REVIEW ARTICLE

DRUG-CYCLODEXTRIN COMPLEXES: CURRENT STATUS AND RECENT ADVANCEMENTS

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ABSTRACT

Cyclodextrins are water-soluble oligosaccharides formed by the action of cyclodextrin glucosyl transferase enzyme (CGTase) on the medium containing starch. Cyclodextrins are proven to be a cost-effective breakthrough in the pharmaceutical industry by formulating them with polymers and drugs to improve the safety, bioavailability, and solubility of APIs. This review describes the current status and advancement of cyclodextrin research in drug delivery. The use of cyclodextrins to improve the solubility and dissolution properties of poor water-soluble products has been reviewed exhaustively with a specific focus on their physicochemical property, practical methods, toxicity, the drug-cyclodextrin compatibility and its applications.

Keywords: Cyclodextrin, cyclodextrin complex, drug delivery, inclusion complex

INTRODUCTION

Cyclodextrin (CD) is an oligosaccharide produced through enzymatic starch conversion[1]. On starch-containing media, the enzyme cyclodextrin glucosyltransferase (CGTase) produces cyclodextrin. Polysaccharide with sixD-(+)-glucopyranose units bonded to α (1 - 4) linkages. The outer shell of cyclodextrin is hydrophilic, while the core is relatively hydrophobic. Cyclodextrin is a fine white crystalline powder with a pleasant, sweet taste and no odour. In both solid and liquid states, inclusion complexes are formed by the diffusion of guest molecules into cyclodextrin cavities[2,3]. A wide range of industries use CDs, including pharmaceuticals, medical devices, cosmetics, food and chemicals. These are typically found in tablets, eye drops and ointments. The drug's solubility is critical to it's bioavailability. The drug discovery process and a clinical trial process both require this method. The chemical structure of many newly developed medications contribute to their limited solubility in water. A wide variety of methods is used to enhance solubility, including solid dispersion, salt generation, co-solvency, micellar solubilization, as well as CD complexation, nanosizing and particle engineering[4].

Recently, lipid drug delivery methods or nano-emulsions have been studied[5,6]. Each of these traditional solubilization techniques has disadvantages in solubilizing ability, patient acceptance and safety[7,8].

In this article, it is shown that cyclodextrins are utilized widely to increase the aqueous solubility of drugs with low water-solubility.

Historical background

This type of CD is made up of 6 or more glucopyranose units that are linked by a bond of α- (1→4). The enzyme CD glucosyltransferase[9] initiates intramolecular transglycosylation events from starch breakdown (Fig. 1).

Villiers made the initial discoveries in 1891, while studying the action of butyric ferment *Bacillus amylobacter* on potato starch[10]. Villiers observed a crystalline material he termed "cellulosine." "Crystallized dextrin α" and "Crystallized dextrin β" were isolated by Schardinger in 1903, and afterwards were termed as Schardinger dextrins[1]. From 1930 to 1970, enzymatic CD processing

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Table I: Pharmaceutical products containing cyclodextrin[91, 92]

