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Cyclodextrin In Drug Delivery: A Review

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Review Article

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ABSTRACT

Cyclodextrins (CDs) are a family of cyclic oligosaccharides composed ofα-(1, 4) linked glucopyranose subunits. CDs have been found as potential candidates because of their ability to alter physical, chemical and biological properties of guest molecules through the formation of inclusion complexes. Pure cyclodextrins that were suitable for pharmaceutical applications did not come available until about 25 years later and at the same time the first cyclodextrin-containing pharmaceutical product was marketed in Japan. Later cyclodextrin-containing products appeared on the European market. Cyclodextrin molecules are relatively large with a number of hydrogen donors and acceptors and, thus, in general they do not permeate lipophilic membranes. In the pharmaceutical industry cyclodextrins have mainly been used as complexing agents to increase aqueous solubility of poorly soluble drugs, and to increase their bioavailability and stability.

INTRODUCTION

Cyclodextrins are natural cyclic oligosaccharides that were discovered 100 years ago but only recently did highly purified cyclodextrins become available as pharmaceutical excipients. In the pharmaceutical industry cyclodextrins have mainly been used as complexing agents to increase aqueous solubility of poorly soluble drugs, and to increase their bioavailability and stability. In addition, cyclodextrins can be used to reduce gastrointestinal drug irritation, convert liquid drugs into microcrystalline or amorphous powder, and prevent drug-drug and drug-excipient interactions [1].

Types of Cyclodextrin

- **α -cyclodextrin**: six membered sugar ring molecule
- **β -cyclodextrin**: seven membered sugar ring molecule
- **γ -cyclodextrin**: eight membered sugar ring molecule [1,2]

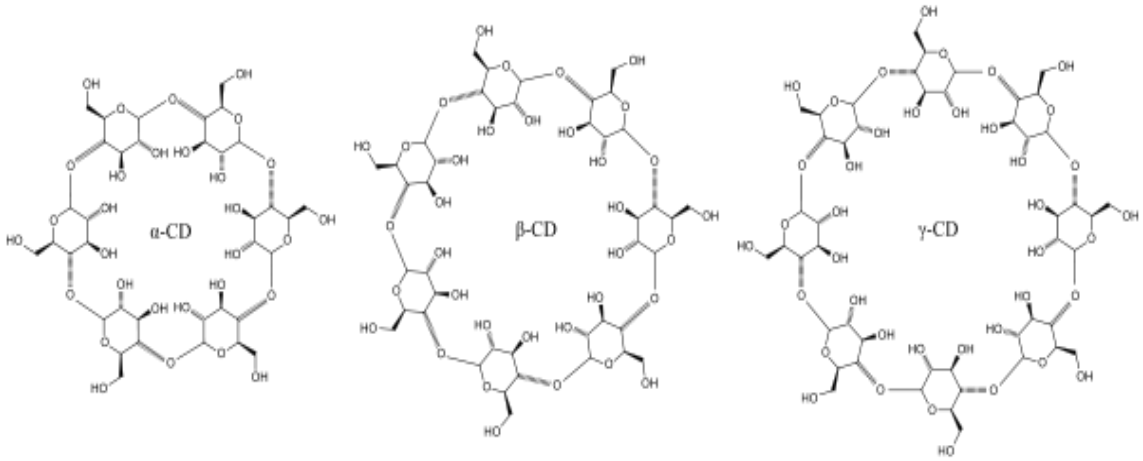

Figure 1: Chemical Structure of the Three Types of Cyclodextrin.

