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REVIEW ARTICLE

Cyclodextrin based novel drug delivery systems

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Abstract The versatile pharmaceutical material cyclodextrin's (CDs) are classified into hydrophilic, hydrophobic, and ionic derivatives. By the early 1950s the basic physicochemical characteristics of cyclodextrins had been discovered, since than their use is a practical and economical way to improve the physicochemical and pharmaceutical properties such as solubility, stability, and bioavailability of administered drug molecules. These CDs can serve as multi-functional drug carriers, through the formation of inclusion complex or the form of CD/drug conjugate and, thereby potentially serving as novel drug carriers. This contribution outlines applications and comparative benefits of use of cyclodextrins (CDs) and their derivatives in the design of novel delivery systems like liposomes, microspheres, microcapsules, nanoparticles, cyclodextrin grafted cellulosic fabric, hydrogels, nanosponges, beads, nanogels/nanoassemblies and cyclodextrin-containing polymers. The article also focuses on the ability of CDs to enhance the drug absorption across biological barriers, the ability to control the rate and time profiles of drug release, drug safety, drug stability, and the ability to deliver a drug to targeted site. The article highlight's on needs, limitations and advantages of CD based delivery systems. CDs, because of their continuing ability to find several novel applications in drug delivery, are expected to solve many problems associated with the delivery of different novel drugs through different delivery routes.

Keywords Cyclodextrin · Complexed · Novel drug delivery · Liposomes · Beads · Nanosponges · Nanogels/nanoassemblies · Nanoparticles · Hydrogels

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Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides derived from starch containing six (α-CD), seven (*β*-CD), eight (*γ*-CD), nine (*δ*-CD), ten (*ε*-CD) or more (α-1, 4)-linked α-D-glucopyranose units (Table 1). CDs take the shape of a truncated cone or torus instead of a perfect cylinder because of the chair conformation of the glucopyranose units (Fig. 1) [3–5]. Among the natural (α, *β*, *γ*) CDs, in particular *β*-CD are of limited aqueous solubility meaning that complexes resulting from interaction of lipophiles with these CDs may also be poorly soluble resulting in precipitation of the solid CD complexes from water and other aqueous systems [6]. So derivative such as hydrophilic, hydrophobic and ionic derivatives came into existence with a view to extend the physicochemical properties and inclusion capacity of parent CDs [7, 8]. The desirable attribute for the drug carrier is the ability to control the rate and/or time profile of drug release. Hydrophilic CDs can modify the rate of drug release, which can be used for the enhancement of drug absorption across biological barriers, serving a potent drug carrier in the immediate release formulations [9]. On the other hand CDs have also been used as stabilizers for protein and peptides. There peripheral hydrophilic zone and hydrophobic cavity can chemically interact with proteins and are supposed to stabilize their conformation against denaturation. However,

Table 1 Characteristics of the natural cyclodextrins α-CD, β-CD and γ-CD [1, 2]

Cyclodextrin	Number of glucose units	Dimensions (nm)			Mean K1:1[a] (M^{-1})
		H	OD	ID	
α-Cyclodextrin (α-CD)	6	0.78	1.37	0.57	130 ± 8
β-Cyclodextrin (β-CD)	7	0.78	1.53	0.78	490 ± 8
γ-Cyclodextrin (γ-CD)	8	0.78	1.69	0.95	350 ± 9

OD, outer diameter; ID, internal diameter; H, height

[a] Stability constants (binding constants) of 1:1 guest/CD complexes in aqueous solutions at 25 ± 5 °C

their use for protein stabilization during encapsulation has not ever been crowned with success [10]. Also hydrophobic CDs may serve as sustained release carriers for the water-soluble drugs including peptide and protein drugs [9, 11]. The delayed release formulation can be obtained by the use of enteric type CDs such as *O*-carboxymethyl-*O*ethyl-β-CDs [9]. A combined use of different CDs and/or pharmaceutical additives will provide more balanced oral bioavailability with prolonged therapeutic effects. Now-a-days CDs polymers and CDs conjugates have been designed and evaluated for pharmaceutical uses. In addition, the preferable combination of CDs and other pharmaceutical excipients or carriers such as nanoparticles, liposome etc. fosters the progress of the advanced dosage forms. Derivatives of CD which are of pharmaceutical interest (Table 2) are hydroxypropyl derivatives of β-CD and γ-CD (i.e., HP-β-CD and HP-γ-CD), the randomly methylated β-CD (RM-β-CD), sulfobutylether β-CD (SBE-β-CD), Monochlorotriaziny beta cyclodextrin (MCT-β-CD), Heptakis-β-CD {Heptakis (2-ω-amino-*O*-oligo(ethylene oxide)-6-hexylthio) beta cyclodextrin} and the so-called branched CDs such as maltosyl-β-CD (G2-β-CD) etc. Thus the use of cyclodextrins (CDs) is a practical and

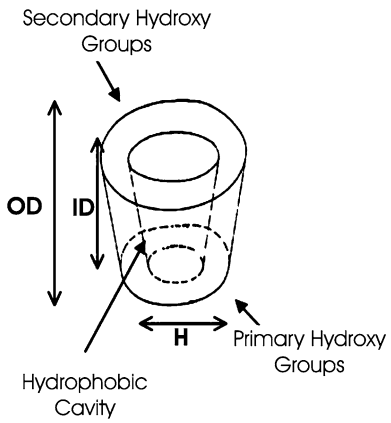

Fig. 1 Truncated cone or torus shape of cyclodextrins

economical way to improve the physicochemical and pharmaceutical properties of administered drug molecules. This review article outlines the current application of natural and chemically modified CDs and their contribution in novel drug delivery to improve the efficiency of various formulations.

Chronological evolution of cyclodextrins

The first publication on cyclodextrins was done by a French scientist Villiers in 1891 [17, 18]. The Austrian microbiologist Franz Schardinger laid the foundation of the cyclodextrin chemistry in 1903–1911 and identified both α- and β-cyclodextrin [17, 18]. Although many of the physicochemical properties of cyclodextrins were still unknown in 1911, when Schardinger published his last article on cyclodextrins [19].

Freudenberg and co-workers in the 1930s identified γ-cyclodextrin and suggested that larger cyclodextrins could exist [20]. They showed that cyclodextrins were cyclic oligosaccharides formed by glucose units and somewhat later Cramer and co-workers described their ability to form inclusion complexes [17, 18]. By the early 1950s the basic physicochemical characteristics of cyclodextrins had been discovered, including their ability to solubilize and stabilize drugs. The first cyclodextrin-related patent was issued in 1953 to Freudenberg, Cramer and Plieninger [17, 18]. However, 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 and in 1997 also in the US. New cyclodextrin-based technologies are constantly being developed and thus, 100 years after their discovery cyclodextrins are still regarded as novel excipients of unexplored potential [17, 18]. More than 30 different pharmaceutical products containing cyclodextrins are now in the market worldwide.

Need

Therapeutic agents are associated with number of limitations to exhibit desired pharmacological response in the body. These limitations can be overcome by means of CD-based modification of therapeutic agents. Generally encountered difficulties while formulation of drug delivery systems are:

- Solubility limited poor bioavailability.
- The drug is soluble only in such organic solvents, which cannot be injected thus formulation of parenteral preparation is not feasible.
- The drug is irritating to mucous membranes, tissues or skin.

