INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com ISSN 2230 – 8407
Review Article

CYCLODEXTRINS: AN EXCIPIENT TOOL IN DRUG DELIVERY

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Article Received on: 10/02/12 Revised on: 25/03/12 Approved for publication: 14/04/12

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ABSTRACT
Cyclodextrins (CDs) are a family of compounds consist of glucose monomers arranged in a donut shape ring. They are non-reducing, crystalline cyclic oligosaccharides which proximate a truncated core generating a hydrophilic outer surface and a lipophilic interior cavity that offers interaction with appropriately sized molecules to result in the formation of inclusion complex. Cyclodextrins are able to form host-guest complexes with hydrophobic molecules given the unique nature imparted by their structure. As a result, these molecules have found a number of applications in a wide range of fields. The proposed review explores the various techniques used and advantages for the formation of inclusion complex. The CDs have a wide range of applications in different areas of drug delivery and pharmaceutical industry due to their use as complexing agent to increase the aqueous solubility of poor soluble drugs and to increase their bioavailability and stability. The article also highlights extensive use of CDs as a polymer in the design of various novel delivery systems like liposomes, microspheres, nanoparticles that can be expected to improve the therapeutic efficacy of drug and patient compliance. The objective of this contribution is to point out the inherent use of chemically modified cyclodextrins as high performance drug carriers in drug delivery systems with emphasis on the current developments. Thus, CDs because of their continuing ability to find several novel applications in drug delivery are expected to solve many problems associated with the delivery of different novel drugs through different delivery routes.
KEYWORDS: Cyclodextrin (CD), Inclusion, Complexes.

INTRODUCTION

CDs are cup-shaped molecular cages composed of cyclic oligosaccharides. They are novel excipients having glucopyranose units that exhibit amphoteric properties of a lipophilic central cavity and a hydrophilic outer surface[1]. CDs are homologous group of cyclic glucans consisting of α-1, 4 bound glucose units. They are obtained by the action of cyclodextrin glucanotransferase (CGTase) on starch or similar substrates to produce a mixture of cyclodextrins comprised of 6, 7 and 8 glucose units (α, β, and γ-cyclodextrin, respectively). Commercially, cyclodextrins are still produced from starch, but specific enzymes are used to selectively produce consistently pure α, β and γ-cyclodextrin, as desired[2]. The hydrophilicity of the outer surface of the CDs is due to the presence of hydroxyl groups while hydrophobic inner cavity is seamed with skeletal carbons and ethereal oxygen thus rendering a microenvironment for appropriately sized non-polar moiety acting as a guest[3]. The group of forces, including Vander Waals, hydrogen bonds and hydrophobic effects contribute to the formation of a stable complex of drugs in the apolar cavity of cyclodextrins. Cyclodextrins possess a cage-like supramolecular structure, similar to the structures formed from spherands, cryptands, calixarenes, cyclophanes, and crown ethers, thus are having truncated cone or torus shape rather than being a perfect cylinder[4]. As a result of their molecular structure and shape, cyclodextrins possess a unparalleled ability to act as complexing ligands capable of hosting a large variety of guest molecules to form non-covalent inclusion complexes[5]. Such type of hosting can camouflage many non-desirable physicochemical characteristics of the various guest moiety and helps in enhancing their aqueous solubility, dissolution, stability and bioavailability, thus evidencing CDs to be greatly relevant in the pharmaceutical, agrochemical, food and cosmetic industry[6].

(Figure 1)

Advantages

1. CDs help in improving the aqueous solubility of many poorly soluble drugs.
2. CDs enhances the dissolution thus helps in enhancing bioavailability of drugs.
3. CDs complexation improves the chemical, physical and thermal stability of drugs.
4. CDs inclusion complexation helps in ameliorating the irritancy of the drug moiety that irritates the stomach, skin or eye.
5. CDs cloak the unpleasant odour and bitter taste of drugs.
6. Complexing oily or sticky substances with CDs into microcrystalline or amorphous powders help in improving the material handling properties.
7. Formulation of modified release preparations.
8. CDs helps in decreasing the toxic effects associated with drugs.
9. CDs have also been used in the novel pharmaceutical applications.

