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Review Article

CYCLODEXTRIN IN DRUG DELIVERY APPLICATION: A REVIEW

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ABSTRACT

The cyclodextrins have a wide range of applications in various areas of drug delivery and pharmaceutical industry due to their complexation ability and other versatile characteristics. The most popular pharmaceutical application of cyclodextrin is to increase the solubility, stability, safety and bioavailability of drug molecules. The idea of this review article is to solve and study any of the findings and application of cyclodextrin (CD) and their derivatives in different areas of drug delivery. This review article introduce the molecular structure, properties like complexation, solubility etc. of cyclodextrins and targeted on its use for parenteral, oral, ophthalmic and nasal drug delivery. Other routes including dermal, rectal, sublingual and pulmonary delivery are again briefly addressed. The aim of this contribution is to focus on the potential application of chemically altared cyclodextrins as high-performance drug carriers in drug delivery systems with emphasis on the other recent developments. Thus cyclodextrins, 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 other novel drugs through different delivery routes.

Keywords: Cyclodextrin, complexing agents, bioavailability, industrial application

History of cyclodextrine

Cyclodextrins, as they are famous today, were called "cellulosine" when first represent by A. Villiers in 1891. Soon after, F. Schardinge ridentified the three naturally occurring cyclodextrins -α,-β, and -γ. These compounds are referred to as "Schardinger sugars". For 25 years, between 1911 and 1935, Pringsheim in Germany was the leading researcher in this area, demonstrating that cyclodextrins formed stable aqueous complexes with many other chemicals. By the mid-1970s, each all of the natural cyclodextrins have been structurally and chemically characterized and many more complexes have been studied. Since the 1970s, major work has been conducted by Szejtli and others exploring encapsulation by cyclodextrins and their derivatives for industrial and pharmacologic applications. Among the process use for complexation, the kneading process seems to be one of the best.[1,2]

Introduction

Cyclodextrins are natural cyclic oligosaccharides that were discovered hundred 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 raise aqueous solubility of poorly soluble drugs, and to raise, their bioavailability and stability.addition, cyclodextrins can be used to lower gastrointestinal drug irritation, translate liquid drugs into microcrystalline or amorphous powder, and to stop drug□drug and drug□excipient interactions [3,4]

Types of Cyclodextrin

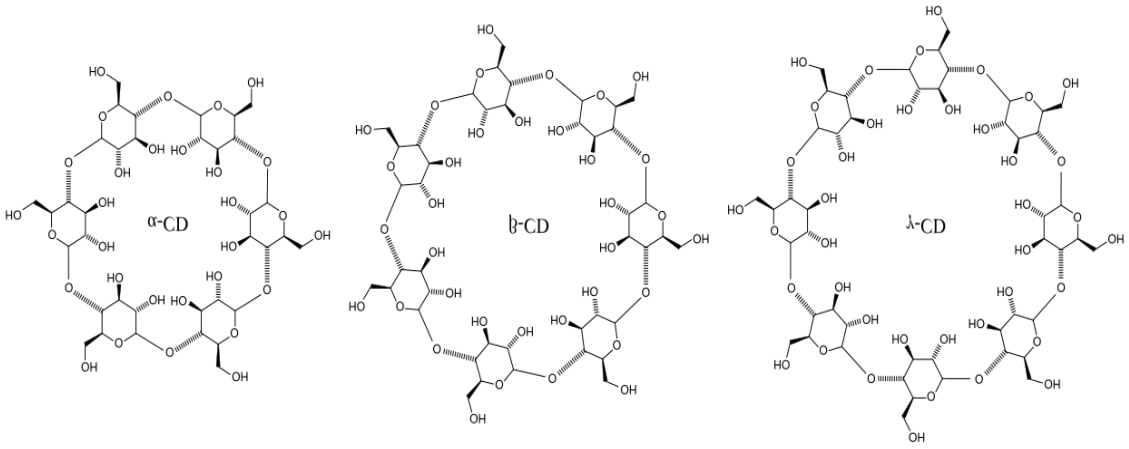

Figure 1: Chemical Structure of the Three Types of Cyclodextrine

- α -cyclodextrin: six membered sugar ring molecule
- β -cyclodextrin: seven membered sugar ring molecule
- γ -cyclodextrin: eight membered sugar ring molecule [3,5]

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 [6,7].

