Chapter 1

Cyclodextrins: Past and Present

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.72736

Abstract

Cyclodextrins (CDs) are cyclic oligosaccharides produced by enzymatic degradation of starch. The most common CDs are the main natural ones, α, β and γ, which are constituted of 6, 7 and 8 glucopyranose units, respectively. The CD structure forms a torus or doughnut ring and the molecule actually exists as a truncated cone. The outer side of the toroid is hydrophilic in nature due to the hydroxyl groups of the glucopyranose units while the internal cavity is relatively apolar. Thus, CDs have a high potential to entrap entirely or partially a wide variety of compounds in a process known as complexation. This gives them new physico-chemical properties and characteristics. The main applications of CDs in drug formulation rely on CD complexation and include the protection of easily oxidizable molecules or the improvement of aqueous solubility. The use of CDs in analytical chemistry is based on his host-guest recognition property, known as supramolecular complex formation. Currently, CDs are successfully used in molecular recognition-based methods like chromatographic separations, spectroscopic and electroanalyses. Quiral analytical separations are a CD area of special relevance. In this work, attention is paid to more recent references, especially to selected reviews.

Keywords: cyclodextrins, applications, encapsulation, controlled release, nano, food, cosmetic

1. Introduction

Cyclodextrins (CDs) at times referred as Schardinger sugars or cycloamylose dextrins, were fortuitously discovered [1, 2] by Vielliers in 1891, who named these compounds as "cellulosing." Later on Schardinger, who is considered the founder of CD chemistry, gave a detailed description about preparation and separation of CD and, more recently, Kurkov and Loftsson [3] also made significant contributions to CD science.

Franz Schardinger, studying microorganisms which play a role in the deterioration of foods and by action of cyclodextrinase-Bacillus macerans amylase on the starch, obtained two distinct crystalline substances with similar properties to the already known partial degradation products of starch, the dextrins, so he named them α-, and β-dextrin. The separation of the cycloalkyls may be carried out by selective precipitation by means of organic compounds or by high temperature chromatography on a cellulose column. French et al. demonstrated that CDs are cyclic oligosaccharides composed of several D-(+)-glucopyranose units in the form of a saddle [4]. In the second half of the 1930s, Freudenberg and his co-workers elucidated the cyclic structure of α-, and β-dextrin [5]. They consist of (α-1,4)-linked glucose units. A Greek letter preceding the abbreviation CD—for cyclodextrin—indicates the number of glucose units (α for 6, β for 7, and γ for 8) entering the composition of the cycloamylose. CDs constituted of less than 6 glucopyranose units cannot be formed due to steric hindrances [6]. Approximately, 1500 CD derivatives have been reported [7] in the literature.

CDs have a truncated cone appearance [7–12], and a doughnut, toroidal- or cylinder-like shape, due to the spatial arrangement characteristic of the various functional groups of the glucose units. As a consequence of this conformation, all the secondary hydroxyl groups (corresponding to the C2 and C3 carbon atoms of the glucose units) are at one of the edges of the cavity, whereas the primary hydroxyls are in the other end of the cavity. Rotation of these –OH groups reduces the effective size of the cavity, making it have a more open conical truncated aspect [13] toward the side of the secondary hydroxyls (**Figures 1** and **2**).

This spatial arrangement gives an apolar character to the interior of the cavity, whereas the presence of the –OH groups at the edges of the cone trunk makes them very water soluble. For instance, hydrophobic hosts will be housed inside the cavity because of the hydrophobic van der Waals type interactions, whereas simultaneously polar interactions