TYPES OF CYCLODEXTRINS

More than 1500 CD derivatives have been reported in the literatures. However, the most common parent cyclodextrins are α-, β- and γ-CDs containing 6, 7 and 8 glucopyranose units respectively. Chemically, they are torus-like macro-ring oligosaccharides containing at least 6 D-(+) glucopyranose units attached by α-(1, 4) glucosidic bonds. CDs with less than 6 units cannot be formed due to stearic hindrance problems. These parent CDs are natural, non-reducing, crystalline, homogeneous, non hygroscopic having limited aqueous solubility due to strong intermolecular hydrogen bonding in the crystal lattice[7]. However, these parent cyclodextrins are also associated with many limitations and to extend their physicochemical properties and inclusion capacity, the chemically modified derivatives of these parental CDs have been prepared which are amorphous, non crystallisable with enhanced aqueous solubility, physical and microbiological stability, and reduced parenteral toxicity[8]. The various derivatives that have gained pharmaceutical interest include:

- Natural CDs: α-, β- and γ-CDs
- Hydroxyalkylated CDs: HPβCD and HPγCD
- Methylated CDs: RAMEB (randomly methylated βCD)

- Acetylated CDs: Acetyl γCD
- SBEβCD (Sulfo butyl ether β-cyclodextrin)
- Branched CDs: maltosyl and glucosyl βCD
- Reactive CDs: chlorotriazinyl βCD **(Table 1)**

APPROACHES FOR MAKING INCLUSION COMPLEXES

Physical Blending Method: The method involves homogenous blending of the physical mixture of drug and CD followed by passing the mixture through an appropriate sieve to get the desired product.

Kneading Method: In this method, drug and CD are grinded with intense trituration for approx. 30 min. The mixture is then kneaded with hydroalcoholic solution to get a pasty consistency. The mass is then dried at 40°C for 1 hour, stored overnight in vacuum desiccators and passed through no. 80 sieve to get the desired product[9].

Solvent Evaporation Method: Also known as solid dispersion method, involves mixing of the alcoholic solution of drug and aqueous solution of CDs with stirring to get a molecular dispersion, followed by evaporation of the solvent under vacuum until dried mass is obtained. The dried mass is then pulverized and sieved to get the complexed product[10].

Spray Drying Method: Also known as atomization method, a common technique involving preparation of monophasic solution of drug and cyclodextrin using a suitable solvent system generally in ethanol: water 50% v/v. The resulting mixture is then stirred for 24 hr. at room temperature to attain equilibrium following which the solvent is removed by spray drying. The sufficient and effective interaction between the drug and CDs to form a perfect complex is the plus advantage of this technique[11].

Freeze Drying Technique: Also known as lyophillisation technique suitable to get a porous, amorphous powder. In this technique, stoichiometric amount of drug and CDs are dispersed in hydro alcoholic solution using a magnetic stirrer. After agitating for a specific time, the resulting solution is frozen and lyophilised under reduced pressure in a freeze dryer. This technique is suitable for thermolabile substances as they can be successfully made into complex form[12].

Microwave Irradiation Technique: This method involves the microwave irradiation reaction between drug and complexing agent using a microwave oven. This is a novel method for industrial scale preparation which requires a shorter reaction time and higher aim product[13].

Melting: This method involves melting excess amount of guest followed by mixing with powdered CD. The drug-CD mixture is cooled and the excess amount of guest is then removed by carefully washing with weak complex forming solvent or by sublimation under vaccum[14].

Supercritical Antisolvent Technique: In this technique, carbon dioxide is used as antisolvent for the solute but act as a solvent with respect to the organic solvent. Drug and CD are dissolved in a suitable solvent followed by feeding the solution through a nozzle into a pressure vessel containing supercritical fluid anti-solvent. When the solution is sprayed, 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. This is a non toxic and fast process [15].

High Pressure Homogenization Method: In this technique, drug and CD in an appropriate solvent are mixed together and the passed through a high-pressure homogenizer causing the disintegration of particles and dispersion throughout the product. The eventual solution was filtered and evaporated to dryness until the solid complex was acquired[16].

CYCLODEXTRINS APPLICATION IN DRUG DELIVERY SYSTEMS

Cyclodextrins are able to form host-guest complexes with hydrophobic molecules given the unique nature imparted by their structure. As a result of this multifunctional characteristic of CDs, enabling them to be used in almost every drug delivery system, be it oral drug delivery or ocular drug delivery or in novel drug delivery systems. An update on the recent work done in different fields is presented below.