Table 2 Structural and physiochemical properties of some cyclodextrin of pharmaceutical interest (adapted from reference 12) [5, 6, 12–16]

Cyclodextrin	*n*	R=H or	Substitution[a]	MW[b] (Da)	Solubility[c] (mg/mL)
α-Cyclodextrin	0	^{-}H	0	972	145
β-Cyclodextrin	1	^{-}H	0	1,135	18.5
2-Hydroxypropyl-*β* Cyclodextrin (HP-*β*-CD)	1	$^{-}CH_2CHOHCH_3$	0.65	1,400	>600
Sulfobutylether-*β*-Cyclodextrin sodium salt (SB-*β*-CD)	1	$^{-}(CH_2)_4SO_2{}^{-}Na^{+}$	0.9	2,163	>500
Randomly methylated-*β*-Cyclodextrin (RM-*β*-CD)	1	$^{-}CH_3$	1.8	1,312	>500
6-*O*-Maltosyl-*β*-Cyclodextrin (G_2-*β*-CD)	1	Maltaosyl^{-}	0	1,459	>1,500
γ-Cyclodextrin (*γ*-CD)	2	−H	0	1,297	232
2-Hydroxypropyl-*γ*-Cyclodextrin (HP-*γ*-CD)	2	$-CH_2CHOHCH_3$	0.6	1,576	>500

[a] Average number of substitution per glucose repeat unit

[b] MW, molecular weight

[c] Solubility in pure water at approx. 25 °C; *n*, number of glucopyranoside ring

- The drug is very bitter, astringent tasting.
- The drug is sensitive to destructing factors, like oxygen, light, water, etc.
- The drug is a liquid, volatile and/or sublimable, bad smelling or a hygroscopic solid.
- The drug is sticky, lipid like consistence or incompatible with formulation components [4, 13, 21, 22].

So, molecular encapsulations of the drug and other modifications with appropriate cyclodextrin able to overcome such problems and facilitate safe and efficient delivery of drugs. The potential benefits of drug–cyclodextrin complexation and relevant examples are as follows:

- By cyclodextrin complexation, rate of dissolution and the solubility limit increases (frequently by a factor of 101–103), resulting in an accelerated and significantly improved bioavailability. Cases where bioavailability of drug is less because of the poor or limited solubility of drug, cyclodextrin complexation have demonstrated an overall improvement in bioavailability in comparison to drug alone. The reported increase in bioavailability is typically expressed as a change in an area under the plasma concentration vs. time curve (AUC) value, a change in the time to reach maximum plasma levels of the given compound (T_{max}), and/or the maximum plasma level achieved (C_{max}) [22–26]. Albendazole on complexation with HP-*β*-CD showed increase in AUC 1.4 times and C_{max} 1.2–2.8 mg/mL in comparison to pure drug alone [27]. While change in AUC and C_{max} in case of artemisinin and flurbiprofen was found to be 1.7 times, 0.27–0.46 mg/mL and 7.2–13.6 mg/mL, respectively [25, 28].
- Drugs like voriconazole (antifungal) and ziprasidone (anti-schizophrenia agent) shows poor water solubility which was major hurdle in the development of there parenteral formulation. But sulfobutylether-*β*-cyclodextrin (Captisol®) is used now were days to obtain their parenteral formulations. Moreover i.v. formulations of mitomycin a poorly water soluble drug was developed with the use of HP-*β*-CD (MitoExtra®, Novartis, Switzerland) [29].
  Melarsoprol, a very poorly water-soluble drug, commercially available as solution in propylene glycol (Arsobal®, Aventis Pharma). This non-aqueous solution exhibits a local intolerability (severe pains, burns, and necrosis) and must always be administered by slow intravenous injection. However complexation of melarsoprol with RAME-*β*-CD and HP-*β*-CD showed better result which may results in development of its aqueous based I.V formulation [29].
- The astringent, irritating effect and bitter taste of many therapeutically active compounds limits their dosage form development as sublingual tablet or a chewing gum. However it can be strongly reduced or fully eliminated, if the bitter component forms an inclusion complex with an appropriate cyclodextrin (CD). Cyclodextrin enwrapped such compounds molecularly and thus complexed molecules cannot react with the taste buds in the buccal cavity so no bitter taste is perceived [30]. For example if cetirizine is administered in saturated *β*-CD solution no bitter taste can be observed. The very bitter and anaesthetizing effect of libexin, an antitussivum, was efficiently reduced by *β*-CD [31]. Similarly, the bitter taste of femoxetine HCl was greatly suppressed by complexing with *β*-CD [32]. Uekama et al. found that the bitter taste of clofibrate was significantly quenched by complexing it with *β* or *γ*-CD [33].
- Drugs (Amlodipine) [34], Phytoconstituent (Astaxanthin) [35] and compounds, like vanillin [36], bisphenol, cinnamaldehyde, volatile oils (clove oil), flavoring agents (Lemon and orange peel oil) are rapid lost from solid formulations (due to volatilization, oxidation, polymerization, light (photo degradation). But it was investigated that there complexation with different cyclodextrin derivatives in all the mentioned cases demonstrated to overcome the problem up to satisfactory level. Light catalyzes oxidation of amlodipine to

pyridine derivatives, lacking any therapeutic effect. The results of amlodipine complexed with cyclodextrins reveled that it can definitely be protected from light [34].

Astaxanthin a highly unsaturated molecule shows antioxidant, anticancer, antiinflammatory and immunostimulants activities. Because of unsaturation it is unstable in heat or light, which lead to loss of its biological properties. But the inclusion complex between β-CD and astaxanthin found to greatly enhance its heat stability under light [35]. Moreover, a complexation of vanillin with β-cyclodextrin was found to protect the light sensitive vanillin from oxidation [36].

- Flavoring agents and volatile oils are completely destroyed by atmospheric oxygen when present in powdered formulation, within few days. Contrary to this, when present in complexed form with cyclodextrin are found to last there effect for years. Such cyclodextrin based powder are produced, and marketed in countries like France, Japan, Hungary, etc. [19].

  Popular paramedical products like cinnamon leaf, garlic oils (antimicrobials) etc. which are very bad smelling, losses their active ingredient content rapidly and also their volatility complicates their application can be stabilize by their inclusion complex with β-cyclodextrin [37]. β-cyclodextrins glucopyranose rings are able to form inclusion complexes with flavor substances of low molecular mass. The following advantages of their stable β-cyclodextrin complexes are known: constant composition, macroscopic and microbiological purity, decreased sensitivity to storage circumstances heat, light, time/and stability to oxidation, polymerization and sublimation [38]. The very first cyclodextrin-containing drug that got the approval from the German Health Authorities was a garlic oil/β-cyclodextrin complex containing tablet, marketed under the names XUND and TEGRA [19].
- For many potent therapeutically active entities preparation of suitable dosage form is a challenge because of their sticky, lipid like consistence, incompatibility with formulation components etc. Cyclodextrin complexation is one of the most promising possibilities in such cases [19].

  High hydrophobicity and sensitivity to external agents such us air, light and oxidative enzymes constitute a serious problem for formulation of resveratrol (trans-3,5,40-trihydroxystilbene). However resveratrol complexation with β-CD and G2 β-CD was found to delay its oxidation due to its entrapment in the internal cavity of cyclodextrins, which act as substrate reservoir in a dosage-controlled manner [39].

  A new type of potent anticancer agent, CKD-732 is labile at room temperature, which has been a serious obstacle to the formulation of CKD-732 into a parenteral dosage form. However CKD-732/HP-β-CD complex showed fairly good long-term stability and solubility. After reconstitution and parenteral administration of the lyophilized CKD-732/HP-β-CD complex, CKD-732 was rapidly released from the complex with no loss of pharmacological activity but with better tolerance [40]. Prostaglandin E1 (very oxygen sensitive, poorly soluble) is marketed successfully by the use of cyclodextrin. Its marketed product (PROSTAVASIN, EDEX, VIRIDAL) contains besides the 20 µg PGE1 also 646 µg α-cyclodextrin, which stabilizes, and solubilizes the Prostaglandin [19].

Limitations [6, 22, 41]

All the categories of drugs are not suitable substrates for CD complexation. Drug molecule to be complexed with CD should have certain characteristics explained below. These characteristics are generally favored for pharmaceutical and medicinal benefits, however exceptions cannot be neglected.

- More than five atoms (C, P, S, N) form the skeleton of the drug molecule.
- Melting point temperature of the substance is below 250 °C.
- Solubility in water is less than 10 mg/mL.
- The guest molecule consists of less than five condensed rings.
- Molecular weight between 100 and 400.

Generally inorganic compounds are not suitable for complexation. However halogens, non-dissociated acids (H_3PO_4, HI, etc.), gases (Xe, CO_2 etc.) are exceptions.