Production of Cyclodextrins

Treatment of starch with amylase from Bacillus macerans gives a crude mixture of cyclodextrin, The mixture was challenging to purified it frequently contained several other linear and branched dextrins together with small amounts of proteins and other impurities.The biotechnological growths that occurred in the 1970s lead to dramatic improvements in their production. Genetic engineering made different types of CGTases available that were both extra active and extra specific towards production of or cyclodextrin than the previously used enzymes. These enzymes together with other technological innovations made largely purified and cyclodextrin available that could be used as pharmaceutical excipients. In 1970, cyclodextrin was only available as a rare nice chemical at a price of about US$ 2000 per kg. Current the annum cyclodextrin production is near to 10,000 tonnes and the bulk price has lowered to about US$ 5 per kgr [8].

Cyclodextrin Derivatives

The aqueous solubility of and cyclodextrin is much lower than that of comparable linear dextrins, most probably due to relatively heavy binding of the cyclodextrin molecules in the crystal state (i.e.approximately large crystal energy). In addition, cyclodextrin molecules form intramolecular hydrogen bonds that reduce their ability to form hydrogen bonds with the surrounding water molecules. different semisynthetic water-soluble cellulose derivatives (e.g. carboxymethyl cellulose and hydroxypropyl methylcellulose) had been synthesized and were used in big quantities in a variety of industrial products. Similar chemical modifications were now applied to have water-soluble cyclodextrin derivatives.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 reduce again upon further methylation. Afterward, we found some of 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 solubiliti improvement in the alkyl derivatives is hat chemical manipulation transforms the crystalline and cyclodextrin into amorphous mixtures of isomeric derivatives. [9].

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 250º 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 placed within the lipophilic central cavity are change 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 alternative molecules and cyclodextrins can, like non-cyclic oligosaccharides and polysaccharides, form water soluble complexes with lipophilic water-insoluble compounds. i.e.1, 4-linked linear glucose oligomers, have been shown as to require fluorescence probes but the required constants are significantly smaller than those for their cyclic counterparts. Cyclodextrine It has been shown that forms both inclusion and non-inclusion complexes with dicarboxylic acids and that the two types of complexes coexist in aqueous solutions. In socked aqueous solutions cyclodextrin complexes frequently consist of a mixture of formation and noninclusion complexes. This could explain why the value of the equilibrium constant for the complex formation is sometimes concentration dependant and why their numerical value is frequently dependant on the process method applied .[11,12]

Methods to enhance cyclodextrin complexation

The complexation effective is the product of the observe solubility (i.e. apparent S0) of the drug in absence of CD and the suppose stability constant (K1:1) of the drug/CD complex formed assuming formation of 1:1 drug-CD complex and in aqueous solutions increase CE will result in increase solubilization. In other words, CD solubilization of poorly soluble drug can be enhancing by increasing S0 and/or K1:1 (Loftsson and Brewster, 2012). Various methods that have been used to raise the solubilizing reply of CDs are Increasing S0 in aqueous complexation media by, for example, ionization of the drug molecules, salt formation, formation of co-complexes, addition of cosolvents, and transformation of a crystalline drug to an amorphous one can lead to enhanced CD solubilization. Methods that increase K1:1 include addition of water-soluble polymers to the aqueous media, charge charge interactions between ionized CDs and counter ionic

drug molecules and formation of ternary complexes. Other methods that temporarily increase S0 can be applied to prepare solid drug/CD complexes.[13,14]

Drug Availability from Cyclodextrin-Containing Products

It has been generally 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 absolutely close to diffusion controlled limits with complexes being continually formed and break down. Consequently, presence of water soluble drug/cyclodextrin complexes good 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 (low aqueous solubility, high permeability) drugs but they can block bioavailability of Class I (high solubility, high permeability) and Class III (high solubility, low permeability) drugs .[15,16]

Cyclodextrins in Dispersed Systems

Cyclodextrins and there derivatives have been use in disperse 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 properly together with there ability to form aggregates frequently result in formation of separate systems. In other cases cyclodextrins have been uses to raise drug loading of polymeric microspheres or to increase drug availability from dispersed systems. Novel surface active cyclodextrin derivatives have also been synthesis and use as drug delivery systems [17,18]