Synthesis of Cyclodextrins

The production of cyclodextrins is relatively simple and involves treatment of ordinary starch with a set of easily available enzymes. Commonly cyclodextrin glycosyltransferase is employed along with α-amylase. First starch is liquified either by heat treatment or using α-amylase, then CGTase is added for the enzymatic conversion. CGTases can synthesize all forms of cyclodextrins, thus the product of the conversion results in a mixture of the three main types of cyclic molecules, in ratios that are strictly dependent on the enzyme used: each CGTase has its own characteristic α:β:γ synthesis ratio. Purification of the three types of cyclodextrins takes advantage of the different water solubility of the molecules: β-CD which is very poorly water soluble can be easily retrieved through crystallization while the more soluble α- and γ-CDs (145 and 232 g/l respectively) are usually purified by means of expensive and time consuming chromatography techniques. As an alternative a "complexing agent" can be added during the enzymatic conversion step: such agents (usually organic solvents like toluene, acetone or ethanol) form a complex with the desired cyclodextrin which subsequently precipitates. The complex formation drives the conversion of starch towards the synthesis of the precipitated cyclodextrin, thus enriching its content in the final mixture of the products [3,4].

Production of Cyclodextrins

Treatment of starch with amylase from *Bacillus macerans* gives a crude mixture of cyclodextrin, The mixture was difficult to purify and it frequently contained several other linear and branched dextrins together with small amounts of proteins and other impurities. The biotechnological advances that occurred in the 1970s lead to dramatic improvements in their production. Genetic engineering made different types of CGTases available that were both more active and more specific towards production of or cyclodextrin than the previously used enzymes. These enzymes together with other technological innovations made highly purified and cyclodextrin available that could be used as pharmaceutical excipients. In 1970, cyclodextrin was only available as a rare fine chemical at a price of about US$ 2000 per kg. Today the annuam cyclodextrin production is close to 10,000 tonnes and the bulk price has lowered to about US$ 5 per kg [5].

Cyclodextrin Derivatives

The aqueous solubility of and cyclodextrin is much lower than that of comparable linear dextrins, most probably due to relatively strong binding of the cyclodextrin molecules in the crystal state (i.e. relatively high crystal energy). In addition, cyclodextrin molecules form intramolecular hydrogen bonds that diminish their ability to form hydrogen bonds with the surrounding water molecules. Various semisynthetic water-soluble cellulose derivatives (e.g. carboxymethylcellulose and hydroxypropyl methylcellulose) had been synthesized and were used in large quantities in a variety of industrial products. Similar chemical modifications were now applied to obtain water-soluble cyclodextrin derivatives. It was discovered that substitution of any of the hydroxyl groups, even by hydrophobic moieties such as methoxy functions, resulted in dramatic increase in their aqueous solubility. With increasing degree of methylation the solubility of cyclodextrin (in cold water) increases until about 2/3 of all the hydroxyl groups have been methylated, and then it decreases again upon further methylation. Later several new derivatives came available including the 2-hydroxypropyl derivatives of both and cyclodextrin, the sulfobutyl ether derivative of cyclodextrin, and the branched (glucosyl- and maltosyl-) cyclodextrins. The main reason for the solubility enhancement in the alkyl derivatives is hat chemical manipulation transforms the crystalline and cyclodextrin into amorphous mixtures of

isomeric derivatives. For example, 2-hydroxypropyl cyclodextrin is obtained by treating a based solubilized solution of cyclodextrin with propylene oxide, resulting in isomeric system that has solubility well in excess of 60% (w/v) . The number of isomers generated based on random substitution is very large. Statistically there are about 130,000 possible cyclodextrin derivatives, and given that introduction of the 2-hydroxypropyl function also introduces an optical center, the total number of isomers, i.e.geometrical and optical, is even much greater. Since the reactivity of the three hydroxyl groups on the cyclodextrin forming glucose units have been shown to be slightly different the substitution is usually not totally random and found to depend on, for instance, the basicity of the aqueous reaction media. This could explain the slight differences found in the complexing abilities of identical cyclodextrin derivatives from different suppliers and sometimes from one batch to another from the same supplier. Fully substituted derivatives were shown to have lower aqueous solubility than partly substituted derivatives which could be related to the fact that the number of possible isomers decreases as the cyclodextrin molecule becomes close to fully substituted. The ability of the cyclodextrin derivatives to form water-soluble complexes is also dependent on the degree of substitution (i.e. the solubility of the cyclodextrin molecule and the access of the guest molecule to the cyclodextrin cavity). Thus, the degree of substitution is in general optimized with regard to the solubilizing abilities of the cyclodextrins. The degree of substitution of the pharmaceutical grades is about 0.65 for 2-hydroxypropyl cyclodextrin (i.e. on the average 0.65 hydroxypropyl-moieties are on each glucose unit) and about 1.8 for randomly methylated cyclodextrin (i.e. on the average 1.8 methoxy-moiety on each glucose unit). Furthermore, since new cyclodextrin derivatives are unlikely to offer broad advantages over the currently used ones availability of new cyclodextrin derivatives will most likely increase very slowly [6].