Drug	Cyclodextrin type	Trade name	Country
SOLUTION			
Alprostadil (PGE1)	α-cyclodextrin	Provastatin®	Japan, Europe, and USA
Iodine	β- cyclodextrin	Mena-Gargle®	Japan
Piroxicam	β- cyclodextrin	Cicladol®	Europe and Brazil
INTRAVENOUS SOLUTION			
Alprostadil (PGE1)	α- cyclodextrin	Rigidur®	Japan, Europe, and USA
Voriconazole	Sulfobutylether-β- cyclodextrin	Vfend®	Europe and USA
Ziprasidone mesylate	Sulfobutylether-β- cyclodextrin	Geodon®, Zeldox®	Europe and USA
Tc-99m teoboroxime	2-hydroxypropyl-γ- cyclodextrin	Cardiotec®	USA
TABLET			
OP – 1206	α- cyclodextrin	Opalmon®	Japan
Cefotiam hexetil hydrochloride	α- cyclodextrin	Pansporin T®	Japan
Cephalosporin (ME 1207)	β- cyclodextrin	Meiact®	Japan
Chlordiazepoxide	β- cyclodextrin	Transillium®	Argentina
Nimesulide	β- cyclodextrin	Nimedex®	Europe
Omeprazole	β- cyclodextrin	Omebeta®	Europe
Piroxicam	β- cyclodextrin	Brexin®	Europe and brazil
Tiaprofenic acid	β- cyclodextrin	Surgamyl®	Europe
CAPSULE			
Benexate hydrochloride	β- cyclodextrin	Ulgut®, Lonmiel®	Japan
CREAM			
Dexamethasone	β- cyclodextrin	Glymesason®	Japan
SUBLINGUAL TABLET			
Diphenhydramine hydrochloride, Chlorotheophylline	β- cyclodextrin	Stada-Travel®	Europe
Nicotine	β- cyclodextrin	Nicorette®	Europe
Nitroglycerin	β- cyclodextrin	Nitropen®	Japan
PGE2	β- cyclodextrin	Prostarmon E®	Japan
CHEWING GUM			
Nicotine	β- cyclodextrin	Nicogum®	Europe
SUPPOSITORY			
Piroxicam	β- cyclodextrin	Flofene®	Europe and Brazil
Cisapride	2-hydroxypropyl-β- cyclodextrin	Prepulsid®	Europe
INTRAMUSCULAR INJECTION AND ORAL SOLUTION			
Itraconazole	2-hydroxypropyl-β- cyclodextrin	Sporanox®	Europe and USA

INTRAVENOUS INFUSION			
Mitomycin	2-hydroxypropyl-β- cyclodextrin	Mitozytrex®	Europe and USA
OPHTHALMIC SOLUTION			
Chloramphenicol	Methyl-β- cyclodextrin	Clorocil®	Europe
Diclofenac sodium	2-hydroxypropyl-γ- cyclodextrin	Voltaren®	Europe
NASAL SPRAY			
17β-estradiol	Methyl-β- cyclodextrin	Aerodiol®	Europe
INTRA-ARTERIAL INJECTION			
PGE1	α-cyclodextrin	Prostavasin®	Japan
SACHET			
Piroxicam	β- cyclodextrin	Cicladol®	Italy
LIQUID			
Hydrocortisone	HPβ-CD	Dexacort®	Island
Itraconazole	HPβ-CD	Sporanox®	Belgium
Chloramphenicol	Mβ-CD	Clorocil®	Portugal
17-β-Estradiol	Mβ-CD	Aerodiol®	France
RECTAL			
Cisapride	β- cyclodextrin	Coordinax®	Belgium
ORAL SACHET			
Nimesulide	β-cyclodextrin	Mesulid Fast®	Italy
TABLET INHIBITOR			
Omeprazole	β-cyclodextrin	Omebeta®	Germany
EYE DROP			
Diclofenac Na	HPγ-CD	Voltaren ophtha®	Switzerland
INTRAMUSCULAR INJECTION			
Ziprasidone mesylate	SBEβ-CD	Zeldox®, Geodon®	USA

