REVIEW

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Chronicle updates in cyclodextrin-based carriers for drug delivery

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Abstract

Background: Cyclodextrins offer a range of biomedical applications in the pharmaceutical and biotechnology industries. Cyclodextrins (CDs) are oligosaccharides composed of glucose as repeating units (6–9 repeating units given terms α, β, γ and δ, respectively). Its inner core size varies with the type of CD, and this variation finds its fitness with small- to larger-sized organic drug molecules to resolve its delivery problems. Employment of CDs in drug delivery was conceptualized since its initial development (Year 1891). However, the very first pharmaceutical product was in the market in 1976. CDs not only act as carrier or as self-assembly hydrogel or hybrid gels for delivery of hydrophobic drugs but also reported as a modifier of the gelling temperature of agarose and make it suitable for drug delivery.

Main body: This review represents the trend of research on CDs with reference to drug delivery. Phase I (1975–1980) CD research trend shows inclination towards β-CD molecules for inclusion complex with a wide range of drugs. Decade of phase II (1981–1990) worked majorly on other natural CDs with a glimpse of its derivative for drug delivery system. Critical literature surveys from the years 1991–2000 (phase III) provide research visualization of CD derivatives supported with animal studies. Phase IV (2001–2010) can be attributed as the golden period of CDs with its extreme exploitation in many novel drug delivery systems (aerosols, microemulsion, polymeric nanoparticles, osmotic pumps, and sustain release), while in most last decade CDs were observed in association with nanoscale systems.

Conclusions: In the view of its incessant utilization in wider applications including drug carrier, gel, gel modifier and nano-composite modifier properties, its chronicle update in the drug delivery knowledge database would inspire the researchers for multidisciplinary research. To sum up, almost every emerging novel drug delivery system in the near future will make the earnest effort to take advantage of the properties of CDs for their better efficacy, stability, prevention of toxicity and patient acceptability.

Keywords: Cyclodextrins, Hydroxyl propyl derivatives, Methyl derivative, Drug delivery, Characterization, In vitro, In vivo

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Background

The significant emergence of novel drugs for effective diagnosis and treatment finds a common difficulty, i.e. successful drug targeting and delivery in the desired target area. Most of the commercialized drug molecules lack solubility, specificity, permeability, immediate metabolism and lesser tolerability, making the drug lacking therapeutic eminence (Hodgson 2001; Loftsson and Brewster 2010). The development of modified drug formulation has been proven to overcome the drawbacks of drugs with above-mentioned problems. Many research works

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have been initiated to bring out novel drug carrier molecules to meet the requirements. Cyclodextrins (CDs) as three-dimensional molecule are one of the highly explored drug delivery/carrier systems as biomedical application. CDs are cyclic oligosaccharides composed of repeated glucose units [6 (α-), 7 (ß-) or 8 (γ-)], resulting in a toroidal or truncated conical structure formed through α(1–4)glycosidic bonds. CDs not only act as carrier or as self-assembly hydrogel (Antoniuk and Amiel 2016) or hybrid gels (Jalalvandi et al. 2016) for delivery of hydrophobic drugs but also reported as a modifier of gelling temperature of agarose and make it suitable for drug delivery (Kim et al. 2019). Recent research trend focuses on its drug carrier, gel, gel modifier and nanocomposite modifier properties. In the view of its incessant utilization in wide range of domains, its chronicle update in the drug delivery knowledge database would inspire the grooming researchers, provide combinatorial possibilities to experienced/flourished researchers and attract other domain audiences. This review encompasses the development of CD for drug delivery system based on Google Scholar/PubMed literature survey with keywords CDs in drug delivery including research papers and patents. Decade-wise CDs indicative development based on drug delivery system has been collected and discussed from the inception of exploratory phase to the commercial applications.
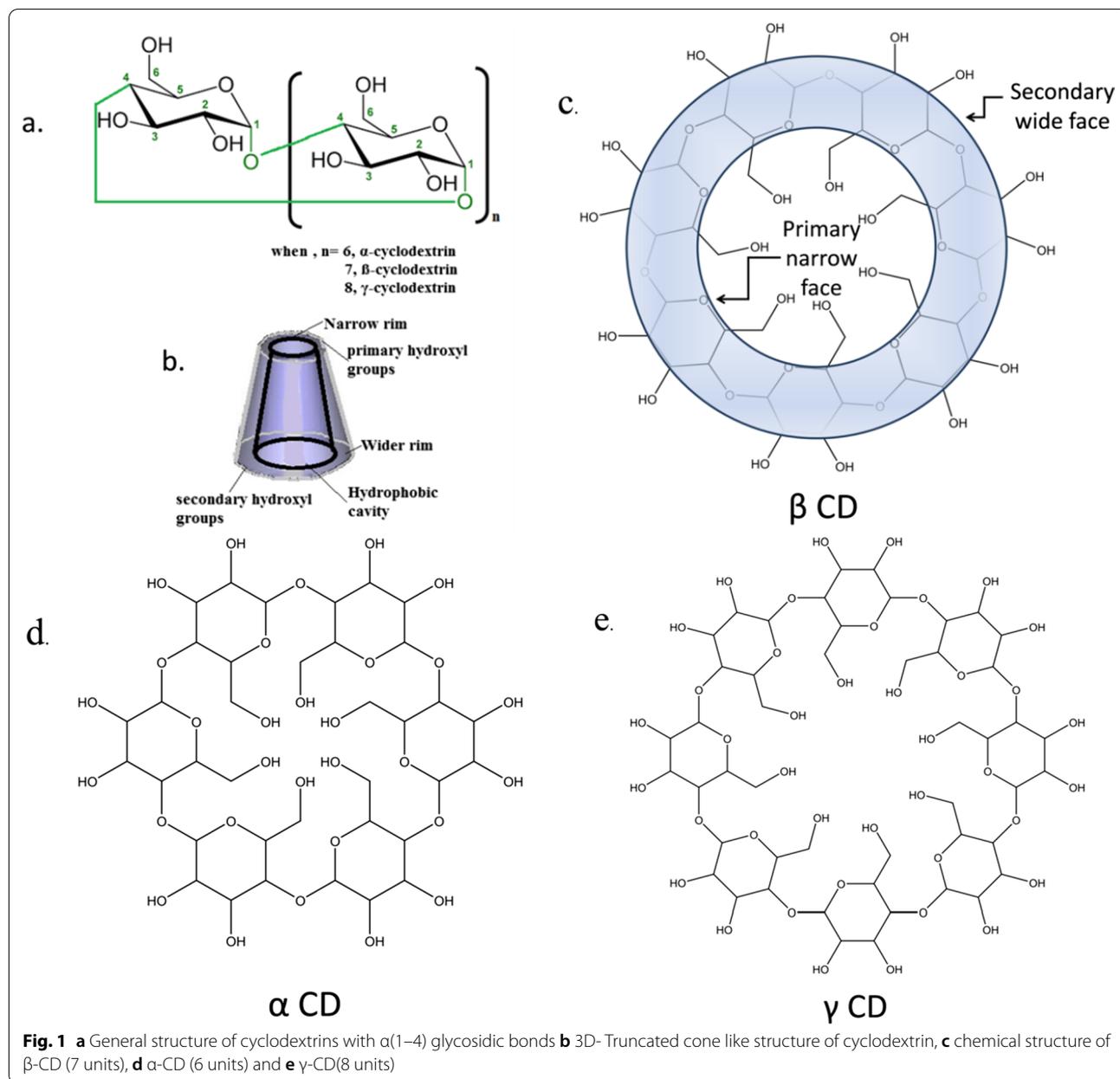
Main text

Professor JozsefSzejtli represented CDs development in three phases, i.e. discovery, exploratory and utility (Szejtli 1998). Viller initially gave the name cellulosine to a bacterially digested crystalline glucose form with yield of 0.3%. This reproducible study raised a new field in carbohydrate chemistry to discover what this carbohydrate form is (Villiers 1891)? In 1911, Schardinger also observed crystalline material after treatment of potato sugar with bacteria (*Bacillus macerans*) and crystalline dextrin was given to it (Schardinger 1911). Freudenberg and Jacobi, with different bacterial treatments, found another form of which was later called gamma (γ) CD with slightly different properties; an important one was solubility (Freudenberg and Jacobi 1935). Finally, its ring and cavity structure was elucidated in 1938 (Freudenberg and Meyer-Delius 1938). Sixteen years later (1954), Carmer described structure, cavity sizes and diameters of CDs (α, β& γ) along with possibility and stability of inclusion complexes. The elucidated structure suggested that it is a molecule with inner diameter of the truncated conical structure with 7.8 Å height, varies as 5.7 to 7.8 and 9.5 Å by the increment in the number of glucopyranose units. The primary hydroxyl groups and secondary hydroxyl groups

of the glucopyranose units occupy the narrow and wider sides of the truncated cone. CD molecules noncovalently form an inclusion complex by the interaction with the guest molecules. The CD consists of external hydrophilic and internal lipophilic surfaces that readily accept the drug molecules to form a complex (Fig. 1a–c). This enhances the guest molecules solubility or protects them throughout the drug delivery process. CD homologs with less than 6 glucose units are difficult to form because of the steric hindrance, and CDs with higher glucose units (9 units) render difficulties in the purification process and meagre yield (Ueda 2002; Challa et al. 2005).