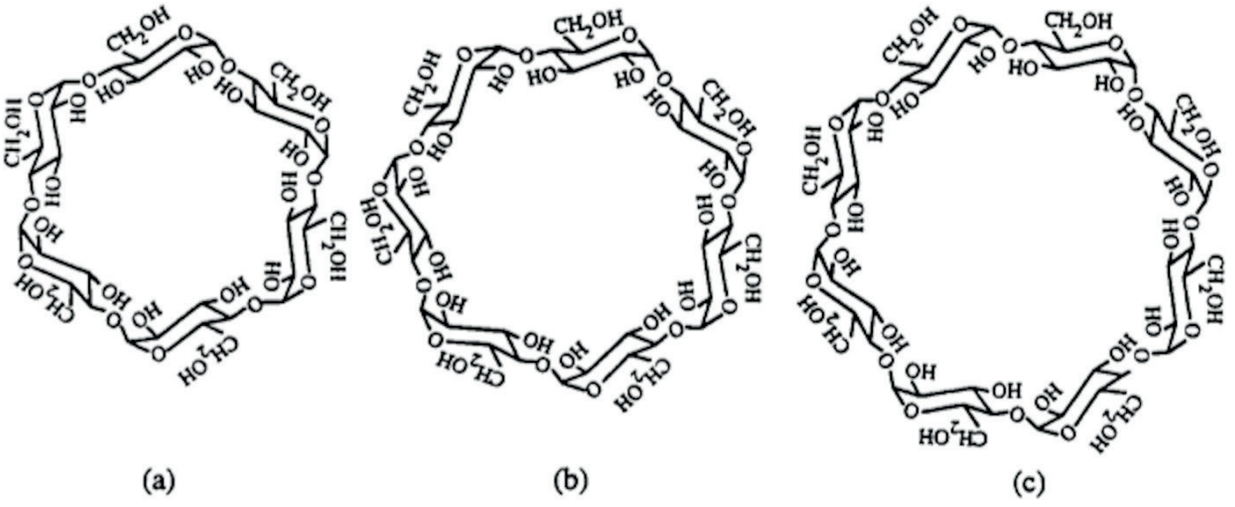

Figure 1. Molecular structure of (a) α, (b) β, and (c) γ-CDs.

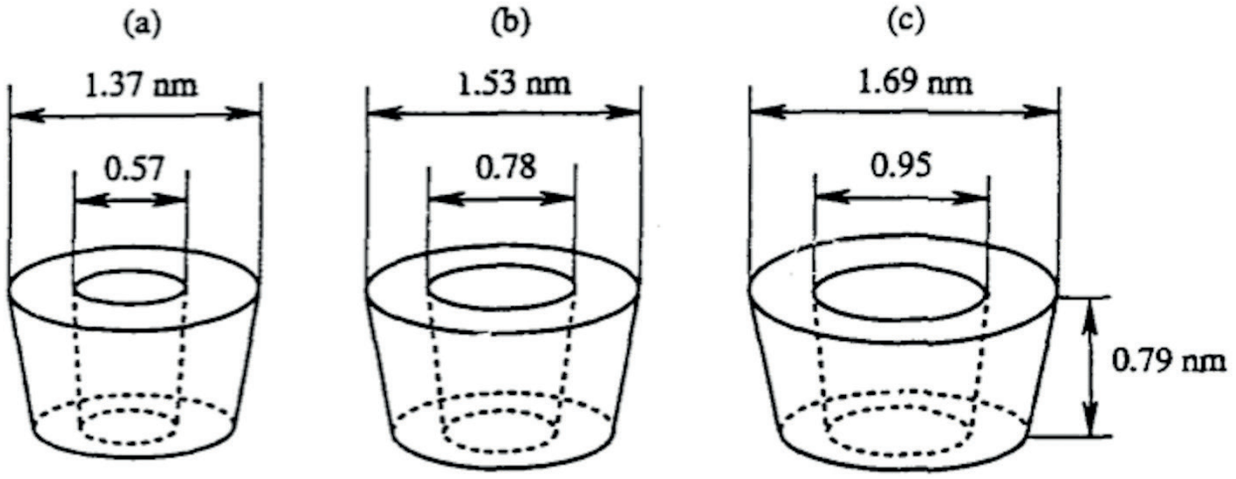

Figure 2. Steric structures of molecules from (a) α, (b) β, and (c) γ-CDs.

can be established by the formation of hydrogen bridges between polar hosts and –OH of the primary hydroxyls. An endless number of physical and chemical processes [10, 14] are usually facilitated, that is, volatile substances may be stabilized by transforming in crystalline substances; oxygen-sensitive materials could find protection against oxidation; solubility and bioavailability of drugs could be improved [15–20] by participating in controlled delivery processes.

CDs have been the subject of a large number of studies dealing with complexation and molecular catalysis [21–25], as well as studies about hydrophobic effects and fine-tune models of biological processes. In 1953, the first patent on CDs and complexes was registered, but until 1970, only small amounts of relatively pure CDs were produced for industrial use due to their high production cost. Although in the beginning it was erroneously thought that CDs were toxic, currently, it is difficult to imagine a world without CDs [3] due to their potential use [26]. The number of possible applications seems to be unlimited, i.e., computer-aided drug design, pharmaceutical, medical, biomedical and biotechnological, drug and gene delivery, foods, foods additives and ingredients, food processing, cosmetic, textiles, industrial and analytical. Currently, patents on CDs are counted by thousands.

