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Review Article

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A REVIEW ON PHARMACEUTICAL APPLICATION OF CYCLODEXTRINS

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ABSTRACT

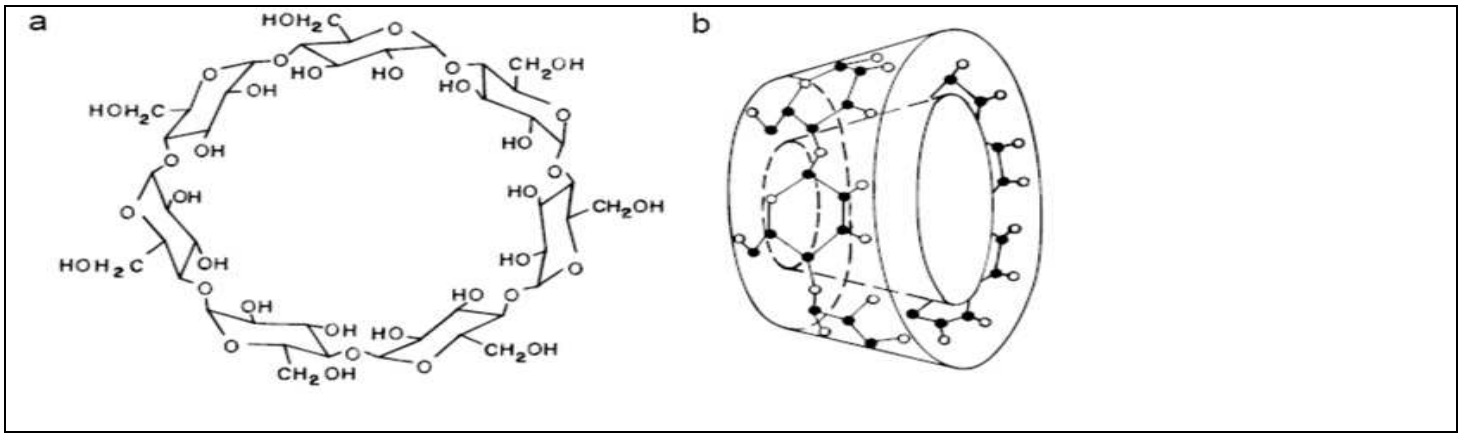
The macrocylic cyclodextrins(enzyme conversion product of starch)were discovered in1891,and the structure were elucidated in mid -1930s.there industrial significance become obvious in 1970s,and by now thousand of tons of cyclodextrins and there chemical derivatives and inclusion complexes are produced industrially. The purpose of this review is to discuss some of the interesting findings and applications of cyclodextrins (CDs) and their derivatives in different areas of drug delivery, particularly in protein and peptide drug delivery and gene delivery. The article highlights important CD applications in the design of various novel delivery systems like liposomes, microspheres, microcapsules, and nanoparticles. In addition to their well-known effects on drug solubility and dissolution, bioavailability, safety, and stability, their use as excipients in drug formulation are also discussed in this article. The 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. This review also covered the factor affecting the complex formation which is required to know at the time of selection in formulation of different drug delivery system.

Keywords: Macrocylic cyclodextrins, Drug delivery system, Nanoparticles.

INTRODUCTION

Cyclodextrins (CDs), with lipophilic inner cavities and hydrophilic outer surfaces, are capable of interacting with a large variety of guest molecules to form noncovalent inclusion complexes (Figure 1)**.** Chemically they are cyclic oligosaccharides containing at least 6 D-(+) glucopyranose units attached by α glucosidic bonds[1, 4]. CDs and their derivatives along with their abbreviations are given in Table 1. The 3 natural CDs, α-, β-, and γ-CDs (with 6, 7, or 8 glucose units respectively), differ in their ring size and solubility (Table 2).[1] CDs with fewer than 6 units cannot be formed due to steric hindrances while the higher homologs with 9 or more.

Figure-1 The chemical structure (a) and the toroidal shape (b) of the β-Cyclodextrins molecules.



glucose units are very difficult to purify. However, recently Endo et al established an isolation and purification method for several kinds of large ring CDs and also obtained a relatively large amount of δ-CD (Cyclomaltonose) with 9 glucose units.[2, 4]

The cavity size of α-CD is insufficient for many drugs and γ-CD is expensive. In general, δ-CD has weaker complex forming ability than conventional CDs. With drugs like digitoxin and spiranolactone, δ-CD showed greater solubilizing effect than α-CD but the effect of δ-CD was less than that of β- and γ-CDs. β-CD has been widely used in the early stages of pharmaceutical applications because of its ready availability and cavity size

suitable for the widest range of drugs. But the low aqueous solubility and nephrotoxicity limited the use of β-CD especially in parenteral drug delivery.[5]

Chemically modified CD derivatives have been prepared with a view to extend the physicochemical properties and inclusion capacity of parent CDs. Several amorphous, noncrystallizable CD derivatives with enhanced aqueous solubility, physical and microbiological stability, and reduced parenteral toxicity have been developed by chemical modification of parenteral CD[6,7].

Table 1. List of Abbreviations of CDs.

Cyclodextrin (CD)	**Abbrevation**
α- cyclodextrins	α- CD
β- cyclodextrins	β- CD
γ- cyclodextrins	γ- CD
Hydroxyethyl-β-CD	HE -β-CD
Hydroxypropyl-β-CD	HP-β-CD
Sulfobutylether-β-CD	SBE-β-CD
Methyl-β-CD	M-β-CD
Dimethyl-β-CD	DM-β–CD (DIMEB)
Randomly dimethylated -β-CD	RDM-β-CD
Randomly methylated-β-CD	RM-β−CD (RAMEB)
Carboxymethyl - β –CD	CM-β-CD
Carboxymethyl ethyl- β-CD	CME-β-CD
Diethyl-β-CD	DE-β-CD

Tri-O-methyl-β- CD	TRIMEB
Tri-O-ethyl–β-CD	TE-β-CD
Tri-O-butyryl–β-CD	TB-β-CD
Tri-O-valeryl–β-CD	TV-β-CD
Di-O-hexanoyl–β-CD	DH-β-CD
Glucosyl-β-CD	G_1-β-CD
Maltosyl-β-CD	G_2 -β-CD
2-hydroxy-3-trimethyl-ammoniopropyl-β-CD	HTMAPCD