Too large molecules (protein, peptides, enzymes, etc.) strongly hydrophilic compounds generally cannot be complexed. But it was found that large water soluble molecules with side chains capable of forming complex react with cycloderxtrins in aqueous solutions, resulting in modified solubility and stability (e.g., the stability of an aqueous solution of insulin, or many other peptides, proteins, hormones, enzymes is significantly improved in presence of an appropriate CD).

Usually mass of tablets and capsules lies in the range of 500–800 mg and cyclodextrins have high molecular weight 972, 1,135 and 1,400 α, β and HP-β-CD. So drugs having molecular weight 100–400 are preferred for complexation so that they can be easily molded into most favored oral dosages form says capsules and tablets.

Advantages

Drug solubility and dissolution

Inclusion complexation or solid dispersion with cyclodextrins can improve drug solubility or dissolution of poorly water-soluble drugs. In case of drugs with inadequate molecular characteristics for complexation cyclodextrin act as hydrophilic carriers, or as tablet dissolution enhancers for drugs with high dose (with which use of a drug/CD complex is difficult) e.g., paracetamol [42]. The magnitude of apparent stability constant for several drug/CD complexes, K in M^{-1}, ranges from 0 to 1,000 [43, 44]. Out of various commercially available CDs, methylated CDs with a relatively low molar substitution appear to be the most powerful solubilizers. Reduction of drug crystallinity on complexation or solid dispersion with CDs also contributes to the CD increased apparent drug solubility and dissolution rate. CDs can enhance drug dissolution even when there is no complexation. CDs can also act as release enhancers, for example β-CD enhanced the release rate of poorly soluble naproxen and ketoprofen from inert acrylic resins and hydrophilic swellable (high-viscosity hydroxypropyl methyl cellulose [HPMC]) tableted matrices. β-CD also enhanced the release of theophylline from HPMC matrix by increasing the apparent solubility and dissolution rate of the drug [44]. Examples of CD-enhanced Solubility and Dissolution are summarized in (Table 3).

Table 3 CD-enhanced solubility and dissolution (adapted from reference 44)

Cyclodextrin	Drugs	References
α-CD	Praziquantel	[45]
β-CD	Piroxicam, Ibuprofen, Lorazepam, Ketoprofen, Praziquantel, Nimesulide, Sulfomethiazole, Chlorthalidone, Etodolac, Itraconazole	[45–54]
γ-CD	Omeprazole, Digoxin, Praziquantel	[45, 55, 56]
DM-β-CD	Camptothesin, Naproxen	[57, 58]
HP-β-CD	DY-9760e, ETH-615, Levemopamil HCl, Albendazole	[59–62]
RM-β-CD	Tacrolimus, ETH-615	[60, 63]
SBE-β-CD	Fluasterone, Spiranolactone, Danazol	[64–66]

Drug absorption/bioavailability

In case of hydrophobic drugs, CDs increase the permeability by increasing drug solubility, dissolution and thus making the drug available at the surface of the biological barrier, from where it partitions into the membrane without disrupting the lipid layers of the barrier. In such cases it is important to use just enough CD to solubilize the drug in the aqueous vehicle since excess may decrease the drug availability (Fig. 2) [44, 67–69].

There are four possible mechanisms affecting the absorption and thus enhancing bioavailability of drugs by various administration routes complexed with hydrophilic CDs which have been extensively studied and are summarized as follows: (a) CDs increase the solubility, dissolution rate, and wettability of poorly water-soluble drugs; (b) CDs prevent the degradation or disposition of chemically unstable drugs in gastrointestinal tracts as well as during storage; (c) CDs perturb the membrane fluidity to lower the barrier function, which consequently enhances the absorption of drugs including peptide and protein drugs through the nasal and rectal mucosa; and (d) competitive inclusion complexation with third components (bile acid, cholesterol, lipids, etc.) to release the included drug [70–72].

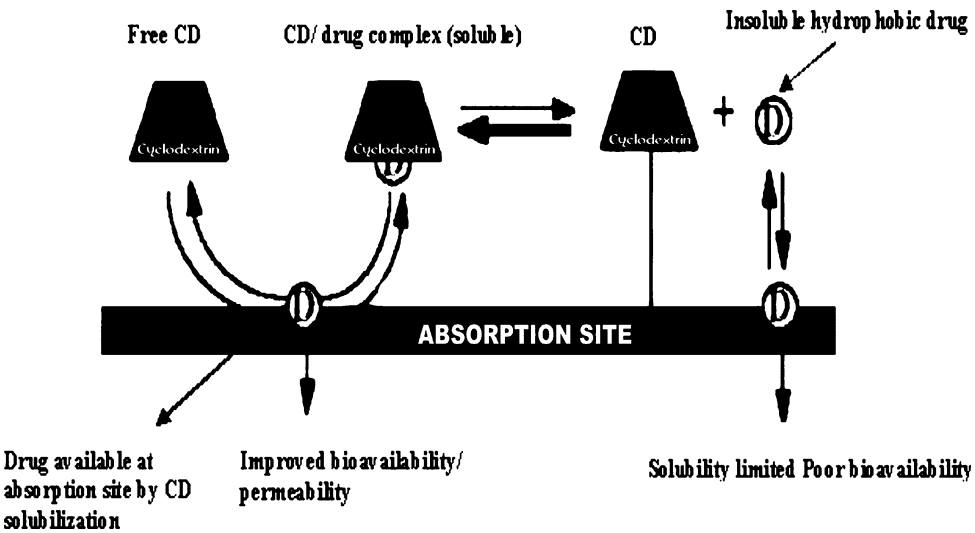

Fig. 2 Mode of penetration enhancement by CDs (adapted from reference 68)

Recently the new enhancing mechanism of 2,6-di-*O*-methyl-b-CDs (DM-β-CDs) with respect to multidrug efflux pump, P-glycoprotein (P-gp) and multidrug resistant-associated protein 2 (MRP2) for oral bioavailability of hydrophobic drugs (e.g., tacrolimus, a typical P-gp substrate) in Caco-2 cell and vinblastine-resistant Caco-2 (Caco-2R) cell monolayers have been revealed. Labile drug stabilization by CDs [56, 73] and their ability to ameliorate drug irritation, and thus improve drug contact time at the absorption site in nasal, ocular, rectal, and transdermal delivery, are some other important factors that contribute to the CD-improved bioavailability. Thus, CDs can enhance the oral bioavailability of drugs in different ways [44].

Control of drug release

There are two types of control on drug release via oral delivery i.e., rate-controlled release and the time-controlled release. The hydrophobic CDs such as ethylated and acylated CDs with low aqueous solubility are known to work as prolonged-release carriers of water-soluble drugs [9, 74]. Among the various acylated CDs, per-Obutanoyl-β-CDs (TB-β-CDs) has the prominent retarding effect for water-soluble drugs, owing to the mucoadhesive property and appropriate hydrophobicity that differ from those of other derivatives having shorter or longer chains. The gel forming property of 2-hydroxypropyl-β-CDs (HP-β-CDs) is also useful to design the prolonged release of water-soluble drugs. Moreover, sulfobutyl ether β-CDs (SBE7-β-CDs) can serve as both a solubility modulating and an osmotic pumping agent for the controlled-porosity osmotic pump tablets, from which the release rate of both highly and poorly water-soluble drugs can be controlled precisely [75].

The combined use of CDs complex and CDs conjugate will be useful for designing various kinds of time-controlled type oral drug delivery preparations. The release of drug from the drug/CDs conjugate after oral administration shows a typical delayed-release behavior. Therefore, when the CDs conjugates are combined with other different release preparations, we can obtain more advanced and optimized drug release system, securing balanced oral bioavailability, and prominent therapeutic efficacy. For example, a repeated-release preparation may be designed by combining the CDs conjugate with a fast releasing fraction, while a combined preparation of the conjugate with a slow-releasing fraction may provide a prolonged release preparation. These modified-releases by means of the combination were demonstrated using the ketoprofen/α-CDs conjugate [72, 76]. The co-administration of the CDs conjugate and the fast-dissolving ketoprofen/HP-β-CDs complex gave a typical repeated release profile after oral administration. Since pharmaceutical preparations are usually composed of considerable amounts of pharmaceutical excipients and additives to maintain the efficacy and safety of the drug molecules, suitable combination of the CDs complex and the third component can markedly extend the actions of CDs for the design of advanced drug release formulations.