In the exploratory phase, starch was treated with purified enzymes from the micro-organisms instead of the whole micro-organism, resulted in specific production. Cyclodextrin-glycosyl-transferase (CGTase) enzyme was found to be responsible for attaching two ends of oligosaccharide detached from starch (Saenger 1980). Later genetically engineered CGTase was developed to make its industrial production scale possible. The solubility of cyclic dextrin was significantly lower than linear dextrin, and solubility of different CDs also varies depending upon the type of bonding (Sallas and Darcy 2008). The size of the inner cavity of α-CDs was found to be inadequate for the drug encapsulation process, whereas γ-CD was found to be expensive for this purpose. The δ-CD was found to possess a reduced complex forming capacity with the drug molecules than that of the native CD molecules. ß- and γ-CDs were found to possess higher solubilizing capacity than δ-CD, whereas δ-CD has a higher solubilizing capacity than α-CD. In ancient times, ß-CD molecules were considered to be most suitable due to their cavity size and easy availability. However, in the parenteral drug delivery process, ß-CDs are refused because of their toxic nature to nephrons and low aqueous solubility nature (Challa et al. 2005).

By subjecting, native CD molecules to chemical modification attributes an amphiphilic nature to it, contributing actively for the self-assembly characteristics. The domains in the CD region enable the encapsulation of the guest or drug molecules into it to facilitate in the targeted drug delivery process (Sallas and Darcy 2008; Fromming and Szejtli 1993). These molecules not only find its application in pharmaceutical industries but also in textile, cosmetics as well as in food industries.

The CD molecules possess different characteristics enabling them to serve as a suitable drug carrier molecule. It includes a distinct chemical structure with recognizable sites for modifying chemically and drug conjugate formation along with varying inner cavity size, less toxic nature and less pharmacological adverse effects, protects the conjugated drug molecules from degradation,

Fig. 1 **a** General structure of cyclodextrins with α(1–4) glycosidic bonds **b** 3D- Truncated cone like structure of cyclodextrin, **c** chemical structure of β-CD (7 units), **d** α-CD (6 units) and **e** γ-CD(8 units)

bioadaptability, low gastrointestinal absorption, solubility nature and many more.

The cavity size, molecular weight and solubility of the naturally occurring CDs are given in Table 1 (Challa et al. 2005).
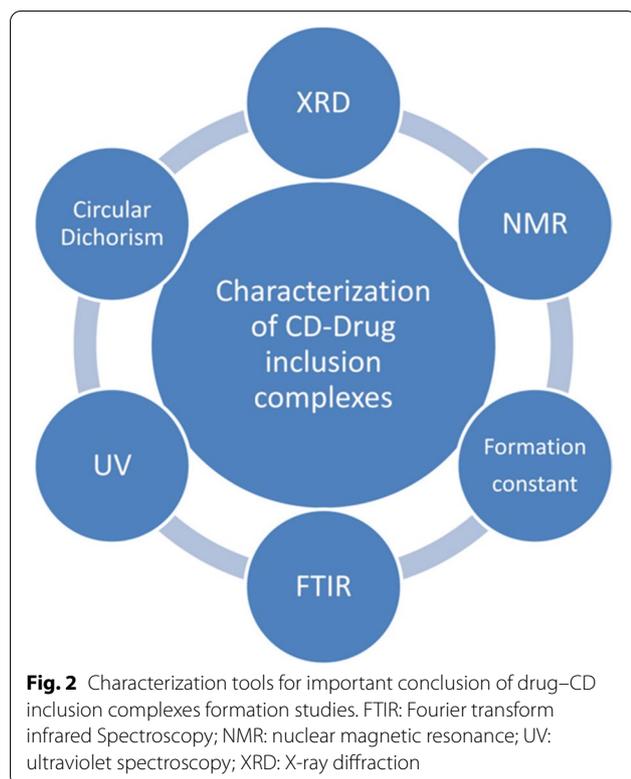
Cyclodextrin in medicines as bioactive compounds and drug delivery systems

The ultimate motive of a drug delivery system is to deliver an appropriate quantity of drug molecules to the predetermined target site for a desired period of time, more accurately and systematically. The undesired side effects of the drug molecules in the body can be restrained by the evolution of novel drug carrier molecules that would redirect the undesired reactions in the body. CDs are one of the most prominent candidates that are capable of altering the physicochemical and biological characteristics of the guest molecules (drug) interacting with it by means of inclusion complex formation by the interaction of the drug with their hydrophobic cavity. The CD molecules have the ability to augment the stability, solubility as well as the bioavailability of the drug molecules complexed with it. In 1976, first pharmaceutical product prostaglandin E2 appeared in the market for

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Table 1 Physicochemical properties of variants of cyclodextrins (CDs)

Cyclodextrin	Glucopyranose units	Diameter of the internal cavity (Å)	Solubility (g/L)	Molecular weight
α- CD	6	4.7–5.3	1.45	972
ß- CD	7	6.0–6.5	0.85	1135
γ- CD	8	7.5–8.3	2.32	1297
δ-CD	9	10.3–11.2	0.82	1459

Fig. 2 Characterization tools for important conclusion of drug–CD inclusion complexes formation studies. FTIR: Fourier transform infrared Spectroscopy; NMR: nuclear magnetic resonance; UV: ultraviolet spectroscopy; XRD: X-ray diffraction

more soluble and thus bioavailable, stable formulation of prostaglandins (Loftsson and Duchene 2007). However, the natural CD molecules are less soluble in water and organic solvent systems than their derivative molecules (Uekama et al. 1998; Duchene 2011).

Phase I (1975–1980): Establishment period of β-cyclodextrin
In this phase of time, a very few groups of researchers were involved in this field of research producing research articles and patents. Most of the studies were taking β-CD for making inclusion compounds and were including preparation of inclusions with CDs and their physical characterization, such as X-ray diffraction (XRD), circular dichroism, thermo-gravimetric analysis (TGA), nuclear magnetic resonance (NMR), formation constant (Fig. 2) (Loftsson and Duchene 2007; Otagiri

et al. 1975,1976; Ikeda et al. 1975; Uekama et al 1978a, 1978b) and a couple to studies showed bioavailability and effect of CD-drug preparation in vivo (Szejtli et al. 1980; Uekama et al. 1979a; Koizumi et al. 1980a) (Table 2). Otagiri et al. observed the increase in optical activity of phenothiazines and its derivatives after attachment with CDs (evaluated using circular dichroism) and termed as induced cotton effect. They also elucidated the mechanism and structure of inclusion complex. Absorbance in circular dichroism and UV spectra of substituted phenothiazine CD inclusion complex was found to be more than phenothiazine CDs complex (although it is more than phenothiazine not complexed); thus, it was concluded that not only phenothiazine but also its N-substituted compounds also contributed in the formation of complexes. NMR spectra showed the changes in chemical shift with internal (strong) and external protons, which suggested the interaction of phenothiazine to interior cavity as well as externally (Otagiri et al. 1975).