Cyclodextrins in Oral Drug Delivery

Nearly 40% of the new chemical entities currently being discovered are poorly water soluble drugs, thus to enhance their efficacy is a challenging task in drug development. The most common pharmaceutical application of CDs in oral drug delivery includes enhanced drug solubility in aqueous solutions thus resulting in an enhanced dissolution and bioavailability, and stability of the drug at the absorption site or in formulation, reduction of drug induced irritation, and taste making. Beside this, CDs are potential candidates for modified release carriers as chemically modified CDs may serve as novel slow release carriers for water soluble drugs including proteins and peptides. Cyproheptadine hydrochloride is a poorly soluble antihistaminic drug, thus motives adjustment to heighten the efficacy. The solubility of the drug was successfully bumped to 9.69mg/ml at pH 6.8 with β-CD inclusion complex by preparing solid dispersion as compared to 2.09mg/ml of that of pure drug. Thus CDs role in enhancing drug solubilisation was found crucial[17]. The use of Cyclosporine A for inhalation therapy of asthma is limited by its hydrophobic properties. However, complex formation with maltosyl α-CD not only reduced the effective drug dose but wider therapeutic safety margin on inhalation of Cyclosporine A was also expected[18]. Complexation of Repaglinide, an antidiabetic drug, with HPβCD using lyophillisation technique showed an enhanced solubility thus improving dissolution profile of the drug also[19]. Bitter taste and odour of drugs can also be masked by forming inclusion complex of drug and CDs thus making the drug to be acceptable orally. e.g. βCD has potential of masking the bitter taste of drug like Oseltamivir Phosphate (OP). In addition, prepared FDC exhibited better drug release at pH 1.2 and less at pH 6.8. The results of TPS indicate effective taste masking as compared to pure drug. In conclusion, the study corroborated that CD can be utilized as an alternative approach for effective taste masking of OP[20]. NSAIDS, like Piroxicam, Indomethacin showed side effects like gastric ulceration. However, it was found that complexing these NSAIDS with β-CD and HPβCD ameliorate the induction of gastric ulcers induced by restraint and cold stress in rats[21]. Oral antifungals like, Itraconazole, Saperconazole showed greatly enhanced bioavailability with HPβCD complexation. The wide variety of CDs available has made possible to modify the drug release and thus providing option for drug to be released either immediately, or sustainly. Molecular complex of glipizide with β-CD play a vital role to obtain a uniform, controlled and complete drug release of a poorly soluble drug from the swellable /erodible matrix tablet. Thus, CD can be applicable in formulating sustained release formulations also[22]. Very limited aqueous solubility and wettability of Vinpocetine (VP) give rise to problems of both formulation and bioavailability. However, VP-CD-Tartaric

acid multi-component complexes when prepared and formulated in HPMC matrix tablets showed controlled and almost complete release behavior of drug over a 12hr period when compared to vinpocetine immediate release dosage form. Thus, CD-VP complexation improves oral bioavailability of drug and controlled release delivery strategies[23]. **(Table 2)**

Cyclodextrins in Ophthalmic Drug Delivery

Various drug formulations in the form of suspensions, eye drops, ointments, gels and solid inserts are available for topical administration into the eye. But most of these formulations are associated with unwanted side effects like eye irritation, blurred vision and discomfort. Also drug solubility, stability criteria have also to be considered while formulating drugs for ocular delivery. CDs, especially 2HP-β-CD and SBE-β-CD are shown to be well tolerated in aqueous formulations and are non toxic to the eye, thus proving to be beneficial excipients for ocular formulation. Eye drops are also associated with the limitability to sustain high concentration of drugs. However, incorporating ocular drugs into gels or polymer matrix have been shown to increase the contact time. Benefits of using CDs in ocular formulations include:

i. Provides sustained release of drug.
ii. Enhancing solubilisation and chemical stabilization of drug.
iii. Enhancement of ocular drug permeability.
iv. Reduced ophthalmic drug irritation and discomfort.