Site-specific drug delivery

Drug targeting to specific organ or tissues by drug/CD complex are sometimes disadvantageous because the complex dissociates before it reaches targeting site. Such problem can be surmounted by binding a drug covalently to CDs.

CDs are known to be scarcely capable of being hydrolyzed and only slightly absorbed in passage through the stomach and small intestine; however, they are fermented to small saccharides by colonic microflora and thus absorbed as maltose or glucose in the large intestine. This biological property of CDs can be exploited for site-specific delivery of drugs to colon [72]. The CDs conjugates of biphenylylacetic acid and ketoprofen, *n*-butylic acid, prednisolone, and 5-fluorouracil, as new candidates for colon-specific delivery prodrugs were studied, which revealed that the prednisolone/CDs conjugate is particularly useful for colon-specific delivery owing to the alleviation of systemic side effects of prednisolone, while maintaining the anti-inflammatory effect. This CDs prodrug approach provided a versatile means for constructions of not only colon-specific delivery systems but also site-specific drug release system including gene delivery.

Davis and co-workers have reported a number of uses of β-CDs-containing polymers with adamantine–PEG or adamantine–PEG–transferrin for gene transfer as well as DNAzyme transfer [77–80]. Kihara et al. have recently demonstrated that Starburst PAMAM dendrimer (generation 2 or 3) conjugate with α-CDs (α-CDE conjugates) in the molar ratio of 1:1 can be utilized as a novel nonviral vector for gene and siRNA delivery in vitro and in vivo [81]. These in vitro and in vivo results highlight the potential use of CDs, CDs conjugates and CDs polymers for gene, antisense and siRNA therapies. A number of bioadaptable CDs derivatives and polymers have been designed and evaluated for practical uses in pharmaceutical field in the form of complex or conjugate.

Drug safety

CDs have been used to ameliorate the irritation caused by drugs [13]. The increased drug efficacy and potency (i.e., reduction of the dose required for optimum therapeutic activity), caused by CD-increased drug solubility, may reduce drug toxicity by making the drug effective at lower doses. β-CD enhanced the antiviral activity of ganciclovir

on human cytomegalovirus clinical strains and the resultant increase in the drug potency reduced the drug toxicity [44, 82]. The toxicities associated with crystallization of poorly water soluble drugs in parenteral formulations can often be reduced by formation of soluble drug:CD complexes. Formulation of phenytoin with HP2-β-CD showed considerably reduced tissue irritation compared with a commercial injection of the drug in a BALB/c mouse model [44, 83]. Further CD entrapment of drugs at the molecular level prevents their direct contact with biological membranes and thus reduces their side effects (by decreasing drug entry into the cells of nontargeted tissues) and local irritation with no drastic loss of therapeutic benefits [19, 44]. Inclusion complexation with HP-β-CD reduced the side effects of 2-ethyl hexyl-*p*-dimethyl aminobenzoate (a UV filter) by limiting the interaction of the UV filter with skin [44, 84]. Inclusion complexation with CDs also reduces ocular drug irritation by limiting the free drug concentration on the precorneal area to a nonirritating level [5, 44, 85].

Drug stability [44]

Cyclodextrin complexation provides molecular shielding by encapsulating labile drugs molecules at molecular level. Thus insulate them against various degradation process and increase the shelf life of drugs [4]. CD-induced enhancement of drug stability is result of inhibition of drug interaction with vehicles and/or inhibition of drug bioconversion at the absorption site [8] e.g., photostability of promethazine on complexing with HP-β-CD, DM-β-CD, stability against hydrolysis of Melphalan and Carmustine by complexation with SBE-β-CD, and HP-β-CD etc.

SBE-β-CD showed greater stability enhancement of many chemically unstable drugs than other CDs [86]. The stabilizing effect of CDs depends on the nature and effect of the included functional group on the drug stability and the nature of the vehicle. HP-β-CD significantly reduced the photodegradation of 2-ethyl hexyl *p*-dimethyl aminobenzoate in solution than in emulsion vehicle [84]. CDs improved the photostability of trimeprazine [87] (when the solution pH is reduced) and promethazine [88]. CDs also enhanced the solid state stability and shelf life of drugs [89–91]. CDs were reported to enhance the physical stability of viral vectors for gene therapy, and the formulations containing sucrose and CDs were stable for 2 years when stored at 20 °C [92]. Since the hydrolysis of drugs encapsulated in CDs is slower than that of free drugs, the stability of the drug/CD complex, i.e., the magnitude of the complex stability constant, plays a significant role in determining the extent of protection. The effect of complexation on drug stability can be represented by the following (Eq. 1) (Fig. 3) [44]:

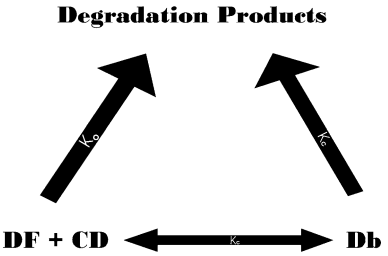

Fig. 3 Model representing the effect of complex stability constant on drug degradation (Adapted from reference 93)

$$\frac{1}{K_0 - K_{obs}} = \frac{1}{K_C(K_0 - K_C)[CD]} + \frac{1}{(K_0 - K_C)} \quad (1)$$

where K_0 is the degradation rate constant of free drug, K_{obs} is the observed degradation rate constant in the presence of CD, K_c is the stability constant for the complex, and [CD] is the concentration of CD [93].

Cyclodextrin in the design of delivery systems

Liposomes

Liposomes are concentric vesicles in which an aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or synthetic phospholipids. Liposomes entrap hydrophilic drugs in the aqueous phase and hydrophobic drugs in the lipid bilayers and retain drugs en route to their destination. Major problems encountered with these vesicular systems appears during their preparation and results from a low water solubility of the drug is rapidly released in the presence of plasma leading to either a low yield in drug loading, or a slow or incomplete release rate of the drug. So these drawbacks were ruled out by a new concept in drug delivery [94, 95]. The concept was to entrap CD–drug complexes into liposomes, which combines the advantages of both CDs (such as increasing the solubility of drugs) and liposomes (such as targeting of drugs) into a single system and thus circumvents the problems associated with each system. By forming water soluble complexes, CDs would allow insoluble drugs to accommodate in the aqueous phase of vesicles and thus potentially increase drug-to-lipid mass ratio levels, enlarge the range of insoluble drugs amenable for encapsulation (i.e., membrane-destabilizing agents), allow drug targeting, and reduce drug toxicity. Problems associated with intravenous administration of CD complexes such as their rapid removal into urine and toxicity to kidneys, especially after chronic use, can be circumvented by their entrapment in liposomes [44, 95–98]. Liposomal entrapment can also alter the pharmacokinetics of inclusion complexes. Liposomal entrapment drastically reduced the urinary loss of

HP-β-CD/drug complexes but augmented the uptake of the complexes by liver and spleen, where after liposomal disintegration in tissues, drugs were metabolized at rates dependent on the stability of the complexes [44, 96]. When the concept of entrapping CD complexes into liposomes was applied to HP-β-CD complexes of dexamethasone, dehydroepiandrosterone, retinal, and retinoic acid, the obtained dehydration–rehydration vesicles (DRV liposomes) retained their stability in the presence of blood plasma [44, 96]. CD complexation can increase liposomal entrapment of lipophilic drugs and also reduce their release from the carrier, i.e., liposomes. Complexation with CDs increased the liposomal entrapment of nifedipine by reducing its interaction with lipid bilayers and also improved the liposomal stability in plasma [44, 99]. Large amounts of lipophilic drugs in liposomes can be encapsulated by selecting a CD molecule having ability to form inclusion complex with high drug:CD ratio. Complexation with CDs can improve the stability of liposomes, e.g., most stable liposomal formulations of metronidazole and verapamil were obtained by direct spray drying of lipid, drug, and HP-β-CD mixture [44, 100]. Inclusion complexation can greatly increase the chemical stability of labile drugs in multilamellar liposomes. Multilamellar DRV liposomes containing a riboflavin/γ-CD complex provided optimal protection to the photosensitive drug [44, 101]. Similarly, multilamellar liposomes containing indomethacin/HP-β-CD inclusion complex showed increased stability of the hydrolysable drug (∼75-fold) [44, 102]. Parent CDs along with sulfated glycolipids were used as starting materials in the synthesis of specific erythrocyte-like liposomes having excellent self-assembling capacity to form stable monolayers at an air water interface [44, 103].

