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Review Article

Industrial Scope of Cyclodextrins in Pharmaceuticals Products: A Review

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ABSTRACT

Cyclodextrins (CDs) belongs to a class of novel excipients used in pharmaceutical fields and have been studied for almost 100 years. Cyclodextrins have been used in almost 35 above products in pharmaceutical industries. Chemically CDs are macrocyclic oligosaccharides that consist of α-(1,4) linkages of dextrorotatory glucopyranose units which show same biological characteristics as that of their linear counterparts however some physicochemical properties are different. CDs have a hydrophilic and lipophilic cavities in their structures. Because of this property they have ability to make inclusion complexes with lipid soluble drugs. CDs are also used to enhance solubility of water soluble drugs and hence increase the bioavailability of these drugs followed by improved absorption. In this way CDs and their derivatives also attractive for their use in the modification of drug profile. CDs are also considered for their use to convert oil and liquid drugs into microcrystalline and amorphous powders, also used to decrease side effects of API. CDs are important for their non-toxic behavior which aids their importance as an inactive excipient in many pharmaceutical and food additives. By combining with CDs many poor water soluble drugs can be manufactured in dosage forms like parenteral solutions, eye, nasal and ear drops. This review will provides an overview for the utility of CDs in diverse nanotechnology dosage forms like liposomes, niososmes, nanoparticles, microspheres and microcapsules etc.

Keywords: Cyclodextrins; Inclusion complex; Solubility; Hydrophobic drugs; Drug carrier

INTRODUCTION

During product development aqueous solubility and rate of dissolution are the parameters to be controlled [1]. To overcome the issues to be faced in these parameters could be resolved by using different carrier molecules during the process of product development [2]. Dosage forms must be developed to attain the desired level of drug delivery at the targeted site which is so obtained by proper use of these carrier molecules. Among which Cyclodextrins CDs have their potential to meet the criteria for these properties and parameters just because of their potency to change the organoleptic, physicochemical and biological properties of interacting chemicals by the principle of inclusion complex formation [3]. Advanced nanotechnologies have resulted in betterment of different delivery systems in which CDs are used and also for improvements in production of cyclodextrins to meet their demand and production expenses [4]. Currently over 35 pharmaceutical products have been marketed made by CDs complexes [5].

Chemically CDs are the organic compounds which make complexes with the guest molecules of drugs following the phenomenon of inclusion complex formation. Molecular weights of cyclodextrin exceed 1000 so they are larger than conventional organic compounds. While their weights are smaller than the enzymes that have molecular weights of 10,000 that may exceed upto 20,000-30,000 [6]. Because of this property they have ability to make inclusion complexes with lipid soluble drugs. CDs are also used to enhance solubility of water soluble drugs and hence increase the bioavailability of these drugs followed by improved absorption [7]. Along with absorption of oral systems this complex formation of CDs with drug also increases absorption of drug via transdermal and rectal drug deliveries. CDs also increase the compatibility of drug with excipients so that there are no chances of crystallization of active pharmaceutical ingredients and hence no appearance of new pattern of crystal lattice or any type of chelation [8].

Similarly CDs make such an inclusion complex with the active drug which protect it from thermal, physical and chemical effects of other ingredients in the formulation and also an aid for prevention

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of any type of unwanted erosion, or diffusion in the drug polymer matrix [9]. As the drugs molecules dissociated from the polymer matrix they readily absorbed in the body due to solubility factor of CDs and hence there will not much concentration of drug at that place to promote irritation and any type of toxicities or adverse effects [10]. CDs could also be used to mask the bitter taste and unpleasant odor of drug substances. This target can be achieved by hiding the functional of API with CDs from receptors by the process of complexation. This leads to gain patient compliance and drug stability as well [11].

LITERATURE REVIEW

Cyclodextrins types and complexation

Natural cyclodextrin: Cyclodextrins are the family of chemically and physically stable macrocyclicoligosaccharadies that are synthesized by enzymatic degradation of saccharides (starch). They lack exact cylindrical shape due to chair confirmation of their saccharide monomers [12]. Scientist Schardinger gave them a unique name hence named Schardinger dextrins because of their enzymatic degradation of starch by amylase enzyme. Schardinger extracted them for the first time from starch and its derivatives while Villiers in the year 1891 discovered them first [13].

