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Review Article

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CURRENT TRENDS IN β-CYCLODEXTRIN BASED DRUG DELIVERY SYSTEMS

Lala Rita*, Thorat Amit, Gargote Chandrashekhar
Prin. K. M. Kundnani College of Pharmacy, Department of Pharmaceutics, Plot No 23, Jote Joy Building, Rambhau Salgaonkar Marg, Cuffe Parade, Colaba, Mumbai-400005, India

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***Corresponding author**
Email: r_r_lala@yahoo.co.in

ABSTRACT
Many compounds identified through various screening programs are poorly soluble in the water. These molecules are difficult to formulate using the conventional formulation approaches. An important tool in this regard is the use of cyclodextrins, especially 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, which leads to additional benefits such as increased solubility, increased bioavaibility, protection of active molecules from physicochemical degradation and decreased side-effects. This review aims to assess the use of cyclodextrins in newer drug delivery systems such as nanosponges, nanoparticles, nanospheres, nanoassemblies, drug-in cyclodextrin-in deformable liposomes and other drug delivery systems. These approaches are useful for resolving many of the current issues associated with developing and commercializing poorly water soluble drugs.
Keywords: β-cyclodextrin, comlpexation, nanosponges, nanoparticles, nanospheres, nanoassemblies, drug-in cyclodextrin-in deformable liposomes

INTRODUCTION

Cyclodextrins (CDs) are cyclic compounds consisting of six to eight glucose units, which are termed α-, β-, and γ-CD, respectively[1]. These cyclic oligosaccharides consist of (α-1,4)- linked α-D-glucopyranose units and contain a somewhat lipophilic central cavity and a hydrophilic outer surface. Because of the chair conformation of the glucopyranose units, the cyclodextrins are shaped like a truncated cone rather than perfect cylinders. The hydroxyl functions are orientated to the cone exterior with the primary hydroxyl groups of the sugar residues at the narrow edge of the cone and the secondary hydroxyl groups at the wider edge. The central cavity is lined by the skeletal carbon and ethereal oxygen atoms of the glucose residues, which gives it a lipophilic character[2,3,4].

About 30 different pharmaceutical products containing CDs are now on the market worldwide (Table 1). In the pharmaceutical industry CDs have mainly been used as complexing agents to increase the aqueous solubility of poorly water-soluble drugs and to increase their bioavailability and stability. In addition CDs can be used to reduce or prevent gastrointestinal and ocular irritation, reduce or eliminate unpleasant smells or tastes, prevent drug-drug or drug-additive interactions, or to convert oils and liquid drugs into microcrystalline or amorphous powders[2,5]. The regulatory status of CDs is evolving. α-CD and β-CD are listed in a number of pharmacopeia sources including the US Pharmacopeia, European Pharmacopoeia and Japanese Pharmacopoeia. γ-CD will soon be included in the US Pharmacopeia and subsequently in the European Pharmacopoeia as well. A monograph for 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) has recently been published in both the European Pharmacopoeia (Ph. Eur. 5th Ed.) and in the US Pharmacopoeia (USP28/NF23). Other derivatives are not yet compendial but efforts are underway for their inclusion. β-CD and γ-CD are also listed in the generally regarded-as-safe list of the US FDA for use as a food additive. CDs are relatively new from a regulatory point of view and policies on their use are still not standardized. Consensus seems to be building among regulators that CDs are excipients and not part of the drug substance, although various opinions have been given and interpretation related to this point can be division- and product-specific.

β-cyclodextrin complexation mechanisms and applications

CDs are able to form dynamic molecular inclusion complexes with many drugs by incorporating the drug molecule, or more commonly a lipophilic moiety of the molecule, into the central cavity. No covalent bonds are formed or broken during the drug/cyclodextrin complex formation. The driving forces leading to the inclusion complex formation include release of enthalpy rich water molecules from the cavity, electrostatic interactions, van der Waals interactions, hydrophobic interactions, hydrogen bonding, release of conformational strains, and charge-transfer interaction[2,6,7]. All these forces are relatively weak, allowing free drug molecules in solution to be in rapid equilibrium with drug molecules bound within the cyclodextrin cavity[3].

Most drug molecules (D) form 1:1 complexes with cyclodextrin molecules (CD) and the value of the stability constant (K 1:1) is most often between 50 and 2000 mol^{-1} with a mean value of 129, 490 and 355 mol^{-1} for α-, β-, and γ-CDs, respectively[3,8,9,10].

$$D + CD \underset{}{\overset{K1:1}{\rightleftharpoons}} D/CD\ Complex$$

$$K_{1:1} = [D/CD] / [D].[CD]$$

This is a somewhat oversimplified description of a much more complex mechanism[11,12] but is sufficient to explain the role of cyclodextrins in the oral drug delivery. In a given aqueous complexation medium, saturated with the drug, the concentration of free drug ([D]) is constant and equal to the apparent intrinsic solubility of the drug in the aqueous medium (i.e. drug solubility in absence of cyclodextrin). CDs encapsulation of a drug will change the drug's physicochemical properties, such as its aqueous solubility and chemical stability. The CD forms a hydrophilic shield around the applicable lipophilic moiety of the drug molecule. This will, in general, increase the apparent aqueous solubility of the drug. The CDs can also protect chemically labile drug molecules from potentially corrosive environments and, in this way, reduce or even prevent drug hydrolysis, oxidation, racemisation and enzymatic decomposition[2,13].

CDs have found numerous applications in many fields due to their ability to complex with a wide range of compounds[14] (Table 2). It has recently been reported that, by reacting CDs with suitable cross-linking agents, a novel nanostructure material consisting of hyper-cross-liked CDs can be obtained; these are known as nanosponges[15,16,17]. This composite material shows interesting characteristics; in particular, cyclodextrin-based nanosponges are characterized by their marked capacity to encapsulate a great variety of substances that can be transported through aqueous media[18,19].

