International Journal of Pharmacy
Journal Homepage: http://www.pharmascholars.com

Review Article **CODEN: IJPNL6**

CYCLODEXTRINS: NANOCARRIERS FOR NOVEL DRUG DELIVERY

Kishore Rapolu[1], Vinaydas Aatipamula[2], Kavitha Jayapala Reddy[3] and Swathi Voruganti[4]

[1]National Institute of Pharmaceutical Education and Research, Balanagar, Hyderabad
[2]National Institute of Pharmaceutical Educational Research, Raja S.C. Mullick Road, Jadavpur ,Kolkata, India.
[3]Centre for Pharmaceutical Sciences, JNTUH, Kukatpally, Hyderabad, Andhra Pradesh, India
[4]Pharmacokinetics and Metabolism Division, CSIR-CDRI, Luck now, India

***Corresponding author e-mail:** ucpsc.kishore@gmail.com

ABSTRACT
Cyclodextrins are cyclic (α -1, 4)-linked oligosaccharides of α -D-glucopyranose containing a relatively hydrophobic central cavity and hydrophilic outer surface. Cyclodextrins, which can serve as solubilising and stabilizing agent of drug, are very significant in improving the bioavailability of drug, increasing the solubility, decreasing the stimulation, and masking the Smell. The objective of this review is to discuss and summarize some of the findings and application of novel cyclodextrin based nanocarriers. The nanoparticles, taking cyclodextrins as the matrix, can enhance the capability of encapsuling the guest molecule; efficiently regulate the drug release rate and targeting of drug. This review also highlights the molecular structure, properties like complexation solubility, etc. of cyclodextrins and focuses on its usage in various nanocarriers like liposomes, dendrimers, carbon nanotubes, magnetic nanoparticles, gold nanoparticles and nanosponges. Thus cyclodextrins, because of their continuing ability to find several novel applications, are expected to solve many problems associated with the delivery of different novel drugs through different approaches of nanotechnology.

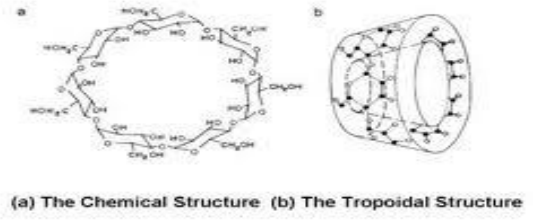
Keywords: Cyclodextrins, Nanocarriers, Complexation solubility, Stability, Bioavailability.

INTRODUCTION

Although cyclodextrins are frequently regarded as a new group of pharmaceutical excipients, they have been known for over 100 years. The foundations of cyclodextrins chemistry were laid down in the first part of this century and the first patent on cyclodextrins and their complexes was registered in 1953. However, until 1970 only small amounts of cyclodextrins could be produced and high production costs prevented their widespread usage in pharmaceutical formulations. Recent biotechnological advancements have resulted in dramatic improvements in cyclodextrins production, which has lowered their production costs. This has led to the availability of highly purified cyclodextrins and derivatives which are well suited as pharmaceutical excipients[1].Use of cyclodextrins in nanoparticulate systems can enhance the capability of encapsuling the guest molecule, improve the stability of drug, and efficiently regulate the drug release rate. Moreover, they can realize the improvement of bioavailability and targeting of drug.

Structure and properties: Cyclodextrins consists of (α-1, 4)-linked α-D-glucopyranose unit with a lipophilic central Cavity and the structures are as shown in fig.1. Due to the chair formation of the Glucopyranose units, cyclodextrins molecules are shaped like cones with secondary Hydroxyl groups extending from the wider edge and the primary groups from the narrow edge. This gives cyclodextrins molecules a hydrophilic outer surface, whereas the. Lipophilicity of their central cavity is comparable to an aqueous ethanolic solution. The naturally occurring cyclodextrins are α, β and γ types containing 6, 7 and 8 glucopyranose units respectively. They have limited aqueous solubility due to the strong intermolecular hydrogen bonding in

the crystal state. Substitution of the H-bond forming -OH group has improved their solubility .The various derivatives that have gained pharmaceutical interest include hydroxyl propyl derivatives of β, γ and methylated β-Cyclodextrins, sulfo butyl ether β-cyclodextrins etc.[2].