Microspheres

The first studies on the role of cyclodextrins in microparticle preparation were carried out by Loftsson et al. [104]. Complexation may not improve the drug dissolution rate from microspheres even in the presence of a high percentage of highly soluble hydrophilic excipients. Nifedipine release from chitosan microspheres was slowed down on complexation with HP-β-CD in spite of the improved drug-loading efficiency, this can be attributed to lesser drug availability from the complex and also due to formation of hydrophilic chitosan/CD matrix layer around the lipophilic drug that further decreases the drug matrix permeability [44, 105]. Sustained hydrocortisone release with no enhancement of its dissolution rate was observed from chitosan microspheres containing its HP-β-CD complex. This sustained hydrocortisone release was due to formation of a layer adjacent to the interface during the dissolution process that makes the microsphere surface increasingly hydrophobic [44, 106]. 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 a result of increased hydrophilicity of the proteins caused by shielding of their hydrophobic residues by HP-β-CD, this also reduces their aggregation and denaturation. CDs were also used to modulate peptide release rate from microspheres, e.g., HP-β-CD coencapsulation in PLGA microspheres slowed down insulin release rate [44, 107].

Microcapsules [44, 108]

The crosslinked β-CD microcapsules, because of their ability to retard the release of water-soluble drugs through semipermeable membranes, can act as release modulators to provide efficiently controlled release of drugs. Terephthaloyl chloride (TC) crosslinked β-CD microcapsules complexed with *p*-nitrophenol rapidly and the amount complexed increased as the size of the microcapsules decreased. TC crosslinked β-CD microcapsules retarded the diffusion of propranolol hydrochloride. Double microcapsules encapsulating methylene blue with β-CD microcapsules inside a crosslinked human serum albumin (HSA) decreases release rate of methylene blue with increasing amount of β-CD microcapsules. HSA microcapsules with parent β-CD due to the hydrating property of the CD can promote the diffusion of water into the microcapsules, resulting increased release rate of methylene blue.

Nanoparticles

Whatever the very promising studies carried out on liposomes and microspheres, it seemed more interesting to work on nanoparticles. First, they present a higher stability than liposomes. Secondly, because of their small size, they present a larger surface area than microparticles, allowing a better contact with the biological membranes leading to a higher bioavailability [44, 109]. However, the safety and efficacy of nanoparticles are limited by their very low drug loading and limited entrapment efficiency that may lead to excessive administration of polymeric material [44, 110, 111]. Two applications of CDs have been found very promising in the design of nanoparticles: one is increasing the loading capacity of nanoparticles and the other is spontaneous formation of either nanocapsules or nanospheres by nanoprecipitation of amphiphilic CDs diesters. Both the techniques were reported to be useful due to great interest of nanoparticles in oral and parenteral drug administration. CDs increased the loading capacity of poly (isobutylcyanoacrylate) nanoparticles. The increased

loading capacity was reported to be a result of increased drug concentration in the polymerization medium on addition of the drug:CD complex and increased number of hydrophobic sites in the nanosphere structure on association of large amounts of CDs to the nanoparticles [108, 110, 111]). HP-β-CD increased saquinavir loading into poly (alkylcyanoacrylate) nanoparticles by providing a soluble drug reservoir in polymerization medium [44, 112, 113]. Steroidal drugs like hydrocortisone (HC) and progesterone (PN) as β-CD or HP-β-CD complexes maintained the sizes of solid lipid nanoparticles (SLN) below 100 nm. CD complexation increased the incorporation of the more hydrophilic drugs e.g., HC than PN, provided lower release of both the drugs from SLN [44, 114]. Amphiphilic β-CDs (β-CDsa) with varying chain lengths (C6–C14) and bond types (ester and amide) on the primary face of the CD, have been characterized and evaluated as potential novel excipients in the preparation of nanocapsules with low hemolytic activity [44, 74, 110, 115]. The chemical structure of β-CDsa derivatives influences their ability to nanoassociate or form stable nanospheres. Amphiphilic β-CD (β-CDa) derivatives, 6-*N*-CAPRO-β-CD and β-CDC6 with 6C aliphatic chains on the primary and secondary face, respectively, enhanced the solubility and therapeutic efficacy of model drugs, bifonazole and clotrimazole. The β-CDa derivatives formed inclusion complexes with the drugs and with the nanoprecipitation technique the derivatives gave nanospheres of less than 300 nm with no use of surfactants. 6-*N*-CAPRO-β-CD, due to its ability to hold drugs longer in its cavity, displayed a higher loading capacity and slower release profile than β-CDC6. A slightly higher loading capacity observed with 6-*N*-CAPRO-β-CD was attributed to the higher drug adsorption onto its particle surface caused by the higher affinity of the 14 alkyl chains surrounding the CD molecule [44, 115].

Cyclodextrin grafted cellulosic fabric

The harmful effects of the solar UV radiation (290–400 nm) on human skin have been the object of several studies that led to improved approaches in photoprotection. The strategies advocated to prevent the sunlight-induced damage include reduced sun exposure, topical application of sunscreening preparations etc. [116]. But problems associated with sunscreen agents are poor solubility (such as an UVA and an UVB filter (4-tert-butyl-4′-methoxydibenzoyl methane and 3-(4-methylbenzylidene) camphor) insoluble in water) [117], photo degradation (butyl methoxydibenzoylmethane (BMDBM) undergoes marked decomposition under sunlight exposure leading to a decrease of its expected UV-protective capacity and it is also desirable to minimize skin penetration of some sunscreens (2-Hydroxy-4-Methoxy Benzophenone (Oxybenzone) [118–121]. Therefore, there is a need to reduce the photoinstability of sunscreens.

The inclusion of the sunscreen agent phenylbenzimidazole sulphonic acid (PBSA) into the HP-β-CD cavity completely inhibit the formation of free-radicals generated by PBSA on exposure to simulated sunlight, thereby suppressing its photosensitising potential [122]. Cyclodextrin complexation phenomenon enhances the stability to air and light of the included molecule. Complexation of BMDBM with hydroxypropyl-β-cyclodextrin (HP-β-CD) decrease the extent of decomposition and free radical formation upon exposure of the UV filter to simulated sunlight. The stabilizing effect of HP-β-CD was more in solution than in lotion vehicles (oil-in-water emulsions) [119, 123, 124]. However the problem of repeated application after washing/bathing, stability, consistency and short shelf life was still a major hurdle on the way of lotions, solution, lipid microparticles (lipospheres) and microencapsulated complex containing complexed sunscreen agent.

A different approach to enhance the sun protection factor by textiles is the incorporation of sunscreens into fabrics was introduced. The incorporation of cyclodextrins onto fabrics by impregnation or spraying of the tissue with a cyclodextrin solution, or through covalent binding (grafting) retains their complexing properties even after handling and repeated washing cycles in contrast to simple surface adsorption [125, 126]. Tencel, a cellulosic fabric obtained from wood pulp was the clothing material for chemical grafting of monochlorotriazinyl-β-cyclodextrin (β-CDMCT) (Fig. 4) [126, 127].

The results revealed enhanced UV screening properties of the prepared clothing fabric [125, 126]. Thus chemical grafting of cyclodextrins onto cotton fibers represents a useful strategy for the production of sun-protective clothing.