Table 2. List of characteristics of α-, β-, γ-, and δ-CD[1,2]

Type of CD	**Cavity Diameter Å**	**Molecular Weight**	**Solubility (g/100 mL)**
α-CD	4.7–5.3	972	14.5
β-CD	6.0–6.5	1135	1.85
γ-CD	7.5–8.3	1297	23.2
δ-CD	10.3–11.2	1459	8.19

Factors influencing inclusion complex formation

Type of CD can influence the formation as well as the performance of drug/CD complex[8]**.** For complexation, the cavity size of CD should be suitable to accommodate a drug molecule of particular size[9]**.** Compared with neutral CDs, complexation can be better when the CD and the drug carry opposite charge but may decrease when they carry the same charge (Table-3). For many acidic drugs forming anions, the cationic (2-hydroxy-3-[trimethylammonio] propyl)-β-CD acted as an excellent solubilizer[1]**.** In the case of ionisable drugs, the

presence of charge may play a significant role in drug/CD complexation and hence a change in the solution pH can vary the complex constant. In general, ionic forms of drugs are weaker complex forming agents than their nonionic forms. but in the case of mebendazole, the un-ionized form was less included in HP-β-CD than the cationic form[10].

Temperature decreased the magnitude of the apparent stability constant of the drug/CD complex and the effect was reported to be a result of possible reduction of drug/CD interaction forces, such as van der Waals and hydrophobic forces with rise of temperature. However, temperature changes may have negligible effect when the drug/CD interaction is predominantly entropy driven (ie, resulting from the liberation of water molecules hydrated around the charges of guest and host molecules through inclusion complexation)[11].

Table 3. List of Factors Affecting Inclusion Complexation[10-11]

Factor	Drug	CDs Studied	Observation
Type of CD	Albendazole, Mebendazole, Ricobendazole	β-, HP-β-, M-β-CDs	More effective enhancement of solubility with substituted CDs.
	Fenoprofen	α-, β-, γ-, HP-β-CDs	Better stability constant values of pharmaceutical interest with only β-CD and HP-β-CD complexes.
	Ketoprofen	M-β-, β-CDs	Better dissolution performance of M-β-CD complex.
	Cocaine	α-, β-, γ- CDs	Drug binding with reasonable affinity only to β-CD in aqueous solution.

Cavity size	Gliclazide	β-, α- CDs	Cavity size of β-CD was suitable for complexation while that of α-CD was insufficient to include GL rings.
	Digitoxin	δ- CD	Enhanced solubility due to partial inclusion of the drug in CD cavity.
	Macrocyclic compounds (MCCs)	α-, β-, γ-, δ-CDs	Complexes of smaller MCCs with α- and β-CDs and those of larger MCCs with γ- and δ-CDs were relatively stable.
	Ibuproxam	α-, β-, γ- CDs	Effective enhancement of dissolution rate with only with β- and γ- CDs but the cavity of α-CD was less suitable.
	Prochloro-methazine	β-, HP-β-, DM-β-CDs	Decreased solubility due to failure of the CD cavities to include phenothiazine ring.
pH and ionization state	DY– 9760e	SBE-β-CD	Strong drug/CD interaction in acidic region, at pH 4.
	NSC-639829	SBE-β-CD	Increased solubility of the cationic drug at pH 1.
	ETH–615	HP- β-, RM-β-, CM-β-, SBE-β-HTMAP-β-CDs	Increased solubility with uncharged RM-β-CD. Complex stability constants were low with the highly polar drug at pH 5 due to its lesser ability to enter the CD cavity but were high with anionic less polar form at pH 10.

	Piroxicam	β-CD	Effective complexation at low pH
	Levemopamil HCl	HP-β-CD	Enhancement of solubility (mg/mL) was 3-fold with the charged drug (by 7.88 to 25.62 at pH 4) and 525-fold with the neutral form (0.0026 to 1.37 at pH 10.6).
	Ziprasdone mesylate	SBE-β-CD	Complexation was more favored with the ion pair over the dissociated ionic form.
	Sulindac	β-CD	Complexation was easier with nonionized form.
	Mebendazole	HP-β-CD	Un-ionized form was less included than the ionized form.
Temperature	DY–9760e	SBE-β-CD	Temperature change showed negligible effect on the stability constant.
	Sulindac	β-CD	Increasing the temperature decreased the apparent stability constant.
	Phenolphthalein	β-CD	Increasing the temperature decreased association constant for binding.
	Danazol	SBE-β-CD	Increasing the temperature decreased the complex stability constant.

CD EFFECTS ON DRUG PROPERTIES IN FORMULATION

Effect on Drug Solubility and Dissolution

CDs have been playing a very important role in formulation of poorly water-soluble drugs by improving apparent drug solubility and/or dissolution through inclusion complexation or solid dispersion, by acting as hydrophilic carriers for drugs with inadequate molecular characteristics for complexation, or as tablet dissolution enhancers for drugs with high dose, with which use of a drug/CD complex is difficult, eg, paracetamol. CD applications as solubilizing agents are summarized in table 4.

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, as a result of their ability to form in situ inclusion complexes in dissolution medium, can enhance drug dissolution even when there is no complexation in the solid state. SBE-β-CD was shown to be an excellent solubilizer for several drugs and was more effective than β-CD but not as effective as DM-β-CD[5]

Table 4. List of CD-enhanced Solubility and Dissolution [5]

CD	Drug(s)
β-CD	Nimesulide, Sulfomethiazole, Lorazepam, Ketoprofen, Griseofulvin, Praziquantel, Chlorthalidone, Etodolac, Piroxicam,, Itraconazole, Ibuprofen
α-CD	Praziquantel
γ-CD	Praziquantel, Omeprazole, Digoxin
HP-β-CD	Albendazole, DY–9760e, ETH–615, Levemopamil HCl, Sulfomethiazole, Ketoprofen,, Griseofulvin, Itraconazole, Carbamazepine Zolpidem, Phenytoin, Rutin

DM-β-CD	Naproxen, Camptothesin
SBE-β-CD	DY– 9760e, Danazol, Fluasterone, Spiranolactone
RM-β-CD	ETH–615, Tacrolimus
	Naproxen