Formulation with HP-β-CD, with and without HPMC, improved the bioavailability and maximal mydriatic response of tropicamide by enhancing the drug's ocular permeability, but reduced the ocular drug irritation probably by maintaining the pH in physiologic range. Gancyclovir, an acyl ester prodrug upon complexing with 5% w/v HPβCD showed an improved stability and corneal permeation by solubilising the hydrophobic prodrug to 2.5 folds and delivering it across the mucin layer at the corneal surface[38]. A formulation consisting of drug zinc-diethyldithiocarbamate with HP-β-CD complexation was prepared along with addition of polymers and penetration enhancers and this drug delivery system increases both the drug solubility in aqueous eye drops and the permeability of drug through the rabbit cornea[39]. An aqueous ocular delivery system for the poor water soluble anti-inflammatory drug Indomethacin was prepared using HP-β-CD as a complexing agent. Besides a sufficient solubility for the drug, many factors were examined in the development of this system, such as stability and safety. Formulated Indomethacin-HP-β-CD eye drops exhibited delayed release and high drug stability compared to the drug solution. In addition, Indomethacin-HP-β-CD eye drops showed promising management to corneal inflammation[40]. Norfloxacin is a poorly water soluble drug, was complexed with β-cyclodextrin. Several ocular patches/inserts of Norfloxacin-β-CD were prepared in hydroxypropyl methyl cellulose (HPMC) matrix. The influence of rate controlling membranes made of ethyl cellulose (EC) alone and in combination with polyvinyl pyrrolidone K30 (PVP K30) on drug release kinetics was studied. The study confirmed the improved solubility of Norfloxacin when complexed with β-cyclodextrin and that it can be delivered through films made of HPMC matrix cast with EC alone or with a combination of PVPK30[41]. **(Table 3)**

Cyclodextrins in Transdermal Drug Delivery

The topical availability of drugs depends on the criteria that the drug should be able to dissolve in the vehicle (base), and should permeate the skin barrier to show the effect. However, most of the drugs fail to meet this unique amphiphillic nature requirement. Hence, formulations require incorporation of excipients like permeation enhancers, solubilizers etc. that can overcome the problems of either or both of the transport processes (i.e. dissolution into vehicle and diffusion across skin). The main limitation of this route is to overcome the stratum corneum, the outermost skin barrier. In order to achieve therapeutic concentrations and to improve the drug flux, permeation enhancers are used to optimize drug permeation through the skin. Besides the potential of CDs in enhancing the solubility, they can be used as membrane permeability enhancer and stabiliser[50]. CDs have been used as permeation enhancers although their mechanism is not yet well known. CDs play an important role in optimizing local and systemic dermal drug delivery. Benefits of using CDs in transdermal drug delivery include:

i. Enhancement of drug release and/or permeation.
ii. Stabilisation of drug in the formulation or at absorptive site.
iii. Enhanced solubilisation of lipophilic drug.
iv. Alleviation of drug induced local irritation.
v. Providing sustained release of drug from vehicle.
vi. Alteration of drug bioconversion in the viable skin.

Piroxicam formed an inclusion complex with β-CD and RAMEB that additionally improved the drug dissolution properties. Incorporation of the drug β-CD inclusion complex in hydrophilic gel effectively enhanced the drug permeation across semi permeable membrane[51]. Drugs must retain sufficient stability, not only during storage but also at the site of application. Various studies report CD as a drug stabilizer in dermal drug delivery. Complex of dermatocorticoid, tixoxortol-17-butyrate-21-propionate, with β-CD included in vaseline and o/w emulsion showed stability after 30 days storage at 40°C. Oral therapy with glipizide comprises problems of bioavailability fluctuations and may be associated with severe hypoglycemia and gastric disturbances. As a potential for convenient, safe and effective antidiabetic therapy, transdermal delivery system was developed. For this purpose, inclusion complexes of the drug in various CDs were prepared. Release studies revealed an improved release of the drug from formulations containing glipizide-CD complexes[52]. Recently, CDs in dermal delivery of proteins and peptides has been noted. For example, a combination of β-CD and the permeation enhancer Azone achieved higher percutaneous absorption of a peptide drug, nafarelin acetate, and a luteinizing hormone releasing analog[53]. **(Table 4)**