Cyclodextrin Complexation

The complexes are formed when a "guest" molecule is partially or fully included inside a "host" molecule, like cyclodextrin, with no covalent bonding . The most widely used approach to study inclusion complexation is the phase solubility method described by Higuchi and Connors, which examines the effect of a solubilizer, i.e., CD or ligand on the drug being solubilized, i.e., the substrate [7,8].

Complexation Techniques

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

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

c. Neutralization method: Drug and CD are separately dissolved in 0.1 N NaOH mixed and stirred for about half an hour, pH is recorded and 0.1 N HCl is added drop wise with stirring until pH reaches 7.5, where upon complexes precipitates. The residue is filtered and washed until free from chlorine, it is dried at 250^0 C for 24 hrs. and stored in a desicators.

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

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

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

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

h. Melting: Complexes can be prepared by simply melting the guest, mixed with finely powdered CD. In such cases there should be a large excess of guest, and after cooling this excess is remove by careful washing with a weak complex, forming solvent or by vacuum sublimation [10].

Inclusion and Non-Inclusion Complexes

It is generally accepted that in aqueous solutions cyclodextrins form what is called "inclusion complexes" where water molecules located within the lipophilic central cavity are replaced by a lipophilic guest molecule or a lipophilic moiety on, for example, a drug molecule. However, the hydroxy groups on the outer surface of the cyclodextrin molecule are able to form hydrogen bonds with other molecules and cyclodextrins can, like non-cyclic oligosaccharides and polysaccharides, form water soluble complexes with lipophilic

water-insoluble compounds. Linear homologs of maltodextrins, i.e.1,4-linked linear glucose oligomers, have been shown to bind fluorescence probes but the binding constants are significantly smaller than those for their cyclic counterparts. It has been shown that cyclodextrin forms both inclusion and non-inclusion complexes with dicarboxylic acids and that the two types of complexes coexist in aqueous solutions. In saturated aqueous solutions guest/cyclodextrin complexes frequently consist of a mixture of inclusion and non-inclusion complexes. This could explain why the value of the equilibrium constant for the complex formation is sometimes concentration dependent and why their numerical value is frequently dependant on the method applied [8,9].

Methods to Enhance the Complexation Efficiency

For a variety of reasons, including toxicological considerations, formulation, bulk, production cost, drug bioavailability and isotonicity, it is important to use as small amount of cyclodextrin as possible in pharmaceutical formulations. Same applies to other industrial products such as cosmetics and food products where excess amounts of cyclodextrins can have less than optimal effects. A number of methods have been applied to enhance the complexation efficiency (or rather the solubilization efficiency) of cyclodextrins and some of them are listed in Table-1. Formation of cyclodextrin complexes is an equilibrium process where free guest molecules are in equilibrium with molecules in the complex. Increasing the solubility of the guest through ionization, salt formation, formation of metal complexes and addition of organic cosolvents to the aqueous complexation media will, if the conditions are right, lead to enhanced complexation [10].