(a) The Chemical Structure (b) The Tropoidal Structure

Figure 1: The chemical structure of β-Cyclodextrins molecule

Complex formation and drug solubility of cyclodextrin: In aqueous solutions, cyclodextrins are able to form inclusion complexes with many drugs by taking up the drug molecule or some lipophilic moiety of the molecule, into the central cavity. No covalent bonds are formed or broken during complex formation, and the drug molecules in complex are in rapid equilibrium with free molecules in the solution. The driving forces for the complex formation include release of enthalpy-rich water molecules from the cavity, hydrogen bonding, Vander Waals interaction, and charge transfer interaction etc[3].The physicochemical properties of free cyclodextrin molecule differ from those in complex. The stoichiometry of the complexes formed and the numerical value of their stability constants can be determined by observing the changes in physicochemical properties like solubility, chemical reactivity, UV/VIS absorbance, drug retention, chemical Stability, effects on drug permeability through artificial membranes etc [4].

Phase-solubility diagram: Higuchi and Connors [5] have classified complexes based on their effect on substrate Solubility and it is indicated by the phase-solubility profiles as shown in Fig. 2. A-type Phase-solubility profiles are obtained when the solubility of the substrate (i.e. drug) increases with increasing ligand (cyclodextrin) concentration. When the complex is first Order with respect to ligand and first or higher order with respect to substrate then A_L-type Phase-solubility profile is obtained. If the complex is first order with respect to the Substrate, but second or higher order with respect to the ligand then A_P-type phase solubility Profile is obtained. It is difficult to interpret the A_N-type phase-solubility profile. The negative deviation from linearity may be associated with cyclodextrin induced changes in the dielectric constant of the aqueous complexation media, changes in complex Solubility or self-association of cyclodextrin molecules. B-type phase-solubility profiles Indicate formation of complexes with limited solubility in the aqueous complexation medium.

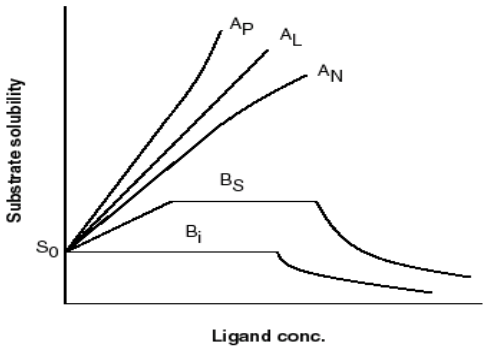


Figure 2: Phase-solubility profiles-

In general, the water-soluble cyclodextrin derivatives form A-type phase solubility profiles, whereas the less soluble natural cyclodextrin forms B-type profiles. Most of the drug/cyclodextrin complexes are thought to be inclusion complexes, but cyclodextrins are Also known to form non-inclusion complexes and the complex aggregates are capable of Dissolving drugs through micelle-like structures. The phase-solubility profiles only describe how the increasing cyclodextrin concentration influences the drug solubility.

The most common type of cyclodextrin complexes is the 1:1 drug/cyclodextrin (D/CD) complex where one drug molecule (D) forms a complex with one cyclodextrin molecule (CD) and is given in equation 1.

$$D + CD \overset{K_{1:1}}{\leftrightarrow} D/CD \qquad (1)$$

Under such conditions an AL-type phase-solubility diagram, with slope less than unity, would be observed and the stability constant ($K_{1:1}$) of the complex can be Calculated from the slope and the intrinsic solubility (S_0) of the drug in the aqueous Complexation media (i.e. drug solubility when no cyclodextrin is present)

$$K_{1:1} = \text{Slope}/S_0(1-\text{Slope}) \qquad (2)$$

The value of K1:1 is most often between 50 and 2000 M-1 with a mean value of 129, 490 and 355 M-1 for α-, β- and γ-cyclodextrin respectively. For 1:1

drug/CD complexes the complexation efficiency (CE) can be calculated from the Slope of the phase-solubility diagram (eq. 3)

$$CE = [D/CD]/CD = S_0.K_{1:1} = Slope/(1-slope) \quad (3)$$

The most common stoichiometry of higher order D/CD complexes is the 1:2 D/CD complex resulting in Ap-type phase solubility diagram. Consecutive complexation is assumed Where 1:2 complex (eq. 4) is formed when one additional cyclodextrin molecule forms a Complex with an existing 1:1 complex.

$$D/CD + CD \xleftrightarrow{K_{1:2}} D/CD2 \quad (4)$$

The various methods that are used to prepare D/CD complexes include solution method, Co-precipitation method, neutralization method, slurry method, kneading method, grinding method etc .and water is essential for the successful complex formation[6].