By classification CDs are either of three groups i.e alpha, beta or gama, alpha group CDs are composed of α–(1,4)–linkages of dextro rotatory glycopyranose subunits and are represented by Greek letter 6, beta group CDs are composed of β–(1,4)–linkages of dextrorotatory glycopyranose subunits and are represented by Greek letter 7, similarly gamacyclodextrins are represented by letter 8 [14]. All these classes are crystalline, non-hygroscopic and homogeneous substances. Beta CDs are the ideal one because of their low cost and high capability to form inclusion complexes. β–cyclodextrin derivatives formed by esterification of methyl and sulfobutyl ether groups are the most preferred choices for the complexation of cyclodextrins with drug molecules [15,16].

Different classes of CDs can be isolated either by the process of precipitation or by using absorption chromatography. For example from a mixture containing three types of CDs, each is precipitated out by adding ethylene-ethane mixture of tetrachloro form. α-CDs can be separated out by precipitation with cyclohexane, β-CDs are precipitated out by the addition of flurobenzene and γ-cyclodextrins can be precipitated out by treating the solution with anthracene [17]. Cyclodextrins are truncated structures, while both top and bottom diameters increases with the increase in glucose units (Figure 1) [18].

Cyclodextrin derivatives

Many types of cyclodextrins have been used in almost 35 above products in pharmaceutical industries and have been synthesized by different ways. These derivatives are produced by reaction of cyclodextrins with amino group containg compounds, reaction called amination, with ester group containing compounds reaction called esterification, with ether group containing compounds reaction called etherification of their primary and secondary alcohols [19]. These derivatives are observed to have better properties than that of parent CDs [20].

Depending on the nature of additional functional group on cyclodextrins, CDs derivatives have varied physical and physicochemical properties like solubility, stability and so have varied behavior towards active ingredients in formulation [21,22]. In Table 1 characteristics of various cyclodextrin derivatives are mentioned [23,24]. These derivatives of CDs can make such changes in the molecular structures of CDs that they become the exact match to use in drug delivery systems [25,26]

Amphiphilic cyclodextrins: Amphiphilic cyclodextrins are the derivatives of cyclodextrins that can be prepared by the addition of alkyl group to parent chain of CDs and are used to enhance the interactive compatibility of cyclodextrins with that of epidermal or transdermal membranes of body [27]. According to conjugated groups cyclodextrins can be categorized into neutral, cationic, anionic CD Amphiphiles.

Neutral cyclodextrin amphiphiles Neutral amphiphilic cyclodextrins polar groups named primary hydroxyl groups [28]. They can also be synthesized by the esterification of secondary hydroxyls at positions 2 and 3. This reaction gives rise to CDs with diacyl groups ranging from 2-14 carbons [29,30].

Neutral amphiphilic cyclodextrins may also be prepared by their conjugation with cholesterol derivatives [31,32]. Amphiphlic derivatives of CDs named heptakis (6-alkylthio-6-deoxy)-ß-CD 2-oligo (ethylene glycol) have functional group of ethylene glycol at secondary position and alkyl group at primary position of CDs. The phenomenon involved here is alkylation and nucleophilic sustitution [33].