Table 1. Methods that can be Used for Complexation are Given in Following Table

Effect	Consequences
Dug ionization	Unionized drugs do usually form more stable complexes than their ionic counterparts. However, ionization of a drug increases its apparent intrinsic solubility resulting in enhanced complexation.
Salt formation	It is sometimes possible to enhance the apparent intrinsic solubility of a drug through salt formation.
Complex-in-complex	It is sometime possible to increase the apparent intrinsic solubility of a drug through formation of metal complexes.
The acid/base ternary complexes	It has been shown that certain organic hydroxy acids (such as citric acid) and certain organic bases are able to enhance the complexation efficiency by formation of ternary drug/cyclodextrin/acid or base complexes.
Polymer complexes	Water-soluble polymers form a ternary complex with drug/cyclodextrin complexes increasing the observed stability constant of the drug/cyclodextrin complex. This observed increase in the value of the constant increases the complexation efficiency.
Solubilization of cyclodextrin aggregates	Organic cations and anions are known to solubilize uncharged drug/cyclodextrin complexes that have limited aqueous solubility. This will enhance the complexation efficiency during preparation of, for example, solid drug/cyclodextrin complex powder.
Combination of two or more methods	Frequently the complexation efficiency can be enhanced even further my combining two or more of the above mentioned methods. For example drug ionization and the polymer method, or solubilization of the cyclodextrin aggregates by adding both polymers and cations or anions to the aqueous complexation medium.

Cyclodextrin Aggregates

Water-soluble polymers and certain organic acids and bases, can be explained by the fact that both cyclodextrins and cyclodextrin complexes self-associate to form nano-scale aggregates that interact with these excipients. Formation of such structures is not easily detected and they have for the most part been ignored until relatively recently. They can, however, be made visible by Cryo-TEM micrographs. The size and shape of cyclodextrin aggregates in water have, for example, been shown to depend on the cyclodextrin concentration and other external factors and to have a minimum hydrodynamic radius of about 90 nm. Other investigations have indicated that the aggregate diameter is much smaller or from 3 to 5 nm. Discovery of these aggregates, as well as the ability of cyclodextrins to form non-inclusion complexes, is likely to have profound influence on future cyclodextrin research [11].

Drug Availability from Cyclodextrin-Containing Products

It has been widely believed that drug availability in cyclodextrin-containing formulations will be hampered by the slow release of drug molecules from the cyclodextrin cavities. However, it has been shown that the rates for formation and dissociation of drug/cyclodextrin complexes are very close to diffusion controlled limits with complexes being continually formed and broken down. Consequently, presence of water-soluble drug/cyclodextrin complexes right at the hydrated epithelial surface will frequently increase the availability of dissolved drug molecules, especially of lipophilic drugs with poor aqueous solubility. Studies have shown that cyclodextrin enhance oral bioavailability of FDA's Class II (poor aqueous solubility, high permeability) drugs but they can hamper bioavailability of Class I (high solubility, high permeability) and Class III (high solubility, poor permeability) drugs [12,13].

Cyclodextrins in Dispersed Systems

Both the parent cyclodextrins and their derivatives have been used in dispersed vehicle systems such as emulsions, microcapsules, microspheres, nanospheres, nanocapsules, liposomes and niosomes. Inclusion complexes of glycerides, fatty acids or fatty alcohols do possess surface activity and this property together with their ability to form aggregates frequently result in formation of dispersed systems. In other cases cyclodextrins have been uses to increase drug loading of polymeric microspheres or to increase drug availability from dispersed systems. Novel surface active cyclodextrin derivatives have also been synthesized and used as drug delivery systems [14,15].

Applications of Cyclodextrins in Drug Delivery

Oral Drug Delivery

Immediate Release

The dissolution rate of poorly water-soluble drugs is mainly responsible for both the rate and extent of oral bioavailability of drugs. Highly hydrophilic CD derivatives, such as HP- β -CD, maltosyl- β -CD and SBE- β -CD have been used to obtain an immediate release formulation that is readily dissolved in GIT, enhancing the oral bioavailability of poorly water soluble drugs through the formation of inclusion complexes.

Delayed Release

CME- β -CD was developed to exhibit pH-dependent solubility for use in selective dissolution of the drug CD-complex. Molsidomine absorption from tablets containing CME- β-CD was studied in gastric acidity-controlled dogs in fasted and fed states. Under high gastric acidity, molsidomine absorption was significantly retarded compared to that found under low gastric acidity conditions.