Nano-sized colloidal carriers have recently been developed and proposed for drug delivery, since their use can solubilize poorly water-soluble drugs and provide prolonged release, as well as improving a drug's bioavailability and in some cases modifying its pharmacokinetic parameters. They can also decrease side-effects and protect drugs from degradation. Among colloidal carriers, liposomes, microparticles and nanoparticles have in particular been described as a new technological approach to drug administration. CDs and their derivatives have been used as solubilizers to enhance the loading capacity of liposomes, microparticles and nanoparticles[20]. Entrapment of CDs inclusion complexes in liposomes[21] increases the drug-to-lipid mass ratio and enlarges the number of insoluble drugs that can be incorporated. Solid lipid nanoparticles (SLN) have since been prepared as carriers of drug complexes of β-CD, and have shown good loading capacity and slower drug release[22]. Polymeric nanoparticles containing CDs nanoparticles of poly (butylcyanoacrylate) have been prepared in the presence of CDs[23], and modified cyclodextrins have been used as matrices to obtain nanoparticulate systems[24].

β-CDs have been the most widely used of all the CDs[25,26,9]. It is also reported that of all the potentially useful polymers in drug delivery systems naturally occurring polysaccharides appear an attractive alternative due to low cost, high biodegradability and biocompatibility[27].

NANOSPONGES

Briefly, Nanosponges can be obtained by cross-linking different types of CDs with a carbonyl or a dicarboxylate compound as cross-linker. They are solid particles with a spherical morphology that have been reported to have a very high solubilizing power for poorly soluble molecules[28], and they are proposed to form inclusion and non-inclusion complexes with different drugs. The CDs cross-linker ratio can be varied during preparation to improve the drug loading and to obtain a tailored release profile[18,19,29].

Two main features of the new type of nanosponges are the microscopic and almost spherical shape of the particles and the polarity of the mesh, which can be tuned through the degree of cross-linking, type of cross-linker and reaction conditions[30].

Synthesis of nanosponges

β-CD nanosponges were prepared as reported in the patent by Trotta and Tumiatti[17]. Briefly, 100 ml of anhydrous DMF was placed in a round bottom flask and 17.42 g of anhydrous β-cyclodextrin (15.34 mmol) was added to achieve complete dissolution. Then 9.96 g of carbonyldiimidazole (61.42 mmol) was added and the solution allowed reacting for 4 h at 100 °. Once condensation polymerization was completed, the transparent block of hyper-cross-linked cyclodextrin was roughly ground and an excess of deionized water added to remove DMF. Finally, residual by-products or unreacted reagents were completely removed by Soxhlet extraction with ethanol.

The white powder thus obtained was dried overnight in an oven at 60 ° and subsequently ground in a mortar. The fine powder obtained was dispersed in water. The colloidal part that remained suspended in water was recovered and lyophilized. The nanosponges recovered are sub-micron in dimension and with a spherical shape.

The synthetic procedure can also be carried out using ultrasound and diphenylcarbonate or pyromellitic anhydride as cross-linker. An amount of anhydrous cyclodextrin was put to react in melted diphenylcarbonate at 90 ° for at least 5 h. Then, the solid was ground in a mortar and Soxhlet extracted with ethanol to remove either impurities or unreacted diphenylcarbonate. After purification, nanosponges were stored at 25 ° until further use.

Preparation of drug loaded β-cyclodextrin nanosponges

Nanosponges for drug delivery were pre-treated to obtain a nanoparticle population with mean size below 500nm. The nanosponges were suspended in water and sonicated to avoid the presence of aggregates and then centrifuged to obtain the colloidal fraction. The supernatant was separated and freeze-dried. Drug-loaded nanosponges were generally prepared by the freeze-drying method; each type of nanosponge tested was mixed with powdered drug and suspended in distilled water. The suspensions were stirred for at least 24 h and then centrifuged at 2500 g for 5 min; undissolved drug was precipitated while drug loaded nanosponges remained in the supernatant. The supernatant was freeze-dried to obtain drug-loaded nanosponges as a free flowing powder[30].

Trotta and Roberta[30] performed phase solubility studies to determine the nanosponge drug solubilization efficiency; drug concentration was determined by HPLC. To evaluate encapsulation efficiency, various drugs with different structures were tested; dexamethasone was taken as model molecule for this study. In vitro release experiments were carried out using the dialysis bag technique (dialysis membrane cut-off 3500 Da) to determine the release kinetics of dexamethasone from the nanosponges. Nanosponges were able to complex dexamethasone, thus increasing its aqueous solubility. The results of loading experiments showed that nanosponges may be used as drug carriers for dexamethasone. The percentage of loaded drug was about 35 % w/w; drug-loading and drug release varied with the degree of cross-linking.

Roberta Cavalli *et al.*[18] found that nanosponges may be used as drug carriers. Due to their structure they can include either lipophilic drugs (e.g. dexamethasone or flurbiprofen) or hydrophilic drugs (e.g. doxorubicin) showing good solubilization capacity. They particularly improved the aqueous solubility of the lipophilic drugs: the percentage incorporated was about 15 wt%, whereas it was only 4 wt% for doxorubicin hydrochloride. This different behavior could be ascribed to the higher number of lipophilic sites available for the complexation of lipophilic drugs in comparison with the hydrophilic sites. The nanosponges drug interaction was confirmed by DSC analyses, since the thermograms did not contain the drug's melting peak. It was speculated that the drugs might be molecularly dispersed in the nanosponges, the lipophilic molecules preferably in the cyclodextrin hydrophobic cavities and the hydrophilic molecules completely or partially in the surrounding network.

Swaminathan *et al.*[31] found that for the crystalline nanosponges camptothecin was loaded in the highest amount in higher cross-linker concentration as much as 37 %w/w. The different camptothecin loading showed that the degree of cross-linking affected the complexation ability of nanosponges. It might be supposed that, the lower amount of cross-linker formed a network with an uncompleted cyclodextrin cross-linking and with decreased sites for the drug complexation; thus, camptothecin might not be included in higher amount in these types of nanosponges. While higher amount of cross-linker might provide a high cross-linking of β-CDs, and consequently a part of camptothecin interaction with β-CDs cavities might be hindered[31].