Applications of Cyclodextrins in Drug Delivery Systems

Oral drug delivery system

Oral route has been the very popular route for designing a drug delivery system. In the oral delivery system, the issue of the drug is other dissolution controlled, diffusion controlled, osmotically controlled, density controlled or pH controlled. CDs have been used as an excipient to transit the drugs through an aqueous medium to the lipophillic absorption surface in the gastrointestinal tract, i.e., complexation with CDs has been used to increase the dissolution rate of badly water-soluble drugs. Hydrophilic CDs have been particularly helpful in this regard. Fast dissolving complexes with CDs have also been formulated for buccal and sublingual administration. In this type of drug delivery system, a fast raise in the systemic drug concentration takes place along with the avoidance of systemic and hepatic first-pass metabolism .[19,20,21]

Table 1: cyclodextrine in oral drug delivery system

S. No.	Improvement	Drug
1.	Enhanced solubility of drugs	Bromazepam, Flavanoids, Napthoquinone, Ibuprofen Campothecin, Thyrotropin-releasing hormone, Gliclazide, Nicardipine, Ketoprofen, Albendazole, Aryl semicarbazones, Itraconazole, Nifedipine, Naproxen, Tolfenamic acid, Phenytoin, Meloxicam, Tropicamide, Prostaglandin, Ibuprofen, Ofloxacin, Danazol, Tacrolimus, Amylobarbitone, Artemisinin, Omeprazole, Ketoralac, Phenothiazine, Nimesulide, Theophylline, Zolpidem, Tolbutamide, Tenoxicam
2.	Enhanced bioavailability of drugs	Sparfloxacin, Artemisin, Terfenadine, Tolbutamide
3.	Enhanced of stability of drugs	Metoprolol, Nifedipine, Quinapril
4.	Reduced gastric ulceration	Meloxicam, Prednisolone

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 [22].

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 [23,24,25]

Limitations

a). SBE 4-β-CD has no effect on pilocarpin bioavailability and it has even a slight decreasing effect at higher concentrations[26]

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 [27]

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 [28]

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 system

The nasal route is another useful way to bypass first-pass metabolism start to order systematic flow of drug the aqueous nasal fluids In nasal formulations, cyclodextrins are Common application to increase the aqueous solubility of lipophilic drugs The methylated cyclodextrin derivatives increase the bioavailability sNasal preparations must be critically evaluated for their possible effect on the nasal mucociliary functions, which are known to depend the respiratory portion against dust, allergens and bacteria The local toxicity of cyclodextrins after nasal administration is very low. In the case of the nasal preparations containing the complexes of steroids with cyclodextrins, the effects of the cyclodextrins on the nasal epithelial membranes seem to be of minor necessary for absorption enhancement, because the cyclodextrins would drope their abilities to connect with the membranes when their cavities are occupied by steroids. [29, 30,31,32]

Table 2-Cyclodextrins in nasal drug delivery system

Improvement	Drug	Reference
Absorption enhancers	Leucine enkephalin	Agu *et al.*, 2002
	Glucagon	Sakr M. (1996)
	Insulin	Zang *et al.*, 2001a
	Peptides	Ahsan *et al.*, 2001
	Calcitonin	Merkus *et al.*, 1996
	Burselin	Tenqamnuay *et al.*, 2000
		Schipper *et al.*, 1995
		Matsubara *et al.*, 1995
Enhanced bioavailability of drugs	Midazolam	Loftsson *et al.*, 2001
	Dihydroergotamine	Vanderkuy *et al.*, 1999
		Martinn *et al.*, 1997a
Controlled release	Estradiol	Gudmundsdottir *et al.*, 2001
Reduced toxicity	Sodium deoxycholate	Zang *et al.*, 2001b

Rectal drug delivery system

The release of drugs from suppository bases is one of the important factors in the rectal combinations of the drugs, therefore the rectal fluid is small in volume and viscous compared to gastrointestinal fluid. In general, hydrophilic cyclodextrins slowly the release of water-soluble drugs from oleaginous suppository bases because of the less interaction of the result complexes with the vehicles. The complexation of lipophilic drugs with hydrophilic cyclodextrins prepare them insoluble in hydrophobic

vehicles, the complex existing as well-dispersed fine particles in the vehicle .In comparison with the parent cyclodextrins, the methylated cyclodextrins significantly enhance the rectal absorption of hydrophobic drugs, that are anti inflammatory agents, such as flurbiprofen , carmofur and biphenyl acetic acid from the oleaginous suppository. The superior effect of the methylated cyclodextrins can be explained by the faster release of the drugs together with the low affinity of the complexed drugs to the oleaginous suppository base .[33 ,34,35,36]