Cyclodextrins in Nasal Drug Delivery

Highly potent drugs can be aimed for systemic delivery through nasal mucosa. This novel approach is beneficial for the drugs with a low oral bioavailability due to extensive gastro-intestinal breakdown and high hepatic first-pass effect. For lipophilic drugs nasal delivery is possible if they can be dissolved in the dosage form. CDs are safe and non toxic, thus are effective excipients for nasal drug delivery as they can enhance either drug absorption by increasing the aqueous solubility or by enhancing drug permeability or both. The hydrophilic CDs enhance membrane permeability by solubilising some specific lipids from biological membrane through the rapid and reversible formation of inclusion complexes. Beside this, they can decrease the nasal toxicity and can act as a carrier for sustained release of drug across nasal mucosa. HP-β-CD and methylated β-CDs have been used mainly as solubilizers and absorption enhancers in nasal

drug delivery system. Administration of lipophilic drugs such as female steroid hormones Estradiol[60] and progesterone with CDs has shown rapid absorption. Progesterone, a poorly water soluble drug possess complications in oral delivery because of high first pass metabolism, thus results in a limited oral efficacy. Formulations of progesterone as gels for nasal administration with carbopol containing β-CD and HPβCD as solubilizers and absorption enhancers were prepared. In vivo studies in rabbits for nasal absorption of progesterone show a rapid increase in plasma levels and promising bioavailability values[61]. Interaction of the antipsychotic drug Risperidone with HPβCD was studied with the aim of overcoming the limitations associated with nasal administration of low solubility drugs. The in vitro dissolution studies showed that formation of the inclusion complex significantly increased the risperidone dissolution rate from the micro particles, thus providing sustained drug release[62]. The use of methylated cyclodextrin derivatives in formulations for enhancing the nasal bioavailability of insulin in rats from about 0-100% was observed[63]. **(Table 5)**

Cyclodextrins in Liposomal Drug Delivery

The main motive of the liposomal drug delivery is to combine the advantages of CDs such as increased drug solubility with the advantages of liposome such as drug targeting. A novel concept in drug delivery takes advantage of certain properties of the drug "containers" cyclodextrins and liposomes to combine them into a single system thus circumventing problems associated with both systems. The concept, entailing entrapment of water-soluble cyclodextrin-drug inclusion complexes in liposomes, would allow accommodation of insoluble drugs in the aqueous phase of vesicles. A combined strategy, based on cyclodextrin complexation and loading in liposomes, has been investigated to develop a new delivery system with improved therapeutic activity of the local anesthetic, prilocaine (PRL). Cyclodextrin complexation not only allowed an efficient encapsulation of PRL base in the aqueous vesicle core, but also increased the anesthetic effect duration and reduced the initial lag time, in comparison with the corresponding formulations containing, respectively, free PRL in the lipophilic phase or PRL hydrochloride in the aqueous vesicle core[67]. Curcumin is water insoluble drug and an effective delivery route is through encapsulation in cyclodextrins followed by a second encapsulation in liposomes. Curcumin-loaded γ-cyclodextrin liposomes indicate significant potential as delivery vehicles for the treatment of cancers of different tissue origin[68]. Conventional drug-loading technologies have typically resulted in undesired drug retention properties. To resolve the problem, a modified gradient loading method was developed for irinotecan encapsulation. The novel SBE-CD gradient could mediate effective irinotecan loading and improve irinotecan retention, thus resulting in highly active liposomal irinotecan formulations[69]. **(Table 6)**

Cyclodextrins in Microspheres

CDs can be used extensively as a polymer in microspheres that can be expected to improve the therapeutic efficacy of drug and patient compliance. The potential of CDs to stabilize α-chymotrypsin upon encapsulation in Poly (lactic-co-glycolic) acid (PLGA) microspheres using a solid-in-oil-in-water (s/o/w) technique was investigated. The results suggest that MβCD can be a suitable excipient to improve protein stability in s/o/w encapsulation procedures[73]. HP-β-CD acted as a promising agent for stabilizing lysozyme and bovine serum albumin during primary emulsification of poly (d, l-lactide-co-glycolide) (PLGA) microsphere preparation. The stabilizing effect was reported to be a result of increased hydrophilicity of the proteins caused by shielding of their hydrophobic residues by HP-β-CD[74]. Sustained release chitosan/β-cyclodextrin microspheres of theophylline were prepared by spray drying method. The effect of several formulation variables on the characteristics of microspheres was studied. The microspheres showed a prolonged release pattern with the release rate of 60.20% (pH 6.8) within 8 h[75]. **(Table 7)**