NANOPARTICLES

The potential of nanoparticles as drug delivery systems have been extensively investigated in recent years. They could provide a means of modifying the distribution of an active substance in vivo and of increasing its concentration in the target tissue, thereby improving efficacy and reducing toxicity[32,33,34]. For these applications, the nanoparticles must not only be composed of a biodegradable and biocompatible polymer but also have a strictly controlled diameter and size distribution, particularly for intravenous administration[35,32]. Indeed, the diameter of drug carriers is a crucial parameter determining the extent and rate at which they are removed from the circulation and their biodistribution[36,37]. Particle size also affects drug loading and release. Numerous methods for the manufacture of polymer nanoparticles have been described[38,39,40]. Monoolein (MO)

cubic phases entrapping HP-β-CD/minoxidil (MXD) complex were prepared by hydrating molten MO with the complex solution[41].

Sharma and Sajeesh[42] developed an oral insulin delivery system based on HP-β-CD–insulin complex encapsulated polymethacrylic acid-chitosan-polyether (polyethylene glycol-polypropylene glycol copolymer) (PMCP) nanoparticles. Nanoparticles were prepared by the free radical polymerization of methacrylic acid in presence of chitosan and polyether in a solvent/surfactant free medium. CDs complexation represents a unique and effective strategy for improving the protein therapy by stabilizing them against aggregation, thermal denaturation and degradation. Hydrophilic β-CD inhibits the adsorption of insulin to hydrophobic surfaces and prevents self-aggregating of insulin at neutral pH[43]. Proteins are mostly hydrophilic and too bulky to be wholly included into a β-CD cavity. Hydrophobic side chains in the peptides penetrate into the β-CD cavity leading to the formation non-covalent inclusion complexes and CDs ability to sequester hydrophobic moieties helps in improving the stability of proteins[4]. CDs complexation perturbs the membrane fluidity to lower the barrier function and this may enhance the absorption of drugs across the biological barriers[44]. However clinical exploitation of CDs based systems has been restricted mainly due to safety concerns. Oral administration of β-CD based systems raises minimal safety concerns since they are poorly absorbed from GI tract. β-CD complexed insulin encapsulated mucoadhesive microparticles seem to be a promising system for improving oral insulin delivery [45,46].

Amphiphilic cyclodextrins are chemically obtained derivatives of natural CDs modified on the primary and/or secondary face with aliphatic chains of varying length (C2 to C18) and structure (linear or branched) linked with different chemical bonds including ester, ether, thiol or amide bonds[47].These derivatives have been used in the last decade to prepare nanospheres and nanocapsules with high drug loading properties that do not require the presence of a surfactant[47, 48,23]. In fact, nanospheres and nanocapsules may be prepared directly from the pre-formed inclusion complexes of drugs with amphiphilic cyclodextrins which ensures high loading and delaying of burst effect[49, 50, 51].

The potential use of nanoparticles made of amphiphilic cyclodextrins as drug carriers has been exploited with success to reduce the toxic side effects of several drugs, thus improving their therapeutic indices[52] and amphiphilic cyclodextrin nanospheres present no toxic reactions[47]. Furthermore, the preferential uptake of nanospheres by liver macrophages opens up important therapeutic perspectives in the particular case of hepatic abscess. A colloidal carrier system prepared from modified cyclodextrins was described[49]. These nanospheres have been characterized and visualized by freeze-fracture electron microscopy[53]. The self-assembling structural properties of several amphiphilic cyclodextrins and the internal organization of the amphiphilic cyclodextrin nanospheres have been described by Gulik *et al*.[54].

Recently, microparticles based on CDs were synthesized as pharmaceutical materials by cross-linking with terephthaloyl chloride[55], epichlorohydrin[56] and glutaraldehyde[57]. The attractive property of CDs is not only inclusion complexation with guest molecules but with also many hydroxyl groups of the glucose units, whose numbers are 18, 21 and 24 for α-, β-, and γ-CD, respectively. Modification of the hydroxyl groups of CD is expected to affect the capability of molecular recognition. In fact, methylation or hydroxyalkylation of the hydroxyl groups of CDs improved their solubility and stabilized their inclusion complexes with guest molecules[58]. Ooya *et al*. introduced carboxyl groups[59] and amino groups[60] via the hydroxyl groups of α-CD to functionalize polyrotaxane.

By combining these two technologies, namely, cross-linking and modification of hydroxyl groups, they have designed a novel functional nanoparticle based on β-CD, aiming at creating a new material of nanobiotechnology. Nanoparticles have been prepared by an interfacial polyaddition between aminoethylcarbamoyl-β-CD (AEC-β-CD) and ethylene glycol diglycidyl ether (EGDGE)[61].

NANOASSEMBLY

Nano-systems assembled by macromolecular amphiphiles have attracted great attention due to their wide applications in areas such as pharmaceutics, bioengineering, medical diagnosis and genetherapy[62-65]. Polymeric micelles with core–shell architecture are among the most widely studied nanocarriers for the delivery of hydrophobic therapeutics. Generally, polymeric micelles with hydrophobic cores are assembled in an aqueous solution due to the hydrophobic interaction between the core-forming segments. The hydrophobic inner core serves as a nanocontainer for hydrophobic drugs, while the outer shell of hydrophilic polymers, such as polyethylene glycol (PEG), provides the micelles with colloidal stability and extends the circulation time in the blood stream after their systemic administration. Until now, most of the polymeric micelles with hydrophobic cores have been constructed using amphiphilic copolymers with block, graft, comb, branch or dendritic architecture[66,67] in which the hydrophobic block/graft segments or groups were covalently linked with the hydrophilic segments. In addition, micelle-like nano-assemblies based on polyelectrolyte complex have been developed as delivery carriers. These assemblies are constructed by the complexation of double hydrophilic block copolymers containing ionic and nonionic blocks with oppositely charged molecules such as polyelectrolytes, proteins, surfactants, or metal ions. These novel nano-vehicles are now widely used for the delivery of genes, proteins, low molecular weight drugs and imaging agents[68,69,70].