While NMR studies in case of mefenamic acid, there was broadening of chemical shift for phenyl ring protons indicating the restriction of electrons after interaction with CDs. This observation suggested that there is formation of inclusion with internal cavity only (Ikeda et al. 1975). Formation constant in such cavity inclusion cases suggested the stoichiometric ratio of CD and drug 1:1 in case of β-CD (Uekama et al. 1978b). XRD characteristic peaks of crystalline drug CDs complexes were at different diffraction angles 2θ value than CDs alone. With a reference to drug delivery, researchers did not give much attention to this potential 3D molecule during this phase. Among few studies related to drug delivery, one widely studied research published in patent included preparation of nitroglycerin (antianginal) β-CD complex, its characterization (XRD, NMR, circular dichroism) and bioavailability studies in human that were carried out. This invention was to overcome the problems associated with nitroglycerin, i.e. volatility of 4-mm size tablets. Decomposition temperature of nitroglycerin in its CD complex was significantly higher (192 °C) than nitroglycerin stand-alone formulation, giving indication of formation of inclusion complex. Evaporation rate of the inclusion compound was reduced to 1/10 to that

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Table 2 Phase I (1975–1980) of cyclodextrin (CDs) development

Year	CD type	Drug	Studies	Reference
1975	β	Phenothiazine	Inclusion formation and characterization	Otagiri et al. (1975)
1975	β	Fenamates	Inclusion formation and characterization	Ikeda et al. (1975)
1976	β	Barbiturates	Inclusion formation and characterization	Otagiri et al. (1976)
1978	β	Stability constants for barbiturates, phenothiazines sulfonylureas, etc.	Inclusion formation and characterization	Uekama et al. (1978a)
1978	β	Sulphonamide	Inclusion formation and characterization	Uekama et al. (1978b)
1978	β	Nitroglycerin	Inclusion formation and characterization, resolving volatility problem of nitroglycerin increasing bioavailability	FAkito et al. (1978)
1979	β	Acetohexamide	animal studies	Uekama et al. (1979a)
1979	β	Prostaglandins	dissolution and chemical stability studies	Uekama et al. (1979b)
1980	β	Indomethacin inclusion complexes	in vivo bioavailability studies, anti-inflammatory activity and ulcer toxicity studies	Szejtli et al. (1980)
1980	β	Barbiturates	animal studies	Koizumi et al. (1980a)
1980	α, β	Prostaglandins attachment changes molecular dynamic of CDs	Inclusion formation and characterization	Hirayama et al. (1980)
1980	β	Tolbutamide chlorpropamide	Inclusion formation and characterization	Ueda and Nagai (1980)

of conventional nitroglycerin product, while sublingual delivery to healthy humans showed nitroglycerin β-CD complex effects (blood pressure, heart rate) significantly higher than placebo and equivalent to conventional formulation of nitroglycerin (Table 3) (FAkitoet al. 1978).

A very interesting study of indomethacin β-CD complex covering physicochemical characterizations (XRD, IR, circular dichroism, pKa values), bioavailability in starved rats, pregnancy protective property in rabbits, anti-inflammatory activity and subacute toxicity (ulcer test) of indomethacin β-CD complex in comparison with indomethacin alone was carried out. Interestingly, in vivo evaluation of the indomethacin-β-CD complex was found to be significantly better/statistically similar than/to its equivalent free indomethacin. The curve of plasma level vs time of indomethacin level by its CD complex was high throughout the study time range. Study of pregnancy protection was evaluating the number of the implantations of the uterus and the number of the alive foeti. Percentage of alive foeti in the control group and

free indomethacin complex was 16.1% and 58.8%, respectively, while the indomethacin–CD complex was found to show 66.7% alive foeti (significantly higher than control and statistically equivalent to free indomethacin). Anti-inflammatory activity of indomethacin–CD complex with respect to standard free indomethacin was determined measuring the weight of carrageenan-induced inflammatory feet (separated above metacarpus) of placebo control and treated animals. Taking weight of control animal's feet as 100% inflammation thus 0% anti-inflammatory condition, the percentage of anti-inflammatory activity of indomethacin–CD complex was equivalent to non-complex indomethacin for acute inflammation, while it was high at higher doses, which were attributed to absorption of the drug in complex form. Duration and speed of anti-inflammatory activity were also better than free indomethacin. While its 1:1 indomethacin–CD complex was having higher ulcerative toxicity than free indomethacin (Szejtli et al. 1980) (Table 4), acetohexamide (hypoglycemic agent) complexation with β-CD showed better

Table 3 Outcomes of nitroglycerin-cyclodextrins (CDs) inclusion complex (FAkito et al. 1978)

Decomposition temperature	Nitroglycerin conventional formulation:very small Nitroglycerin-CD complex: 192 °C
Evaporation rate	Nitroglycerin conventional formulation: 1 Nitroglycerin-CD complex: 1/10
Evaporation content after 10 days 50 °C	Nitroglycerin conventional formulation: 100% Other cellulose-based formulation: 81% Nitroglycerin-CD complex: 42%
Sublingual delivery to healthy human	Nitroglycerin-CD complex: Heart rate and blood pressure significantly higher than placebo and slightly higher than conventional formulation

Table 4 In vivo studies indomethacin–cyclodextrins (CDs) inclusion complex (Szejtli et al. 1980)
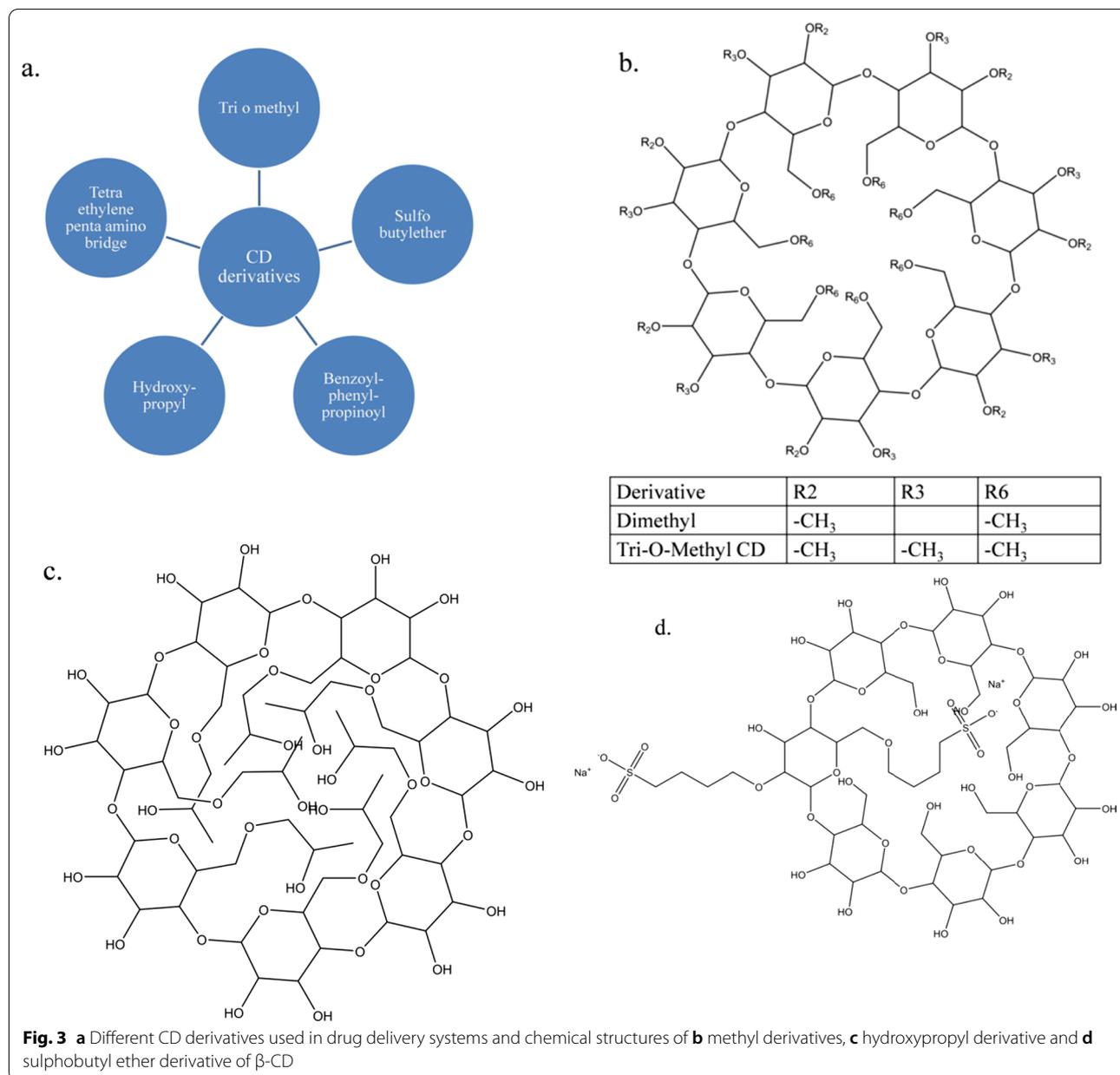
Bioavailability (plasma concentration) in rats	Indomethacin–CD complex: higher than free indomethacin throughout study time range
Pregnancy protection study in rabbit	Control: 16% alive foeti Free indomethacin: 58.8% Indomethacin–CD complex: 66.7% (insignificantly higher than free indomethacin)
Anti-inflammatory activity in rats	Indomethacin–CD complex: insignificant at lower dose while significant at higher dose with respect to equivalent free indomethacin
Duration of anti-inflammatory activity in rats	Indomethacin: showed un-observable activity if given after 48 h of carrageenan induction of inflammation Indomethacin–CD complex: retained activity even if given after 6 h
Speed of anti-inflammatory activity	Indomethacin–CD complex: higher speed of inflammation
Ulcerative toxicity in rats	Indomethacin–CD 1:1 complex caused more ulcerative toxicity than free drug