Novel cyclodextrin based nanocarriers:
Nanoparticulate systems are constructs that possess a unique physical and chemical properties associated with their being of 1–100 nm in size. It includes Liposomes, dendrimers, carbon nanotubes, magnetic nanoparticles, and, and gold nanoparticles[7]. one of the major problems encountered with these vesicular systems during their preparation and result from low solubility leading to low yield in drug loading or incomplete release rate .By using Cyclodextrins as the matrix, can enhance the capability of encapsuling the guest molecule, improve the stability of drug, and efficiently regulate the drug release rate. Moreover, they can realize the improvement of bioavailability and targeting of drug.

Cyclodextrins in Nanoparticles:
Nanoparticles are considered as most stable system than liposomes. An approach in which cyclodextrins as stabilizers for the preparation of drug nanocrystals by the emulsion solvent diffusion method were studied by Abdullah Makhlof[8].Delivering drug in combination of cyclodextrins and nanoparticles improves solubility and permeability as reported in the case of paclitexel[9]. The apparent solubility of saquinavir was increased 400-fold at pH 7.0 in presence of hydroxypropyl- β -cyclodextrin owing to the formation of a drug–cyclodextrin complex as demonstrated mainly by 1H NMR and confirmed by other techniques[10]. Acyclovir-loaded nanoparticles were prepared from inclusion complexes of Acyclovir with β-CD-PACM. Both unloaded and drug-loaded nanoparticles were characterized in terms of particle size distribution, morphology, zeta potential, drug loading and in vitro drug release rate. The antiviral activity of acyclovir loaded into β-CD-PACM nanoparticles against two clinical isolates of HSV-1 was evaluated and found to be remarkably superior compared with that of both the free drug and a soluble β-CD-PACM complex [11]. Amphiphilic cyclodextrins are chemically obtained derivatives of natural cyclodextrins (α, β and γ cyclodextrins) modified on the primary and/or secondary face with aliphatic chains of varying length (C2to C18) and structure (linear or branched) linked with different chemical bonds including ester, ether, thiol or amide bonds . 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. 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[12]. Progesterone-loaded amphiphilic β -CD nanospheres were proved to be a promising non-surfactant injectable delivery system providing high-quantity of water insoluble progesterone rapidly within 1 h[13].

In other approach extend release profile is reduced as tamoxifen citrate loaded α, -CDC6 nanospheres and nanocapsules of appropriate particle size are obtained by nanoprecipitation technique.[14]. Later a new drug nanocarriers consisting of chitosan and hydroxypropyl cyclodextrin was evolved. The complexation with the cyclodextrin permits the solubilization as well as the protection for sensitive drugs, whereas the entrapment in the chitosan network is expected to facilitate their absorption. Chitosan nanoparticles including hydroxypropyl cyclodextrins could be prepared by the ionic cross linking of chitosan with sodium tripolyphosphate in the presence of cyclodextrins.[15].

Then chitosan/SBE-CD nanoparticles developed showed a promising carrier for controlled delivery of drug to the eye[16]. In other approach Inclusion complexes of hydrocortisone and progesterone were formed with β -cyclodextrin or 2-hydroxypropyl- β -cyclodextrin. The formation of the complexes was confirmed by differential scanning calorimetry (DSC).

The inclusion complexes were incorporated in two types of solid lipid nanoparticles (SLN). In the presence of the complexes the sizes of SLN remained below 100 nm. Using the b-cyclodextrin complexes the incorporation of the more hydrophilic drug, hydrocortisone, was higher than that of progesterone. Release of hydrocortisone and progesterone from SLN was lower when they were incorporated as inclusion complexes than as free molecules[17].