Effect on Drug Bioavailability

CDs enhance the bioavailability of insoluble drugs by increasing the drug solubility, dissolution, and/or drug permeability. CDs increase the permeability of insoluble, hydrophobic drugs by making the drug available at the surface of the biological barrier, eg, skin, mucosa, or the eye cornea, 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**.**

In the case of water-soluble drugs, CDs increase drug permeability by direct action on mucosal membranes and enhance drug absorption and/or bioavailability[7, 8] Solubilization of specific membrane lipids of human erythrocytes through inclusion complexation with CDs and their ability to cause perturbation of membrane integrity, were suggested to contribute to CD-induced promotion of drug absorption and toxicity. It was reported that CDs, because of their ability to remove cholesterol, may increase membrane fluidity and induce membrane invagination through a loss of bending resistance and cause cell lysis. On the other hand, removal of phospholipids, especially phosphatidylcholine and sphingomyelin from the outer half of the membrane bilayer by CDs causes bilayer imbalance; the removal may also contribute in part to the formation of stomatocytes through an inward bending of membranes. CDs were reported to solubilize membrane components without entering into the membrane, and hence the perturbing effects of CDs can be mild and reversible. [12]

Labile drug stabilization by CDs 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. α-CD improved the rectal bioavailability of morphine by inhibiting the drug's upward movement from areas impacted by first pass metabolism.[7]

Effect on Drug Safety

CDs have been used to ameliorate the irritation caused by drugs. The increased drug efficacy and potency (ie, 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. The toxicities associated with crystallization of poorly water-soluble drugs in parenteral formulations can often be reduced by formation of soluble drug:CD complexes. 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. -[13]

Effect on Drug Stability

CDs can improve the stability of several labile drugs against dehydration, hydrolysis, oxidation, and photodecomposition and thus increase the shelf life of drugs.[1] Table 5. summarizes CD effects on drug stability. It was reported that CD-induced enhancement of drug stability may be a result of inhibition of drug interaction with vehicles and/or inhibition of drug bioconversion at the absorption site[7]. By providing a molecular shield, CD complexation encapsulates labile drug molecules at the molecular level and thus insulates them against various degradation processes. SBE-β-CD showed greater stability enhancement of many chemically unstable drugs than other CDs.

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. 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. Since the hydrolysis of drugs encapsulated in CDs is slower than that of free drugs, the stability of the drug/CD complex, plays a significant role in determining the extent of protection[14].

Table 5. List of CD Effect on Drug Stability[7]

Effect	**Drug**	**CD**
↑Photostability	Promethazine	HP-β-CD, DM-β-CD
	2–ethyl hexyl p–dimethyl aminobenzoate	HP-β-CD
	Glibenclamide	β-CD
↑ Shelf life with unaffected dissolution rates for 4 years	Diclofenac sodium	β-CD
↑ Thermal stability in solid state	Quinaril	β-CD, HP-β-CD
↑Stability against intramolecular cyclization in solid state	Doxorubicin	HP-β-CD, HP-γ-CD
↑Stability to acid hydrolysis and photodecomposition	Acyl ester prodrugs of Ganciclovir	HP-β-CD
↑Stability against hydrolysis	Digoxin	γ-CD
	Rutin	HP-β-CD
	Camptothesin	RDM-β-CD

	Melphalan and Carmustine	SBE -β-CD, HP-β –CD
	Paclitaxel	γ-CD, HP-γ-CD, HP-β-CD
	Spiranolactone	SBE-α-CD, SBE-β-CD, HP-β-CD, γ-CD,β-CD
↑ Deacetylation or degradation	Flutamide	β-CD

CD APPLICATIONS IN DRUG DELIVERY

Oral Drug Delivery

Applications of CDs in oral drug delivery include improvement of drug bioavailability due to increased drug solubility, improvement of rate and extent of dissolution, and/ or stability of the drug at the absorption site, eg, the gastrointestinal tract (GIT) or in formulation, reduction of drug-induced irritation, and taste masking (Table 6). CD complexation was found to decrease local drug irritation and also modify the time of drug release during GI transit.[8] CDs enhance the mucosal drug permeability mainly by increasing the free drug availability at the absorptive surface**.** CD complexation can provide better and uniform absorption of low-soluble drugs with poor and erratic absorption and also enhance the drug activity on oral administrationCD complexation increased the anthelmentic activity of albendazole and provided a high plasma concentration of the active metabolite. CD complexation increased the absorption of poorly water-soluble drugs, delivered via buccal or sublingual mucosa. Complexation of miconazole, econazole, and clotrimazole with HP-β-CD and genuine CDs increased the toxicity of these drugs on a human buccal cell culture model (TR_{146}) by causing drug supersaturation[15]**.**

Captisol or (SBE)7m-beta-CD, a solubilizer with osmotic property, was used to design osmotic pump tablets of chlorpromazine and prednisolone. Complexation can also mask the undesirable taste of drugs.

Complexation with CDs suppressed the bitter taste of oxyphenonium bromide. With the assumption that only the free drug molecule exhibits bitter taste, the extent of the suppression was reported to be dependent on the availability of free drug, regardless of the kind and concentration of CD[16-18].

Table 6. List of Applications of CDs in Oral Delivery[16-18]

Effect	Drug	CD
↑ Bioavailability by ↑Solubility and dissolution rate	β-CD	Ketoprofen, Griseofulvin, Terfenadine
	HP-β-CD	Albendazole, Ketoprofen, Phenytoin, Gliclazide
	SBE7–β-CD	Spiranolactone
	DM-β-CD	Tacrolimus
	M-β-CD	Albendazole
	ME-β-CD	Phenytoin
↑ Intensity or duration of therapeutic activity	β-CD	Terfenadine, Tolbutamide
	HP- β-CD	Tolbutamide, Amylobarbitone
↑ Permeability	HP-β-CD	Flutamide
↑Gastrointestinal stability	γ-CD	Digoxin
	HP-β-CD	Rutin
↑Sublingual bioavailability	HP-β-CD	Clomipramine, Testosterone
↑Buccal bioavailability	SBE7-β-CD,	Danazole

Parenteral Drug Delivery

CD derivatives such as amorphous HP-β- and SBE-β-CDs have been widely investigated for parenteral use on account of their high aqueous solubility and minimal toxicity. HP-β-CD with much higher aqueous solubility

allows parenteral administration of various drugs with no significant toxicity problems and hence is more often used in parenteral formulations. An itraconazole parenteral injection containing HP-β-CD (40% wt/vol) has been commercialized in the United States and Europe. The solubilizing potentials of both SBE-β- and HP-β-CDs for the drugs melphalan and carmustine were qualitatively similar but the intrinsic reactivities were significantly less with SBE-β-CD. 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 the aqueous environment. Formation of a stable, water-soluble dexamethsone complex with sugar branched β-CDs suggested the potential of these CDs as excellent carriers in steroidal injectable formulations.[19] Aqueous phenytoin parenteral formulations containing HP-β-CD exhibited reduced drug tissue irritation and precipitating tendency because their pH values were significantly closer to the physiological value (7.4)[20].