Hydrogels

Hydrogels have been gaining increased relevance as drug delivery systems, medical devices, scaffolds for tissue regeneration and substitution, and in several chemical applications as well. These hydrogels may offer interesting possibilities as dosage forms, administered by almost any route, if their limited ability for the direct loading of poorly water-soluble drugs is overcome. Thus crosslinked cyclodextrins that enable the combination of the hydrogel versatility with the complexation capability of cyclodextrins could be particularly useful [128–130].

Polymerized cyclodextrins maintain or promote the complexation ability of free cyclodextrins in solution [131]. When solutions of drug–cyclodextrin complexes are diluted in the physiological fluids, the release of the drug is

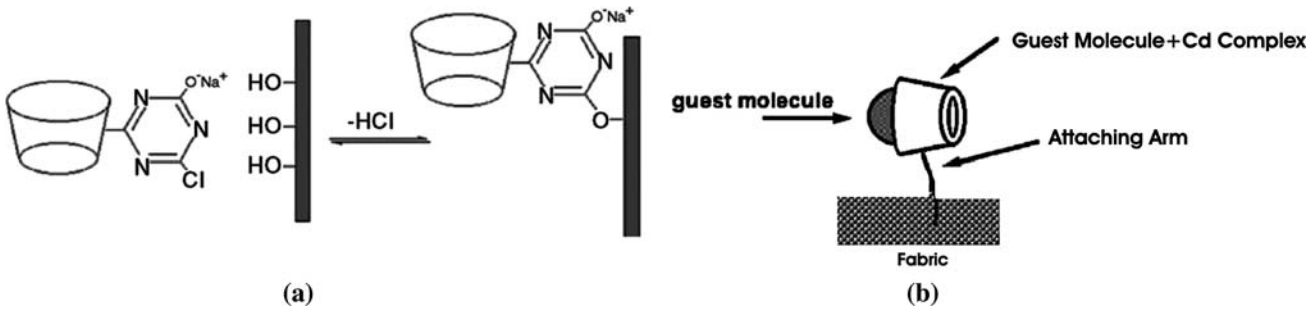

Fig. 4 (**a**) Chemical grafting of monochlorotriazinyl-β-cyclodextrin onto a cellulosic fiber. (**b**) Scheme of a host–guest inclusion complex grafted on the textile surface (Adapted from reference 126)

practically instantaneous. By contrast, in the case of the cyclodextrin hydrogels, the cyclodextrin units are covalently attached to each other and the volume of water which can enter the hydrogel is limited by the own network. This provides a microenvironment rich in cavities available to interact with the surrounding drug molecules. Consequently, delivery systems comprising chemically linked cyclodextrins offer considerable possibilities of achieving sustained release [129, 130, 132].

Cyclodextrin hydrogels are obtained by copolymerization of cyclodextrin monomeric derivatives with other acrylic or vinyl monomers. HPβCD hydrogels using diglycidylethers as cross-linking agents can be developed directly in order to avoid the important drawbacks of the chemical modification of cyclodextrins (low reproducibility of the synthesis or residual toxic monomers).

Hydrogels of different cyclodextrin varieties, cross-linked with ethyleneglycol diglycidylether (EGDE) as sustained delivery systems for estradiol demonstrated increase solubility in physiological environments [133].

Taishi Higashi demonstrated that the pegylated insulin forms polypseudorotaxanes with α and γ-CDs in a similar manner as poly(ethylene glycol) does. The resulting polypseudorotaxanes were less soluble in water and the release rate of the pegylated drug was controlled by regulating the threading and dethreading rates of the polypseudorotaxanes by adjustment of administration conditions such as amount of injection medium and concentration of CDs in the medium. Thus polypseudorotaxane formation can be useful as a sustained drug delivery technique for pegylated proteins and peptides [134].

Nanosponges

Nanosponges are a new class of material made of microscopic particles with cavities a few nanometers wide, characterized by the capacity to encapsulate a large variety of substances that can be transported through aqueous media. In the recent years, β-cyclodextrin-based nanosponges (Fig. 5) have been synthesized for their potential application in drug delivery, water purification, cosmetics (fragrance release) agriculture (controlled release of crop products) analytical (HPLC stationary phase) etc. In the pharmaceutical field, in particular, they could be employed as solubilizing agents or nanocarriers.

The nanosponges contain β-cyclodextrins as building-blocks, linked with carbonate groups to form a high crosslinked network. The reaction is very simple and carried out under relative mild conditions. The final nanosponge structure contains both cyclodextrin lyphophilic cavities and carbonate bridges, leading to a network of more hydrophilic channels [135]. Nanosponges are solid, insoluble in water, and rather crystalline.

The important and innovative aspects of these nanosponges are their lack of toxicity and their ability to be combined in spherical particles on a micrometric scale.

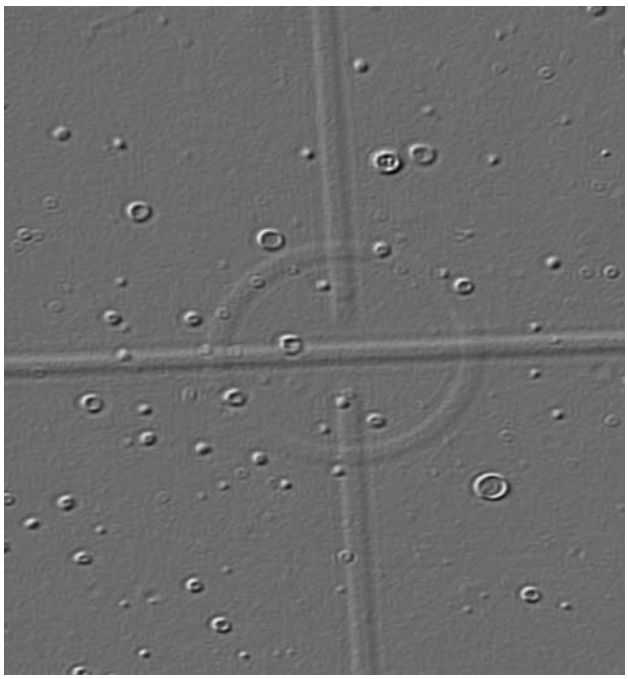

Fig. 5 Microphotograph of β-cyclodextrin nanosponges (Adapted from reference 135)

From the point of view of medical applications, this tiny shape enables the pulmonary and venous delivery of nanosponges. The combined action of micrometric spherical particles and nanometre pores size guarantees the administration of active principles to the sick part, avoiding the addiction of harmful solubilising substances. The efficacy of some pharmaceuticals adsorbed in the nanosponges showed an activity 3–4 times higher and exhibited no detrimental side effects.

Cyclodextrin based nanosponges (of dexamethasone, flurbiprofen and Doxorubicin hydrochloride) demonstrated the ability to include either lipophilic or hydrophilic drugs and to release them slowly into physiological media. Thus nanosponges can be used as a vessel for pharmaceutical principles to improve the aqueous solubility of lipophilic drugs, to protect degradable molecules and to formulate drug delivery systems for various administration routes beside the oral one.

Beads

Potential drawbacks related to the composition and preparation of novel delivery systems viz. poor stability of liposomes in the gastrointestinal tract, use of organic solvents in manufacture of micro/nanocapsules, heating of lipid phase in preparation of SLN undermine the encapsulation of fragile molecules in such systems [136–139].

An innovative particulate "beads", made of safe and well-known materials: α-CD and soybean oil demonstrated potential to surmount above mentioned drawbacks. Beads" can be prepared by using soft conditions (no organic solvent, no cross-linking or surface-active agents, moderate heating). Morphologically, these beads appear as minispheres consisting of a partial crystalline matrix of cyclodextrins surrounding micro-domains of oil (Fig. 6). Beads can be prepared by continuous external orbital shaking of a mixture of an α-cyclodextrin aqueous solution and soybean oil at room temperature. α-CD is employed for its ability to interact with components of vegetable oil and more especially with triglycerides whereas the high oil content offers interesting prospects for the microencapsulation of lipophilic drugs. Freeze-drying advantageously transforms beads into dry powder in which the oil content reaches 80% weight and also facilitates ease of handling and use for oral administration [140, 141].