Cyclodextrins in liposomes:
Liposomes are phospholipids vesicles (50–100 nm) that have a bilayer membrane structure similar to that of biological membranes and an internal aqueous phase .The concept, entailing entrapment of cyclodextrins complexes in liposomes would result in the increase to drug to lipid mass ratio to levels above those attained by conventional drug incorporation into the lipid phase, enlarge the range of insoluble drugs amenable to encapsulation to include[18], for instance, membrane destabilizing agents, allow targeting of complexes to specific sites and reduce toxicity. it has been recently proposed that drugs sensitive to light and photochemical oxidation, such as riboflavin and sodium ascorbate respectively, exhibited a great increase in their stability (270- and 125-fold, respectively) when entrapped as cyclodextrin complexes in multilamellar liposomes (MLV), incorporating light absorbers (such as oil red O, oxybenzone, deoxybenzone, sulisobenzone) and antioxidants (such as *β*-carotene) in their bilayer[19]. The stability of the anti-inflammatory drug indomethacin, which is hydrolysable in alkaline buffered solutions, was increased 75-fold when entrapped in multilamellar liposomes in the form of a hydroxypropyl-*β*-cyclodextrin 1:1 inclusion complex. Complexation with CD can also improve the stability of liposomes, e.g., most stable liposomal formulations of metronidazole and verapamil were obtained by direct spray drying of lipid, drug and HP-β-CD mixture. Another approach showed increase encapsulating efficiency and release kinetics of betamethasone in cyclodextrins in-liposomes[20]. The presence of the cyclodextrin complex affected MLV dimensions but not their lamellar structure. The complex with HP-cyclodextrin, in virtue of its greater stability than the β-cyclodextrin one, allowed higher percentages of encapsulation and gave rise to more stable MLV systems in the case of liposomes-ketoprofen cyclodextrin complexes [21].

Cyclodextrins in dendrimers:
Dendrimers are three-dimensional, highly ordered oligomeric and polymeric compounds formed by reiterative reaction sequences starting from smaller molecules Dendrimers can mimic various properties of large biomolecules and, thus, numerous applications are conceivable. By attaching chemical moieties to dendrimers, a variety of biomimetic functional molecules can be designed. Dendrimers with hydrophilic exteriors and hydrophobic interiors may be regarded as covalently fixed assemblies of amphiphiles. In view of intensive studies on catalytic reactions of micelles, dendrimers may be exploited as biomimetic catalysts. Without specific binding sites, major principles of enzymatic catalysis can be hardly reproduced. Many cyclodextrin (CD) derivatives have been examined for their ability to recognize guest molecules and to catalyze chemical transformation of the included molecules In order to devise effective biomimetic catalysts using CD derivatives, it is necessary to introduce catalytic groups to CDs in positions suitable for high catalytic efficiency. It is not easy to introduce a catalytic group in the productive position by using a short spacer to connect CD and the catalytic group. When a long spacer is used, however, conformational freedom of the resulting cyclodextrin derivative should be suppressed to freeze the molecule in the productive conformation. Thus, reactions of compounds included in the CD cavity would be affected by the dendrimer moiety. In addition, the conformation and the chemical behavior of the dendrimer would be in turn influenced by the presence of b-CD in the molecular framework The interactions between drugs and dendrimers can also increase the solubility of poorly soluble drugs. The interactions that lead to an increase in solubility include physical entrapment of the drug molecules inside the dendrimer structure or the drug being attached onto the dendrimer surface to prepare dendrimer-drug conjugates. From the phase solubility studies, when the fold enhancement in solubility of niclosamide combined with full generation amine terminated PAMAM(Polyamidoamine) dendrimers was compared with that obtained when the drug was combined with β- or hydroxypropyl-β-cyclodextrin, the results showed that, except for G-0 dendrimer at pH 7, the solubility of niclosamide was significantly higher in the presence of the dendrimers. [22].Another approach showed the growing body of data on the binding interactions between dendrimers and two types of well-established molecular hosts: cyclodextrins and cucurbit[*n*]urils [23]. In a different approach koke wada et al evaluated in vitro and in vivo gene delivery efficiency of Polyamidoamine (PAMAM) starburst dendrimers (generation 2, G2) conjugate with α-cyclodextrins (α-CDE conjugate (G2)) [24].In another approach gokhan temel et al studied the BP/Me-β-CD inclusion complex was synthesized and used in photo induced free radical polymerization of acrylamide as a type II photo initiator in the presence of a dendritic co-initiator [25].