Cyclodextrins in Nanoparticles

The safety and efficacy of nanoparticles are limited because of their very low drug loading and limited entrapment efficiency. CDs played an important role in designing nanoparticles by enhancing drug loading capacity and the spontaneous formation of either nanocapsules or nanospheres of amphiphilic CDs diester's nanoprecipitation. Thus, opted suitable to provide targeted drug delivery and to enhance the efficacy and bioavailability of poorly soluble drugs. Paclitaxel is a potent anticancer agent with limited bioavailability due to side-effects associated with solubilizers used and the tendency of the drug to precipitate in aqueous media. Amphiphilic cyclodextrin nanoparticles emerged as promising alternative formulations for injectable paclitaxel administration with low toxicity and equivalent efficacy. Hydroxyapatite (HA) containing levels of β-CD of upto 0.9 wt% has been produced by co-precipitation method. The results show that an increase in concentration of β-CD in the prepared samples that leads to an increase in hydrophobicity seems to promote an affinity for albumin adsorption. The results indicate that HA/β-CD complexes have immense potential in targeted delivery of drugs[76]. Captopril (CAP) was the first angiotensin I-converting enzyme (ACE) inhibitor to be developed and is widely used in hypertension treatment. The nanoparticles obtained by the kneading method (CAP/α-CD: KM) showed a potent and long-lasting inhibitory activity (~22 hours) on the angiotensin I pressor effect. The results suggest that the inclusion complex of CAP and α-CD can function as a novel antihypertensive formulation that may improve therapeutic use of CAP by reducing its oral administration to once a day[77]. **(Table 8)**

CONCLUSION

The proposed review on Cyclodextrins (CDs) explores its utility as useful functional excipients that have enjoyed widespread attention and use in the pharmaceutical industry. The bioadaptability and multi-functional characteristic of CDs make them capable of alleviating the undesirable properties of drug molecules in various routes of administration through the formation of inclusion complexes. CDs, as a result of their complexation ability and other versatile characteristic are continuing to have different applications in different areas of drug delivery, thus proving CDs to be greatly applicable in the pharmaceutical, agrochemical, food and cosmetic industry. CDs use as a polymer in NDDS like liposomes, nanoparticles and microspheres is expected to improve the therapeutic efficacy of drug and patient compliance. In future, CDs may solve various problems associated with drug delivery through complexation.

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TABLE 1. PARAMETERS OF NATURAL CYCLODEXTRINS

Parameters	α- CD	β-CD	γ-CD
Empirical formula	$C_{36}H_{60}O_{30}$	$C_{42}H_{70}O_{35}$	$C_{48}H_{80}O_{40}$
Glucose residue	6	7	8
Molecular mass	973	1135	1297
Cavity diameter	0.47-0.53	0.6-0.66	0.75-0.83

TABLE 2. EFFECT OF CDs IN ORAL DRUG DELIVERY

Drug	Type of CDs	Effect
Diacerein[24]	HP-β-CD	Enhanced stabilization against hydrolysis.
Etoricoxib[25]	HP-β-CD	Enhanced solubility and efficacy.
Mefenamic acid, Niflumic acid Flufenamic acid[26]	HP-β-CD	Enhanced solubilisation of drug.
Carvedilol[27]	β-CD	Enhanced oral bioavailability of carvedilol.
Siymarin[28]	β-CD	Enhanced dissolution and sustained effect.
Aceclofenac[29]	β-CD	Enhanced dissolution and faster action.
Felodipine[30]	β-CD	Enhanced dissolution.
Clotrimazole[31]	β-CD	Enhanced solubility and bioavailability.
Olanzapine[32]	β-CD	Enhanced dissolution and absorption.
Curcumin[33]	HP-γ-CD	Enhanced release and bioavailability.
Nimesulide[34]	β-CD	Enhanced physical stability.
Indomethacin[35]	α-CD, γ-CD	Enhanced solubility and dissolution.
Asiatic Acid[36]	HP-β-CD	Enhanced aqueous solubility of drug.
Valsartan[37]	β-CD	Enhanced solubility and efficacy.