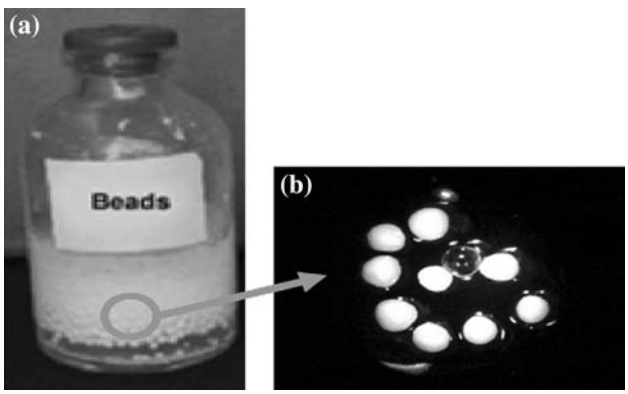

Fig. 6 Photograph of beads: (**a**) at the end of the fabrication process; (**b**) zoom of beads after washing (Adapted from reference 140)

Encapsulation of isotretinoin (poorly stable and lipophilic molecule) in "beads, for oral delivery demonstrated high drug loading/encapsulation efficiency which can be attributed to inner structure (micro-domains of oil) and increase oral bioavailability in rats. Thus beads may open up new prospects for oral delivery of lipophilic drugs [140, 141].

Nanogels/nanoassemblies

In the past few decades, submicronic polymeric particles have attracted considerable attention as potential drug delivery devices for the controlled release of active molecules and targeting. So the technical roadblock in their use is the fact that their preparation needs to employ large amount of potentially toxic organic solvents and surfactants, which is often not acceptable, at least for parenteral administration. Therefore to overcome these technological issues new self assembling nanogels/nanoassemblies were developed avoiding the use of organic solvents and surfactants.

They consist of a hydrophilic polymer backbone, on which hydrophobic moieties are grafted [142]. Among the associative polymers, hydrophobized polysaccharides, such as cellulose derivatives [143], dextran [144, 145], chitosan [146, 147] or pullulan [148, 149] are particularly attractive due to their biocompatibility, biodegradability and low toxicity, which are advantageous for biological and pharmaceutical applications.

The development of supramolecular assemblies, in which CDs were associated to macromolecules, attracted much attention. Harada et al. reported on the design of supramolecular structures consisting of CDs and poly(ethylene oxide) with a relevant crosssectional area for its inclusion into CD cavities [150–152]. Huh and coworkers described systems, in which CDs formed inclusion complexes with poly(ethylene oxide)-grafted polysaccharides [153, 154]. More recently, supramolecular gel-like networks were obtained by mixing a CD-bearing host polymer and a hydrophobically modified guest polymer.

Spherical supramolecular nanoassemblies (nanogels) may be obtained in pure water just by mixing two neutral polymers which instantaneously associate together. Colloidal systems generally result from the association of amphiphilic polymers in water, from the complexation of

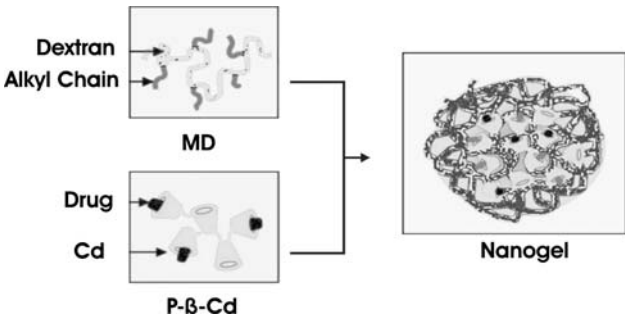

Fig. 7 Schematic representation of the formation of self-assembling MD-pβCD nanogels (Adapted from reference 155)

oppositely charged polyions or from hydrogen-bonding interactions.

S. Daoud-Mahammed prepared nanoassemblies by combining the properties of both polysaccharides and CDs. They showed that these nanoassemblies spontaneously form by mixing two aqueous solutions of soluble polymers: a hydrophobically modified dextran obtained by grafting alkyl moieties onto the polysaccharide backbone (MD) and a β-cyclodextrin-epichlorohydrin polymer (pβCD).

S. Daoud-Mahammed, P. Couvreur, R. Gref studied the stability of new supramolecular nanoassemblies (nanogels), based on the association of a hydrophobically modified dextran (MD) and a β-cyclodextrin polymer (p β-CD) (Fig. 7). They concluded that freeze-drying was a convenient method for the long-time storage of MD-pβ-CD nanoassemblies. Thus the new supramolecular nanoassembly concept avoids some of the inconveniences of the currently employed nanotechnologies [155].

Cyclodextrin-containing polymers [156]

Cyclodextrin-containing polymers are now being explored as vehicles for delivering nucleic acids into cells. The structures of the cyclodextrin-containing polycations affect the nucleic acid delivery efficiencies and their toxicities. The cyclodextrin-containing polymers reveal lower toxicities than polymers that lack the cyclodextrins. The cyclodextrins endow the nucleic acid delivery vehicles with the ability to be modified by compounds that form inclusion complexes with the cyclodextrins, and these modifications can be performed without disruption of the polymer–nucleic acid interactions.

The development of polyplexes (cationic polymer + nucleic acid) for use as DNA delivery agents is based on hypothesis that it may be possible to prepare low toxicity polycations from cyclodextrins because numerous individual cyclodextrins (CD) were known to reveal low toxicity and to not elicit immune responses in animals. These new families of cyclodextrin-containing, cationic polymers (CDP) were able to provide effective DNA delivery to cultured cells with low toxicity. Numerous cyclodextrin-containing, cationic polymers currently exist. For example, within the class of cyclodextrin pendent polymers (Table 4), several are polycations, e.g., PEI, poly (allylamine), dendrimers.

Polyplex formulations (cationic polymer + nucleic acid) optimized for in vitro delivery are typically not appropriate for in vivo use because successful systemic delivery requires different particle properties. After intravenous injection, cationic polyplexes interact with serum proteins and are quickly eliminated from the bloodstream by phagocytic cells. But use of cyclodextrin-containing polycations for polyplex formation provides the means to create modified particles in an entirely new manner. Pun and Davis recently developed methodologies to modify the surface of polyplexes formed with cyclodextrin-containing polymers whether they are of the CDP-type or not. This concept exploits the use of cyclodextrin/guest compound complexation to provide modified polyplexes appropriate for systemic application as gene delivery vehicles. As an example of this methodology, adamantane was conjugated to PEG and the resulting compound exposed to CDP based polyplexes for self-assembly between the adamantane and the cyclodextrins. This methodology can provide CDP-based particles that are appropriate for systemic gene delivery.

Table 4 Examples of cyclodextrin pendent polymers (adapted from reference 156)

Type of cyclodextrin	Preparation method	Prepared polymer
α, β	Polymerization of vinyl cyclodextrin derivatives	Polyacrylic esters
β	Grafting of cyclodextrin to preformed polymer	Poly(Allylamine)S
β	Grafting of cyclodextrin to preformed polymer	Acrylonitrile-Methyl Acrylate Copolymer
α, β, γ	Polymerization of cyclodextrin methacrylate monomers	Polymethacrylates
β	Grafting of cyclodextrin to preformed polymer	Chitosan
β	Grafting of cyclodextrin to preformed polymer	Polyester
β	Grafting of cyclodextrin to preformed polymer	Polyethylenimine