More recently, the host–guest interactions between host and guest molecules have been adopted to assemble polymer nanoparticles for drug/gene delivery. Due to their excellent biocompatibility, CDs including α-CD, β-CD and γ-CD, have been widely used as host units to construct host–guest delivery carriers. For instance, excellent in vivo therapeutic efficacy has been observed for nanoparticles assembled from camptothecin-conjugated β-CD polymers[71]. On the other hand, cationic β-CD polymers derived nanoparticles were found to be efficient non-viral delivery vectors for siRNA in humans[72]. Additionally, α-CD based polyrotaxanes have also been employed a delivery carriers[73,74,75]. To the best of our knowledge, fewer efforts have been made to fabricate host–guest assemblies based on a double hydrophilic copolymer and small molecules, in which inclusion interaction is the main driving force.

A good example for nanoassemble drug delivery system is of meglumine antimoniate (MA) for treatment of leishmaniasis[76]. It was reported previously that the association of MA with β-CD enhances the absorption of Sb by oral route and renders MA orally active in a murine model of cutaneous leishmaniasis[77]. Progress was recently achieved towards the understanding of the mode of action of the MA/β-CD composition[78]. The unexpected behaviour of the MA/β-CD composition was attributed, in part, to the physicochemical properties of MA in aqueous solution. MA consists of a mixture of oligomeric structures with the general formula (NMG–Sb)n, (NMG–Sb)n–NMG and (Sb–NMG)n–Sb, where NMG represents N-methyl-d-glucamine[79]. It was found that the first step of preparation of the MA/β-CD composition, which consists in heating of an equimolar mixture of MA and β-CD at 55° for 48h, induces the dissociation of MA from high-molecular weight Sb complexes into 1:1 Sb–NMG complex. Furthermore, the observation that MA, after heating, was more effectively absorbed by the oral route led to propose that the dissociation of MA may contribute to the enhanced absorption of Sb promoted by the MA/β-CD composition[78]. However, the serum Sb levels achieved after heated MA were still significantly lower than those achieved after MA/β-CD composition,

indicating that additional factors related to specific interactions of MA with β-CD should be involved in the mode of action of MA/β-CD. The characterization of the heated MA+β-CD mixture, using circular dichroism and electrospray ionization mass spectrometry (ESI-MS), indicated the formation of a ternary NMG–Sb–-CD complex which may also contribute to the enhanced oral absorption[78]. As the second step of preparation of the MA/β-CD composition consists of freeze-drying of the heated MA+β-CD mixture, the freeze-drying step may promote additional interactions. However, it should be investigated to which extent each step (heating and freeze-drying) contributes to the enhanced Sb absorption by oral route and how the induced interactions mediate such an effect. In the present work, the interactions between MA and β-CD induced by heating and freeze-drying were investigated using CD, 1H NMR, ESI-MS and photon correlation spectroscopy and their impact on Sb absorption by oral route was evaluated. Importantly, the freeze-drying process was found to generate supramolecular nanoassemblies which contributed most significantly to the enhanced Sb absorption by oral route. Upon dilution, MA/β-CD composition was found to act as a sustained release system for MA.

DRUG-IN CYCLODEXTRIN-IN DEFORMABLE LIPOSOMES

A new delivery system for cutaneous administration combining the advantages of CDs inclusion complexes and those of deformable liposomes was developed, leading to a new concept: drug-in cyclodextrin-in-deformable liposomes. Deformable liposomes made of soybean phosphatidylcholine (PC) or dimyristoylphosphatidylcholine (DMPC) and sodium deoxycholate as edge activator were compared to classical non-deformable liposomes. Recently, it became evident that, in most cases, classical liposomes are of little or no value as carriers for transdermal drug delivery as they do not penetrate skin deeply, but rather remain confined to upper layers of the stratum corneum[80]. In order to target deeper underlying skin tissue, intensive research led to the introduction and development of a new class of lipid vesicles, the highly deformable (elastic or ultraflexible) liposomes, which have been called Transfersomes®[81]. Several studies have reported that deformable liposomes are able to improve in vitro skin delivery of various drugs[82].

The important difference between deformable liposomes and traditional liposomes is the high and stress-dependent adaptability of such deformable vesicles, which enables them to squeeze alone between the cells in the stratum corneum, despite the large average vesicle size[83]. Thus, they can pass through the intact skin spontaneously, under the influence of the naturally occurring, in vivo transcutaneous hydration gradient[84]. These vesicles consist of phospholipids and an edge activator. An edge activator is often a single chain surfactant, with a high radius of curvature, which destabilizes lipid bilayers of the vesicles and increases their deformability[80].

Liposomes are able to encapsulate hydrophilic drugs in their aqueous compartment, while lipophilic drugs are encapsulated in their lipid bilayer. However the accommodation of lipophilic compounds in the lipid phase can be problematic as some drugs can interfere with bilayer formation and stability. This accommodation is often limited in terms of drug to lipid mass ratio[85,86]. In the case of the encapsulation of betamethasone into liposomes, the use of CDs was shown to increase the drug to lipid mass ratio[87]. Entrapping water-soluble drug–cyclodextrin inclusion complexes in the aqueous compartment of liposomes has been proposed in order to avoid such drawbacks[85,86]. The entrapment of hydrophobic drugs in the aqueous core of liposomes as soluble inclusion complexes with CDs has been proposed as an interesting alternative to avoid the use of organic solvents, thus obtaining drug-in cyclodextrin-in liposome systems[85,88]. This approach can be useful to increase both drug solubility and stability[89] and better control the in vivo fate of poorly soluble drugs, avoiding the rapid release observed after conventional incorporation into the liposome lipid phase [85,88]. Moreover, complexation with CDs increases drug solubility and permeation across the skin, thus improving drug bioavailability through topical route[90,91]. The effectiveness of such a combined approach, which simultaneously exploits the CDs solubilizing power towards the drugs and the liposome carrier function through the skin, has been recently demonstrated by using both classic[92,86,93,94] and deformable[95] liposomes. Further advantages can be obtained by the use of a double-loading technique, i.e. by preparing liposomes loaded with the plain drug in the lipophilic phase and its cyclodextrin complex in the aqueous phase of the vesicles, so as to obtain both a fast onset action and a prolonged effect[96].