2. Inclusion complexes

An inherent interest surrounds these compounds due to their physical and chemicals properties [26–38]. The common feature of CDs is their ability to form inclusion complexes with a variety of molecules and ions, both in the solid state (crystalline substances) and in solution. As results of the structure of CDs, they can establish apolar-apolar interactions encapsulating other apolar molecules which may undergo structural changes [33–38], acting as molecular capsules [27–32]. However, the idea that one molecule could envelop another one to form a

new compound (adduct, inclusion complex) was not accepted until X-ray diffraction showed the formation of an inclusion complex between α-CD and iodine [37]. They constitute a significant example of relatively simple organic compounds showing complex formation with other organic molecules. They are excellent models of enzymes that lead to their use as catalysts [21, 24, 39], both in enzymatic and non-enzymatic reactions. Additionally, they are natural products and readily available to most researchers.

It is accepted [18, 38, 40–43] that the binding forces involved in complex formation are, in general:

i. van der Waals type interactions (or hydrophobic interactions) between the hydrophobic unit of the guest molecules and the CD cavity.

ii. Hydrogen bond between the polar functional groups of the guest molecules and the hydroxyl groups of the CD.

iii. Release of high energy water molecules from the cavity in the complex formation process.

iv. Release of strain energy into the ring structure system of the CD.

The role of the hydrogen bond is not universal since stable complexes are formed with hosts such as benzene, which do not form hydrogen bonds.

2.1. Factors affecting stability

Regardless of which type of stabilizing force is involved, the most important factors in determining the stability of the inclusion complex are [36, 40–45]:

the geometric capability

polarity of the guest molecules

the medium

temperature

Geometric, rather than chemical factors, are critical in determining the type of "guest" molecules that can penetrate into the cavity. If the guest is too small, it passes easily through the cavity and the bond will be weak or will not occur. The formation of complexes with molecules significantly larger than the cavity is also possible, but only some limited groups or side chains penetrate into the CD cavity.

The stability of an inclusion complex also depends on the polarity of the "guest" molecule. Only substrates that are less polar than water may form inclusion complexes with the CDs. The stability of a complex is proportional to the hydrophobic character of the "guest" molecule. Highly hydrophilic molecules form complex CDs very weakly or do not complex at all.

On the other hand, stability depends heavily on the nature of the medium used for complexation. In principle, the inclusion complexes may be formed either in solution [46–49] (generally carried out in the presence of water) or in the crystalline [40, 50–52] state. Although the formation of inclusion complexes also takes place [53] in an organic solvent, the guest molecules

are weakly complexed. Additionally, although a 1:1 stoichiometry between the substrate and the CD molecule is typical [46, 54–56], with certain systems (**Figure 3**), 1:2 and 2:1 complex formations are possible. Experimentally determined formation constant can be the function (**Figure 4**) of the formation constants of the isomeric complexes [46]. In addition, substitution of one or more hydroxyls results in most cases in better water-soluble derivatives. For example, CDs can be polymerized [32, 36, 40, 42, 44, 45, 57] by suitable bio- or polyfunctional agents to oligomers, long-chain polymers or crosslinked or immobilized networks in various supports. Low molecular weight oligomeric CDs are readily soluble in water. Polymers (molecular mass over 10,000) are swollen gels which can be prepared in bead forms. The rigid structure of CDs "host" translates into well-defined and differentiated inclusion complex depending on the nature of the "guest" molecule.

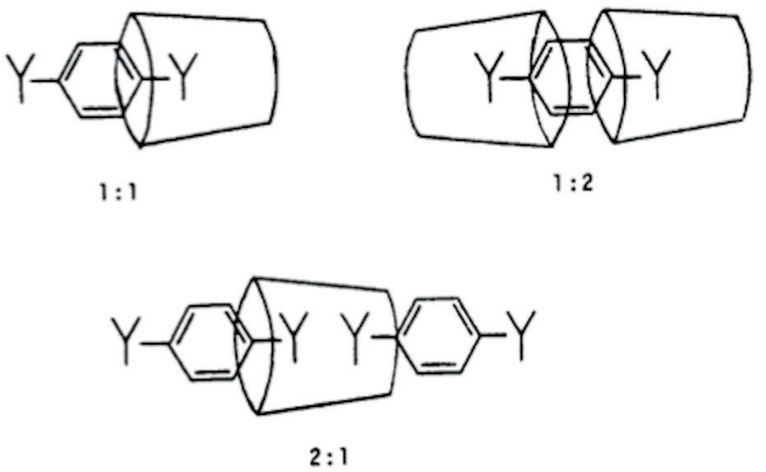

Figure 3. Complexes of α-CDs and 1,4-disubstituted benzene [13].