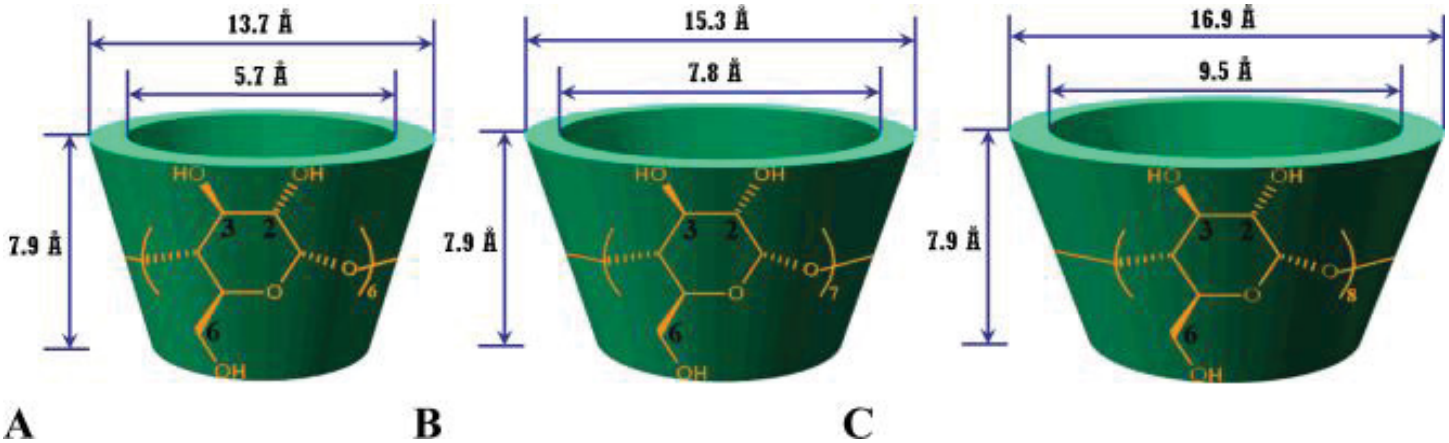

Figure 1: Molecular structures and dimensions of various CDs: **A)** α-CD, **B)** β-CD and **C)** γ-CD. (The positions 2, 3, and 6 are indicated with the numbers of 2, 3, and 6, respectively).

Table1: Characteristics features of different types of cyclodextrins.

Name of Cyclodextrin	Solubility (mg/mL)	Mol.Wt.(Da)
Natural Cyclodextrins		
α–cyclodextrins	145	972
β–cyclodextrins	18.5	1135
γ–cyclodextrins	232	1297
Chemically Modified Cyclodextrins		
Hydroxypropyl β–cyclodextrins	≥600	1400
Sulfobutyl ether β–cyclodextrins	≥500	2163
Randomly methylated β–cyclodextrins	≥500	1312
Hydroxypropyl γ–cyclodextrins	≥500	1576
Polymerized Cyclodextrins		
Epichlorohydrin β–cyclodextrins	>500	112000
Carboxy Methyl Epichlorohydrin β–cyclodextrins	>250	2000000-15000000

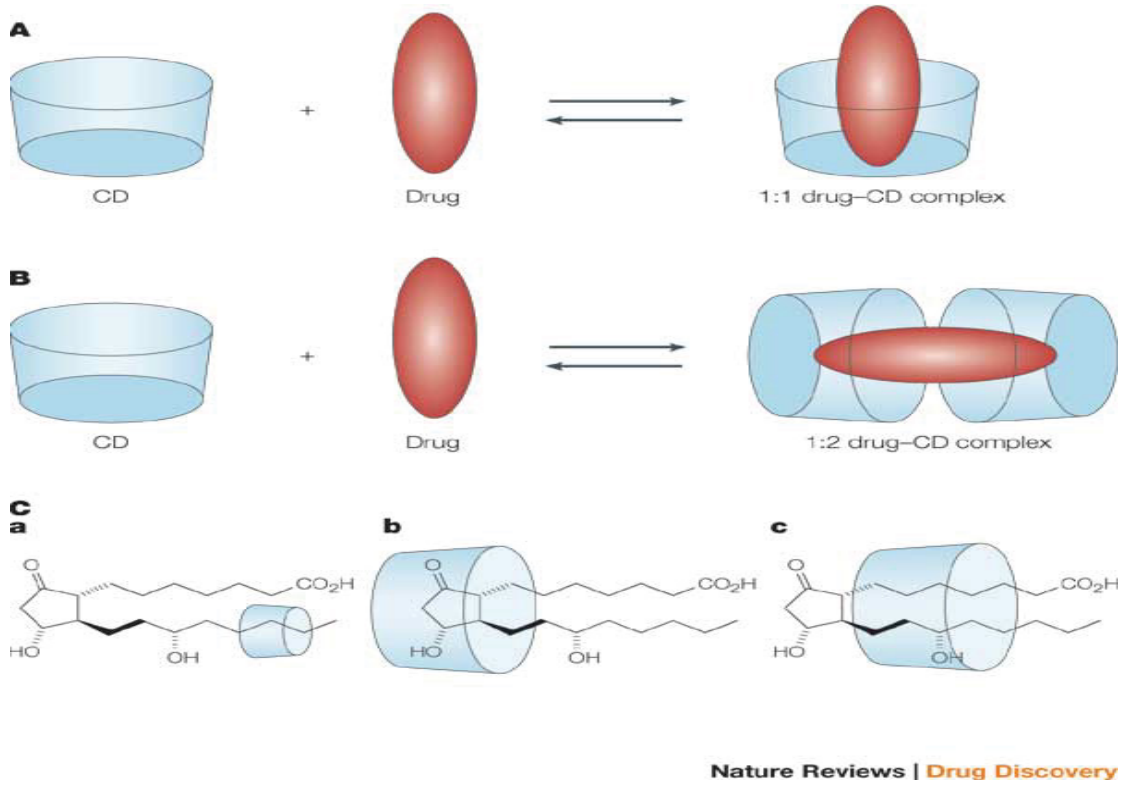

Figure 2: Equilibrium binding of drug and cyclodextrin to form 1:1, 1:2. Complex the interaction of a drug with a cyclodextrin to form an inclusion complex.