Cyclodextrins in carbon nanotubes:
Carbon nanotubes (CNTs) are a new type of carbon nanostructure material that possesses outstanding properties, such as high electrical conductivity, large surface area, good chemical stability and significant mechanical strength [26]. Owing to their unique structure and physical properties, as an example, the large surface area together with good conductive

properties has made CNTs and their derivatives attractive as sensing materials. Cyclodextrins could interact with CNTs. Chen et al. proposed that CDs could efficiently disperse SWNTs (single walled nanotubes) and they possibly adsorb at the surface of the nanotubes via Vander Waals force. Subsequently, Chambers et al. and Liu et al. reported the similar results. CDs adsorbed on the surface of CNTs by Vander Waals force and the hydrogen-bonding interaction between adjacent CD molecules was responsible for the formation of CNT–CD complexes. CDs are excellent reagents to disperse CNTs, and their composites in the construction of CD/CNT based electrodes could be used as electrochemical sensor and therefore, it is crucial to investigate the interactions between CDs and CNTs to guide the choice of CDs in their applications. In recent years, computer simulations have been widely used to investigate the "wrapping" of CNTs. It has been proved by molecular dynamics (MD) simulations that polymers and biological macromolecules and can smoothly wrap around or insert into the nanotubes therein, they focused on the physisorption of CDs on SWNTs to investigate their interactions by MD simulation. A work describes a highly sensitive amperometric biosensor for organophosphates (OPs) pesticides based on immobilization of acetylcholinesterase (AChE) on multiwall carbon nanotubes (MWCNTs)-β-cyclodextrins (β-CD) composite modified glassy carbon electrode[27]. A simple and reliable method based on electrochemical technique at β-cyclodextrins incorporated carbon nanotubes-modified electrodes (β-CD-CNT/E) was proposed for simultaneous or individual determination of guanine and adenine as studied by Zonghua Wang etal.[28].In other approach, a highly selective dopamine sensor was fabricated by doping polypyrrole with a sulfonated β-cyclodextrins. This composite material enabled the selective sensing of dopamine in the presence of a large excess of ascorbic acid and prevented the regeneration of dopamine through the homogeneous catalytic reaction of the ascorbate anion with the dopamine-o-quinone. A single redox wave, corresponding to the oxidation of dopamine, was observed in dopamine/ascorbate mixtures, giving a truly selective dopamine sensor [29].

Cyclodextrins in magnetic nanoparticles:

During the past decades, advances in nanoscience and nanotechnology have pushed forward the synthesis of functional magnetic nanoparticles (MNPs), which is one of the most active research areas in advanced materials and. MNPs that have unique magnetic properties and other functionalities (such as electronic and optical properties) have enabled a wide spectrum of applications. Owing to their unique magnetic properties and relatively small size to biologically important objects, these MNPs are very useful for biomedical applications. Their responses to external magnetic fields allow biomolecules to be tagged and detected magnetically, enabling some exciting new approaches to bio-separation, bio-detection and targeted drug delivery and it is widely known that CDs can form inclusion complexes with a wide variety of organic compounds in its hydrophobic cavity through host–guest interactions. The formation of these complexes has been attributed to weak interactions such as hydrophobic effect, Vander Waals interactions, and hydrogen bonding and so on. This molecular encapsulation ability is widely utilized in many industrial products, technology and analytical methods and. recently; efforts are being made to graft β-CD, which forms a whole new family of pharmaceutical excipients on the surface of magnetic nanoparticles for biomedical applications. In 2007, Banerjee and Chen first reported the designing of magnetic nanoparticles functionalized with β-CD/β-CD-citrate as nanocarriers for hydrophobic drug delivery. They demonstrated from the loading and release experiments for drug-like ketoprofen that the system can be a promising vehicle for the administration of hydrophobic drugs. In a study, Badruddoza et al. explored the potential of using β-CD-conjugated magnetic nanoparticles (CD-APES-MNPs) as stripping agents for protein refolding. In addition, cyclodextrins functionalized graphane nanosheets with high supermolcular recognition capability has also been reported. Although there are some previous works carried out on using CDs grafted on Fe_3O_4-MNPs as nanocarriers for drug delivery or as nano-absorbents for dye absorption, no or limited work has been done, on using CDs decorated MNPs as modified working electrode for detecting uric acid. It should be noted here that introducing a number of CDs onto the surface of MNPs cannot only improve the stability and dispersion of MNPs, but also be expected to enhance the sensitivity of detection for some important biomolecules and drugs through the formation of supramolecular complexes between CDs and the guest molecules[30].In a study β− cyclodextrins (β−CD)-based inclusion complexes of $CoFe_2O_4$ magnetic nanoparticles (MNPs) were prepared and used as catalysts for chemiluminescence (CL) system using the luminol–hydrogen peroxide CL reaction as a model. . It was found that inclusion complexes between β−CD and $CoFe_2O_4$ magnetic nanoparticles could greatly enhance the CL of the luminol–hydrogen peroxide system[31].In other work Prussian-blue-modified iron oxide magnetic nanoparticles as

effective peroxidase-like catalysts to degrade methylene blue with hydrogen peroxide [32].