The liposomes were characterized for morphological properties using confocal laser scanning microscopy (CLSM), while their particle size, Zeta potential, and entrapment efficiency were determined by using, respectively, light scattering, and dialysis techniques.

CONCLUSION

β -cyclodextrin based drug delivery systems currently developed have shown a marked increase in drug loading capacity which is very important from a pharmaceutical point of view. They are also beneficial in improving the aqueous solubility of poorly water-soluble molecules, to protect degradable substances, to obtain sustained delivery systems or to design innovative drug carriers. From the standpoint of medical applications, the small sizes and spherical shape provides a variety of drug delivery systems to improve patient's compliance.

REFERENCES

1. Easton CJ, Lincoln SF. Modified Cyclodextrins: Scaffold and Templates for Supramolecular Chemistry. Imperial College Press, Imperial College, London;1999.
2. Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins:1. Drug solubilization and stabilization. J Pharm Sci 1996; 85(10):1017-25.
3. Stella VJ, Rajewski RA. Cyclodextrins: their future in drug formulation and delivery. Pharm Res 1997; 14(5):556-67.
4. Irie T, Uekama K. Cyclodextrins in peptide and protein delivery. Adv Drug Deliv Rev 1999; 36:101–123.
5. Uekama K. Recent aspects of pharmaceutical application of cyclodextrins. J Incl Phenom Macroc Chem 2002; 44:3-7.
6. Bergeron R. Cycloamylose-substrate binding. In: Attwood JL, Bavies JE, MacNicol DD, editors. Inclusion compounds. London: Academic Press; 1984. p. 391-443.
7. Liu L. Guo Q. The driving forces in the inclusion complexation of cyclodextrins. J Incl Phenom Macrocycl Chem 2002; 42:1-14.
8. Connors K. Population characteristics of cyclodextrin complex stabilities in aqueous solution. J Pharm Sci 1995; 84:843-848.
9. Connors K. The stability of cyclodextrin complexes in solution. Chem Rev 1997; 97:1325-57.
10. Rao M, Stella VJ. When can cyclodextrins be considered for solubilizing purposes?. J Pharm Sci 2003; 92:927-932.
11. Loftsson T, Magnusdottir A, Masson M. Self-association and cyclodextrin solubilization of drugs. J Pharm Sci 2002; 91:2307-2316.
12. Loftsson T, Masson M, Brewster M. Self-association of cyclodextrins and cyclodextrin complexes. J Pharm Sci 2004; 93:1091-1099.
13. Loftsson T. Effects of cyclodextrins on chemical stability of drugs in aqueous solutions. Drug Stability 1995; 1:22-33.
14. Martin Del Valle E.M. Cyclodextrins and their uses: a review. Proc Biochem 2004; 39:1033–1046.
15. Garcia-Zubiri X, Gonzales G, Isasi, J. Thermal stability of solid dispersions of naphatelene derivatives with β-cyclodextrin and β-cyclodextrin polymers. Termochim Acta 2006; 444:57–64.
16. Ma M. Li D. New organic nanoporous polymers and their inclusion complexes. Chem Mater 1999; 11:872–876.
17. Trotta F, Tumiatti W. Cross-linked polymers based on cyclodextrin for removing polluting agents. 2003; WO 03/085002.
18. Cavalli R, Trotta F, Tumiatti V. Cyclodextrin-based nanosponges for drug delivery. J Incl Phenom Macrocycl Chem 2006; 56:209–213.
19. Swaminathan S, Vavia P, Trotta F, Torne S. Formulation of betacyclodextrin based nanosponges of itraconazole. J Incl Phenom. Macrocycl Chem 2007; 57:89–94.