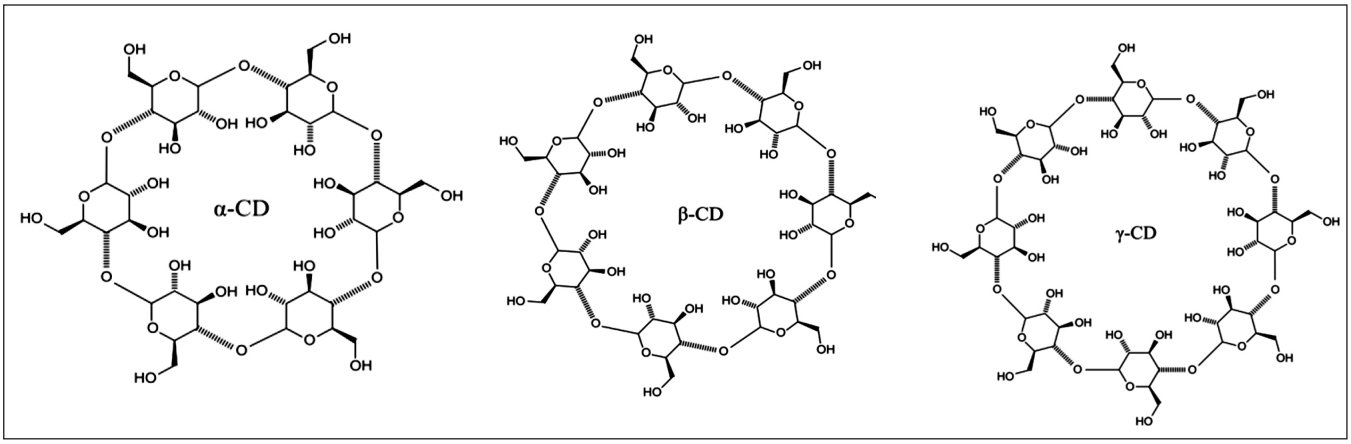

Fig. 1: Cyclodextrins: Formation and types (α, β, and γ-cyclodextrins chemical structure)[9]

Table II: Recent patents in cyclodextrin

US Patent Number	Title	Remark	Ref.
10,933,083	Hydroxypropyl beta-cyclodextrin compositions and methods	Hydroxypropyl beta cyclodextrin had been used as pharmaceutical ingredient and for the treatment of Niemann-Pick disease Type C	93
10,888,621	Injectable tissue adhesive hydrogel including gamma-cyclodextrin and biomedical use thereof	Excellent cell viability and used for adhesion of a skin incision	94
10,882,023	Porous cyclodextrin polymeric materials and methods of making and using same	The polymeric cyclodextrin had been used to remove the organic contamination from water	95
10,876,099	Preparation and application of cyclodextrin glucosyltransferase mutant	The CGTase is used in industrial production and purification	96
10,874,609	-cyclodextrin-based star-shaped polymer, a preparation method thereof and an integrated unimolecular micelle system for diagnosis and treatment thereof	β-cyclodextrin star shaped polymer is used for the treatment and diagnosis	97
10,869,884	Cyclodextrin based polymers, methods, compositions, and applications thereof	Improved biocompatibility, retention time, prolonged duration of action in cells, and increased efficacy in treating a variety of kidney diseases	98
10,842,883	Aqueous oral solution of steroid hormones and hydroxypropyl-beta-cyclodextrin with optimized bioavailability	Formulated drug-cyclodextrin complex for oral administration to achieve effective plasma concentration	99
10,799,599	Inhalant formulation containing sulfoalkyl ether cyclodextrin and corticosteroid	The formulation is employed in an improved nebulization system for administering drug by inhalation	100
10,709,730	Hydroxypropyl beta-cyclodextrin compositions and methods	Hydroxypropyl beta cyclodextrin used as pharmaceutical ingredient and for the treatment of Niemann-Pick disease Type C	101
10,646,586	Aqueous oral solutions of steroid hormones and hydroxypropyl-beta-cyclodextrin with optimized bioavailability	Formulated drug-cyclodextrin complex for oral administration to achieve effective plasma concentration	102
10,646,532	Method of preparing water extract of Ashwagandha leaves which has enhanced anti-cancer activity utilizing cyclodextrin, and pharmaceutical composition containing Ashwagandha leaves	Formulated drug-cyclodextrin complex for anti-cancer activity	103
10,633,462	Manufacturing process for cyclodextrin derivatives	It provides cyclodextrin derivatives in substantially shorter time and with fewer side products than previous processes	104
10,398,785	Pharmaceutical compositions containing taxane-cyclodextrin complexes, method of making and methods of use	Formulated drug-cyclodextrin complex for parenteral administration to treat cancer patients	105
10,363,316	Pharmaceutical formulation comprising NSAID and cyclodextrin	Formulated drug-cyclodextrin aqueous solution spray for throat	106
10,239,961	Cyclodextrin	It produces material with a high average degree of substitution and enables the production of sulphobutylether. Beta-cyclodextrin small manufacturing footprint	107