Cyclodextrins in gold nanoparticles:
Gold nanoparticles (Au NPs) are a fascinating material owing to their unique optical (Plasmon band), electronic, catalytic, and supramolecular properties. S. Rodríquez-Llamazares introduce in their work the use of cyclodextrins (CD) inclusion compounds. Although unmodified and thiolated α- and β- cyclodextrins have been used for preparation of colloidal gold nanoparticles and or for the phase transfer in liquid of different polarity and , the method described there utilizes the well defined surface functionality of CD inclusion compounds, in which the surface functional groups can be adjusted by the guest molecules. Hence, two actually very interesting chemistry areas converge, i.e. the molecular recognition phenomenon applied to the CD inclusion compounds and the assembly of metal nanoparticles [33].In a study a new method for preparing β-cyclodextrins/poly (*N*-vinylpyrrolidone) composite nanofibers containing gold nanoparticles by electrospinning. β-Cyclodextrins is mixed into fibers as a new material, and it acts as stabilized reagent and reducing reagent in the synthesis of gold nanoparticles. TEM observation confirms that the gold nanoparticles are completely encapsulated within the composite nanofibers.

Cyclodextrin in nanosponges:
Nanosponges are a new class of material made of microscopic particles with cavities a few nanometers wide, characterized by the capacity to encapsulate a large variety of substances that can be transported through aqueous media. In the pharmaceutical field, in particular, they could be employed as solubilizing agents or nanocarriers. The nanosponges contain β -cyclodextrins as building blocks, linked with carbonate groups to form a high cross linked network. The reaction is very simple and carried out under relative mild conditions. The final nanosponge structure contains both cyclodextrin lyphophilic cavities and carbonate bridges, leading to a network of more hydrophilic channels [34].Recently cyclodextrin based nanosponges for delivery of resveratrol have been developed [35].

Recent trends and future directions:
Calando pharmaceuticals, Inc. has developed proprietary therapeutic cyclodextrin-containing polymer RNA interference (RNAi) delivery technology and demonstrated the first clear in vivo sequence specific inhibition in tumours. Calando's technology for RNAi called RONDEL.specifically it employs small interfering RNA (siRNA) as the therapeutic RNA[36]. Recently Cerulean pharma by using cyclodextrin nanoparticle technology (CDP) has developed CRLX101 which is in phase 2a trials. CRLX101 is comprised of the high potency anti-tumor agent camptothecin coupled to a cyclodextrin based polymer that self-assembles into nanoparticles of consistent size and other physical attributes.

CONCLUSION
Cyclodextrins are useful functional tools that had wide use in the pharmaceutical industry. The bioadaptability and multi-functional characteristics of Cyclodextrins, Makes them capable of alleviating the undesirable properties of drug molecules in various areas of nanotechnology through the formation of inclusion complexes. Knowledge of different factors that can influence complex formation in order to prepare economically drug/Cyclodextrins complexes with desirable properties are necessary. 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 nanoparticles, liposome, dendrimers, and carbon nanotubes.

REFERENCES

1. Thorstenin Loftsson, Marcus E.Brewster. Pharmaceutical Applications of Cyclodextrins. J. Pharm. Sci., 1996; 85:10.
2. Thorsteinn Loftsson, Pekka Jarho, Már Másson & Tomi Järvinen, Cyclodextrins in drug delivery, Expert opin.2005; 2: 335-51.
3. Liu L, Guo QX, The driving forces in the inclusion complexation of cyclodextrins. Incl. Phenom. Macro Chem., 2002; 42: 1–14.
4. Arun rasheed, Asok kumar CK, Sravanthi VVNS. Cyclodextrins as Drug Carrier Molecule: A Review. Sci. Pharm., 2008; 76: 567–98.
5. Higuchi T, Connors KA. Phase solubility techniques. Adv Anal Chem. Instrum, 1965; 4:117–212.