Prolonged Release

Slow-release preparations have been designed to achieve zero-order or pH-independent release of drugs to provide a constant blood level for a long period of time.

Modified Release

Complexation of drug with CD also suited for sublingual or buccal administrations, which avoid the hepatic first-pass metabolism of the drug. Biphosphonate derivative of CD, ALN-β-CD/ Dexamethasone complex bound to hydroxyapatite (HA) more than 15 extractions to release 90% of the loaded Dex. For β- CD/ Dex complex nonspecifically bound to HA, 2 extractions will remove over 95% of the initial drug content . Elementary osmotic pump (EOP) tablets were prepared to improve the solubility and dissolution rate of lovastatin by complexation with β-CD by kneading method. The release rate of drug can be effectively modified using PVP with higher molecular weight. The EOPs with thicker coating films showed longer dissolution time which is in agreement with the theoretical prediction. The results confirmed that dissolution rate of lovastatin β -CD were greatly enhanced and this system has suitable solubility behavior in EOP tablet formulations [16].

Parenteral Drug Delivery

HP-β-CD and SBE-β-CDs have been widely investigated for parenteral use because of their high aqueous solubility and minimal toxicity. Applications of CDs in parenteral delivery are solubilization of drugs, reduction of drug irritation at the site of administration and stabilization of drugs unstable in aqueous environment etc [17].

Ophthalmic Drug Delivery

Topically applied drug formulations such as suspensions, oily drops, gels, ointments and solid inserts have been used, but most of these formulations give rise to unwanted side effects e.g., eye irritation and blurred vision. CDs work as an anti irritant by formation of inclusion complex and thereby masking the irritating drugs or by replacing the irritating additives from the formulation. Pilocarpine irritation is due to the rapid absorption of the lipophilic prodrug into the lipophilic corneal epithelium and/or precipitation of prodrug molecules in the pre-corneal area. Pilocarpin/SBE7 β-CD complexes can be considered to act as a depot that limits the free prodrug concentration in the precorneal area to a non-irritating level . CDs enhance drug permeability through biological membranes such as eye cornea and skin by disrupting the membrane, either by permeating into the membrane or by extracting or complexing with some lipophilic components such as cholesterol and phospholipids from the membrane. But, the correct mechanism is when CD acts as a true carrier by keeping the hydrophobic drug molecules in solution and delivers them through the aqueous mucin layer to the surface of the ocular barrier (i.e., cornea or conjunctiva) where they partition into the barrier [18].

Limitations

a). SBE 4-β-CD has no effect on pilocarpin bioavailability and it has even a slight decreasing effect at higher concentrations[19].

b). Eye drops are usually delivered in a multi-dose container and thus should contain an antimicrobial preservative. CD complexation with the preservative can reduce their antimicrobial activity[20].

c). The order cytotoxicity of CDs on human corneal cell line was found to be α-CD > DM-β- CD > SBE-β-CD = HP-β-CD > γ-CD. It was suggested that ocular toxicity with SBE-β- CD (100mM) after 1 hr of its exposure could be possibly due its high osmotic pressure [21].

d). Ophthalmic delivery of drugs can be limited by the dissociation of drug/CD complexes in the precorneal area due to the limited dilution in this area [10]

Nasal Drug Delivery

For nasal drug delivery, the volume delivered must be 25-200 ml. complexation with cyclodextrin is one the best approach for making the nasal drug delivery for poorly water soluble drug by improving the solubility of drug. However, large interspecies differences were found in CD enhanced nasal drug absorption. The safety and non-toxicity of CDs in nasal drug formulations have been demonstrated by the clinical data with CDs showing no adverse effects. Large hydrophilic drugs like peptides and proteins show insufficient nasal absorption that decreases with increasing molecular size. At a 5% concentration CDs can be safely used to improve nasal bioavailability of drugs, especially peptides [22].