10,195,227	Method of using cyclodextrin	Prevention and cure of obesity, metabolic syndrome, and diabetes related complications	108
10,188,664	Injectable pharmaceutical compositions compromising a cyclodextrin a hydrophobic drug, a co-solvent, and a preservative	Studied the effectiveness of hydrophobic drug and cyclodextrin through injectables	109
10,182,567	Cyclodextrin compositions, articles, and methods	Cyclodextrin composition is useful to cure the packaging of respiring plant materials	110
9,949,946	Inclusion complexes of pinocembrin with cyclodextrin or its derivatives	It improves the neurobehavioral injury and relieve the decreasing degree of the cerebral blood flow in the cortex medium-sized arterial blood-supplying area	111
10,149,912	Dehydrated hydrogel inclusion complex	Formulated controlled release biodegradable polymer for the administration of bioactive agents	112

was researched. Each round of a linear polysaccharide contains α (1→4)- -linked glucose units[11]. This is called cyclic dextrin[12]. Sicard and Saniez examined the ability of *Bacilli, Micrococcus*, and *Klebsiella* strains to produce CDs. Splicing enabled the building of more sophisticated and active CGTases for α/β/γ CDs after the 1980s. Other innovative technologies permitted the assembly of highly distilled, α, β and γ CDs as medicinal excipients. The crystal structures of α, β, and γ CD were determined in 1948[11].

Cramer demonstrated how CDs might act as refuge molecules, ready to shape reversibly complex molecules absorbed into their interior cavity, giving birth to inclusion complexes. In 1965, the French determined the structure and thus size of the δ -and ε dextrins along with the ζ -and η -dextrins (9-12 residues)[10].

Types of cyclodextrins

- α cyclodextrin-It has 6-component sugar ring molecules; it is moderately irritating after IM injection, it attaches lipids.
- β cyclodextrin-It has a 7-membered sugar ring molecule that binds cholesterol. It is less irritating than α cyclodextrin after IM injections.
- γ cyclodextrin-It has an 8-membered sugar ring molecule, with an absorption rate of 0.1 per cent after oral administration.

The physicochemical properties of cyclodextrin are exhaustively described in the literature[13].

Cyclodextrin toxicity

Natural cyclodextrin and its derivatives were designated by the USFDA as inactive substances and are now accepted as excipients in pharmaceutical products[13]. Routes of delivery influence cyclodextrin toxicity. Oral administration of natural cyclodextrins is safe and well tolerated. Because they are resistant to human amylase, αCD and βCD are easily metabolized by gut microflora. However, αCDs and βCDs are excreted intact in feces[14], whereas γCD is degraded by gut bacteria. Parenterally given cyclodextrins are promptly removed from the body without being metabolized. CDs and certain of their derivatives are unsuitable for intravenous use. Their recrystallization and buildup in kidney tissues induces nephrotoxicity[13]. Natural αCDs and βCDs are substantially more hazardous than their water-soluble derivatives. The use of surface active methylated cyclodextrins is limited. Safe cyclodextrins in parenteral solutions include hydroxypropyl and sulfobutylether[15]. RMβCD cytotoxicity in buccal mucosa was assessed by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide. The inflammatory effects of 10% RMβCD vary on the exposure time. 2% and 5% RMβCD are safe for buccal medication delivery systems[16]. Some commercial products including nasal sprays (Aerodil)® and eye drops (Clorocil)® include methylated cyclodextrins (RMβCD). MeβCD[17] can remove cholesterol from triglycerides. Aqueous settings may have favored native cyclodextrins. Compared to native cyclodextrins, γCD exhibits lower lipid extraction selectivity. The quantity of -CH_3 methyl_ groups in the CD molecules affects extraction of cholesterol from cell membranes. The ionic replacement of methyl group[18] reduces the extraction of cholesterol. CDs are not surfactants. They generate lipid complexes outside of membranes rather than inside. αCD and βCDs show a temperature-dependent aggregation and unfolding tendency in some proteins[19]. The cyclodextrins have hemolytic action *in vitro*, which is explained by the low concentration of CD. This occurs post-parenterally. Cyclodextrins are said to have negligible hemolytic activity *in vivo*.