Cyclodextrin-containing polymers

Cyclodextrins in combination with various types of polymers are used to enhance the compatibility of drug molecules with polymer matrix for better diffusion of drug-polymer complex in plasma and hence to provide better drug delivery system. Structures of these polymers are as simple as a linear un-branched structure and as complex as hyper-branched and dendritic structures, where CDs are:

1. Attached to the main chain of linear or branched polymer
2. Conjugated to the polymer chain

Polymers with cyclodextrins in the main chain: These can be obtained by poly-condensation of CDs with epichlorohydrin in alkaline solution [34,35]. CDs obtained by this attachment could cover the drug either by making lipid soluble interaction of CD Polymer with drug or by making host guest interaction [36].

By introducing other functional monomers such as charged compounds in there action mixture of CD-epichlorohydrin, CD-based poly-cations can be obtained by a similar poly-condensation reaction [37].

Cyclodextrin-conjugated polymers: Cyclodextrins are covelantly conjugated with drug molecules to enhance biocompatibility of drugs. Polymers are used for this bonding [38]. These CDs polymers were used to make assemblies of nano, micro and macro molecules. These polymers could be either biodegradable or non-biodegradable and can be prepared by direct polymerization of CDs or copolymerization with other monomers [39-42].

Cyclodextrins and inclusion complexation phenomenon

Chemically CDs are the saccharides of five carbon atom rings of glucose units that contains two types of characteristics in their structures:

1. Hydrophobic central cavity
2. Hydrophilic outer surface

They are not perfectly cylindrical in shape but have cone shaped structures [43]. Due to this characteristic structure they can bind guest drug molecules perfectly and enhance the solubility and absorption of hydrophobic drugs in the body by increasing diffusion of drug-polymer matrix. Drug-CD complex formation does not involve the formation or breaking of covalent bonds [44]. The driving forces responsible for drug-CD complex formation includeelectrostatic interactions, van der Waals forces, hydrogenbonding, the release of conformationalstrain and charge-transfer interactions.

{LOFTSON}In aqueous solution drug-CD complexes readily diffuse and free drug molecules always remain in equilibrium with the molecules within the CD cavity (Figure 2).

Applications of cyclodextrins in drug delivery systems

CDs are used in almost every drug delivery system because of their multifunctional characteristics. The commercial feasibility of CD-based oral product formulations has been established with worldwide marketing of more than 20 products [45].

Oral drug delivery system: Oral route is the most common and popular route for drug delivery since time immemorial. In the oral delivery of drugs, drug release is either controlled through dissolution, diffusion or osmotically and also may be density controlled or pH controlled [46]. CDs are being used as an excipient for transportation of drugs through an aqueous medium to the lipophillic absorption site in the GIT i.e., complexation of drugs with CDs has been used to boost the dissolution rate of poorly water-soluble drugs. Hydrophilic CDs are mainly useful in this respect. For buccal and sublingual administration of drugs rapidly dissolving CD-drug complexes have been formulated. In these types of delivery system, a prompt increase in the systemic drug concentration takes place and along with the avoidance of systemic and hepatic first-pass metabolism [47].

Cyclodextrins in oral drug delivery system

Drugs with enhanced drug solubility: Bromazepam, Nifedipine, Ketoprofen, Itraconazole, Naproxen, Tacrolimus, Tropicamide, Prostaglandins, Omeprazole, Nimesulide, Ketorolac, Theophylline, Tolbutamide, Gliclazide are the drugs with which CDs are used to enhance drug delivery. Metoprolol, Nifedipine, Quinapril are the drugs with which CDs are used to enhance stability. Sparfloxacin, Artemisin, Terfenadine, Tolbutamide are the drugs with which CDs are used to enhance drug bioavalability. Meloxicam, Along with prednisolone CDs reduce gastric ulceration.

Rectal drug delivery system: Cyclodextrins are used in rectal dosage forms for the drugs that are bitter in taste or degraded in low pH of stomach. Patients facing coma like diseases and children can also get benefit from these rectal drug delivery systems. CDs are used in rectal delivery systems to increase the surface area for absorption, also they are non-irritant and inhibit reverse diffusion of drugs [48].