glucose control in rabbits over a long period of time than non-complex acetohexamide. The effect was also compared with "physical mixture of drug and β-CD". The mixture showed the hypoglycemic activity same as that of the free acetohexamide (Uekama et al. 1979a). Overall, this phase of CD development was paving its utility in the drug development field of research.

Phase II 1981–1990: exploration of natural cyclodextrins and emergence of its derivatives for drug delivery

This decade and onward showed overwhelmed research publications and patents with concerned keywords. This phase can also be characterized by the development of CD derivatives for its next version of properties. The research during this phase represented that CDs are generally biodegradable in the aqueous state that enables them to be used in pharmaceutical applications. β-CD contains 7 primary and 14 secondary –OH groups at the smaller and larger entrance of torus. The hydroxyl groups present in their molecular structure make them water soluble to a great extent. But, due to the presence of secondary hydroxyl groups and inter-hydrogen bond networks, ß- CDs are less soluble (2% (w/w)) than α-CDs (13% (w/w)) at ambient environmental conditions, whereas γ-CDs are more soluble (26% (w/w)) than the other two (Muankaew et al. 2014). β-CD retains the best drug inclusion property among other natural CDs, but its insolubility limits its potential. As a solution to the above problem, γ CDs were used instead where the molecule fits its cavity size, while CDs, mainly its β form, were derivatized with hydrophilic moieties (Fig. 3). Even hydrophobic methyl derivative was increasing its aqueous solubility. This unexpected behaviour was attributed to the breakage of intermolecular hydrogen bonding with hydrophilic or hydrophobic functional group attachment to hydroxyl group of CDs. Up to 2/3rd hydroxyl group consumption of the β-CD with functional group progressively increasing the solubility (Loftsson and Duchene 2007). The dynamic equilibrium is maintained between the free

drug and the CD molecule by an appropriate interaction between them by means of their adequate inner cavity size and their physicochemical properties. This leads to the formation of an inclusion complex. For instance, the host–guest interaction between α- and β-CD molecules with prostaglandin E_2 led to the complex interaction with aliphatic groups and aromatics groups, respectively (Del and Martin 2004). In a recent supporting study, utilizing a molecular dynamic simulator, it has been predicted that structure distortion of β-CD was maximum in polar solvents in comparison with its derivatives. That means β-CD retains its structure and shape suitable for making inclusion compounds when there is proper intramolecular hydrogen bonding (Khuntawee et al. 2017). So, this decade started exploring drug inclusions with derivatized β- or α/γ-CDs with respect to its delivery and were evaluated by in vivo, in vitro or ex vivo systems/models. In this decade (phase II 1981–1990), representative studies in this phase relate to β-CD utilization with different problems in delivery, more of other natural CDs with problems in which β-CD was not suitable or compatible, and studies with derivatives of CDs have been compiled (Additional file 1) and high impacting/interesting ones are discussed (Table 5). With solubility, bioavailability increases thus low dose required to achieve therapeutic concentration ultimately showing efficacy with low concentration. In an interesting study by Szejtli and Szente, CHINOIN-137 (indomethacin & β-CD 1:2 molar ratio) movement with respect to location (*in loco*) was studied using C^{14}radiolabelling technique. Significant higher activity (68%) of complex CHINOIN-137 than indomethacin (54%) alone was observed. The bioavailability in rat was also higher (25%) in this complex (Szejtli and Szente 1981). Dose with 50% effect (ED_{50}) of barbiturates (barbital, amobarbital, Phenobarbital, allobarbital and pentobarbital) and its respective inclusion complex with β-CD were determined evaluating sleeping lag and sleeping time in rats. The ratio (CD complex to its free form) of ED_{50} was found to be minimum in case of phenobarbital

Fig. 3 **a** Different CD derivatives used in drug delivery systems and chemical structures of **b** methyl derivatives, **c** hydroxypropyl derivative and **d** sulphobutyl ether derivative of β-CD

inclusion complex (Koizumi et al. 1980b). Phenobarbital β-CD suppository formulation was further used for rapid release and absorption (IwAoKu et al. 1982).

Digoxin tablets used for cardiac patients were showing problems of variable bioavailability due to its low aqueous solubility and its uncontrollable degradation in stomach due to its acidic pH. So, on the above ground, its inclusion complex with γ-CD was prepared and characterized. α and β CDs were not suitable due to their low cavity size for digoxin, and thus, the yield of inclusion complex was poor. Dissolution rate was 30 times higher than the digoxin due to both solubility and reduced

particle size (increased surface area of dissolution) of the digoxin-γ-CD preparation. Tablet of fine powder from digoxin γ-CD was given to the dog. Its plasma concentration profile was always remained higher than profile of free digoxin. After 45 min of administration, the complex was having 3 times higher plasma concentration than free digoxin, while after 24 h the same was 5.4 times. Such preparation was claiming a smaller dose and thus lower toxicity of treatment paradigm (Uekama et al. 1981a). Tri-o-methyl derivatization of β-CD increased both hydrophilicity and hydrophobicity. So, this unique property has been checked for increased bioavailability

Table 5 Phase II 1981–1990: Exploration of natural cyclodextrins and emergence of its derivatives for drug delivery

Sr. No.	Year	CD type/ derivative	Drug	Class of drug	system/model	Problem of drug delivery/ result	Reference
1	1981	γ –CD	Digoxin	Cardiac glycoside	In vivo (dog)	Variable bioavailability, toxicity	Uekama et al. 1981a)
2	1981	β-CD	Indomethacin	Anti-inflammatory	In vivo (rat)	Bioavailability	Szejtli and Szente (1981)
3	1981	β-CD	Barbiturates	Hypnotic agent	Sleeping time studies in mice	Solubility thus bio-availability	IwAoKu et al. (1982)
4	1981	α-, β- and γ-CD	Chlorpromazine	Anti-psychotic	In vitro and in vivo rats	Reduced haemolysis with no reduction in central nervous system effect	Uekama et al. (1981b)
5	1982	β-CD	Phenobarbital	Anti-convulsant	Rectal delivery in mice	Required rapid release and absorption in child	IwAoKu et al. (1982)
6	1982	tri-o-methyl-β- CD	Flurbiprofen	Anti-inflammatory	Oral delivery to rabbits	Bioavailability studies of tri-o-methyl-β-CD/ 5 times early and 3 times higher C_{max} was achieved	Otagiri et al. (1982)

of its drug inclusion. Oral delivery of drug CD inclusion complex to rabbits increased its concentration in plasma (C_{max}) to highest, i.e. approximately 3 times higher than its free drug form in 35 min (free drug took 2.4 h to reach its C_{max}) (Koizumi et al. 1980a; Otagiri et al. 1982).