Ocular Delivery

Applications of CDs in aqueous eye drop preparations include solubilization and chemical stabilization of drugs, reduction of ocular drug irritation, and enhancement of ocular drug permeability. Vehicles used in ophthalmic preparations should be nonirritating to the ocular surface to prevent fast washout of the instilled drug by reflex tearing and blinking. Hydrophilic CDs, especially 2HP-β- and SBE-β -CDs, are shown to be nontoxic to the eye and are well tolerated in aqueous eye drop formulations, eg, increased ocular absorption and shelf life of pilocarpine in eye drop solutions by SBE-β-CD and decreased ocular irritation of a lipophilic pilocarpine prodrug by SBE-β- and HP-β-CDs.[1] **(Table 7)**[21].CDs enhance drug permeability by making the drug available at the ocular surface. HP-β-CD enhanced the ocular permeability of dexamethasone acetate and also inhibited the conversion of acetate salt to less permeable dexamethasone[9]. Since only the free drug can permeate biological membranes, 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. The dissociation of drug/CD

complexes depends more on the binding of drugs to precorneal proteins, absorption by corneal tissue, and displacement of drugs from CD complexes by precorneal fluid components. The ability of CDs to decrease membrane lipophilicity by interacting with the lipophilic compounds of epithelium was indicated by the reduction in the bioavailability of highly lipophilic pilocarpine prodrugs on addition of CDs[22]. Complexation with HP-β-CD significantly decreased hydrocortisone (HC) transport from the aqueous to the organic phase, the effect was dependent on the drug partition coefficient and the relative magnitude of the stability constant of the inclusion complex. The polymer interactions with the drug, HC, and its complex in each system were reported to be responsible for the observed solubility and different release behaviors of HC and its inclusion complex from high molecular weight cellulose and polyvinyl alcohol (PVA) polymeric films for ocular delivery. Formulation with HP-β-CD, with and without HPMC, improved the bioavailability and maximal mydriatic response of tropicamide by enhancing the drug's ocular permeability, but reduced the ocular drug irritation probably by maintaining the pH in physiologic range[23]. HP-β-CD also enhanced the permeability and miotic response of pilocarpine nitrate without damaging the rabbit corneal tissue[24].

Table 7. List of Usage of CDs in Aqueous Eye Drop Solutions[43]

Drug	**CD**
Acetazolamide	HP-β-CD, α-CD, HP-β-CD
Arachidonylethanolamide	HP-β-CD
Cyclosporine	α-CD
Dexamethasone	HP-β-CD
Dexamethasone acetate	HP-β-CD
Diclofenac	HP-β-CD, M-β-CD
Ethoxyzolamide	HP-β-CD, α-CD, β-CD,
Pilocarpine	HP-β-CD, SBE-β-CD

Nasal Drug Delivery

CDs are effective excipients in nasal drug delivery. CDs improve nasal drug absorption either by increasing aqueous drug solubility and/or by enhancing nasal drug permeability. However, large interspecies differences were found in CD-enhanced nasal drug absorption. The safety and nontoxicity of CDs in nasal drug formulations have been demonstrated by the clinical data with CDs showing no adverse effects. Merkus et. al[25] demonstrated that CDs can be safely used to improve nasal bioavailability of drugs, especially peptides. DM-β-CD improved the nasal bioavailability of estradiol in rats and rabbits. Nasal absorption of melatonin, a drug with high first pass metabolism was rapid and efficient when administered with β-CD and the peak levels were ~50 times higher than those observed after oral administration. Midazolam was absorbed rapidly when administered as an aqueous nasal spray (pH 4.3) containing SBE-β-CD (14% wt/vol), HPMC (0.1% wt/vol), and other additives[26].

CDs can also be used to reduce the nasal toxicity of other enhancers without affecting their absorption-enhancing property. β-CD or DM-β-CD reduced the serious nasal toxicity of sodium deoxycholate by inhibiting the leucine aminopeptidase activity in nasal mucosa without affecting the absorption-enhancing property of the bile salt for insulin[27]. Salbutamol release from the powder inhaler formulations containing γ-CD and DM-β-CD was faster than that from control with lactose; at the amount studied γ-CD was safer than DM-β-CD[28]. Midazolam nasal formulation in aqueous SBE-β-CD solution approached an IV form of the drug in speed of absorption, serum concentration, and sedation effect, with no serious side effects[29].

Rectal Drug Delivery

Applications of CDs in rectal delivery include enhancing drug absorption from a suppository base either by enhancing drug release from the base or by increasing drug mucosal permeability, increasing drug stability in the base or at the absorption site, providing sustained drug release, and alleviating drug-induced irritation[7,9]