Applications in drug delivery

Nano and micro-particles can significantly affect the pharmaceutical application in the drug/CD complex formation. They can help drug distribution across biological membranes. The solubilizing abilities of nano- and microparticles are important. Particle generation occurs in aqueous cyclodextrin solutions. As a result, they act more like liposomes, microemulsions, and nano-suspensions than solutions. Water-soluble polymers can help CDs complex in medicinal excipients by stabilizing nanoparticles and micelles. Aqueous solubilization of cyclodextrins and drug/CD complexes is improved by adding organic acid salts. It is thought that the salts associate with the nanoparticles, causing them to become soluble and less likely to combine with other particles to produce larger ones that precipitate out of the solution. When Unstirred Water Layer (UWL) is present, it improves lipophilic membrane permeability, but when UWL is absent, CDs decrease drug permeation[20].

The mucus layer of the gastrointestinal system enhances total drug permeability of the permeability barrier[21]. Although not established, some lipophilic medicines diminish interactions and thereby promote drug penetration into the mucus layer[20]. The ability to distribute medications to specific organs is another benefit of drug/aggregate-drug complexes. Hair follicles can get medications from nanoparticles and liposomes. Hair follicles also have clear medication solution concentrations[22]. *In vitro* investigations have demonstrated no substantial improvement in drug delivery as determined by drop concentrations, whereas aqueous skin testing shows an extraordinary tenfold increase in topical bioavailability[23,24].

Inclusion complexes

Cyclodextrins are a major class of inclusion complexes[25]. Cyclodextrins partially or completely encase any medication; modify drug delivery location and/or time profile; reduce or eliminate bad taste and odour; avoid drug-drug or drug-excipient reactions; convert liquid medications to microcrystalline or amorphous powder.

CDs must be able to build inclusion complexes. Host-guest complexes can be formed using a wide variety of solid, liquid, and gaseous substances. It is retained within the cyclodextrin host by a dimensional match[26]. Host-guest inclusion complexes can have better chemical or biological characteristics than host molecules alone.

Chemical compounds that are poorly water soluble are often made more water soluble by adding cyclodextrins CDs[27]. The ensuing non-covalent inclusions or host complexes are of contemporary scientific and technical interest. In addition to increasing water solubility, non-covalent interactions can also govern guest molecule release. Hydroxypropyl-β-cyclodextrin, a hydroxyl derivative, is a more water-soluble and less toxic alternative to parent cyclodextrins. HP-β-cyclodextrin has been used in medicine, pharmaceuticals, and agriculture since it was originally approved by the FDA[27].

Method of preparation of cyclodextrin complex

- Conventional techniques- co-grinding method, kneading method, solvent evaporation, melting method, co-precipitation methods.
- Comparatively newer techniques- spray drying, lyophilization, hot-melt extrusion.

Co-precipitation method

Co-precipitation method creates an inclusion complex. This is followed by an aqueous CD solution containing the guest. Heating dissolves additional cyclodextrin if the molecule accepts it. Hydration of complex precipitates following filtering or centrifugation is common. This relies on the guest's chemistry and the likelihood of complexation[28].

Solvent evaporation method

By using the solvent evaporation method, a drug-β-cyclodextrin combination is prepared using two molar ratios: 1:1 and 1:2. A mixture of drug and β-cyclodextrin molar weights as per the ratio is prepared. This solution is then lyophilized at – 45°C and 0.5 torr, and the dry residues are gathered and put in a vacuum desiccator overnight[29]. In another reported method, in a round bottom flask, drug and a CD are mixed with water. A three-day cooling-off period is allowed for the solution. A rotary vacuum evaporator is used to dry wet solvents and lyophilize them[30].