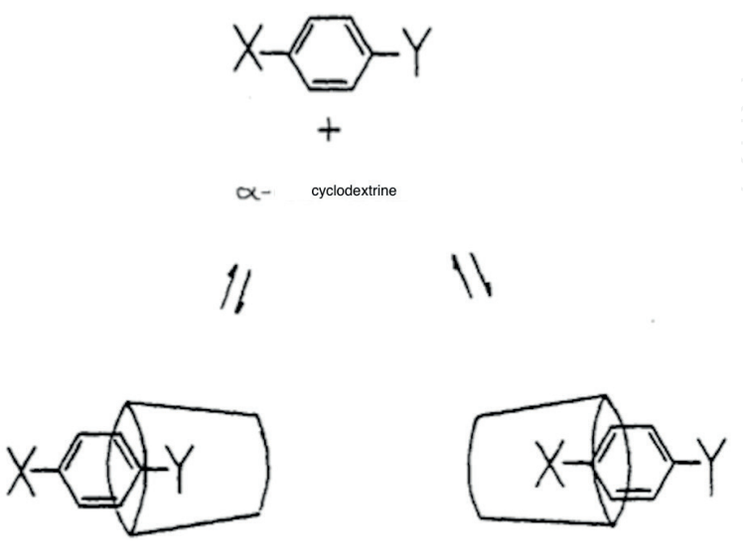

Figure 4. Isomeric complexes from substrate and free ligand [55].

Finally, the stability of the inclusion complex, in general, decreases when temperature increases [46]. Enthalpy and entropy changes can be obtained from the temperature dependence of the equilibrium constant. An important issue, often overlooked in the CD field, is that the magnitudes of the standard free energy and entropy changes are dependent on the standard state chosen by the experimentalist.

3. Analytical and physicochemical applications

In the last years, CDs and their derivatives have been used in a variety of fields of analytical chemistry, especially in analytical separations [45, 58–63]. Spectral properties of CD and guest molecules can be altered due to the changes of the electrons distribution in the CD hole. CDs are used as reagent in different analyses such as UV-visible spectrophotometry, fluorescence [64, 65], phosphorescence [66, 67], and nuclear magnetic resonance methods [45, 68, 69].

The complexation of the analyte and/or the colored reagent can effectively change its properties. Among the most notable uses of this effect are: (i) enhancing the solubility of polar or non-polar analyte; (ii) enhancing the stability in polar or non-polar solution of reagents and colored complexes; (iii) increasing UV-visible absorption which improves the sensitivity of the colored reactions; and (iv) enhancing colored reactions selectivity. Luminescence techniques, in terms of fluorimetry and phosphorimetry, have reached a rapid development in routine analysis. However, many compounds luminesce very weakly in aqueous solution and the addition of CDs protects the excited (singlet or triplet) states of the possible dampers present in the solution since the rotation of the molecules is impeded due to the formation of the complex of inclusion with the result of a decrease in vibrational relaxation processes. The formation of inclusion complexes also increases the quantum fluorescence yield and hence the fluorescence intensities of numerous compounds. Sensitivity to certain characteristic reactions also increases.

CDs also increase the emission intensity of the chemiluminescent reactions. This improvement can be attributed to a number of factors, including an increase in the reaction rate and a greater efficiency in the process of excitation and protection of species that emit quenching phenomena. One of the most relevant applications of CDs is to allow the observation of phosphorescence at room temperature [67]. This is because they protect the excited triplet state of the molecules of the shock absorbers present in the solution, and in the case of molecular quenching phosphorescence. They are used as chiral reagents in NMR. In many cases, the formation of inclusion compounds modifies the general characteristics and chemical shifts of two enantiomers. Differences in the chemical shifts of two diastereoisomers can be used for the determination of the isomeric purity of the samples. The formation of inclusion complexes can very significantly modify the redox characteristics [13, 70, 71] of the included molecules. Voltammetric sensors capable of responding to anionic compounds have been developed. The changes produced after the complexation (selective interaction) allow the voltammetry to be used in the study of the complexation between CDs and organic molecules.