TABLE 3. EFFECT OF CDs IN OCULAR DRUG DELIVERY

Drug	Type of CDs	Effect
Econazole nitrate[42]	SBE-β-CD	Sustained release of drug.
Ketotifen fumerate[43]	2HP- β-CD	Enhanced solubility, stability, permeability.
Tropicamide[44]	HP-β-CD	Enhanced permeability and reduced irritation.
Pilocarpine[45]	SBE-β-CD	Improved tolerability of drug.
Gancyclovir prodrugs[46]	HP- β-CD	Improved chemical and enzymatic stability.
Indomethacin[47]	HP-β-CD	Enhanced solubility, aqueous stability, permeation.
Dexamethasone[48]	CD	Enhanced tolerability.
Fluconazole[49]	β-CD	Enhanced solubility and penetration.

TABLE 4. EFFECT OF CDs IN TRANSDERMAL DRUG DELIVERY

Drug	Type of CDs	Effect
Ibuprofen[54]	HP-β-CD	Enhanced transdermal permeation
Nicotine[55]	β-CD	Sustained release of drug.
Avobenzone[56]	HP-β-CD	Enhanced photo stability of drug.
Ascorbic acid[57]	α-CD	Enhanced stabilization and transdermal permeation.
Human Growth Hormone[58]	2HP-β-CD	Enhanced permeation across the skin.
Asiaticoside[59]	β-CD	Enhanced encapsulation and release features.

TABLE 5. EFFECT OF CDs IN NASAL DRUG DELIVERY

Drug	Type of CDs	Effect
Fexofenadine HCl[64]	HP-β-CD	Enhanced plasma concentration.
Artemether[65]	HP-β-CD	Enhanced drug release.
Granisetron[66]	HP-β-CD	Enhanced release profile of drug.

TABLE 6. EFFECT OF CDs IN LIPOSOMAL DRUG DELIVERY

Drug	Type of CDs	Effect
Prilocaine[67]	HPβCD	Enhanced anesthetic effect and duration.
Curcumin[68]	2HP-γ-CD	Enhanced efficiency.
Irinotecan[69]	SBECD	Prolonged release and protection against hydrolysis.
Benzocaine ,Butamben[70]	HPβCD	Enhancement of intensity and duration of anesthetic effect.
Colchicine[71]	βCD	Prolonged drug release and improved site specificity.
Asialofetuin[72]	γ-CD	Increased gene transfer activity.

TABLE 7. EFFECT OF CDs IN MICROSPHERES DELIVERY

Drug	Type of CDs	Effect
α-chymotrypsin[73]	M-β-CD	Enhanced stabilization of drug.
Bovine Serum Albumin[74]	HP-β-CD	Stabilization of protein.
Theophylline[75]	β-CD	Prolonged release of drug.

TABLE 8. EFFECT OF CDs IN NANOPARTICLES DELIVERY

Drug	Type of CDs	Effect
Diazepam[78]	β-CD	Effective as haemoadbsorbant for drug removal.
Diclofenac Na[79]	HP-β-CD	Effective colon-targeted delivery of drugs.
Silver Acetate[80]	β-CD	Enhanced efficacy of drug.

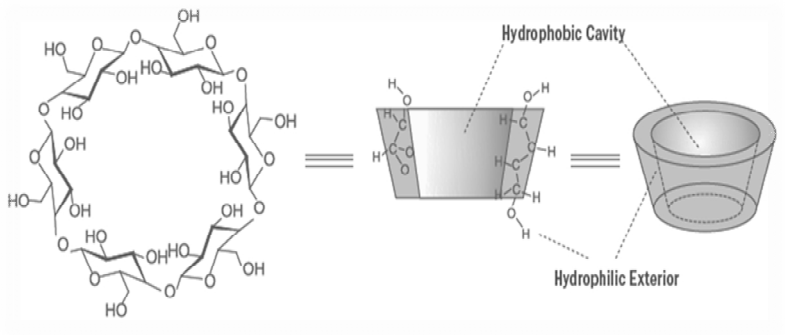

Figure 1. OVERVIEW OF CYCLODEXTRIN MOLECULE GEOMETRY