Rectal Drug Delivery

Applications of CDs in rectal delivery include-

- Enhancing drug absorption from suppository base either by enhancing drug release from the base or by increasing drug mucosal permeability.
- Increasing drug stability in the base or at the absorption site either by inhibiting the drug/ vehicle interaction or by inhibiting the drug bioconversion in the rectum.
- Providing sustained drug release, alleviating drug induced irritation [23].

Colon Specific Drug Delivery

CDs are barely hydrolysed and only slightly absorbed in stomach and small intestine but are absorbed in large intestine after fermentation into small saccharides by colonic microbial flora. The peculiar hydrolyzing property of CDs makes them useful for colon drug targeting. Biphenyl acetic acid (BPAA) prodrugs for colon specific delivery were developed by conjugation of the drug onto one of the primary hydroxyl groups of α-, β-, and γ- CDs through an ester or amide linkage [24].

Peptide and Protein Delivery

Various problems associated in practical use of therapeutic peptides and proteins are their chemical and enzymatic instability, poor absorption through biological membranes, rapid plasma clearance, peculiar dose response curves, and immunogenicity. P-glycoprotein (P-gp) is an efflux transporter present in the apical region of epithelial cells in the brain, kidney, liver and GI tract. P-gp opposes the transcellular drug movement in the epithelial cells and many peptide drugs. DM- β-CD can inhibit or impair the efflux function of P-gp and multidrug resistance associated proteins (MRP2), also decreased the level of P-gp in the apical membranes of the monolayers probably by allowing its release from the apical membranes into the transport buffer [22].

Gene and Oligonucleotide Delivery

CDs can solve many of the problems associated with *in vivo* delivery of ONs such as,

- Their limited ability to extravasate from blood stream and traverse cellular membranes,
- High degree of susceptibility to endonucleases with potential toxicity of their breakdown products,
- Polyanionic nature leading to non-specific interactions with extra and intracellular cationic molecules, and
- Potential immunogenicity.

CDs can improve cellular uptake of ONs and also delay their degradation by increasing their stability against endonucleases. ON-adamatane conjugates associated with HP-β-CD provided significantly increased cellular uptake of ONs. CDs can also modulate undesirable side-effects of ON treatment such as, immune stimulation and reduction of platelet counts. Polyethylenimine (PEI) was derivatized with β-cyclodextrin on 10% of the polymer's amines (termed CD-PEI). Human insulin was also derivatized with a hydrophobic palmitate group (pal-HI), which could anchor the protein to CD-PEI/DNA polyplexes. CDPEI was essentially nontoxic to HEK293 cells at concentrations optimal for gene delivery and mediated nearly 4-fold higher gene expression than unmodified PEI, which is relatively toxic to these cells. More importantly, addition of the pal-HI to CD-PEI enhanced gene expression by more than an order of magnitude compared to unmodified PEI, either with or without the pal-HI. Because of the relative ease with which CD-binding moieties may be attached to various types of ligands, CD-PEI may be a generally useful material for testing novel cell specific targeting compounds [25].

Topical Drug Delivery

Applications of CDs in transdermal drug delivery include

- Enhancement of drug release and permeation,
- Drug stabilization in formulation or at absorptive site,
- Alleviation of drug induced local irritation, sustaining of drug release from vehicle and alteration of drug bioconversion in the viable skin. CDs may alleviate drug induced skin irritation by lowering the extent of free drug resulting from inclusion equilibrium [26].

Brain Drug Delivery or Brain Targeting

It was reported that P-gp mediated peptide transport may play an important role in greatly reducing the peptide delivery to central nervous system *in vivo*. CDs such as DM-β- CD, due to their inhibitory effect on P-gp efflux function, may enhance drug delivery to brain [27].

Applications of Cyclodextrins in Novel Delivery Systems

Liposomes

The concept of entrapping CD-drug complexes into liposomes in drug delivery combines the advantages of both CDs by increasing the solubility of drug and liposomes for drug targeting into a single system. Liposomes entrap hydrophilic drugs in the aqueous phase and hydrophobic drugs in the lipid bilayers and retain drugs until the drug reach to their destination . The fact that some lipophilic drugs may interfere with bilayer formation and stability limits the range and amount of valuable drugs that can be associated with liposomes. Liposomal entrapment drastically reduced the urinary loss of HP-β-CD/drug complexes but augmented the uptake of the complexes by liver and spleen. Inclusion complexation can greatly increase the chemical stability of labile drugs in multilamellar liposomes.