CDs increase the selectivity of chromatographic separations [72–74], because the separation process is more selective than that between the eluent and the stationary phase alone. In HPLC, the application of the CDs has achieved a spectacular success. Their incorporation into the mobile phase allows improving the separations, since they are soluble in water and provide reversible and selective complexation. In addition, they are stable and show no absorption in the UV-visible region of the electromagnetic spectrum. These characteristics mean that CDs are generally used in reverse phase separation processes, achieving the separation of isomers, diastereoisomers, and enantiomers [75–78]. The high resolution obtained is due to the differences in the stability constants of the complexes in the mobile phase and the different adsorption of these complexes in the stationary phase. CDs may also be incorporated as support for the stationary phases. Capillary electrophoresis has also found use in chiral analytical separations [79–82].

4. A primer on pharmaceutical, food and cosmetic cyclodextrin studies

4.1. Bioavailability

CDs have mainly been used as complexing agents to improve the aqueous solubility of molecules. This allows the use of CDs to reduce or prevent gastrointestinal or ocular irritation by lowering the local concentration of the free drug below the irritancy threshold. Also, unpleasant odor or taste of drugs can be hidden by complexation of the functional groups that produce them with CDs, occulting them from the sensory receptors [83–85], furthermore, reducing their hydrophobicity using CDs. Finally, CDs can increase percutaneous or rectal absorption of drugs and their derivatives can increase the guest molecule bioavailability [84]. Recently, CDs and their derivatives have been used in dispersed vehicle systems such as emulsions, microcapsules, microspheres, nanospheres, nanocapsules, liposomes, and beads [86]. Additionally, the host-guest property allows CDs to be used as building blocks in supramolecular chemistry [7]. Suvarna et al. [87] explain an insight in the use of CDs to increase the bioavailability to resolve the problem of solubility and stability of phytochemicals. The authors describe that some chemicals as quercetin, curcumin, arteminsinin, resveratrol or naringenin increased their bioavailability due to the inclusion complexes with CDs. Authors concluded that CDs need to be more explored to cover some molecules that have potential biological activity but have not been approached.

4.2. Encapsulation

The encapsulation with CDs is gaining interest in different industries; this is reflected in the large number of publication and products related with it, such as drug delivery systems [7, 35]. This capacity of encapsulating compounds is used for a wide variety of things, among them is to protect the compounds, or to transport them to a target. This ability is due to the toroidal shape of CDs which makes possible to encapsulate hydrophobic molecules fully or

partially in their cavity [14, 35]. This characteristic let the CDs being used for oral, sublingual, ocular, nasal, rectal, pulmonary, dermal, and other drug delivery systems, especially in systems of type 1/1 (one molecule per CD). The encapsulation with CDs enhanced the bioavailability of lipophilic drugs, as they are 17β-estradiol, androstenediol, clomipramine, and others. A limitation of CD in sublingual route is that the quantity used for a proper formulation is too large to be considered. This increase in the bioavailability is also observed in the oral route for drugs such as diltiazem, flufenamic acid, molsidomine, salbutamol, having all of them a sustained release [88].

4.3. Controlled release

In order to optimize pharmacotherapy, drug release should be controlled in accordance with the therapeutic purpose and the pharmacological properties of the active substances. In recent years, the interest regarding the control of rate or time of delivery has significantly increased [88]. The multifunctional characteristics of CDs allow them to be used in most drug delivery systems [84]. The design process of drug delivery systems is currently more focused on the oral route, in which the release of the drug can be controlled by dissolution, diffusion, osmosis, density or pH. Challa et al. [89] give several examples of different uses in oral delivery. The use of β-CD increased the bioavailability of ketoprofen, terfenadine, and griseofulvin; but, the same CD, also demonstrated higher intensity or longer duration of therapeutic activity in tolbutamide or terfenadine. Although there are different effects depending on the modified CD used, for example, the solubility and dissolution rate can be increased using HP-β-CD, for drugs as albendazole, ketoprofen, phenytoin, and gliclazide; or an improvement of hydrolysis stability γ-CD, for drugs as digoxin, camptothesin and paclitaxel. For oral administration, all CDs can be used because they are not toxic.