6. Thorsteinn Loftsson, Pekka Jarho, Mar Masson, Tomi Järvinen. Cyclodextrins in drug delivery. Expert Opin., 2005; 2: 335-51.
7. Nuria Sanvicens, M. Pilar Marco. Multifunctional nanoparticles– properties and prospects for their use in human medicine, Trends Bio., 2008; 26(8):425-33.
8. Abdullah M, Yuta M, Yuichi Tozuka, Hirofumi Takeuchi. Cyclodextrins as stabilizers for the preparation of drug nanocrystals by the emulsion solvent diffusion method. Int. J. Pharm., 2008; 357:280–5.
9. M Agüeros, V Zabaleta, S Espuelas, MA Campanero, JM Irach. Increased oral bioavailability of paclitexel by its encapsulation through complex formation with cyclodextrins in poly (anhydride) nanoparticles, J. Control. Re., 2010; 145(1): 2-8.
10. H Boudad, P Legrand, G Lebas, M Cheron, D Duchene, G Ponchel.Combined hydroxypropyl -β-cyclodextrin and poly (alkylcyanoacrylate) nanoparticles intended for oral administration of saquinavir, Int. J. Pharm, 2001; 218: 113-24.
11. Roberta Cavalli, Manuela Donalisio, Andrea Civra, Paolo Ferruti, Elisabetta Ranucci, Francesco Trotta, David Lemb., Enhanced antiviral activity of Acyclovir loaded into β-cyclodextrin-poly(4-acryloylmorpholine) conjugate nanoparticles, J.Control.Release, 2009; 137(2): 116-22.
12. Annabelle Geze, Soad Aous, Isabelle Baussanne, JeanLuc Putaux, Jacques Defaye, Denis Wouessidjewe. Influence of chemical structure of amphiphilic β-cyclodextrin on their ability to form stable nanoparticles. Int. J. Pharm., 2002; 242(1-2): 301-5.
13. Erem Memişoğlu, Amelie Bochot, Murat Şen, Dominique Duchene. Non-surfactant nanospheres of progesterone inclusion complexes with amphiphilic β-cyclodextrins Int. J. Pharm., 2003; 251(1-2): 143-53.
14. Erem Memisoglu-Bilensoy, Imran Vural, Amelie Bochot' Jack Michel Renoir, Dominique DucheneA. Atilla Hıncal, Tamoxifen citrate loaded amphiphilic β-cyclodextrin nanoparticles: In vitro characterization and cytotoxicity. J.Control. Rel., 2005; 104(3): 489-96.
15. Maestrelli F, Fuentes GM, Mura P, Alonso MJ.A new drug nanocarriers consisting of chitosan and hydroxypropyl- cyclodextrin. Eur. J. Pharm. Biopharm., 2006; 63:79–86.
16. Azza. Mahmoud, Gina S. El-Feky Rabab Kamel Ghada E. Awad.Chitosan /sulfobutylether -β cyclodextrin nanoparticles as a potential approach of ocular drug delivery. Int. J. Pharm, 2011; 413(1-20): 1-286.
17. Roberta Cavalli, Elena Peira, Otto Caputo, Maria Rosa Gasco. Solid lipid nanoparticles as carrier of hydrocortisone and progesterone complexes with β-cyclodextrins, Int. J. Pharm, 1999; 182(1): 59-69.
18. Brenda Mccormcak,Gregory gregoridis. Drugs-in-cyclodextrins-in liposomes: A novel concept in drug delivery, Int. J. Pharm, 1994;112(3):249-58.
19. Yannis L Loukas, Vassilia Vraka, Gregory Gregoridis. Drugs, in cyclodextrins, in liposomes: A novel approach to the chemical stability of drugs sensitive to hydrolysis. Int. J. Pharm., 1998; 162(1-2): 137-42.
20. Skalko BN, Pavelic Z, Becirevic LM. Liposomes containing drug and cyclodextrin prepared by the one-step spray-drying method. Drug Dev. Ind. Pharm. 2000; (26): 1279–84.
21. Francesca Maestrelli, Maria Luisa Gonzalez Rodriguez, Antonio Maria Rabasco. Paola Mura**.** Preparation and characterization of liposomes encapsulating ketoprofen cyclodextrin complexes for transdermal drug delivery. Int. J. Pharm, 2005; 298(1) :5-67.
22. Bharathi Devarakonda, Ronald A. Hill, Wilna Liebenberg, Marius Brits, Melgardt M. de Villiers. Comparison of the aqueous solubilization of practically insoluble niclosamide by polyamidoamine (PAMAM) dendrimers and cyclodextrins, Int. J. Pharm., 2005; 304(1-2): 193-209
23. Wei Wang, Angel E. Kaifer. Cucurbituril and cyclodextrin complexes of dendrimers Inclusion. Adv. Polym. Sci., 2009; 222: 205-35.
24. Koki Wada, Hidetoshi Arima, Toshihito Tsutsumi, Yuko Chihara, Kenjiro Hattori, Fumitoshi Hirayama, Kaneto Uekama. Improvement of gene delivery mediated by mannosylated dendrimer/α-cyclodextrin conjugates, J. Control. Rel., 2005; 104(2): 397-413.
25. Gokhan Temel, Tezcan Parali, Metin Tulu, Nergis Arsu.Photo polymerization of acrylamide with benzophenone/methylated-β-cyclodextrin inclusion complex in the presence of jeffamine based dendrimers as co initiators in aqueous media, J. Photochem. Photobio A: Chem., 2010; 213(1): 46-51.
26. Lizhu Yang, Ying Xu, Xiuhua Wang, Jing Zhu, Renyi Zhang, Pingang He, Yuzhi Fang. The application of β-cyclodextrin derivative functionalized aligned carbon nanotubes for electrochemically DNA sensing *via* host–guest recognition,Anal. Chem Acta., 2011; 689(1):39-46.
27. Dan Du, Minghui Wang, Jie Cai, Aidong Zhang. Sensitive acetylcholinesterase biosensor based on assembly of β-cyclodextrins onto multiwall carbon nanotubes for detection of organophosphates pesticide, Sens. Actuators B: Chem., 2010; 146,(1): 337-41.