Microspheres

HP-β-CD acted as a promising agent for stabilizing lysozyme and bovine serum albumin (BSA) during primary emulsification of poly (d, l-lactide-co-glycolide) (PLGA) microsphere preparation. The stabilizing effect was reported to be due to increased hydrophilicity of the proteins caused by shielding of their hydrophobic residues by HP-β-CD; this also reduces their aggregation and denaturation by keeping them away from methylene chloride water interface. HP-β-CD enhanced BSA conformational stability and also increased its recovery from w/o emulsion by preventing the adsorption of the protein to PLGA. CDs were also used to modulate peptide release rate from microspheres.

Nanoparticles

CDs increasing the loading capacity of nanoparticles and the spontaneous formation of either nanocapsules or nanospheres is achieved by nanoprecipitation of amphiphilic CDs diesters. CDs increased the loading capacity of poly (isobutylcyanoacrylate) nanoparticles. Amphiphilic β-CDs (β-CDsa) have been characterized and evaluated as potential novel excipients in the preparation of nanocapsules [28].

Uses of Cyclodextrins

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. Other than the above mentioned pharmaceutical applications for drug release, cyclodextrins can be employed in environmental protection: these molecules can effectively immobilise inside their rings toxic compounds, like trichloroethane or heavy metals, or can form complexes with stable substances, like trichlorfom(an organophosphorus insecticide) or sewage sludge, enhancing their decomposition.

In the food industry cyclodextrins are employed for the preparation of cholesterol free products: the bulky and hydrophobic cholesterol molecule is easily lodged inside cyclodextrin rings that are then removed. Alpha-, beta-, and gamma-cyclodextrin are all generally recognized as safe by the FDA.

Weight loss supplements are marketed from alpha-cyclodextrin which claim to bind to fat and be an alternative to other anti-obesity medications. Other food applications further include the ability to stabilize volatile or unstable compounds and the reduction of unwanted tastes and odour. Alpha-cyclodextrin is used as emulsifier in food and cosmetic applications. Reportedly cyclodextrins are used in alcohol powder, a powder for mixing alcoholic drinks.

The strong ability of complexing fragrances can also be used for another purpose: first dry, solid cyclodextrin microparticles are exposed to a controlled contact with fumes of active compounds, then they are added to fabric or paper products. Such devices are capable of releasing fragrances during ironing or when heated by human body. Such a device commonly used is a typical 'dryer sheet'. The heat from a clothes dryer releases the fragrance into the clothing.

The ability of cyclodextrins to form complexes with hydrophobic molecules has led to their usage in supramolecular chemistry. In particular they have been used to synthesize certain mechanically-interlocked molecular architectures, such as rotaxanes and catenanes, by reacting the ends of the threaded guest.

The application of cyclodextrin as supramolecular carrier is also possible in organometallic reactions. The mechanism of action probably takes place in the interfacial region. Wipff also demonstrated by computational study that the reaction occurs in the interfacial layer. The application of cyclodextrins as supramolecular carrier is possible in various organometallic catalysis.β-cyclodextrins are used to produce HPLC columns allowing chiral enantiomers separation [28,29].