4.4. Nano

The improvement of the efficacy and bioavailability of poorly soluble drugs can be achieved by nanoparticles, which are stable systems that are used to create drug delivery systems [83]. Nanoparticles are 100–10,000 times smaller than human cells and their uses revolutionize diagnosis, treatment, therapeutic efficacy, and patient compliance [83, 90]. However, nanoparticles are limited by their low drug loading and entrapment ability, which compromises their safety and efficacy [84]. The use of CDs as a polymer increases the loading capacity of nanoparticle systems [89]. Furthermore, the optimal drug bioavailability and biodistribution can be achieved with a proper manipulation of physico-chemical and biological mechanisms, which can be provided by the hybrid functionalities of CD nanosystems [91]. A new class of colloidal polymer is nanosponges, which consist of solid nanoparticles with colloidal shape and nanocavities. Examples of nanosponges are those based on CDs. It should be noted that the type, number, and position of the substituent on the CD affect the complexation ability of nanosponges. Thus, it is crucial to know which CD derivative to use. Tejashri et al. [92] expose the use of CD to make nanosponge, and the use of it to load drugs and use as carriers. The crosslinking of CDs with compounds, as carbonyl or dicarboxylate, creates the different types of nanosponge, polyamide, carbonate, etc. Authors concluded that this novel class of

CD-based nanosponge let drugs to be released in a controlled form at the target place, and its spherical shape let nanosponge to be administered as parental, aerosol, topical, tablets, and capsules forms.

4.5. Food

In last years the application of CDs in the food-industry have increased mainly due to the use of them as a protective agent against oxygen, to protect flavor of volatile compounds, to enriched food with vitamins and color components (such as anthocyanins) or to stabilize them [93, 94]. Another advantage for the food industry is that CD are tasteless, odorless, and non-caloric saccharides, and that they have an antidiabetic effect due to their low glycemic index and their capability to decrease the glycemic index of the food, and also to improve the cholesterol index. Human gastrointestinal enzymes cannot digest them, so it can be used as a dietary fiber, which is fermented by microflora, what makes them a prebiotic compound. All these properties make them nutraceuticals and bioactive food supplements [95, 96]. López-Nicolás et al. [97] analyzed the positive effects of CDs in the encapsulation of antioxidant, and the repercussion on important factors as K_F or pH values. They also reviewed the antioxidant capacity of CDs, but they concluded that there is a necessity of more studies in this aspect.

4.6. Cosmetic

The cosmetic industry is looking for products with a good biological activity and adequate delivery on the skin [98]. The applications of CDs in cosmetics are similar to the pharmaceutical ones, e.g., stabilizing substances or increasing their solubility [99–101]. Centini et al. [98] associated ferulic acid, which is a photoprotector agent and an antioxidant compound, and CD. However, ferulic acid is not too much used due to the instability of it in the presence of air, UV-light, and heat; so, the aim of the work was to enhance the physico-chemical stability. The authors concluded that the complex ferulic acid/CD have a better photostability and do not generate degradation products. Buschmann and Schollmeyer [99] explained the use of CD against the vaporization of slow release of the volatile compounds in perfumes; or the opposite, they also explained the use of CD to eliminate undesired odors, such as mercapto derivate used in waving lotion. More applications will become possible when CDs price decreases. CDs can also be used in the textile industry as depots of cosmetic molecules providing new cosmetic formulations.

4.7. Miscellaneous applications of cyclodextrins: tabular form

A more detailed picture of most recent selected applications in various areas, ranging from general reviews to inclusion complexes, metal and organometallic complexes, food, pharmaceutical, pharmacological, medical and biomedical, environmental chemistry, personal care and toiletry, industrial, nanotechnological, industrial and analytical applications to enzyme, biomimetic, bioactive assembles and recognition, as well as miscellaneous applications is compiled in **Table 1**, which gives an idea of the importance and relevance of the CDs field. **Figure 5** shows the number of publications cited per year, whereas in **Figure 6**,