Cyclodextrins in rectal drug delivery system: Ethyl-4-biphenylyl acetate (EBA) insulin are the drugs along which CDs help the drugs to enhance drug release. Human granulocyte colony stimulating factor can show enhanced chemical stability in combination with CDs. Morphine have their enhanced rectal absorption and drug bioavailability along with CDs. Prednisolone along with CDs have reduced rectal irritations.

Nasal drug delivery system: CDs are also used in most of the nasal drug delivery systems for better penetration and drug absorption in to blood streams. This application of CDs is applicable for highly potent drugs and the drugs with low rate and extent of drug absorption in body tissues. CDs help in the enhancement of permeation in blood stream through intranasal drug delivery, this characteristic make them biological barrier for better penetration of drug and hence improved bioavalability.

As excipient for the nasal delivery system CDs should have no effect on secretory functions of ciliac cells of nasal mucosa. They should not produce ciliostatic effect. Must be non-irritating and should be safe for allergic patients. CDs help in the enhancement of permeation in blood stream through intranasal drug delivery system [49].

Cyclodextrins in nasal drug delivery system: Drugs like Glucagon, Insulin, Calcitonin and Leucine encephalin when combined with CDs show improved absorption. Estradiol is the drug that in combination with CDs is available in controlled release dosage forms. Midazolam could increase its bioavailability in presence of CDs. Sodium deoxycholate decreases its toxic effects with CDs.

Transdermal drug delivery system: Transdermal drug delivery system is a very convenient drug delivery system. CDs are used as chemical enhancers in this system and so enhances the chemical and therapeutic activity of drug. CDs for this purpose should have no therapeutic effect on skin. They should be friendly for epidermal membranes of skin to avoid any irritation and allergic reaction. They should have no effect on pH of skin i.e must have pH round about 5 (pH of skin) [50].

Cyclodextrins in transdermal drug delivery system: Miconazole enhances its stability in the presence of CDs. Dexamethasone, Hydrocortisone, Oxybenzone show enhanced permeation in combination with CDs. Ketoprofen show minimal side effects while combined with CDs.

Ocular drug delivery system: Eye drops are the most preferred dosage form in ocular drug delivery system because of easy instillation in the eye. Inability to sustain high local drug concentration is the major disadvantage of this dosage form. CDs are being used to increase the drug's solubility, stability and to prevent the side effects such as irritation and discomfort. CDs used as excipients in ocular drug delivery system, should be non-irritating and non-allergic to ocular surface. They should be therapeutically in active and non-toxic [51].

Cyclodextrins in ocular drug delivery system: Pilocarpine, Dexamethasone, Hydrocortisone enhance their solubility when combined with CDs. Acyclovir, Acetazolamide are the drugs that show enhanced bioavailability in combination with CDs. Thalidomide, Pilocarpine, Diclofenac show enhanced corneal permeability (*in vitro*) when combined with CDs. Methazolamide decreases its intraocular pressure effects with CDs.

Controlled and targeted drug delivery system: CDs are used in controlled and targeted release dosage forms as they help in the

release of drug molecules from CD-drug complex in a controlled manner. CD derivatives formed by alkylation and acylation of parent CD at primary or secondary sites have property to enhance drug absorption and release rate from CD-drug matrix. So the drug delivery is controlled and fast from matrix according to patient demand and need. The improvements of drugs formulated as controlled and targeted delivery systems using different CDs [52,53].

Cyclodextrins in controlled and targetted drug delivery system: Prednisolone, Furosemide, Testosterone, Diltiazem and piroxicam are drugs that could be designed as controlled release dosage forms when combined with CDs. Verapamil, Prednisolone, Metronidazole, Dihydroergosterol enhances their release in combination with CDs.

Peptide and protein delivery: Peptides and proteins that are used for therapeutic purposes endure many of the problems like poor absorption through GIT, enzymatic instability or rapid excretion and clearance [54-56]. In such cases CDs are used to interact with the cellular membranes and can act as carriers for the delivery and controlled absorption of peptides and proteins. These carriers are used for the absorption of hydrophobic drug molecules. An apically polarized verapamil-sensitive efflux system for small lipophilic peptides is being found in the BBB of rats [57].