Kneading method

A CD paste is made using a small amount of water. The guest is assembled and processed for grinding without using any solvent or ethanol. When the solvent evaporates, the complicated shape becomes a powder. For large-scale kneading, extruders or other machines are necessary. The amount of water and time required to remove the paste varies[26,31,32].

Melting method

The inclusion complex is prepared by merely melting a significant excess of guests and inserting

cyclodextrin in a stable state; the reaction mixture is stirred. After cooling, the excess is eliminated by vacuum sublimation[33].

Co-grinding method

On modest scales, a simple mix of some guests with the CD can trigger inclusion complex development; on big scales, a granulator is required to prepare complexes. If the guests are oils or liquids, this kind of kneading is best performed at room temperature. It takes a long time and doesn't guarantee a fair complexation[34].

Co-evaporation method

It is obtained by taking a desired quantity of drug, dissolving it in an organic solvent, stirring it slowly with a magnetic stirrer at a high temperature, and then evaporating the resulting aqueous solution containing cyclodextrin and then the complex shaped would appear as a dried mass[32].

Spray drying

It is a common pharmaceutical application procedure for converting a liquid to a dry powder. The CD is either dissolved or suspended in hot water and vigorously agitated. One part CD to ten parts water is standard. The guest, either as is or dissolved is added. Spray drying the produced solution separates the complexes. Precipitation must be closely monitored to avoid blocking the atomizer or spray nozzle. Drying conditions must be optimized when volatile guests are present to reduce losses.

As a result, this technique is not suited for guest molecules which are easily agitated. Spray drying is still utilized to prepare CD complexes in solutions. The biggest drawback of this approach is the low final product yield[35].

Lyophilization method

Under the newer methods for producing cyclodextrin complexes, first, the cyclodextrin is dissolved in solution, and then the complex is prepared in an aqueous phase with the aid of continuous stirring and then filtering the cyclodextrin to -80 °C. The lyophilization method of the final product obtained is the cyclodextrin drug inclusion complex[32].

Hot-melt extrusion method

Hot-melt extrusion method was reported to show a more effective mixing ability than co-grinding, freeze-drying, and heat treating. Due to aggregated particles and a reduced surface area for dissolution, co-grinding and freeze-drying samples have a reduced drug release rate. Unlike hot-melt extrusion, which has no aggregated particles and virtually no change in drug release rate, hot-melt extrusion increases drug release properties and solubility without using solvents[36].

Advantages of CD complex

Some developed forms are possible in almost any dosage form through the usage of CD complexation techniques. It has been shown that CD inclusion enhances bioavailability of substances delivered by ocular, topical, nasal and rectal routes in addition to oral and injectable forms.

- There are several drugs from Class II (glibenclamide, glimepiride, nimesulide, etc.) and Class IV (e.g., furosemide) which require the addition of complexes to make them more solubility and stable.
- In general, solubility and dissolution rate improvement are expected to enhance cyclodextrin complexation enhancement process bioavailability.
- The lipid barrier at the absorption site can also be changed by CDs, resulting in better drug absorption. A CD's ability to form membrane complexes such as cholesterol, PLs, and proteins may explain their impact on the lipid barrier.
- Among the significant benefits of CD complexation is the enhancement of the guest's chemical stability, which includes the ability to resist oxidation, photolysis, and hydrolysis[37].

Limitations of the CD complexion

Despite some benefits, there are still several limitations to the CD complexation.

- There must be a possibility of complex formation between the compound and the ligand. To begin with, there is a limited ability to improve solubility for substances with minimal solubility.
- For the complexes of Ap type, dilution of a system may still result in precipitation. It is also possible to precipitate Ap form complexes when the system is diluted. Solubilization through combined techniques like complexation with pH adjustment can produce the same results.
- It is possible that the presence of ligands could add to the complexity and cost of the development process because of toxicity concerns, regulatory issues, and quality management issues.
- It is always impossible to achieve a solubilization effect with a minimal amount of CDs since complexation efficiency is always abysmal[37].