Table 5 Novel drug delivery systems incorporating cyclodextrin–drug complex

Cyclodextrin type	Drugs	Delivery system prepared/form in which study is performed	Objective/purpose/work done	References
β-CD, HP-β-CD	Ketoprofen	Liposomes	Transdermal drug delivery	[157]
HP-β-CD, DM-β-CD, OM-β-CD	Gonadorelin, Leuprolide acetate, Recombinant human growth hormone, Lysozyme	Injectable microspheres	Protein stability and sustained release	[158]
β-CD, HP-β-CD	Niclosamide	Dendrimers	Solubility enhancement and controlled release	[159]
β-CD	poly(propylene glycol) bisamine	Hydrogel	Biomedical materials for tissue engineering and drug carriers with controlled release	[160]
β-CD	Dexamethasone, Flurbiprofen, Doxorubicin hydrochloride	Nanosponges	Nanoparticulate system as drug carriers	[102]
2-HP-β-CD	Glutathione	Microparticles	Oral sustained-release delivery systems for tripeptide with reduced peptide degradation	[161]
HP-α-CD, HP-β-CD	Triclosan, Furosemide	Nanoparticles	Transmucosal delivery of hydrophobic compounds	[162]
α-CD, β-CD, γ-CD	Insulin	Pegylated insulin/CD polypseudorotaxanes	Polypseudorotaxanes as sustained release system	[134]
β-CD, M-β-CD, HP-β-CD, SB-β-CD	Estradiol	Hydrogels	Hydrogels as controlled release delivery system	[133]
γ-CDC6	Progesterone	Nanospheres	Feasibility of preparing nanospheres	[163]
HP-β-CD	Nifedipine	Microspheres	Solubility enhancement	[99]
HP-β-CD	Hydrocortisone	Microspheres	Release and stability were investigated	[106]
2-HP-β-CD	Insulin	Nanoparticles	Oral insulin delivery	[164]
HP-β-CD	Carvedilol	Buccal tablet	Bioadhesive sustained-release buccal delivery	[165]
HP-β-CD	Insulin	Large porous particles	Dry powders for the sustained release for pulmonary delivery	[166]
β-CD hydrate	Amlodipine	Liposomes	Stability against photodegradation	[34]
HP-β-CD	Methoxydibenzoylmethane	Lipospheres	Photostability	[123]
HP-β-CD	Insulin	Microspheres	Protein release kinetics	[167]
β-CDMCT	Octyl methoxycinnamate	Cellulose fabric	Incorporation of the sunscreen agent into cyclodextrin bounded to cloth fiber and evaluate its sun protective capacity	[126]
Heptakis-β-CD	TPPS	Nanoparticles	Photodynamic activity	[168]
HP-β-CD	Saquinavir	Nanoparticles	Improve oral delivery	[113]
β-CD, 2-HP-β-CD	Hydrocortisone, Progesterone	Solid lipid nanoparticles	To modulate the release kinetics	[114]
Bis-CD	Bovine serum albumin	Nanoparticles	As protein delivery system	[169]
HP-β-CD	Bovine serum albumin	Microspheres	To investigate the conformational stability of protein	[170]
α, β, γ-CD	Gabexate Mesylate	Bioadhesive microspheres	Bioadhesive nasal delivery system	[171]
β-CDC6	Tamoxifen citrate	Nanoparticles, nanospheres, nanocapsules	Developed nanoparticulate drug delivery systems	[172]
HP-β-CD	Itraconazole	Vaginal cream	Developed mucoadhesive vaginal cream	[173]
α, β, γ-CD	Indomethacin, Furosemide, Naproxen	Nanoparticle	Developed nanoparticles as delivery systems and solubility enhancement	[174]
β-CD, HP-β-CD	Nifedipine	Suppositories	To improve the release property	[175]

Table 5 continued

Cyclodextrin type	Drugs	Delivery system prepared/form in which study is performed	Objective/purpose/work done	References
β-CD	Amikacin	Microparticles microspheres for pulmonary drug delivery	Pulmonary drug delivery	[176]
HP-β-CD, γ-CD, RM-β-CD	Methacholine	Nebulized aerosol	Pulmonary administration	[177]
$(SBE)_{7m}$-β-CD	Chlorpromazine hydrochloride	Osmotic pump tablet	Controlled release of poorly water-soluble drugs	[178]
α-Cyclodextrin	Isotretinoin	Oil beads	Oral bioavailability of lipophilic drugs	[141]
MCT-β-CD	Miconazole	Fabric with antibacterial abilities	Incorporation of the antibacterial agent into cyclodextrin on to covalently bonded cloth fibers	[179]
SBE7-β-CD	Carbamazepine	Beads	Sustained release and Solubility enhancement	[180]
β-CD	Retinoic acid	Hydrogel topical formulation	Improve efficacy and tolerability of retinoic acid	[181]
HP-β-CD	Rh-interferon α-2a	Lipidic implants	Controlled protein release	[182]
a-cyclodextrin	Droepiandrosterone	Matrix tablet	Sustained-release	[183]
β-CD, HP-β-CD, Me-β-CD	Flurbiprofen	Fast-dissolving tablets	Solubility enhancement	[184]
β-CD	Naproxen, Ibuprofen	Water-soluble epichlorohydrin-β-cyclodextrin polymer	To modulate the kinetic release and solubility enhancement	[185]
β-CD, Me-β-CD	Piroxicam	Gel	Development of topical dosage form to overcome side effects connected with the oral use	[186]
α-CD, β-CD, HP-β-CD, RAME-β-CD	Melarsoprol	Oral form and parenteral aqueous solution	Solubility enhancement and to improve tolerability and safety	[29]
HP-β-CD, PM-β-CD	Bupranolol	Solution/suspension	Transdermal penetration enhancement	[187]
β-CD	Diclofenac	Solutions	Permeation enhancement studies using silicone as a model membrane	[188]

β-CD, Beta cyclodextrin; HP-β-CD, Hydroxypropyl beta cyclodextrin; DM-β-CD, 2,6-di-*O*-methyl beta cyclodextrin; OM-β-CD, 6-*O*-maltosyl beta cyclodextrin; 2HP-β-CD, 2-hydroxypropyl beta cyclodextrin; HP-α-CD, Hydroxypropyl alpha cyclodextrin; α-CD, Alpha cyclodextrin; γ-CD, Gamma cyclodextrin; M-β-CD, Methyl-β-cyclodextrin; SB-β-CD, Sulfobutyl beta cyclodextrin; γ-CDC6, Gamma cyclodextrin C6 or amphiphilic 2,3-di-*O*-hexanoyl gamma cyclodextrin; β-CDMCT, Monochlorotriazinyl beta cyclodextrin; Heptakis-β-CD, Heptakis (2-ω-amino-*O*-oligo (ethylene oxide)-6-hexylthio) beta cyclodextrin; bis-CDs, Ethylenediamino or diethylenetriamino bridged bis(beta cyclodextrin)s; RM-β-CD, randomly methylated beta cyclodextrin; $(SBE)_{7m}$-β-CD, Sulfobutyl ether-β-cyclodextrin; MCT-β-CD, Monochlorotriaziny beta cyclodextrin; Me-β-CD, Methyl beta cyclodextrin; SBE-β-CD, Sulfobutylether-β-cyclodextrin; TPPS, Anionic 5,10,15,20-tetrakis(4-sulfonatophenyl)-21H,23H-porphyrin

Thus cyclodextrin-containing polymers are revealing new and exciting properties when used as gene delivery vehicles. The cyclodextrins endow the gene delivery vehicles with low toxicity and can serve as hosts that can form inclusion complexes with appropriate guest species to decorate the surfaces of polyplexes.

Table 5 is a compilation indicating contribution of cyclodextrins and its derivative for encountering various problems in formulating drugs. It also highlights novel drug delivery systems incorporating cyclodextrin–drug complexes. The prepared novel delivery systems using cyclodextrin/drug complexes will be of dual advantage comprising cyclodextrin complexation ability along with potential of inherent properties of the novel delivery system.

Conclusion

The purpose of this contribution is to outline how well the CDs satisfy the requirements for a drug carrier in novel drug delivery systems. An important tool in this regard is the use of chemically modified cyclodextrins. These starch

derivatives interact via dynamic complex formation and other mechanisms in a way that camouflages undesirable physicochemical properties, including low aqueous solubility, poor dissolution rate and limited drug stability. Thus because of the multi-functional characteristics and bioadaptability CDs are capable of alleviating the undesirable properties of drug molecules in different areas of drug delivery. The final requirement of the drug carrier is its ability to deliver a drug to a targeted site. Owing to the increasingly globalized nature of the CDs-related science and technology, development of the CDs-based drug formulation is also rapidly progressing. We are looking forward to seeing numerous pharmaceutical products containing CDs in the near future.

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