Content	Authors	Refs.
General reviews		
Overview about the work carried out on CDs concerning with: the general characteristics of CDs and derivatives, the preparation and evaluation of inclusion complexes, the use of CDs in the preparation of drug delivery systems, and their use for the preparation of biomaterials and nanoparticles.	Duchêne and Bochot (2016)	[14]
Comprehensive overview on the methods used for analysis of CDs and CD-derivatives. The paper intends to act as a guide in looking around the classical and modern instrumental analytical methods suitable for identification, characterization and determination of CDs themselves, CDs in finished products or even in biological samples.	Szente et al. (2016)	[2]
Current review on various aspects of CDs with regard to their chemical characteristics, properties, approaches used for complexation, characterization techniques, uses along with and future potential.	Khan and Durakshan (2013)	[7]
Pharmaceutical applications of CDs with an emphasis on their solubilizing properties, their tendency to self-assemble to form aggregates, CD ternary complexes, and their metabolism and pharmacokinetics.	Kurkov and Loftsson (2013)	[3]
Overview about several aspects related to the physico-chemical properties of CDs and their potential applications illustrated by recent examples.	Venturini et al. (2008)	[102]
Inclusion complexation and CDs: physicochemical parameters of the guest molecule and improvements in the molecule's solubility, stability, taste, safety, bioavailability, etc.	Mosher and Thompson (2007)	[103]
CDs and their use in industrial products, technologies and analytical methods.	Martin del Valle (2004)	[93]
Overview about past, present, and future of CD research. Potential uses of CDs in pharmaceuticals, foods, cosmetics, and chemical products and technologies.	Szejtli (2004)	[26]
CDs: structure, complex formation, drug solubility and non-conventional CD complexes.	Loftsson (2002)	[9]
Scientific and technological aspects of CDs: from computational chemistry to industrial uses of CDs.	D'souza and Lipkowitz (1998)	[104]
History (the three stages in the development of CD chemistry), fundamentals of CD chemistry and future trends.	Szejtli (1998)	[105]
The properties and potential uses of CD derivatives: dimethyl- and dimethyl-βCD (DIMEB and TRIMEB).	Szejtli (1992)	[106]
Catalyses by CDs leading to practical usages: covalent, non-covalent and asymmetric catalyses by CDs.	Bender and Komiyama (1978)	[107]
Inclusion complexes		
The inclusion complex of oxyresveratrol in modified CDs: a thermodynamic, structural, physicochemical, fluorescent and computational study.	Matencio et al. (2017)	[108]

Content	Authors	Refs.
Summary of method for inclusion complex formation of CD with its guests and its applications.	Cheirsilp and Rakmai (2016)	[42]
Literature review to characterize the formation of inclusion complexes by different techniques in the solid and in the solution state complexation.	Maazaoui and Abderrahim (2015)	[44]
Use of CDs as complexing agents to enhance the solubility of poorly soluble drugs and hence to resolve the many issues associated with developing and commercializing poorly water-soluble drugs.	Chaudhary and Patel (2013)	[16]
Survey of crystal structures of pure CD hosts and CD inclusion compounds carried out during the last six years. The entries range from simple alkylated derivatives to elegant multi-substituted target CD molecules, with and without included guests.	Caira (2011)	[40]
CD inclusion of four phenylurea herbicides: determination of complex stoichiometries and stability constants using solution ^{1}H NMR spectroscopy.	Smith et al. (2010)	[69]
Comparison of the inclusion complexation between host and guest in CD chemistry with the coordination interaction between central ion (M^{x+}) and ligands in coordination chemistry.	Song et al. (2009)	[36]
Threading CDs molecules onto polymer chains to form crystalline inclusion complexes organized by non-covalent interactions.	Martinez and Gomez (2007)	[109]
Practical considerations in development of solid dosage forms that contain CD.	Miller et al. (2007)	[110]
CD inclusion complexes with a solvatochromic fluorescent probe: an undergraduate physical chemistry lab experiment to establish the solvatochromic nature of PRODAN and then use the changes in the emission spectra upon inclusion in β- or γ-CD to determine stoichiometry and formation constants for the complexes.	Baker et al. (2002)	[111]
Some applications of CD/ substrate inclusion complexes.	Crini et al. (2001)	[8]
Determination of thermodynamic parameters of the CD inclusion processes: an undergraduate physical chemistry lab experiment.	Valero et al. (1999)	[112]
Complexation thermodynamics of CDs.	Rekharsky and Inoue (1998)	[113]
Applications of CDs to pharmaceutical industry and chemical catalysis. Analytical applications are also considered, since CDs inclusion improves the sensitivity and selectivity of most analytical methods.	Muñoz-Botella et al. (1995)	[37]
β-CD inclusion complexes with iodine: an advanced and inexpensive undergraduate chemistry experiment.	Diaz et al. (1994)	[114]
Critical overview about past, present and future of CDs: properties, studies on CD inclusion compounds and its applications.	Davies et al. (1983)	[115]
Metal and organometallic complexes		
Synthesis, reactivity and structural diversity of well-defined metal complexes derived essentially from native CDs. Structural motifs for metal complexes based on CDs: from monomeric species, dinuclear systems, homo- and heterometallic sandwich-type complexes to cylindrical, extended structures.	Prochowic et al. (2016)	[116]

