug being formulated.CDS are cyclic oligomers of glucose that can form water soluble inclusion complexes with small molecules and portions of large compounds, because of its biocompatible and multi-functional characteristics they do not elicit immune response and have less toxicity in humans and animals. The complex formation of drug with CDS have been used for constructing a new class of novel drug delivery systems like Liposomes, Microspheres, Nanopartide and Targeted drug delivery system.

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