Phase III 1991–2000: exploration of α, β and γ cyclodextrin derivatives for drug delivery involving animal studies to support

This decade of CD development can be attributed to expanding the research on natural CD variants and corresponding novel derivatives in drug delivery systems, which are mainly supported by animal studies (Table 6 and Additional file 2). The year 1991 showed manifold number of studies on exploration of CD derivatives for drug delivery, which included a study of CD inclusion complexes III. The pulmonary absorption of β-CD, dimethyl-β-CD (DM-β-CD) and 2-hydroxypropyl-β-CDs (HP-β-CD)in rabbits was studied (Marques et al.

1991). The pulmonary release drug used on animals showed absorption and pharmacokinetics of β-CD, DM-β-CD and HP-β-CD. Similarly, Merkus et al. studied the absorption-enhancing effect of CD on intranasally administered insulin in rats using α-, β- and γ-CD type. The nasal insulin given to rats in vivo showed absorption enhancing effects of α-, β-, and γ-CD, DM-β-CD, and HP-β-CD (Merkus et al. 1991). Another study by Stuenkel et al. was related to sublingual administration of testosterone-HP-β-CD inclusion complex simulating episodic androgen release in hypogonadal men, showing that HP-β-CD quickly metabolized without sustained elevations of dihydrotestosterone (Stuenkel et al. 1991). In the year 1992, Hirayama et al. monitored prominent inclusion effect of DM-β-CD on photo-isomerization of the thromboxane synthetase inhibitor (E)-4-(1-imidazoylmethyl) cinnamic acid (IMC) (Hirayama et al. 1992). The thromboxane synthetase inhibitor drug showed ultraviolet, circular dichroism and nuclear magnetic

Table 6 Phase III 1991–2000: Exploration of α-, β- and γ-cyclodextrin derivatives for drug delivery supported by animal studies

S. No	Year	CD type/Derivative	Studies involved	System/Model	Reference
1	1991	β-CD, DM-β-CD and HP-β-CD	Absorption and pharmacokinetics study was conducted	In vivo (Rabbit)	Marques et al. (1991)
2	1991	α-CD, β-CD, γ-CD, DM-β-CD and HP-β-CD	Absorption enhancing effect on intra-nasal insulin with different CDs and derivatives was investigated	In vivo (Rats)	Merkus et al. (1991)
3	1991	HP-β-CD	Metabolization was quickly improved by using HP-β-CD without the sustained elevations of dihydrotestosterone	In vivo	Stuenkel et al. (1991)
4	1992	β- CD	Suppressing outcome of β CD on the photo-isomerization of IMC was confirmed by nuclear magnetic resonance, ultraviolet and circular dichroism	—	Hirayama et al. (1992)
5	1993	β- CD	β- CD improves the ocular bioavailability of pilocarpine	In vivo	Freedman et al. (1993)
6	1994	β- and γ-CD derivatives	In presence of L-α-lysophosphatidylcholine and glycodeoxycholate enhancers the nasal absorption of insulin were studied	In vivo	Gill et al. (1994)

resonance, thereby suppressing the effect of β-CDs on the photo-isomerization of IMC. In 1993, Pedersen et al. studied the formation and antimycotic effect of CD inclusion complexes of econazole and miconazole (Pedersen et al. 1993). The antimycotic drug was tested on bacterial strain and resulted in increased ionization of the imidazole derivatives, thereby decreasing the size of the stability constants; inhibitory effect of β-CD on the growth of the test organism was observed. Another study of β-CD-enhancing bioavailability of pilocarpine was conducted by Freedman et al. This ophthalmic drug using β derivative resulted in improved drug solubility, stability and absorption for oral and parenteral administration. Scanning electron microscopic (|SEM) and electrophysiology studies showed a significant improvement in the ocular bioavailability of pilocarpine (Freedman et al. 1993). Gill et al. in their study of CDs were used as a preventive agent in nasal delivery system against the damaging effects of the enhancer. In vivo studies showed effect on absorption of insulin and histopathology of nasal membrane with β and γ-CD derivatives (Gill et al. 1994).

Bernards (Bernards 1994) studied the effect of HP-β-CD on flux of fentanyl, alfentanil, sufentanil and morphine by injecting through the spinal meninges of monkey in varying concentrations of HP-β-CD. ABE et al.'s, in year 1995, studies observed the enhanced nasal delivery of luteinizing hormone releasing hormone agonist buserelin by oleic acid, which was solubilized and stabilized by HP-β-CD complex. Significantly enhanced effect was observed by using three α, β and γ CD derivatives (Abe et al. 1995). In another study, Lee and Lee also observed the enhanced solubility of lesser water-soluble naproxen with complexation with HP-β-CD, which provides better bioavailability and lowers the gastrointestinal toxicity, when consuming orally (Lee and Lee 1995). The effect of HP-β-CD on percutaneous absorption of methyl paraben was conducted by Tanaka and team. It was observed that HP-β-CD significantly improved the water solubility of methyl paraben, and HP-β-CD is helpful in liquid preparations of methyl paraben for topical medication (Tanaka et al. 1995). Year 1996 included the studies related to fate of free and liposome-entrapped HP-β-CD/drug complexes after intravenous injection into rats. Its importance in drug delivery signifies that the administration of drug-CD inclusion complexes via liposomes can be used in wider range of therapeutic applications (McCormack and Gregoriadis 1996). Hirayama et al. studied the in vitro assessment of biphenyl acetic acid-β-CD conjugates as colon-targeting prodrugs. Drug release behaviour in rat biological media investigated that the ester-type drug conjugate of β-CD may serves as a colon-targeting prodrug (Hirayama et al. 1996). In 1997, Davies et al. determined the outcomes of HP-β-CD

on the water solubility and chemical stability of hydrocortisone (HC) for the formulation of stable topical ophthalmic solution of HC. The water solubility of HC was noticeably increased upon addition of HP-β-CD due to the formation of a soluble 1:1 inclusion complex(Davies et al. 1997). In 1998, Tenjarla in his preparation, characterization and evaluation of miconazole-CD complexes for improved oral topical delivery showed that human cadaver skin retained 2.6-fold more drug from the miconazole-CD complex and hairless mice skin retained 8.4-fold more drug from the HP-β-CD complex than from miconazole solution alone in 24 h (Tenjarla et al. 1998). McCormack and Gregoriadis in their study of drugs-in-CDs-in-liposomes found out that the administration of drug-CD inclusion complexes via liposomes could serve as a means to control the action of a wide range of therapeutic agents(McCormack and Gregoriadis 1998). Towards the end of the decade (1999) after enormous studies conducted by a range of scientists, Jacobsenet al.in their study of CD inclusion complexes of antimycotics intended to act in the oral cavity-drug supersaturation, toxicity on TR146 cells and release from a delivery system showed that genuine econazole-β-CD complex only increased the drug release moderately when compared with the release from the neat econazole gum, and miconazole HP-β-CD gum had a much higher drug release in vitro than the neat miconazole gum(Jacobsen et al. 1999). Overall, this phase of CD exploration can be recognized as derivatization of CDs with small molecules to change their physical properties with success in researcher's endeavour.