20. Duchene D, Ponchel G, Wouassindjewe D. Cyclodextrins in targeting. Application to nanoparticles. Adv Drug Del Rev 1999; 36:29.
21. McCormack B, Gregoriadis G. Drug-in–cyclodextrins liposomes: An approach to controlling the fate of water insoluble drugs in vivo. Int J Pharm 1998; 162:59 -69.
22. Cavalli R, Peira E, Caputo O, Gasco, M. Solid lipid nanoparticles as carriers of hydrocortisone and progesterone complexes with β-cyclodextrins. Int J Pharm 1998; 182:59.
23. Silveira A, Ponchel G, Puisieux F, Duchène D. Combined poly(isobutyl cyanoacrilate)/cyclodextrins for enhanced the encapsulation of lipophilic drugs. Pharm Res 1998; 15:1051-1055.
24. Dubes A, Parrot-Lopez H, Abdelwahed W, Degobert G, Fessi H, Shahgaldian P, *et al*. Scanning electron microscopy and atomic force microscopy imaging of solid lipid nanoparticles derived from amphiphilic cyclodextrins. Eur J Pharm Biopharm. 2003; 55 (3):279– 282.
25. Zejtli J. Introduction and general overview of cyclodextrin chemistry. Chem Rev 1998; 98: 1743–1754.
26. Rekharsky M, Inove Y. Complexation thermodynamics of cyclodextrins. Chem Rev 1998; 98:1875–1918.
27. Rossi S, Ferrari F, Bonferoni M, Caramella C. Characterization of chitosan hydrochloride–mucin interaction by means of viscosimetric and turbidimetric measurements. Eur J Pharm Sci 2000; 10:251–257.
28. Trotta F, Cavalli R. Characterization and application of new hyper-cross-linked cyclodextrins. Composite Interfaces 2009; 16:39–48.
29. Vavia P, Swaminattan S, Trotta F, Cavalli R. Applications of Nanosponges in Drug Delivery XIII International Cyclodextrin Symposium, Turin, 2006;14-17.
30. Trotta F, Roberta C. Characterization and Applications of New Hyper-Cross-Linked Cyclodextrins. Composite Interfaces 2009; 16:39–48.
31. Swaminathan S, Linda P, Loredana S, Trotta P, Vavia P, Aquilano D. Cyclodextrin-based nanosponges encapsulating camptothecin: Physicochemical characterization, stability and cytotoxicity. Eur J Pharm Biopharm 2010; 74: 193–201.
32. Panyam J, Labhasetwar V. Biodegradable nanoparticles for drug and gene delivery to cells and tissue. Adv Drug Deliv Rev 2003; 55: 329–347.
33. Moghimi SG, Hunter AC, Murray JC. Long-circulating and target specific nanoparticles: theory to practice. Pharmacol Rev 2001; 53:283–318.
34. Brannon-Peppas L, Blanchette JO. Nanoparticle and targeted systems for cancer therapy. Adv Drug Deliv Rev 2004; 56:1649–1659.
35. Jeon HJ, Jeong YI, Jang MK, Park YH, Nah JW. Effect of solventon the preparation of surfactant-free poly(dl-lactide-co-glycolide) nanoparticles and norfloxacin release characteristics. Int J Pharm 2000; 207:99–108.
36. Uliano RL. The role of drug delivery systems in cancer chemotherapy. Prog Clin Biol Res 1976; 9:21–32.
37. Allen TM, Chonn A. Large unilamellar liposomes with low uptake into the reticuloendothelial system. FEBS Lett. 1987; 223:42–46.
38. De Jaeghere F, Doelker E, Gurny R. Nanoparticles. In:Mathiowitz E. editor, The Encyclopedia of Controlled Drug Delivery. Wiley and Son, New York; 1999. p. 641–664.
39. Delair T. Colloidal particles: elaboration from preformed polymers. In: Elaissari, A. editors, Colloidal Biomolecules, Biomaterials, and Biomedical Applications. Marcel Dekker Inc., New York; 2004. p. 329–347.
40. Vauthier C, Fattal E, Labarre D. From polymer chemistry and physicochemistry to nanoparticular drug carrier design and applications. In: Yaszemski,M.J., Trantolo,D.J., Lewamdrowski,K.U.,Hasirci,V.,Altobelli, D.E., Wise, D.L. editors, Biomaterial Handbook-Advanced Applications of Basic Sciences and Bioengineering. Marcel Dekker, Inc., New York; 2004. p. 563–598.
41. Jin Chul Kim, Teak Kwan Kwon. In vitro skin permeation of monoolein nanoparticles containing hydroxypropyl β-cyclodextrin/minoxidil complex. Int J Pharm 2010; 302:268-273.
42. Sharma CP, Sajeesh S. Cyclodextrin–insulin complex encapsulated polymethacrylic acid based nanoparticles for oral insulin delivery. Int J Pharm 2006; 325:147–154.
43. Lovatt M. Cooper A, Camilleri P. Energetics of cyclodextrin-induced dissociation of insulin. Eur Biophys J 1996; 24:354–357.
44. Uekama K. Design and evaluation of cyclodextrin-based drug formulation. Chem Pharm Bull 2004; 52:900–915.
45. Victor PV, Sharma CP. Stimuli sensitive polymethacrylic acid microparticles (PMAA)—oral insulin delivery. J Biomater Appl. 2004; 17:125–134.
46. Moses LR, Dileep KJ, Sharma CP. Beta cyclodextrin–insulin encapsulated chitosan/alginate matrix: oral delivery system. J Appl Polym Sci 2000; 75:1089–1096.
47. Memisoglu A, Bochot A, Xen M, Charon D, Duchene D, Hincal A. Amphiphilic β-cyclodextrins modified on the primary face: synthesis, characterization and evaluation of their potential as novel excipients in the preparation of nanocapsules. J Pharm Sci 2002; 91 (5):1214–1224.
48. Geze G, Aous S, Baussanne I, Putaux J, Defaye J, Wouessidjewe D. Influence of chemical structure of zamphiphilic β-cyclodextrins on their ability to form stable nanoparticles. Int J Pharm. 2002; 242:301– 305.
49. Memisoglu E, Bochot A, Ozalp M, Xen M, Duchene D, Hincal A. Direct formation of nanospheres from amphiphilic β-cyclodextrin inclusion complexes. Pharm Res 2003;20 (1):117– 125.
50. Memisoglu E, Bochot A, Xen M, Duchene D, Hincal A. Non-surfactant nanospheres of progesterone inclusion complexes with amphiphilic β-cyclodextrins. Int J Pharm 2003; 251:143–153.
51. Memisoglu E, Vural I, Guc D, Dogan L, Hincal A. Evaluation of in vitro cytotoxicity of amphiphilic β-cyclodextrin nanospheres and nanocapsules on human fibroblasts and granulocytes. Eur J Pharm Sci 2002; 17 (Suppl. 1):81.
52. Skiba M, Morvan C, Duchene D, Puisieux F, Wouessidjewe D. Evaluation of gastrointestinal behaviour in the rat of amphiphilic β-cyclodextrins nanocapsules loaded with indomethacin Int J Pharm 1995; 126:275–279.
53. Skiba M, Duchene D, Puisieux F, Wouessidjewe D. Development of a new colloidal drug carrier from chemically modified cyclodextrins: nanospheres, and influence of physicochemical and technological factors on particle size. Int J Pharm 1996; 129:113–121.
54. Gulik A, Delacroix H, Wouessidjewe D, Skiba M. Structural properties of several amphiphile cyclodextrins and some related nanospheres. An X-ray scattering and freeze-fracture electron microscopy study langmuir. 1998; 14:1050–1057.
55. Pariot N, Edwards LF, Andry MC, Levy MC. Cross-linked β-cyclodextrin microcapsules: preparation and properties. Int J Pharm 2000; 211:19–27.
56. Fundueanu G, Constantin M, Dalpiaz A, Bortolotti F, Cortesi R, Ascenzi P, *et al.* Preparation and characterization of starch/cyclodextrin bioadhesive microspheres as platform for nasal administration of Gabexate Mesylate (Foy®) in allergic rhinitis treatment. Biomaterials 2004; 25:159–170.
57. Constantin M, Fundueanu G, Bortolotti F, Cortesi R, Ascenzi P, Menegatti E. Preparation and characterization of poly(vinyl alcohol)/cyclodextrin microspheres as matrix for inclusion and separation of drugs. Int J Pharm 2004; 285:87–96.
58. Uekama K, Hirayama F, Irie T. Cyclodextrin drug carrier systems. Chem Rev 1998; 98:2045–2078.
59. Ooya T, Eguchi M, Ozaki A, Yui N. Carboxyethylesterpolyrotaxanes as a new calcium chelating polymer: synthesis, calcium binding and mechanism of trypsin inhibition. Int J Pharm 2002; 242:47–54.
60. Ooya T, Yamashita A, Kurisawa M, Sugaya Y, Maruyama A, Yui N. Effects of polyrotaxane structure on polyion complexation with DNA. Sci Techn Adv Mater 2004; 5:363–369.
61. Eguchi M, Du YZ, Taira S, Kodaka M. Functional nanoparticle based on β-cyclodextrin: preparation and properties. Nanobiotechnology 2005; 1:165–170.
62. Wu Y, Sefah K, Liu H, Wang R, Tan W. DNA aptamer–micelle as an efficient detection/delivery vehicle toward cancer cells. Proc Natl Acad Sci U. S. A. 2010; 107:5–10.
63. Peters D, Kastantin M, Kotamraju VR, Karmali PP, Gujraty K, Tirrell M, Ruoslahti E. Targeting atherosclerosis by using modular, multifunctional micelles, Proc Natl Acad Sci U. S. A. 2009; 106:9815–9819.
64. Ruenraroengsak P, Cook JM, Florence AT. Nanosystem drug targeting: facing up to complex realities. J Control Release 2010; 141:265–276.
65. Kabanov AV, Gendelman HE. Nanomedicine in the diagnosis and therapy of neuro degenerative disorders. Prog Polym Sci 2007; 32:1054–1082.
66. Hirao A, Hayashi M, Loykulnant L, Sugiyama K, Ryu S, Haraguchi N, *et al.* Precise syntheses of chain-multi-functionalizedpolymers, star-branched polymers, star-linear block polymers, densely branched polymers, and dendritic branched polymers based on iterative approach using functionalized 1,1-dipheny-lethylene derivatives. Prog Polym Sci 2005; 30:111–182.
67. Harada A, Kataoka K. Supramolecular assemblies of block copolymers in aqueous media as nanocontainers relevant to biological applications, Prog Polym Sci 2006; 31:949–982.
68. Lee Y, Kataoka K. Biosignal-sensitive polyion complex micelles for the delivery of biopharmaceuticals. Soft Matter 2009; 5:3810–3817.
69. Kim S, Kim J, Jeon O, Kwon I, Park K. Engineered polymers for advanced drug delivery, Eur J Pharm Biopharm 2009; 71:420–430.
70. Kabanov AV, Vinogradov VS. Nanogels as pharmaceutical carriers: finite networks of infinite capabilities. Angew Chem Int Ed 2009; 48:5418–5429.
71. Davis ME. Design and development of IT-101, a cyclodextrin-containing polymer conjugate of camptothecin. Adv Drug Deliv Rev 2009; 61:1189–1192.
72. Davis ME. The first targeted delivery of siRNA in humans via a self-assembling, cyclodextrin polymer-based nanoparticle: from concept to clinic. Mol Pharm 2009; 6:659–668.
73. Moon C, Kwon Y, Lee W, Park Y, Yang V. In vitro assessment of a novel polyrotaxane-based drug delivery system integrated with a cell-penetrating peptide. J Control Release 2007; 124:43–50.
74. Yamashita A, Kanda D, Katoono R., Yui N, Ooya T, Maruyama A, Akita H, *et al.* Supramolecular control of polyplex dissociation and cell transfection: Efficacy of amino groups and threading cyclodextrins in biocleavable polyrotaxanes, J Control Release 2008; 131:137–144.
75. Li J, Loh J. Cyclodextrin-based supramolecular architectures: syntheses, structures, and applications for drug and gene delivery. Adv Drug Deliv Rev 2008; 60:1000–1017.