Table 3-Cyclodextrins in rectal drug delivery system

Improvement	Drug	Reference
Enhanced drug release	Ethyl-4-biphenylyl acetate (EBA)	Arima *et al.*, 1998
	Insulin	Watanbe *et al.*, 1992
Enhanced rectal absorption	Morphine	Uekama *et al.*, 1995
	Bis (acetato) ammine dichloro (cyclohexylamine) platinum (IV)	Tanaka *et al.*,1999
Enhanced chemical stability	Human granulocyte colony stimulating factor	Watanbe *et al.*, 1996
Reduced rectal irritation	Prednisolone	Yano *et al.*, 2001a Yano *et al.*, 2001b
Enhanced bioavailability	Morphine	Kondo *et al.*, 1996
	Human chorionic gonadotrophin	Kowari *et al.*, 2002
	Allopurinol	Samy *et al.*, 2000

Transdermal drug delivery system

The primary barrier for dermal drug absorption through the skin is the outer most layer stratum corneum. Penetration are like fatty acids, alcohol etc. are used to peptide barrier its loss properties. Cyclodextrins devlop the solubility and stability of drugs in the topical preparations, Increase the transdermal absorption of drugs, sustains the drug deliver from the vehicle and avoids undesirable side effects associated with dermally applied drugs (Hashimoto H et al 1999). The cyclodextrins enhance drug delivery through aqueous diffusion barriers, but not throughlipophilic barriers like stratum corneum. Cyclodextrins alleviate drug induced skin irritation by lower the extent of free drug resulting from inclusion equilibrium. [37, 38 ,39,40]

Table 4: Cyclodextrins in transdermal drug delivery system

Improvement	Drug	Reference
Enhanced solubility of drugs	Miconazole	Tenjarla *et al.*, 1998
Enhanced stability of drugs	Miconazole	Tenjarla *et al.*, 1998
Enhanced permeation of drugs through Stratum corneum	Dihydroepiandrosterone	Ceshel *et al.*, 2002
	Oxybenzone	Felton *et al.*, 2002
	Gliquidone	Sridevi and Diwan, 2002a
	Levosimendan	Valjakka-Koskela *et al.*, 2000
	Dexamethasone	Lopez *et al.*, 2000
	Hydrocortisone	Chang *et al.*, 1998
	5-Fluorouracil	Williams *et al.*, 1998
	Insulin	Uchida *et al.*, 2001
	Ethyl 4-biphenyllyl acetate	Arima *et al.*, 1998
Sustained release of drugs through the vehicle	Piroxicam	Doliwa *et al.*, 2001
Reduced side effects	Ketoprofen	Sridevi and Diwan, 2002b

Peptide and Protein Delivery

Various problems associated in practical use of therapeutic peptides and proteins are their chemical and enzymatic instability, low absorption through biological membranes, rapid plasma clearance, peculiar dose response curves, and immunogenicity. P-glycoprotein (P-gp) is an efflux transporter present in the sharp region of epithelial cells in the brain, kidney, liver and GI tract. P-gp resists the transcellular drug movement in the epithelial cells and more peptide drugs. DM- β-CD can inhibit or impair the efflux function of P-gp and multidrug resistance associate proteins (MRP2), also reduce 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 [41,42,43].

Colon Specific Drug Delivery

Cyclodextrins 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 hydrolyzing property of cyclodextrine makes them useful for colon drug targeting. Biphenyl acetic acid (BPAA) prodrugs for colon specific delivery have been developed by conjugation of the drug one primary hydroxyl groups of α-, β-, and γ- CDs through an ester or amide linkage .[44]

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 cyclodextrine by increasing the solubility of drug and liposomes for drug targeting into a single system. Liposomes capture 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 lipophilicdrugs may prevent with bilayer formation and stability limits the range and amount of valuable drugs that can be associated with liposomes. Liposomal entrapment drastically are reduced the urinary loss of HP-β-CD/drug complexes but augmented the uptake of the complexes by liver and spleen. Inclusion complexation can largely development the chemical stability of labile drugs in multilamellar liposomes.[45,46]