Table 2: Marketed Products Containing Cyclodextrin

Drug	Administration route	Trade name	Market
α-Cyclodextrin			
Alprostadil (PGE_1)	IV	Prostavastin	Europe, Japan, USA
Cefotiam hexetil HCl	Oral	Pansporin T	Japan
β-Cyclodextrin			
Benexate HCl	Oral	Ulgut, Lonmiel	Japan
Dexamethasone	Dermal	Glymesason	Japan
Iodine	Topical	Mena-Gargle	Japan
Nicotine	Sublingual	Nicorette	Europe
Nimesulide	Oral	Nimedex, Mesulid	Europe
Nitroglycerin	Sublingual	Nitropen	Japan
Omeprazol	Oral	Omebeta	Europe
PGE_2	Sublingual	Prostarmon E	Japan
Piroxicam	Oral	Brexin	Europe
Tiaprofenic acid	Oral	Surgamyl	Europe
2-Hydroxypropyl-β-cyclodextrin			
Cisapride	Rectal	Propulsid	Europe
Hydrocortisone	Buccal	Dexocort	Europe
Indomethacin	Eye drops	Indocid	Europe
Itraconazole	Oral, IV	Sporanox	Europe, USA
Mitomycin	IV	Mitozytrex	USA
Randomly methylated β-cyclodextrin			
17β-Estradiol	Nasal spray	Aerodiol	Europe
Chloramphenicol	Eye drops	Clorocil	Europe
Sulfobutylether β-cyclodextrin			
Voriconazole	IV	Vfend	Europe, USA
Ziprasidone maleate	IM	Geodon, Zeldox	Europe, USA
2-Hydroxypropyl-γ-cyclodextrin			
Diclofenac sodium	Eye drops	Voltaren	Europe

Industrial Applications of Cyclodextrins

Until the late 1960s almost all cyclodextrin related chemistry was carried out in Europe but the obtained technological advances did not lead to notable industrial explorations of these oligosaccharides. However, in the early 1970s a number of industrial applications were being investigated, such as within the food and cosmetic industry. In Japan, there is a tradition for industrial usage of natural products and the Japanese regarded the parent cyclodextrins as natural materials originating from starch and thus as "non-toxic" natural products. By 1970, the Japanese were already actively studying the chemistry of cyclodextrins as well as their production and in the early 1980s cyclodextrins were introduced as industrial raw materials, mainly for the food and cosmetic industries. Within the next decade Japan became the largest cyclodextrin consumer in the world with an annual consumption of about 1800 tonnes, 80% of which went into the food industry and just over 10% into the cosmetic industry. Less than 5% were used in the pharmaceutical and agricultural industries. The industrial usage of cyclodextrins progresses somewhat slower in Europe and America. In the early 1990s, Procter & Gamble, an US based company, launched cyclodextrinbased fabric softener with "longer lasting freshness" which was followed by couple of other cyclodextrin-based products and today the company is the largest single industrial user of cyclodextrins. Introduction of new excipients to the pharmaceutical industry is much more restricted than introduction of new excipients into toiletry and food products. However, in 1976 the world first pharmaceutical product, prostaglandin E2/ cyclodextrin (Prostarmon ETM sublingual tablets), was marketed in Japan

by Ono Pharmaceutical Co. It was not until about 12 years later that piroxicam/cyclodextrin tablets were marketed in Italy by Chiesi Farmaceutici and the first cyclodextrincontaining formulation to be introduced to the US market was itraconazole/2-hydroxypropyl cyclodextrin oral solution which was approved in 1997.Worldwide 30-40 different drugs are nowmarketed as cyclodextrin complexes. In pharmaceutical formulations cyclodextrins are generally used as solubilizers but sometimes as stabilizers or to reduce local drug irritation [30,31].

CONCLUSION

It took cyclodextrins 100 years to evolve from interesting chemical oddities to enabling pharmaceutical excipients.In the pharmaceutical industry cyclodextrins have mainly been used as complexing agents to increase aqueous solubility of poorly soluble drugs, and to increase their bioavailability and stability. In the classical cyclodextrin chemistry, it is assumed that when a drug molecule forms a complex with cyclodextrin, then some given lipophilic moiety of the drug molecule enters into the hydrophobic cyclodextrin cavity. Studies in both humans and animals have shown that cyclodextrins can be used to improve drug delivery from almost any type of drug formulation. However, addition of cyclodextrins to existing formulations without further optimisation will seldom result in acceptable outcome. Currently there are worldwide about 30 different pharmaceutical products containing drug cyclodextrin complexes on the market.

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