Drug release from the suppository base is important in rectal absorption because of the high viscosity of rectal fluids. The effect of CDs on rectal drug absorption can be influenced by partition coefficient of the drug and its CD complex, magnitude of the complex stability constant, and nature of the suppository base (oleaginous or hydrophilic). Hydrophilic CDs (especially methylated and hydroxylpropyl CDs) enhance the absorption of lipophilic drugs by improving the drug release from oleaginous vehicles and/or by increasing the drug dissolution rate in rectal fluids. Formation of hydrophilic CD complexes was found to inhibit the reverse diffusion of drugs into oleaginous vehicles by reducing the drug/vehicle interaction. Rectal absorptions of flurbiprofen and biphenylacetic acid were improved by DM-β-CD and HP-β-CD, respectively. CDs may not affect drug release if the drug/CD complex dissociates in the vehicle itself. For example, although the dissolution rate of ethyl 4-biphenylylacetate (EBA) was highest from the DM-β-CD complex, only the HP-β-CD complex enhanced EBA release from the oleaginous suppository base because of lower dissociation of the HP-β-CD complex in the vehicle. The CD complex, once released from the base, mostly releases the free drug for absorption. The competing sites for the free drug released at the absorption site are CD cavity, suppository base, and the rectal mucosa. The extent of drug diffusion into these sites depends on drug's partition coefficient, magnitude of the stability constant of the drug/CD complex, and the relative lipophilicity of the competing sites. In the case of lipophilic drugs with a high partition coefficient, there might be some back diffusion of the released free drug into the lipophilic base. Since a part of drug may get absorbed as the CD complex, the partition coefficient of the complex also becomes important, eg, rectal absorption of a part of EBA as HP-β-CD complex. In the presence of hydroxyl propyl methyl cellulose (HPMC), β-CD markedly reduced the bioavailability of acetaminophen from both aqueous solution and hydrogels by forming a complex with a lower partition coefficient or higher hydrophilicity[7].

CDs enhance the rectal absorption of inabsorbable, hydrophilic drugs such as antibiotics, peptides, and proteins by their direct action on the rectal epithelial cells [7].α-CD enhanced the rectal absorption of morphine and human chorionic gonadotropin by increasing their mucosal permeability and reducing their degradation[30,31]

CDs enhance rectal drug stability either by inhibiting the drug/vehicle interaction (by making the drug insoluble in oleaginous base) or by inhibiting the drug bioconversion in the rectum. α-CD improved the rectal bioavailability of morphine by inhibiting the upward movement of the drug from areas impacted by first pass metabolism[7]

Controlled Drug Delivery

CDs, due to their ability either to complex drugs or to act as functional carrier materials in pharmaceutical formulations, can serve as potential candidates for efficient and precise delivery of required amounts of drugs to targeted site for a necessary period of time. β-CD derivatives are classified as hydrophilic, hydrophobic, and ionizable derivatives. The hydrophilic derivatives improve the aqueous solubility and dissolution rate of poorly soluble drugs, while the hydrophobic derivatives retard the dissolution rate of water-soluble drugs from vehicles. Hence hydrophilic and hydrophobic CD derivatives are used in immediate and prolonged release type formulations, respectively. The ionizable CD derivatives, on the other hand, improve inclusion capacity, modify drug dissolution rate, and alleviate drug irritation, eg, use of CME-β-CD to obtain delayed release–type formulations. Highly hydrophilic derivatives, such as 2HP-β-, G2-β-, and SBE-β-CDs were used in immediate release formulations that dissolve readily in the GIT and enhance the oral bioavailability of poorly soluble drugs. CDs, both natural and chemically modified, are used in the design of immediate, delayed release, and targeted drug delivery systems (Table 8).The pH-dependent solubility of CME-β-CD (ie, limited solubility under the acidic conditions of stomach with the complex solubility increasing with pH), which

provides selective dissolution of drug/CD complex, makes it useful in the design of enteric formulations. When molsidomine tablets containing CME-β-CD were studied in gastric acidity–controlled dogs, the absorption of the drug was significantly retarded under high gastric acidity compared with low gastric acidity conditions[32,33]

Table 8. Modification of the Drug Release Site and/or Time Profile by CDs[51]

Release Pattern	Aim	Use of CD
Immediate realease	Enhanced dissolution and absorption of poorly water-soluble drugs	HP-β-, DM-β-, SB-β-, and branched-β-CDs
Prolonged release	Sustained release of water-soluble drugs	Ethylated β-CDs, acylated β-CDs
Modified release	More balanced oral bioavailability with prolonged therapeutic effects	Simultaneous use of different CDs and/or other excipients
Delayed, pH-dependent release	(Enteric) Acid protection of drugs	CME-β-CD
Site-specific release	Colon-targeting	Drug/CD conjugate

Hydrophobic CDs, such as alkylated and acylated derivatives, are useful as slow-release carriers in prolonged release formulations of water-soluble drugs. Among the alkylated CDs, DE-β- and TE- β-CDs were the first used slow release carriers and their hydrophobic complexes with diltiazem[33] and isosorbide dinitrate[34] provided slow drug release on oral administration in dogs. Peracylated CDs, particularly those with medium alkyl chain lengths (C_4–C_6) are useful as hydrophobic carriers (Table 9) and have broad applicability in various routes of administration. Combination of short-chain and long-chain peracylated β-CDs in an appropriate molar ratio was suggested to be useful to provide an effectively controlled release rate of water-

soluble drugs, eg, markedly retarded release rate of molsidomine on complexation with peracylated β-CDs.[55] TB-β-CD was suggested to be a useful carrier for oral administration of water-soluble drugs, especially those that are metabolized in the GIT. In beagle dogs, oral administration molsidomine as TB-β-CD complexes resulted in suppressed peak plasma level of the drug while maintaining sufficient drug levels for long periods. The increased hydrophobicity and mucoadhesive properties on complexation were reported to be responsible for the observed sustained effect with TB-β-CD. Nanospheres of amphiphilic CDs such as DH-β-CD were also reported to have bioadhesive effects on gastrointestinal mucosa. [32]

CDs can also be used along with other carrier materials to optimize drug release rate. Improved nifedipine bioavailability with reduced first pass metabolism was observed from a modified oral dosage form containing a fast release portion of the drug with HP–β-CD and HCO-60, a nonionic surfactant (ie, amorphous drug form obtained by spray drying with the CD and surfactant) and a slow release portion with hydroxy propyl celluloses (HPCs) of different viscosity grades. [34]**.** Quaglia et alreported that CDs can be used to modulate drug delivery from swellable systems, eg, β-CD significantly affected the delivery of nicardipine from swellable crosslinked polyethylene glycol matrix by decreasing effective drug diffusivity through the matrix. SBE-β-CD has been used in the design of sustained release matrix tablets of poorly soluble drugs. Directly compressed tablets containing prednisolone with SBE-β-CD and polymer physical mixture showed more enhanced drug release than the control (with lactose instead of the CD) due to formation of an in situ drug:CD complex in the gel layer**.** HP-β-CD, because of its dissolution enhancing effect, was found to be more effective than β-CD in the development of controlled release nicardipine formulations[35]