28. Zonghua W, Sufang X, Yue Chen. β-Cyclodextrin incorporated carbon nanotubes-modified electrodes for simultaneous determination of adenine and guanine. J. Elect. anal. Chem., 2006; 589(2): 237-42.
29. Claire C. Harley, A. Denise Rooney, Carmel B. Breslin. The selective detection of dopamine at a polypyrrole film doped with sulfonated β-Cyclodextrins, Sens. Actuators B: Chem., 2010; 150(2): 498-504.
30. Jie Zhu, Jiang He, Xiaoyan Du, Ruihua Lu, Lizhen Huang, Xia Ge. A facile and flexible process of β-cyclodextrin grafted on Fe_3O_4magnetic nanoparticles and host–guest inclusion studies. Appl.Surf.Sci., 2011; 257(21):9056-9062.
31. Shaohui He**,** Wenbing Shi, Xiaodan Zhang, Jian Li, Yuming Huang. *β*−cyclodextrins based inclusion complexes of $CoFe_2O_4$ magnetic nanoparticles as catalyst for the luminol chemiluminescence system and their applications in hydrogen peroxide detection, Talanta, 2010; 82(1): 377-83.
32. Hui Wang, Yuming Huang. Prussian-blue-modified iron oxide magnetic nanoparticles as effective peroxidase-like catalysts to degrade methylene blue with H_2O_2. J. Haz. Mat., 2011; 191(1-3): 163-9.
33. S. Rodríquez-Llamazares, P Jara, N Yutronic , M Noyong, J Bretschneider, U Simon, Face preferred deposition of gold nanoparticles on *α*-cyclodextrin/octanethiol inclusion compound, J. Colloid. Inter Sci., 2007; 316(1): 202-5.
34. Cavalli R, Trotta F, Tumiatti W. Cyclodextrin-based nanosponges for drug delivery. J. Incl. Phenom. Macrocycle Chem., 2006; 56: 209–13.
35. Khalid Ansari, Pradeep Vavia, Francesco Trotta, Roberta Cavelli. Cyclodextrin based nanosponges for delivery of resveratrol: invitro charcterisation, stability, cyctotoxicity and permeation study.APPS Pharmsci. Tech., 2011; 12(1): 279-86.
36. Derek WB, Mark E. Davis. Impact of tumor specific targeting and dosing schedule of tumour inhibition after intravenous administration of siRNA-Containing nanoparticles. US Patent No. 72708089.