Phase IV 2001–2010: exploration of α, β and γ cyclodextrin polymeric derivatives and utilization in novel drug delivery

2001–2010 research on CDs reveals the extension of the phase III but with novel polymeric derivatives and novel drug delivery systems utilized to overcome specific problems of drug or requirement to treat disease (Table 7 and Additional file 3). As increase in bioavailability became an obvious outcome with drug CD inclusion complexes, this decade research seems to mainly focus on characterization and dissolution studies with different formulations. CDs were almost utilized in almost all range of delivery systems, formulations, polymeric microspheres (Filipovic et al. 2000), aerosols (Srichana et al. 2001), microemulsion, polymeric nanoparticles (Boudad et al. 2001), nanospheres (Memisoglu et al. 2003), buccoadhesive formulation (Jug and Becirevic-Lacan 2004; Arakawa et al. 2005), microemulsions (Dalmora et al. 2001), osmotic pump (Gan et al. 2002), sustain release (Kamada et al. 2002) and so on. In an interesting study, presented by Memisogluet al., nanospheres of amphiphilic β-CDs itself were prepared with

Table 7 Phase IV 2001–2010:A decade exploring of α, β and γ cyclodextrins polymeric derivatives and utilization in novel drug delivery

Sr. No.	Year	CD type	Polymer/encapsulate	Drug	Problem solved/purpose	Reference
1	2000	HP-β-CD	Chitosan microsphere	Hydrocortisone	–	Filipovic et al. (2000)
2	2001	HP-β-CD	Poly(alkylcyanoacrylate) nanoparticles	Saquinavir	To increase drug loading	Boudad et al. (2001)
3	2001	β-CD	Microemulsion	Piroxicam	–	Dalmora et al. (2001)
4	2001	γ-CD and DM- β –CD	Aerosol	Salbutamol	To evaluate delivery efficiency and toxicity of formulation in Aerosol	Srichana et al. (2001)
5	2002	β-CD	Osmotic pump tablets	Glipizide	Constant delivery required	Gan et al. (2002)
6	2002	6^A-O-[2-(3-Benzoyl-phenyl) propinoyl]-α-CD, HP-β-CD	Sustain release dosage form	Ketoprofen	Novel derivative of CD was studied	Kamada et al. (2002)
7	2003	β-CD	Nanosphere	Bifonazole and clotri-mazole	High load delivery of poorly soluble drugs	Memisoglu et al. (2003)
8	2004	HP-β-CD	Buccoadhesive tablets	Piroxicam	To increase buccal bioavailability	Jug and Becirevic-Lacan (2004)
9	2005	β-CD self-polymer, epichlorohydrin as spacer	Buccal delivery, bioadhe-sive polymer	Lidocaine and keto-profen, lipophilic drugs	To check permeation of lipophilic drugs with novel polymer	Arakawa et al. (2005)
10	2009	β-CD	Porphyrin conjugate	Doxorubicin	Photodynamic drug release	Kralova et al. (2009)

high loading of model drugs. Modification in β-CD included 6 carbon chain attachments with ester bond (β-CD C6) and amide bond (CAPRO β-CD) converting β-CD to more soluble form. CAPRO-β-CD showed higher drug loading than-CD C6 more specifically with bifonazole (173 μg), which can be attributed to its affinity for β-CD cavity. Preloaded drug nanospheres were showing slower release than post-loaded drug nanospheres, while pre- and post-loaded nanospheres act like loading dose release and maintenance dose release. RBC and WBC lysis by both amphiphilic β-CD treatment was significantly lower than β-CD. In both cases, i.e. RBC and WBC, lysis by β-CD C6 was significantly and insignificantly lower than CAPRO β-CD, respectively (Memisoglu et al. 2003).

With the vision to reduce the problems associated with buccal delivery (i.e. immediate dilution thus washes out), drug-CD inclusion polymer (low molecular weight) as bioadhesive material was investigated by Arakawa et al. This unique β-CD self-polymerization was assisted with reagent epichlorohydrin. Model drugs taken here were lipophilic in nature (lidocain and ketoprofen). Such a polymer when mixed with existing formulation, i.e. hydroxypropyl alcohol and polyvinyl alcohol, retarded the drug release from the formulation significantly when checked in artificial saliva. Differential scanning calorimetric study showed the more retention of crystal form of lidocaine in HP-β-CD polymer as compared to hydroxypropyl alcohol only formulation, while in the case of ketoprofen it remained as amorphous in both the formulations. Ultra-filtration experiments showed its association constant, which was very high (520 M^{-1}) for ketoprofen with β-CD polymer, while the same was 6.9 ± 0.6 M^{-1}. High binding of ketoprofen was also supported by its high competitive reduction in fluorescence of probe-β-CD inclusion complex (Arakawa et al. 2005).

A combination of chemotherapy and photodynamic therapy (PDT) was studied taking peclitaxel with β-CD and doxorubicin with γ-CD attached with porphyrin as photosensitizer. Porphyrin functionalization with CD showed effect in accommodating drugs in CD along with polarity control of the formulation. In vitro study of chemo-PDT CD preparation with carcinoma cell lines with and without light exposure was carried out, taking drug-loaded β and γ CD as control to compare. Drug-loaded porphyrin CD controls showed 5–8% increase in mortality than drug-loaded CDs only, while with PDT mortality raised to 30% indicating synergistic effect. In vivo study also supported the synergistic treatment with β- and γ-CD derivatives of drug porphyrin complexes, which is superior to individual treatments (Kralova et al. 2009).

Phase V 2010-current: natural, derivative and polymeric CDs in alliance with nanoproperties

Recent research in almost all the fields of development attempted to explore nano-effect on material properties hence respective outcomes (Alimohammadi et al. 2012, 2013, 2018; Mozaffari et al. 2020). This encompasses but not limited to the formation of nanocomposites, nanoparticles (magnetic or polymeric), material surface engineering, nanoemulsions and nano-matrix for enzyme immobilization and latest gel-based systems (Verma 2017; Chamundeeswari et al. 2019; Verma et al. 2020a, 2020b, 2013a, 2013b; Verma and Rani 2020; Parvinzadeh et al. 2010; Kumar et al. 2014a, 2014b, 2013). The role of CDs in drug targeting in phase-V is basically incorporating the use of nanomaterials (nanoparticles, nanogels, hydrogels, etc.), which is evident in Table 8. Cho et al., 2010 reported that new formulation using poloxamer 407 (P407)/HP-β-CD-based thermo-reversible gels with chitosan enhanced the permeation and solubility of intranasal delivery system of fexofenadine hydrochloride (Cho et al. 2010). The potential of novel HP-β-CD and chitosan nanocarriers (NCs) for effective delivery of model drug, i.e. poorly water soluble drug simvastatin, was investigated (Vyas et al. 2010). It was reported that the in vitro release profile of prepared NCs showed initial fast release (burst effect) followed by a delayed release pattern. In conclusion, these nanocarriers constituted a novel and efficient system for encapsulation and oral delivery of poorly soluble drugs. Targeting the poorly soluble drug paclitaxel was studied by loading it with β-CD functionalized hyperbranched polyglycerol (HP-β-CD)(Zhang et al. 2011a). In vitro studies showed high loading capacity and high encapsulation efficiency of paclitaxel. The release profiles of different co-polymer compositions showed a burst release followed by continuous extended release. Chitosan nanoparticles using sulfobutylether-β-cyclodextrin (SBE-β-CD) as polyanionic crosslinker were developed to investigate the targeting of econazole nitrate (ECO)(Mahmoud et al. 2011). The in vivo studies revealed that the prepared muco-adhesive nanoparticles had better ability in sustaining the antifungal effect of ECO than the ECO solution. Chitosan/SBE-β-CD nanoparticles showed a promising carrier for controlled delivery of drugs to the eye. Tacrine hydrochloride nasal delivery was investigated by means of albumin nanoparticles and two different β–CD derivatives (HP-β-CD and SBE-β-CD) (Luppi et al. 2011). Results showed that the permeation and bioavailability of Tacrine hydrochloride increased. In year 2011, CD in combination with nanogels, nanoparticles, and nanosponges has been used to target various antibiotics such as ciprofloxacin (Blanchemain et al. 2011), doxycycline (He et al. 2011), nasal insulin delivery (Zhang et al. 2011b), which increased

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Table 8 Phase V 2010- Current:Natural, derivative and polymeric CDs in alliance with nanoproperties