Microspheres

HP-β- CD act 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 information to be due to increase hydrophilicity of the proteins caused by shielding of their hydrophobic residues by HP-β-CD; this also lower their aggregation and denaturation by keeping them away from methylene chloride water interface. HP-β-CD increase BSA conformational stability and also increased its recovery from w/o emulsion oil by preventing the adsorption of the protein to PLGA. CDs are also use to modulate peptide release rate from microspheres. [47,48]

Nanoparticles

CDs raise the loading capacity of nanoparticles and the simple formation of other nanocapsules or nanospheres is achieved by nanoprecipitation of amphiphilic CDs diesters. CDs raise the loading capacity of poly (isobutylcyanoacrylate) nanoparticles. Amphiphilic β-CDs (β-CDsa) have been characterized and calculate as potential novel excipients in the preparation of nano capsules. [49,50,]

Uses of Cyclodextrins

The food industry cyclodextrins are occupied for the study 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 CV identify as safe by the FDA

Use of cyclodextrin as supramolecular carrier is also free in organometallic reactions.The mechanism of action possiblytake place in the interfacial region. Wolff also demonstrated by computational study that the reaction occurs interfacial layer. The use of cyclodextrins as supramolecular carrier is possible in different organometallic catalysis.β-cyclodextrins are use to produce HPLC columns allowing chiral enantiomers separation.

Cyclodextrins are capable to form host-guest complexes with hydrophobic molecules given the different nature imparted by the structure. As a result, these molecules have organaized number of applications in a wide range of fields. Other than the above mentione pharmaceutical applications for drug release, cyclodextrins can be employed in environmental protection: these molecules can effectively immobilise inside the rings toxic compounds, like trichloro ethane or heavy metals, or can form complexes with stable substances.

Weight loss supplements are marketed from alpha-cyclodextrin which interest to cover to fat and be a different to other anti obesity medications. Other food applications more include the ability to stabilize volatile or unstable compounds and the cut of unwanted tastes and odor. Alpha-cyclodextrin is used as emulsify in food and cosmetic applications. Cyclodextrins are usein alcohol powder, a powder for mixing alcoholic drinks.[51,52]

Industrial Applications cyclodextrine

The late 1960s practically all cyclodextrin related chemistry was carried out in Europe but the obtained technological progress did not lead to notable industrial study of these oligosacharides. However, in the previous 1970s a number of industrial applications were being surveyed, such as within the of cosmetic and food industry. In Japan, is a practice for industrial usage of natural products

and the Japanese scene the parent cyclodextrins as natural materials original from starch as “non-toxic” common products? By 1970, the Japanese were already active chemistry study of the cyclodextrins as well as their production and in the early 1980s cyclodextrins were introduced as industrial raw materials, mainly for the cosmetic and food industries. Within the next decade Japan became the largest cyclodextrin consumer in the world with an annual consumption of about 1800 tones, 80% of which went into the food industry and just over 10% into the cosmetic industry. Less than 5% were use in the pharmaceutical and agricultural industries. The industrial uses of cyclodextrins progress somewhat slowly in Europe and America. In the early 1990s, Proceed & Gamble, a US based company, launched cyclodextrin based 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 recipients to the pharmaceutical industry is much many restrict than introduction of new recipients in to food products. However, in 1976 the world first pharmaceutical products, prostaglandin E2/ cyclodextrin (Prostration ETM sublingual tablets), was market in Japan by Pharmaceutical Co. It was not until about 12 years later that proximal/cyclodextrin tablets were marketed in Italy by Chaise Farmaceutici and the first cyclodextrin containing formulation to be announced to the US market was itraconazole/2-hydroxy produstrial Applications cyclodextrin In pharmaceutical formulations cyclodextrins are generally used as solubilizers but sometimes as stabilizers or to reduce local drug irritation.[53,54]

Conclusion

CDs, as a result of their complexation ability and other functional characteristics, are continuing to have different applications in different areas of drug delivery and pharmaceutical industry. However, it is necessary to find out any possible interaction between these agents and other formulation additives because the interaction can adversely affect the performance of both. It is also important to have knowledge of different factors that can influence complex formation in order to prepare economically drug/CD complexes with desirable properties.

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