76. Berman JD. Human leishmaniasis: clinical, diagnostic, and chemotherapeutic developments in the last 10 years. Clin Infect Dis 1997; 24:684–703.
77. Demicheli C, Ochoa R, da Silva JB, de Melo AL, Falcao CA, Sinisterra RD, Frezard F. Oral delivery of meglumine antimoniate–-cyclodextrin complex for treatment of leishmaniasis. Antimicrob Agents Chemother 2004; 48:100–103.
78. Martins PS, Ochoa R, Pimenta MC, Sinisterra, RD, Demicheli C, Frezard, F, *et al.* Mode of action of -cyclodextrin as an absorption enhancer of the water-soluble drug meglumine antimoniate. Int J Pharm 2006; 325:39–47.
79. Demicheli C, Ochoa R, Lula IS, Gozzo FC, Eberlin M, Frezard F. Pentavalent organoantimonial derivatives: two simple and efficient synthetic methods for meglumine antimonate. Appl Organomet Chem 2003; 17:226–231.
80. Elsayed MM, Abdallah OY, Naggar VF, Khalafallah NM. Lipid vesicles for skin delivery of drugs: reviewing three decades of research. Int J Pharm 2007; 332:1–16.
81. Cevc G, Blume G. Lipid vesicles penetrate into intact skin owing to the transdermal osmotic gradients and hydration force. Biochem Biophys Acta 1992; 1104:226–232.
82. Trotta M, Peira E, Carlotti ME, Gallarate M. Deformable liposomes for dermal administration of methotrexate. Int J Pharm 2004; 270:119–125.
83. Cevc G, Schatzlein A, Richardsen H. Ultra deformable lipid vesicles can penetrate the skin and other semi-permeable barriers unfragmented. Evidence from double label CLSM experiments and direct size measurements. Biochim Biophys Acta 2002; 1564:21–30.
84. Cevc G, Blume G. New, highly efficient formulation of diclofenac for topical, transdermal administration in ultra deformable drug carriers, transfersomes. Biochem Biophys Acta 2001; 1514:191–205.
85. McCormack B, Gregoriadis G. Drugs-in-cyclodextrins-in liposomes: a novel concept in drug delivery. Int J Pharm 1994; 112:249–258.
86. Maestrelli F, Gonzales-Rodriguez ML, Rabasco AM, Mura P. Preparationand characterisation of liposomes encapsulating ketoprofen–cyclodextrin complexes for transdermal drug delivery. Int J Pharm 2005; 298:55–67.
87. Piel G, Piette M, Barillaro V, Castagne D, Evrard B, Delattre L. Betamethasone-in-cyclodextrin-in-liposome: the effect of cyclodextrins on encapsulation efficiency and release kinetics. Int J Pharm 2006; 312:75–82.
88. McCormack B, Gregoriadis G. Drugs-in-cyclodextrins-in-liposomes: an approach to controlling the fate of water insoluble drugs in vivo. Int J Pharm 1998; 162:59–69.
89. Loukas YL, Vraka V, Gregoriadis G. Drugs in cyclodextrins, in liposomes: a novel approach to the chemical stability of drugs sensitive to hydrolysis. Int J Pharm 1998.; 162:137–142.
90. Matsuda H, Arima H. Cyclodextrins in transdermal and rectal delivery. Adv Drug Deliv Rev 1999; 36:81–99.
91. Loftsson T, Masson M. Cyclodextrins in topical drug formulations: theory and practice. Int J Pharm 2001; 225:15–30.
92. Fatouros DG, Hatzidimitriou K, Antimisiaris SG. Liposomes encapsulating prednisolone and prednisolone-cyclodextrin complexes: comparison of membrane integrity and drug release. Eur J Pharm Sci 2001; 13:287–296.
93. Maestrelli F, González-Rodríguez ML, Rabasco AM, Mura P. Effect of preparation technique on the properties of liposomes encapsulating ketoprofen–cyclodextrin complexes for transdermal drug delivery. Int J Pharm 2006;.312:53–60.
94. Lira MC, Ferraz MS, Cortes ME, Teixeira KI, Caetano NP, Sinisterra RD, *et al.* Inclusion complex of usnic acid with cyclodextrin: characterization and nanoencapsulation into liposomes. J Incl Phenom Macrocycl Chem 2009; 64:215–224.
95. Gillet A, Grammenos A, Compere P, Evrard B, Piel G. Development of a new topical system: drug-in–cyclodextrin-in-deformable liposome. Int J Pharm 2009; 380:174–180.
96. Bragagni M, Maestrelli F, Mennini N, Ghelardini C, Mura P. Liposomal formulations of prilocaine: effect of complexation with hydroxypropyl-β-cyclodextrin on drug anaesthetic efficacy. J Liposome Res 2010;1–8.