Sr. No.	Year	CD type/ derivative	Drug	Class of drug	System/Model	Problem of drug delivery/ result	Reference
1	2010	Poloxamer407 (P407)/ HP-β-CD	Fexofenadine hydrochloride	Anti-histamine	In vitro	Bioavailability enhanced	Cho et al. (2010)
2	2010	HP-β-CD and chitosan nanocarriers	Simvastatin	HMG CoA reductase inhibitors	In vitro	Controlled release	Vyas et al. (2010)
3	2011	β-CD functionalized HPG	Paclitaxel	Anti-cancer	In vitro	High loading capacity and high encapsulation efficiency burst release followed by continuous extended release	Zhang et al. (2011a)
4	2011	SBE-β-CD	Econazole nitrate	Anti-fungal	in vivo (rabbit)	Controlled released	Mahmoud et al. (2011)
5	2011	HP-β-CD, SBE-β-CD (albumin nanoparticles)	Tacrine hydrochloride	Acetylcholinesterase inhibitor	Ex vivo/ sheep nasal mucosa	Bioavailability/permeation increased	Luppi et al. (2011)
6	2011	Methyl-β-CD	Ciprofloxacin	Antibiotics	In vitro	Anti-microbial activity enhanced Sustained release	Blanchemain et al. (2011)
7	2011	β-CD Nanosponges	Resveratrol	Polyphenolic phytoalexin	In vivo (rabbit)	Enhanced permeation	Ansari et al. (2011)
8	2011	Insulin-loaded HPG-γ-CD nanoparticles	Insulin	Hormonal therapy	In vivo (rats)	Nasal insulin delivery	Zhang et al. (2011b)
9	2011	HP-β-CD	Doxycycline	Antibiotics	In vitro	Stability and sustained release	He et al. (2011)
10	2012	β-CD hydrogels	Naproxen and nabumetone naftifine and terbinafine	NSAIDs anti-fungal	In vitro	Controlled released	Machín et al. (2012)
11	2012	Methyl-β-CD	Olanzapine	Anti-psychotic drug	Study in rabbit's eye	Higher solubility, consequently, higher bioavailability	Freitas et al. (2012)
12	2012	Randomly methylated-β-CD	Benznidazole	Anti-parasitic medication	In vivo	Effective, standardized and safe drug delivery	Soares-Sobrinho et al. (2012)
13	2012	β-CD-epichlorohydrin polymer, CM-β-CD-epichlorohydrin polymer	Ketoprofen	NSAIDs	In vitro	Permeation enhancement	Cirri et al. (2012)
14	2013	β-CD-crosslinked alginate gel	Ondansetron	Anti-emetic drug	In vitro	Controlled release	Izawa et al. (2013)
15	2013	Chitosan (CS) grafted with γ-CD nanoparticles	Ketoprofen	NSAIDs	In vitro	Controlled drug release	Yuan et al. (2013)
16	2013	Mono- and multi-methacrylate substituted CD	Doxorubicin	Anti-cancer	In vitro	Enhanced doxorubicin delivery	Zhang et al. (2013)
17	2013	β-CD	p-cymene	Anti-nociceptive and anti-inflammatory effects	In vivo (mice)	Improved analgesic and anti-inflammatory effects	Quintans et al. (2013)
18	2014	β-CD-poly(ethylene glycol)-b-12 polylactide	Doxorubicin	Anti-cancer	In vitro & In vivo (mice)	Anti-tumour activity decreased cardiotoxicity	Li et al. (2015)

Table 8 (continued)

Sr. No.	Year	CD type/ derivative	Drug	Class of drug	System/Model	Problem of drug delivery/ result	Reference
19	2014	β-CD	Tetracycline	Antibiotics	In vitro	Greater drug loading efficiency slower drug release	Gogoi and Chowdhury (2014)
20	2014	β-CD and HP-β-CD	Natamycin	Anti-fungal	In vitro	Increased drug released	Phan et al. (2014)
21	2014	β CD	Ciprofloxacin and prednisolone	Antibiotic & NSAID	in vitro, in vivo (in humans)	Enhanced release Control For Drug Delivery Applications	Hernandez-Montelongo et al. (2014)
22	2014	Polyacrylates functionalized with adamantane and β-CD	Doxorubicin	Anti-cancer drug	In vivo (mice)	Enhance the therapeutic effects of DOX for effectively inhibiting the tumour growth	Ang et al. (2014)
23	2015	β-CD grafted carboxymethyl chitosan hydrogels	Acetylsalicylic acid	NSAID	In vitro	Biodegradable active material with controlled drug release ability	Kono and Teshirogi (2015)
24	2013	β-CD-Gold Glyco-nanoparticles	Methotrexate	Anti-cancer	in vitro	Site-specific delivery systems	Aykac et al. (2013)
25	2016	β- CD/cellulose nanocrystals	Curcumin	Anti-cancer	In vitro	Anti-proliferative effect on colorectal and prostatic cancer cell lines	Ntoutoume et al. (2016)
26	2016	Chitosan coated magnetic nanoparticles with acrylic acid and grafted with ethylene–diamine derivative of β-CD	Curcumin	Anti-cancer	In vitro	Controlled release, increased cytotoxicity, enhancement of biocompatibility	Anirudhan et al. (2016)
27	2015	Heptakis(6-amino-6-deoxy)-β-CD	Sorafenib	Anti-cancer	In vitro	Sustained drug release	Correia et al. (2015)
28	2015	HP-β-CD	Sulfisoxazole	Anti-bacterial	In vitro	Controlled Release	Aytac et al. (2015)
29	2016	CD nanoparticles	Polyhydroxyalkanoates, poly-(lactic-co-glycolic acid)	Anti-cancer	In vitro	Controlled release	Masood (2016)
30	2016	CD-polyhydrazine degradable gels	Nicardipine	Calcium channel blockers	In vitro	Sustained release	Jalalvandi et al. (2016)
31	2017	polyβ-CD	Polylactide	Lung cancer	In vitro	Sustained drug delivery	Feng et al. (2017)
32	2017	β-CD with thermo-responsive nanogels	Dexamethasone	Anti-inflammatory	In vitro/in vivo (human skin)	Enhanced penetration	Giulbudagian et al. (2018)
33	2018	HP-β-CD modified carboxylated single-walled carbon nanotubes	Formononetin	antiviral, antioxidant	In vitro	Slow and sustained release	Liu et al. (2018)
34	2018	β-CD grafted polypyrrole magnetic nanocomposites	Doxorubicin	Anti-cancer	In vitro	Controlled release and targeted delivery	Hong et al. (2018)

Table 8 (continued)

Sr. No.	Year	CD type/ derivative	Drug	Class of drug	System/Model	Problem of drug delivery/ result	Reference
35	2019	β-CD modified with Maleic anhydride and NIPAM	Doxorubicin and Curcumin	Anti-cancer	In vivo (mice)/In vitro	Enhanced bioavailability	Das et al. (2019)
36	2019	Biotin & arginin + HP-β-CD nanoparticles	Paclitaxel	Anticancer	In vitro & In vivo	Increase cellular uptake	Yan et al. (2019)
37	2019	2- HP-β-CD -PLGA-nanoparticles	Triamcinolone acetonide	Corticosteroid used in rashes, redness & swelling	In vitro/In vivo	Enhance drug penitation	Li et al. (2019)
38	2019	Folic acid (FA) + Polyethylene glycol(PEG) + β-CD nanoparticles	Doxorubicin	Liver cancer	In vitro	Enhance solubility & control drug delivery	Fan et al. (2019)
39	2020	Chitosan citric acid crosslinked with β-CD nanoparticles	Curcumin	Multiple diseases	In vitro	Increase release time	Karpkird et al. (2020)
40	2021	HP-β-CD nanofibres	Acyclovir	Antiviral	In vitro	Improve bioavailability by enhancing solubility	Celebioglu and Uyar (2021)
41	2021	2 HP-β-CD nanofibre	Kenamycin, chloromphinicol,gentamycin, ampicillin	Antibiotics	In silico and in vitro	Enhance dissolution in oral drug delivery system	Topuz et al. (2021)
42	2021	HP-β-CD nanoemulsion	Doxibuprofen	Analgesic, Antipyretic, NSAID	In vitro	Enhance oral bioavailability	Kim et al. (2021)
43	2021	β-CD as a nanocarrier	Lenalidomide	Anticancer	Quantum chemical approach	β-CD suitable nano carrier for lenalidomide	Harati et al. (2021)
44	2021	CD nanosponge	Doxorubicin	Anticancer	In vitro & in vivo (Wistar rat)	Enhanced solubility & bio-availability	Deng et al. (2021)
45	2021	β-CD nanocomposite			In vivo (rabbit eye sclera)		Xu et al. (2021)
47	2022	Folate-appended-polyethylenimine-β-CD	Doxorubicin and Human telomerase reverse transcriptase-small interfering RNA	Anticancer	In vitro (Cell lines)	Co-delivery enhanced efficacy and reduced toxicity of Doxorubicin as anticancer drug	Mousazadeh et al. (2022)
48	2022	Gelatin and hyaluronic acid functionalized CD	Paclitaxel and Vit-E derivative	Anticancer	In-vivo(rats)	CD and Vit-E derivative combination to improve solubility and bioavailability of drug	Zou et al. (2022)