APPLICATIONS

Due to their unique properties, cyclodextrins are used as complexing agents for food and cosmetics, agriculture, environmental, chemical, analytical and pharmaceutical industries.

Agricultural and chemical industries

CD complexes are used in agricultural compounds such as pesticides and growth regulators[38]. Reduced pesticide instability, improved solubility, light stability and biochemical stability are just a few of the various uses and benefits of CD has identified in agriculture[39]. The latest strategies use CDs as growth regulators to transition experimental crops to medium-sized crops. In the literature, CDs are used to enhance mycelium growth in desert truffles (*Terfezia claveryi*), increasing colony diameter, growth rate and fresh weight. However, the use of CDs as a carbon source is sometimes omitted[40]. Today, isomers and enantiomers are separated by HPLC or gas chromatography. These methods utilize immobilized CDs or derived supramolecular structures as stationary phases. CDs also help to accelerate reactions, eliminate waste and aid processes[40].

Environmental field and research

CDs have a very significant role to play in the environmental field. These are utilized in a variety of areas, such as soil, water, and environment solubilization, and reduce organic and heavy metal contaminants[41,42]. In this regard, they have been used in soil washing procedures[43-45] for the full elimination of toxins and the processing of CDs. Butterfield *et al.* showed how β-CD contains and extracts vapor phase polycyclic aromatic hydrocarbons (PAHs) that minimize their volatilities[46]. α, β and β-CD derivatives (RANDOMβ-CD, CRYSMEB, HPβ-CD, SBEβ-CD) are used to trap toluene in processes of bioremediation and phytoremediation of contaminated soils[47,48]. Bardi *et al.* have demonstrated how *in situ* PAH bioremediation is enhanced by associating β-CD with phytoremediation[49].

Foods and flavours

CDs have several uses in the food business. Due to their favorable toxicological characteristics, α-CD and γ-CD do not have any defined limit of Acceptable Daily Intake (ADI) unlike β-CDs (defined limit of ADI in foods is 5 mg kg^{-1} day^{-1}) [50]. β-CD forms inclusion complexes with lipids, colours, and colourants. In addition to removing/suppressing unwanted elements like taste and odour, they can also control the release of certain food components over time. CDs can also be used to preserve and minimize food odours. The use of CDs gives an alternative to typical encapsulation technologies for the safe storage of volatile liquids[51]. For example, aspartame is stabilized and enhanced by cyclodextrin complexation[52]. CDs can also hide unpleasant flavours like harsh grapefruit juice[53] or coffee[54]. CDs[55,56] stabilize water-in-oil emulsions like salad dressing or mayonnaise. 0.2 % β-CD is also used to retain food colours like tomato ketchup. CDs to cheese, meat, and emulsified foods[55] enhance growing time and water preservation of food items. Most commonly, it is used to remove cholesterol from animal foods. CD-treated items, like eggs and dairy products, have 80% less cholesterol[57]. In frying, CDs and free fatty acids can strengthen fats, reducing haze, foaming, browning, and buildup on leftover oil surfaces[58]. Because of their limited water solubility and unpleasant taste, flavonoids and terpenoids cannot be utilized as food. These compounds' characteristics were discussed by Tommasini et al[59]. Another key application is to minimize residual organic volatile contaminants and improve barrier qualities of CD packaging materials. By reducing the degradation of flavour components, CDs or antimicrobial agents complexed with CDs can improve microbiological safety during storage. Adding essential oils, to chitosan film enhances its antibacterial capabilities for active food packaging[60,61].