Gene and oligonucleotide delivery: Immunogenicity and toxicity which are associated with viral vectors led to the development of nonviral vectors for gene delivery. Further the plasmid or virus based vector systems and "naked" nucleotide derivatives are also being investigated for potential use as therapeutic agents through different routes of administration. Now-a-days gene delivery technologists are testing the CD molecules in the hope of finding an ideal carrier for the delivery of therapeutic nucleic acids. However, the limitations of CDs like CD-associated toxicity (e.g., DM-β-CD) need to be considered before their clinical use [58].

Dermal and transdermal delivery: Parent CD i.e (α, β, and γ CDs) and their derivatives are used to increase and modify the delivery systems of dermal and transdermal drug deliveries. These could enhance the absorption and penetration capacity through formation of inclusion complexes [59].

Brain drug delivery or brain targeting: Cyclodextrin derivatives like 1-methyl-1,4dihydronicotinic acid at primary and secondary positions of parent CD molecule are used to enhance the lipophilicity of drugs that are brain targeting delivery systems [60-63].

Novel delivery systems

Liposomes: Liposomes are the delivery systems in which a hydrophilic head is entrapped in a hydrophobic outer surface. CDs are used to entrap drug molecules to form liposomes in which CD helps in the enhancement of solubility of drug and drug molecule will be targeted to the specific site for therapeutic effects. Hydrophilic end of liposomes is attractive for water soluble drugs and hydrophobic end is the mean for enhancing absorption of lipid soluble drugs [64]. However in case of parenteral drug administration, especially after chronic use, can be circumvented by their entrapment in liposomes [65].

Microspheres: In microsphere delivery systems CDs asexcipient may not increase the absorption and distribution of drug. For example release of niphedipine from its microspheres becomes slow on addition of CD [66]. This is due to smaller extent of drug absorption and dissolution from CD-drug complex due to formation of chitosan [67,68]. Chitosan is the layer of CD –drug matrix formed around the microsphere that causes decreased in absorption and hence permeability of drug molecules in to plasma [69,70]. Sustained release delivery systems of microspheres make the surface of microsphere more lipid soluble so the drug molecules becomes increasingly soluble and dissociate from matrix after a sustained period of time [71].

Microcapsules: Microcapsules of CD-drug molecule have ability to decrease the dissolution and diffusion of water soluble drugs through the matrix and used in controlled drug delivery systems. For example CD complex of terephthaloyl chloride is used to decrease the solubility of drugs like atenolol, propranolol [72,73]. Double microcapsules, prepared by encapsulating methylene blue with different amounts of β-CD microcapsules inside a cross-linked human serum albumin (HSA), showed decreasing release rate of methylene blue with increasing amount of β-CD microcapsules [74,75].

Nanoparticles: Nanoparticles are used for CD-drug complex to make the sustained and controlled release of drug molecules in enhanced order of drug dissolution and bioavailability of lipid soluble drugs. Nanoparticles have limited use as drug delivery systems because of low entrapment [76]. However by the use of CD nanoparticles become advantageous over others like:

1. CD increases the capacity of nanoparticles to penetrate drug in the blood stream.
2. Esterification of CD in the formation of nanoparticles [76,77,78].

Future prospects of cyclodextrins

Unique properties of complex formation with drugs make future prospects of cyclodextrins and their derivatives quite bright. As the number of drugs being developed today have been increased which have problem of poor solubility, bioavailability and permeability [79-82]. In pharmaceutical industry, for optimization the drug delivery of such problematic drugs, CDs and their derivatives can be quite useful. They also serve as tools for the drugs having other undesirable properties such as objectionable odor and taste, poor stability, and irritation potential [83-89]. Instead of being useful in dosage forms like tablets, capsules, solutions, syrups, ointments etc. cyclodextrins are also have diverse application as discussed above in novel drug delivery systems. CD used to enhance the permeability and penetration of drug molecules as nanoparticles, nanocapsules, microspheres liposomes.

However, it is necessary to work on any possible interaction between these agents and other formulation components because the interactions can badly affect the performance of both. To have the knowledge of different factors that have impact on complex formation is also very important in order to prepare drug/CD complexes economically having desirable properties [89-92]. Also it is necessary to work for the development of other economical derivatives of cyclodextrins having desired properties and no toxic potential.

CONCLUSION

Cyclodextrins have diverse applications in different drug delivery areas and pharmaceutical industry. These diverse applications

are due to their complexation ability and other versatile features. But it is needed to find out possible interactions of cyclodextrins with other formulation components because the interactions may adversely affect the overall performance of both. It is also necessary to gather knowledge of different factors which can possibly influence the complex formation in order to prepare the economical complex with needed properties.

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