Table I : EXAMPLES OF MARKETED PRODUCTS CONTAINING CYCLODEXTRINS.

Drug	Administration route	Trade name	Market
α-Cyclodextrin			
Alprostadil (PGE1	IV	Prostavastin	Europe, Japan, USA
Cefotiam hexetil HCl	Oral	Pansporin T	Japan
β-Cyclodextrin			
Benexate HCl	Oral	Ulgut, Lonmiel	Japan
Dexamethasone	Dermal	Glymesason	Japan
Iodine	Topical	Mena-Gargle	Japan
Nicotine	Sublingual	Nicorette	Europe
Nimesulide	Oral	Nimedex, Mesu	Europe
Nitroglycerin (glyceryl trinitrate)	Sublingual	Nitropen	Japan
Omeprazol	Oral	Omeeta	Europe
PGE2	Sublingual	Prostarmon E	Japan
Piroxicam	Oral	Brexin	Europe
Tiaprofenic acid	Oral	Surgamyl	Europe
2-Hydroxypropyl-β-cyclodextrin			
Cisapride	Rectal	Propulsid	Europe
Hydrocortisone	Buccal	Dexocort	Europe
Indomethacin	Eye drops	Indocid	Europe
Itraconazole	Oral, IV	Sporanox	Europe, USA
Mitomycin	IV	Mitozytrex	USA
Randomly methylated β-cyclodextrin			
17β-Estradiol	Nasal spray	Aerodiol	Europe
Chloramphenicol	Eye drops	Clorocil	Europe
Sulfobutylether β-cyclodextrin			
Voriconazole	IV	Vfend	Europe, USA
Ziprasidone maleate	IM	Geodon, Zeldox	Europe, USA
2-Hydroxypropyl-γ-cyclodextrin			
Diclofenac sodium	Eye drops	Voltaren	Europe

Table II: EXAMPLES OF CYCLODEXTRIN CONTAINING FORMULATIONS.

Drug	CD	Formulation	References
Tamoxifen	β	Nanoparticles	Bilensoy,2005
Nicotine	β	Transdermal Patch	Hashemi,2005
Insulin	HPβCD	Nanoparticles	Sharma,2006
Metronidazole	β	Nanospheres	Skiba,2006
Ketoprofen	HPβCD	Liposomes	Maestrelli,2006
Doxorubicin	D-galactose-β	Carriers	Yamanoi,2008
Meglumine Antimoniate	β	Nanoassemblies	Frezard,2008
Paclitaxel	β	Nanoparticles	Bilensoy,2008
Oxytocin	β	Targeted Drug Carrier	Masereel,2008
Rifampicin	HPβCD	Aerosol	Tewes,2008
Ketoprofen	HPβCD	Microspheres	Maestrelli,2008
Metformin	β	Matrix Tablets	Mura,2008
Betamethasone	HPβCD	Deformable Liposome	Gillet,2009
Kavalactones	β	Carriers	Bergonzi,2010
Insulin	β	Nanoparticles	Li,2010
Ibuprofen	β	Nanoassemblies	Ma,2010
Indomethacin	β	Nanoassemblies	Ma,2010
Dexamethasone	β	Nanoassemblies	Ma,2010
Minoxidil	HPβCD	Nanoparticles	Kim,2010
Benzocaine	HPβCD	Deformable Liposome	Maestrelli,2010
Butamben	HPβCD	Deformable Liposome	Maestrelli,2010
Curcumin	HPγCD	Aqueous Formulations	Aggarwal,2010

α= α-cyclodextrin
β= β-cyclodextrin
γ = γ-cyclodextrin
HPβCD = hydroxypropyl-β-cyclodextrin
HPγCD= hydroxypropyl-γ-cyclodextrin