Combination of drug complexes with hydrophilic and hydrophobic CDs in appropriate ratios can be a promising drug delivery system for prolonged therapeutic effect and balanced bioavailability. In rabbits, a sustained release nicardipine formulation, developed by mixing the drug complexes with HP-β-CD (fast

release fraction) and with hydrophobic TA-β-CD (sustained releasing portion) in appropriate ratios, showed markedly retarded drug release with prolonged maintenance of plasma levels[36] A sustained release 2-layered nifedipine tablet formulation was developed by using the drug complexes with β- and HP-β-CDs[37] Use of CDs with a hydroxyapatite matrix was indicated to control the release of chemotherapeutic agents containing toxic metals, such as Rhodium II citrate and butyrate, and to provide localized antitumor chemotherapy with minimal side effects[38]

Table 9. List of applications of Various CD Derivatives in the Formulation of Modified Release Preparations[32-33]

Derivative	Drug	Summary
Diethyl-β-CD	Diltiazem	Sustained release for oral use
	Buserelin acetate	Sustained release for subcutaneous use
	Nitroglycerine	Sustained release for percutaneous use
	Isosorbide dinitrate	Sustained release
	Tiaprofenic acid	Delayed release
Triacetyl-β-CD	Flufenamic acid	Prolonged release for oral use
Peracylated-β-CD (TB-β-CD)	Molsidomine	Sustained release for oral use
	Salbutamol	Prolonged release for oral use
	Captopril	Sustained release
Al-β-CD-sulfate	Recombinant human basic fibroblast growth factor	Sustained release for oral use; enhanced stability
O-carboxymethyl-O-β-CD	Molsidomine Diltiazem HCl	Delayed release

Colon-Specific Drug Delivery

CDs are rarely hydrolyzed and only slightly absorbed in the stomach and small intestine but are absorbed in the large intestine after fermentation into small saccharides by colonic microbial flora. The peculiar hydrolyzing property of CDs makes them useful for colon drug targeting. Biphenyl acetic acid (BPAA) prodrugs for colon-specific delivery were developed by conjugation of the drug onto one of the primary hydroxyl groups of α-, β-, and γ-CDs through an ester or amide linkage. In the case of ester prodrugs, the maltose and triose conjugates released the free drug after initial hydrolysis of the susceptibile ester linkage, but in the case of amide prodrugs, the conjugates remained as such providing delayed release due to the resistance of the amide bond to hydrolysis. The CD-based prodrug approach was used for colon-specific and delayed drug delivery. When studied in rats, it was found that both sugar-degrading and ester-hydrolyzing enzymes are necessary for colon-specific release of butyric acid from its β-CD ester conjugates Drug conjugation with α-CD resulted in a delayed release–type prodrug formulation for colon-specific delivery that alleviates the side effects of drugs while maintaining their therapeutic effect, eg, site-specific degradation of prednisolone/α-CD conjugates in the large intestine alleviated the side effects of the drug while maintaining its anti-inflammatory action[38].

Complexation of triamcinolone acetonide (TA) with β-CD improved the sphericity of microcrystalline cellulose (MCC)–β-CD-TA spherical pellets (5:90:5) prepared by extrusion and spheronization for colon targeting. TA complexation with the CD also facilitated the application of coating resistant to gastric and small intestinal media and maintained the pellet integrity in dissolution medium with no premature bursting of coatings on granule swelling[39]

Peptide and Protein Delivery

Various problems associated in practical use of therapeutic peptides and proteins are their chemical and enzymatic instability, poor absorption through biological membranes, rapid plasma clearance, peculiar dose response curves, and immunogenicity. CDs, because of their bioadaptability in pharmaceutical use and ability to interact with cellular membranes, can act as potential carriers for the delivery of proteins, peptides, and oligonucleotide drugs [40]

The existence of efflux pumps may serve as an additional barrier for nonspecific uptake of peptides and thus can cause low peptide bioavailability. P-glycoprotein (P-gp) is an efflux transporter present in the apical region of epithelial cells in the brain, kidney, liver, and GI tract. P-gp opposes the transcellular drug movement in the epithelial cells and many peptide drugs, especially hydrophobic peptides like cyclosporin A D, N-acetyl-leucyl-leucylnorleucinal, valinomycin, gramicidin, and ditekiren are reported to be substrates for this efflux transporter. Therapeutic use of peptides across the blood brain barrier (BBB) is greatly hindered by their very low penetration and it was reported that P-gp substrates, such as synthetic hydrophobic peptides, can stimulate the transport of drugs across the BBB. An apically polarized verapamil sensitive efflux system for small hydrophobic peptides has been found in the BBB of rats.[41]

It was found that CDs can inhibit or impair the efflux function of P-gp and multidrug resistance associated proteins (MRP2). Out of various β-CD derivatives studied, DM-β-CD was found to be most effective and significantly impaired the efflux function of P-gp and MRP2 in Caco cell monolayers (Caco2, Caco-2R) without changing the cell viability and membrane integrity. The inclusion ability of DM-β-CD, causing the release of the transporters (P-gp, MRP2) from the apical membranes of monolayers, was reported to be the possible reason for the observed impaired efflux function of the transporters in the presence of the CD. Not only the extraction of cholesterol but also that of phospholipids from the monolayers were found to

be required for the CD-induced inhibitory effect on the efflux function[42]. In addition to the solubilizing effect of DM-β-CD, its ability to inhibit P-gp efflux of tacrolimus from intestinal epithelial cells contributed to the CD-induced enhancement of the drug's oral bioavailability. Pretreatment of the apical membranes of the Caco cell monolayers with DM-β-CD decreased the efflux of tacrolimus and rhodamine with no associated cytotoxicity. DM-β-CD also decreased the level of P-gp in the apical membranes of the monolayers probably by allowing its release from the apical membranes into the transport buffer. β-CD or DM-β-CD reduced the serious nasal toxicity of sodiumdeoxycholate (a bile salt) by inhibiting the leucine aminopeptidase activity in the nasal mucosa without affecting the absorption-enhancing property of the bile salt for insulin. [43].