Pharmaceutical applications

A drug must be hydrophobic to pass through cell membranes, while also being soluble in water to ensure membrane release[62]. In solution, CDs can transfer hydrophobic medicines to bio-membranes (like mucous membrane of eye cornea and skin)[63]. For example, HPβ-CD enhances corneal permeability by solubilizing and transferring hydrophobic ganciclovir prodrug to the corneal surface[64]. Not only are CDs non-irritating, but they also protect active substances from hydrolysis, oxidation, heat, and sunshine. CDs' impact on smells and flavour masking are both important parameters. Acceptable palatability is important for pediatric patients[65,66]. For example, oxyphenonium bromide[67] can be neutralized by cyclodextrin complexation.

Because CDs are complexed or scattered, their apparent solubility and dissolution rates improve. CDs are also capable of functioning as release enhancers[68]. Theophylline, naproxen, and ketoprofen are released from inert acrylic resins more efficiently when they are complexed with βCD [69,70]. Shewale *et al.* focused on the effects of pH and HPβ-CD on carvedilol solubility and stability, finding that it is often improved by adding HPβ-CD or pH reducing agents[71].

CDs are commonly utilized in nanosystems as molecular valves[72]. Temperature, redox, enzyme, and light

all influence the reversible transition of open to closed nanovalves. The mesoporous surface has supramolecular nanovalves made of β-CD-functionalized monobenzimidazole. Silica nanoparticles have been used to study p-coumaric acid release, tumor-specific medication delivery and smart anticorrosion coatings[73]. The antibacterial efficacy of pipemidic acid-β-CD complex against *E. coli* and *S. aureus* was reported to be greater than that of pipemidic acid alone[74]. Moreover, the usage of CDs improves medication solubility in the aqueous climate[75,76]. The bioavailability of Δ9-THC following sublingual administration of Δ9-THCβ-CD complex powder is larger than that following oral administration of ethanolic Δ9-THC solution[77]. Many medications, including neuroleptics, anti-inflammatory treatments, and antibiotics, cause erythrocyte hemolysis as a side effect that is covered by CDs. This safety may be due to a lower effective concentration of the chemical in contact with the membrane[78]. Proteins and peptides can also form CD complexes, increasing the size of the drug molecule[79,80]. Adding CDs slows the hydrolysis catalysed by glycoside linkages in digoxin[81]. Cyclodextrins can resolve racemic mixtures[82]. Inclusion complexes govern the dissociation of its components based on the relevance of the corresponding stabilizing constant. Notably, medication potency remains unchanged. A drug's optimum binding constant range: CD complexes is 0 to 1000 M^{-1} [83]. In solution, cyclodextrin complexes typically agglomerate. CDs self-assemble to create nanospheres, nano-reservoirs, micelles, and nanogels, which are effective drug delivery systems[83-86]. These complexes tend to be more successful in delivering medicines topically than standard eye drops[84-87].

New therapies for chronic renal disease combine polycationic cyclodextrin nanoparticles with small interfering RNA to deliver gene-specific silencing to glomerular mesangium, decreasing glomerular aggregation[88]. The initiative therapeutics for rare and neglected diseases has led to the adoption of HPβ-CD as a potential orphan medicine in clinical practice for Niemann-Pick type C1 disorder (NPC1). HPβ-CD appears to be important in avoiding unesterified cholesterol and associated lipid aggregation in neuronal cell lines[89]. Recent research has shown that cyclodextrin can slow the spread of leukemic cells by suppressing tyrosine kinase activation, indicating its potential as an anticancer agent[90]. In the pharmaceutical business, cyclodextrin is used to change medication properties[91, 92] (Table I).

Recent patents in cyclodextrins

An inventor receives a patent when a sovereign authority grants him intellectual property rights. Because of exhaustive research on cyclodextrin based drug delivery, several patents on cyclodextrin have been awarded and are reported in Table II.

CONCLUSION

Apart from application in various other industries, CDs are commonly used in pharmaceutical formulations, drug delivery systems and formulations. The time-tested safety profile with cost effectiveness makes the CDs a vital component to improve solubility, dissolution and permeability of APIs for pharmaceutical industry. The scientific community is working on exploring its role in site-specific drug delivery and for nanoparticle development to prepare more effective dosage forms and delivery systems.

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