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permeation, stability and sustained release. β-CD hydrogels were used to target the naproxen and nabumetone, naftifine and terbinafine, which resulted in the sustained release of these antifungal and anti-inflammatory drugs (Machín et al. 2012). Methyl-β-CD and HP-β-CD have been used for targeting of antipsychotic drug such as olanzapine, which increased the solubility of this drug (Freitas et al. 2012). Methyl-CD has been used for the targeting of benznidazole and ketoprofen, which enhanced the permeation and safety drug delivery (Cirri et al. 2012; Soares-Sobrinho et al. 2012). β-CD-crosslinked alginate gel was used to target ondansetron, which resulted in the controlled release of the drug (Izawa et al. 2013). CDs in combination with nanoparticles and has been used for the targeting of various anti-cancer drugs such as doxorubicin (Zhang et al. 2013; Li et al. 2015; Ang et al. 2014; Hong et al. 2018; Das et al. 2019), curcumin(Das et al. 2019; Anirudhan et al. 2016; Ntoutoume et al. 2016), methotrexate (Aytac et al. 2015), polylactide(Feng et al. 2017), polyhydroxyalkanoates, poly-(lactic-co-glycolic acid) (Masood 2016). The use of new delivery systems enhanced the controlled and sustained release, increased bioavailability and reduced cardiotoxicity. CDs have also been used to deliver various antibiotics such as tetracycline (Gogoi and Chowdhury 2014), ciprofloxacin (Hernandez-Montelongo et al. 2014), anti-fungal such as natamycin (Phan et al. 2014), anti-bacterial like sulfisoxazole(Aykac et al. 2013), anti-viral with enhanced effect, increased bioavailability and controlled release. CDs have been explored in the targeting of non-steroidal anti-inflammatory drugs (NSAIDs) such as acetylsalicylic acid (Kono and Teshirogi 2015), which enhanced the controlled release of drugs. CD-polyhydrazine degradable gels have been used for the targeting of nicardipine a calcium channel blocker drug for its sustained release (Jalalvandi et al. 2016).

β-CD with thermo-responsive nano gels has been studied for the targeting of dexamethasone to enhance its penetration and thus its anti-inflammatory activity (Giulbudagian et al. 2018). The phase-V of the CD usage mainly concentrated on the delivery of various types of drugs like anti-cancer, anti-inflammatory, antibiotics, anti-bacterial, anti-viral, etc., with the help of nanotechnology including nano-gels, nano-materials, nanoparticles, nano-structures, which enhanced the bioavailability, penetration/permeation, sustained/controlled release, site-specific targeting, etc.

The current scenario emphasized the various approaches of β-CD in the drug delivery system. Nanofibre of HP- β -CD proved to be an effective carrier for antiviral drugs, i.e. acyclovir. That nanofibre formulation of HP- β -CD when incorporated with the low-soluble drug (acyclovir) shows enhancement in the solubility of that drug (Topuz et al. 2021). Nanosponge formulation of β CD also showed a noticeable increase in the bioavailability of anticancer drug. i.e. doxorubicin. The drug doxorubicin was encapsulated with β CD and by crosslinkage of the β CD, a compound nanosponge had been prepared (Deng et al. 2021). Nowadays this beneficial β CD compound combines with many other compounds and broad the spectra of its usefulness in many drug delivery systems. For example, FA & PEG when incorporated with nano-β CD had shown a markable increase in bioavailability of doxorubicin. FA incorporated with β-CD by using PEG as a linker. During the analysis, it was found that the drug loading capacity of this formulation was found only 11.9%, and on another side in the case of encapsulation efficacy was found 95.2% in this formulation. The in vitro and in vivo study found extra complimentary drug control release activity along with solubility. This study highlights the control drug release approach associated with CD nanoformulation (Fan et al. 2019). When chitosan citric acid crosslinked with β CD nanoparticles found effective in the slow release of curcumin. Nanofibre approach of β CD also enhanced the oral bioavailability of many antibiotics. By using arginine as a spacer, the hydroxy group of CD had been coupled with the biotin carboxyl group. After loading paclitaxel with that carrier, the nanoparticle had been prepared by using the emulsion solvent evaporation method. The in vitro and in vivo studies carried on that compound and that data provided evidence regarding cellular uptake enhancement (Yan et al. 2019). The use of CD in nano-formulation in various forms like nano-sponge, nanofibre, nano-encapsulation, etc., has the ability to produce an era of evolution in medical science to resolve many problems associated with drug delivery systems. Slow-release of drug approach along with various advantages, i.e. drug target release, sustains release is the new application or approaches of using nano- β-CD drug carrier.

The contemporaneous CD nano-drug delivery example is the utilization of folate- and polyethylenimine-functionalized β-CD nanosystem (pH responsive) for the successful co-delivery of two different class of therapeutic, i.e. doxorubicin and siRNA (human telomerase reverse transcriptase) for the treatment of breast cancer. Its efficacy and toxicity was reduced with such co-delivered formulation (Mousazadeh et al. 2022). In another recent reported study, the solubility and toxicity issue of paclitaxel were addressed in CD preparation with gelatin, and hyaluronic acid was checked. Along with CDs property, solubility enhancement property of vit-E derivative was also taken as support. In vivo study showed C_{max} 54.53 μg/L for this preparation, which was higher than that of the paclitaxel suspension (41.13 μg/L) (Zou et al. 2022).

Conclusions

CDs alone, its derivatives, self-polymeric state, attached polymers and many other forms of drug delivery had been exploited to solve some specific problems in drugs and drug delivery systems. Despite orthodox thinking that there is nothing new in the research field involving CDs in the drug delivery system, still all upcoming novel formulations research has inclination towards CDs for different problems in which CDs are capable of resolving. Its utilization in every aspect of drug delivery ranges from bioavailability, solubility, bitterness, stability, lipophilicity and so on. Literature survey showed that this is a magical molecule and is promising, reproducible and of versatile nature. As suggested in the discussion in the last decade, its future lies in every upcoming field of research with special reference to nanotechnology in drug delivery system.

Abbreviations

Azone: 1 Dodecylazacycloheptane 2 one; CD: Cyclodextrin; CGTase: Cyclodextrin-glycosyl-transferase; CM-β-CD: Carboxymethyl-β-cyclodextrin; CME-β-CD: O-carboxymethyl-O-ethyl-β-cyclodextrin; DM-β-CD: Dimethyl-β-cyclodextrin; DRV: Dehydration-rehydration vesicles; DSC: Differential scanning calorimetry; ECO: Econazole nitrate; FTIR: Fourier transform infrared spectroscopy; HC: Hydrocortisone; HP-β-CD: Hydroxypropyl-β-cyclodextrin; HPE-101: 1[2-(Decylthio)ethyl]azacyclopentane-2-one; HPG: Hyper-branched polyglycerol; HPLC: High-performance liquid chromatography; IMC: (E)-4-(1-imidazoylmethyl) cinnamic acid; IR: Infrared spectroscopy; NMR: Nuclear magnetic resonance; NSAIDs: Non-steroidal anti-inflammatory agents/drugs; PGE1: Prostaglandin E1; SBE-β-CD: Sulfobutyl ether-β-cyclodextrin; UV: Ultra violet spectroscopy; XRD: X-ray diffraction.

Supplementary Information

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Additional file 1. Phase II 1981-1990:Exploration of natural cyclodextrins and emergence of its derivatives for drug delivery.

Additional file 2. Phase III 1991-2000: Exploration of α-, β- and γ-cyclodextrins derivatives for drug delivery supported by animal studies.

Additional file 3. Phase IV 2001-2010:A decade exploring of α, β and γ cyclodextrins polymeric derivatives and utilization in novel drug delivery.

Author contributions

JS did methodology and plan mapping, original document writing with the highest contribution; ID done methodology and plan mapping, original document writing, review and editing with overall equal contribution as that of first author; HM provided original document writing; NK reviewed and edited the article; S and M supported document writing; MLV contributed to conceptualization, methodology and plan mapping, review and editing; SK was involved in conceptualization, methodology and plan mapping, original document writing. All authors have read and approved the manuscript.

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