CDs were found to be useful in the absorption enhancement of calcitonin, glucagon, insulin, and recombinant human granulocyte colony-stimulating factor. DM-β-CD (5%) enhanced the intranasal calcitonin absorption in rats and rabbits. In rabbits, a nasal spray of liquid and powder formulations of glucagons containing DM-β-CD provided improved bioavailability (> 80%) of glucagons compared with their subcutaneous administration. The absolute bioavailability of insulin in rats was also increased to ~100% on nasal administration with DM-β-CD (3% to 5%). β-CD improved insulin loading of alginate microspheres prepared by an emulsion-based process. The process was suggested to be useful in the development of an oral insulin drug delivery system as the absorption of insulin from optimized microspheres was found to take place from the GI region[44]

Gene and Oligonucleotide Delivery

The toxicity and immunogenicity associated with viral vectors led to the development of nonviral vectors for gene delivery. Besides the plasmid or virus-based vector systems, "naked" nucleotide derivatives have also been investigated for possible use as therapeutic agents through several routes of administration. Gene delivery technologists are now testing CD molecules in the hope of finding an optimal carrier for the delivery

of therapeutic nucleic acids, however, the limitations of CDs, such as CD-associated toxicity (eg, DM-β-CD) have to be considered before their clinical use[45].

CDs can solve many of the problems associated with in vivo delivery of oligonucleotides (Ons), such as their limited ability to extravasate from blood stream and traverse cellular membranes, high degree of susceptibility to endonucleases with potential toxicity of their breakdown products, polyanionic nature leading to nonspecific interactions with extracellular and intracellular cationic molecules, and potential immunogenicity. CDs can improve cellular uptake of ONs and also delay their degradation by increasing their stability against endonucleases. ON-adamatane conjugates associated with HP-β-CD provided significantly increased cellular uptake of ONs. Substitution of at least a single nucleotide of ONs with CDs improved the cellular uptake and/or stability of ONs. On conjugation with CDs, ONs may be delivered to the colon, an advantageous absorption site to achieve acceptable therapeutic levels of ONs. CDs can also modulate undesirable side effects of ON treatment such as immune stimulation and reduction of platelet counts[46-47].

Neutral and amphipilic as well as cationic CDs have been used for synthesis of novel gene delivery vectors. Neutral CDs like β-, DM-β-, and HP-β-CDs were reported to increase DNA cellular uptake by increasing its permeability. The increased DNA permeability was reported to be a result of interaction of the CDs with membrane components such as cholesterol, but not due to their complexing ability for DNA. Cationic polyamino CDs, because of their polycationic polyanionic interaction with mononucleotides, neutralized the multiple charges on DNA and thus made DNA compact into a particle of suitable size for cellular internalization. Amphiphilic CDs, because of their vesicle-forming potential, offer an additional possibility for polar nucleotides to complex into aqueous vesicle core while allowing hydrophobic agents to complex into individual cavities or interior of the bilayer with multiple lipophilic hydrocarbon chains.[82]Polyplexes (polycation polymer/DNA composite structures) of linear, cationic, β-CD–containing

polymers (βCDPs) were found to be suitable for DNA delivery due to their increased transfection efficiency and stability against enzymatic degradation with low in vitro and in vivo toxicity. The ability of CDs to complex hydrophobic adamantane was exploited for steric stabilization of βCDPs with hydrophilic polymers like poly(ethylene glycol). Steric stabilization of βCDPs prevents their self-aggregation but facilitates their targeted delivery by preventing their undesired interactions with non–self-entities[48].

CDs were also found to enhance plasmid or viral-vector–based delivery of genes. Positively charged quarternary amino and tertiary amino β-CDs significantly enhanced the transfection efficiency of negatively charged adenoviral vector-based gene formulations. It was reported that the transfection enhancement by the cationic β-CDs could be a result of increased viral internalization caused by increased viral binding to cell and improved cell membrane permeability. CDs also enhanced the physical stability of viral vector formulations for gene therapy[49]

Dermal and Transdermal Delivery

Cyclodextrins have a significant safety margin in dermal application and can be used to optimize the transdermal delivery of drugs intended either for local or systemic use. They also improves the solubility and stability of drugs in the topical preparations, enhances the transdermal absorption of drugs, sustains the drug release from the vehicle and avoids undesirable side effects associated with dermally applied drugs. The main barrier for dermal drug absorption through the skin is the outer most layer stratum corneum. Penetration enhancers like alcohols, fatty acids etc. are used to decrease its barrier properties. The cyclodextrins enhance drug delivery through aqueous diffusion barriers, but not through lipophilic barriers like stratum corneum. A suitable vehicle must be selected so that cyclodextrins fully exert their functions. If the drug release is from an aqueous based vehicle or if an aqueous diffusion layer at outer surface of skin is a rate determining factor, then cyclodextrins can acts as penetration enhancers. But if drug penetration through the lipophilic stratum

corneum is the main rate determining factor then cyclodextrins are unable to enhance the drug delivery. For instance, the in vitro release rate of corticosteroids from water-containing ointments is markedly increased by hydrophilic cyclodextrins, whereas in other ointments the cyclodextrins retard the drug release. The enhancement of drug release can be described to an increase in solubility, diffusibility and concentration of the drug in the aqueous phase of the ointment through water-soluble complex formation. In ointments, as with suppositories, the drug in its cyclodextrin complex may be displaced by some components of the ointment, depending on the magnitude of the stability constant of the complex. Thus, an optimized release of the drug from the preparation containing its cyclodextrin complex may be obtained by using a vehicle in which the complex is barely dissociated and maintains a high thermodynamic activity. Generally, cyclodextrins do not enhance drug delivery from non aqueous vehicles. Cyclodextrins have also been used to reduce permeability of compounds into skin.It has been indicated that complexation of sunscreen enhances its photo protective effects by preventing permeation of the sunlight into the skin[50].

Brain Drug Delivery or Brain Targetting

The concept of Bodor's chemical delivery system (CDS) (ie, covalent coupling of drugs to 1-methyl-1, 4-dihydronicotinic acid through an enzymatically labile linkage, which increases drug lipophilicity) was applied for targeting drugs such as steroids, antitumor agents, and calcium channel antagonists to brain. However, presence of the lipophilic moiety makes prodrugs of CDS poorly water-soluble. HP-β-CD, due to its ability to solubilize drugs and also to enhance the chemical stability of dihydronicotinic acid in aqueous solution solved the solubility problems of CDS. Formulation is an important and integral concern in the development of CDS, especially those for brain targeting. Formulation development of CDS is based on the need for appropriate dosage form, stability, solubility, and dissolution characteristics. Brewster and Loftsson discussed the use of chemically modified, especially water-soluble, CD derivatives such as HP-β-CD in the formulation

development of CDS. HP-β-CD contributed to the development and preclinical testing of several CDS by providing a stable and water-soluble dosage form suitable for parenteral administration. Use of CDs in the formulation of CDS can be demonstrated by the significantly improved solubility, stability, and pharmacologic activity of CDS of thyrotropin-releasing hormone analogs on complexation with HP-β-CD[51].

The very low penetration across the BBB greatly hinders the therapeutic use of peptides, and whenever unexplainable poor peptide absorption is seen the role of the efflux pumps should be examined. It was reported that P-gp–mediated peptide transport may play an important role in greatly reducing the peptide delivery to the central nervous system in vivo. It was also indicated that CDs such as DM-β-CD, due to their inhibitory effect on P-gp efflux function, may enhance drug delivery to brain[43].

CD Applications in the Design of Some Novel Delivery Systems

Liposomes

In drug delivery, the concept of entrapping CD-drug complexes into liposomes 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. Liposomes entrap hydrophilic drugs in the aqueous phase and hydrophobic drugs in the lipid bilayers and retain drugs en route to their destination. The fact that some lipophilic drugs may interfere with bilayer formation and stability limits the range and amount of valuable drugs that can be associated with liposomes. 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 (ie, 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[52-55].

Complexation with CDs can improve the stability of liposomes, eg, most stable liposomal formulations of metronidazole and verapamil were obtained by direct spray drying of lipid, drug, and HP-β-CD mixture.[101] 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. Similarly, multilamellar liposomes containing indomethacin/HP-β-CD inclusion complex showed increased stability of the hydrolysable drug (~75-fold) [56].

Parent CDs (α-, β-, and γ-) 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[57].

Microspheres

In the presence of a high percentage of highly soluble hydrophilic excipients, complexation may not improve the drug dissolution rate from microspheres. Nifedipine release from chitosan microspheres was slowed down on complexation with HP-β-CD in spite of the improved drug-loading efficiency. Since it is highly unlikely for CD molecules to diffuse out of the microspheres, even with a low stability constant, the complex must first release the free drug that can permeate out of the microspheres. Hence the observed slow nifedipine release from the microspheres was reported to be due 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[58].Sustained hydrocortisone release with no enhancement of its dissolution rate was observed from chitosan microspheres containing its HP-β-CD complex. The sustained hydrocortisone release was reported to be due to formation of a layer adjacent to the interface by the slowly dissolving drug during the dissolution process that makes the microsphere surface increasingly hydrophobic[59].

Study of in vivo release behavior (over 24 hours) of β-CD from β-CD/poly (acrylic acid) (PAA) microspheres, prepared by a water/oil solvent evaporation technique, indicated a high encapsulating efficiency (>90%) with potential covalent binding of the CD[60]. β-CD caused no alteration of the in vitro release kinetics of dyes, phenolphthalein, and rhodamine B (with different solubilities and strengths of association with β-CD) from the microspheres. The reasons suggested for the unaltered release kinetics were rapid hydration of the polymer matrix because of limited cross-linking; perturbation of dye/β-CD complex by oil, organic solvent residues and/or conformational changes; and reduction of β-CD complexing ability on covalent binding with PAA due to steric hindrance of its cavity[61].

Microcapsules

It was suggested that 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 were found to complex 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 through dialysis membrane. Double microcapsules, prepared by encapsulating methylene blue with different amounts of β-CD microcapsules inside a crosslinked human serum albumin (HSA), showed decreasing release rate of methylene blue with increasing amount of β-CD microcapsules. Dissociation of methylene blue complex with β-CD microcapsules was found to serve as an additional mechanism in controlling the release kinetics of HSA double microcapsules. In the case of HSA microcapsules with parent β-CD, the hydrating property of the CD, by promoting the diffusion of water into the microcapsules, caused an increased release rate of methylene blue compared with those without the CD. However, in the case of HSA double microcapsules (ie, with β-CD microcapsules), the hydrophobic groups introduced during crosslinking suppressed the CD hydration and

provided controlled release without enhancing the diffusion of water that can impair the complexation of methylene blue[62]

Nanoparticles

Nanoparticles are stable systems suitable to provide targeted drug delivery and to enhance the efficacy and bioavailability of poorly soluble drugs. However, the safety and efficacy of nanoparticles are limited by their very low drug loading and limited entrapment efficiency (with classical water emulsion polymerization procedures) that may lead to excessive administration of polymeric material[62-63]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.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[63-64].HP-β-CD increased saquinavir loading into poly (alkylcyanoacrylate) nanoparticles by providing a soluble drug reservoir in polymerization medium that feeds the nanoparticle-formation process. A dynamic equilibrium was observed between the complex, the dissociated species, and the forming polymeric particle. It was indicated that during nanoparticle formation the free drug gets progressively incorporated into polymer network, driven by the drug partition coefficient between the polymer and polymerization medium though there may be a simultaneous direct entrapment of some drug/CD complex[64-65]

CONCLUSIONS

Cyclodextrins are useful functional excipients that have enjoyed widespread attention and use in the pharmaceutical industry. Studies in both humans and animals have shown that cyclodextrins can be used to

improve the drug delivery from almost any type of drug Formulations.The bioadaptability and multi-functional characteristics of cyclodextrins, makes them capable of alleviating the undesirable properties of drug molecules in various routes of administration through the formation of inclusion complexes. The knowledge of different factors that can influence complex formation inorder to prepare economically drug/cyclodextrin complexes with desirable properties are necessary. However, additions of cyclodextrins to existing formulations without further optimization will seldom result in acceptable outcome. This review outlines the current application of natural and chemically modified CD in the design of advanced dosage forms. Since CD are able to extend the function of pharmaceutical additives, the combination of molecular encapsulation with other carrier materials will become effective and a valuable tool in the improvement of drug formulation. Moreover, the most desirable attribute for the drug carrier is its ability to deliver a drug to a targeted site. The conjugates of a drug with CD can be a versatile means of constructing a new class of novel drug delivery systems like liposome, microspheres, osmotic pump, peptide delivery, and nanoparticle.

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