Content	Authors	Refs.
Overview of recent advances of CD catalyzed reactions, which is organized in the order of the following reaction types: the modified CD catalyzed organic reaction, CD catalyzed organic reaction of metal ion present, CD catalyzed organic reaction without metal ion, and CD catalyzed organic reactions in application of asymmetric synthesis and photochemical reactions.	Hong et al. (2015)	[117]
Research and application of CDs and their derivatives in asymmetric and stereospecific syntheses, with their division into three main groups: (1) CDs promoting asymmetric and stereospecific catalysis in water; (2) CDs' complexes with transition metals as asymmetric and stereospecific catalysts; and (3) CDs' non-metallic derivatives as asymmetric and stereospecific catalysts.	Macaev and Boldescu (2015)	[118]
Preparation and analysis of CD-based metal–organic frameworks: laboratory experiments adaptable for high school students.	Smith et al. (2015)	[49]
Selectively functionalized CDs and their metal complexes: recent applications as chiral receptors and catalytic center in the mimicking of metalloenzymes.	Bellia et al. (2009)	[119]
Metal complexing properties of native CDs (including deprotonation in alkaline medium) and a report on some recent results on composition and stability of metal–CD complexes.	Norkus (2009)	[120]
CDs as supramolecular hosts for organometallic complexes.	Hapiot et al. (2006)	[121]
Food applications		
Complexation of poorly water-soluble phytochemicals (flavonoids, phenolic derivatives, coumestans to triterpenes) with CDs to improve their aqueous solubility, stability, rate of dissolution and bioavailability.	Suvarna et al. (2017)	[87]
CDs in food technology and human nutrition: benefits and limitations. The recent applications of CDs for reducing unwanted components, such as trans-fats, allergens, mycotoxins, acrylamides, bitter compounds, as well as in smart active packaging of foods are also overviewed.	Fenyvesi et al. (2016)	[95]
History, chemistry, methods of complexation and application of CDs into different areas, particularly in the pharmaceutical and food industry.	Maazaoui and Abderrahim (2015)	[44]
Properties, enzymatic production, and food applications of α-CD, as well as its differences with β- and γ-CDs.	Li et al. (2014)	[122]
Studies on the complexes formed between several important types of antioxidant compounds and CDs.	López-Nicolás et al. (2014)	[97]
Applications of CDs as food additives and in food processing: transport of previously nontransportable foods and prevention of the spread of microbial infections.	Martina et al. (2013)	[123]
CDs as novel solutions for the food industry concerning with their role as dietary fiber, in food and drink with health-promoting additives, protect sensitive ingredients, improve taste and odor, or their positively influence to the texture and consistency of food.	Zipp (2012)	[96]
Factors controlling flavors binding constants to CDs and their applications in foods.	Astray et al. (2010)	[124]

Content	Authors	Refs.
CD encapsulation of essential oils and volatiles: methods for the preparation of inclusion complexes, analytical techniques and applications.	Cabral Marques (2010)	[33]
Practical aspects of the utilization of CDs and CD inclusion compounds to food manufacture, focusing on the technical advantages of their use in food processing and as food additives.	Moreira da Silva (2009)	[125]
Use of CDs in the food industry: properties from a technological point of view, such as solubility and their capability to form inclusion complexes are described.	Astray et al. (2009)	[94]
Isolation and identification of native and branched-type (glucosylated and maltosylated) CDs in different enzyme- and heat-processed starch-containing food products.	Szente et al. (2006)	[35]
Practical aspects of the utilization of CDs and CD complexes in the food industry: molecular encapsulation of lipophilic food ingredients, long-term storage stability and technological advantages and food processing technologies.	Szente and Szejtli (2004)	[126]
CDs: application to food processing.	Yoshii (2004)	[127]
Pharmaceutical applications		
Reviews		
CDs: history, chemical structure, synthesis, physicochemical properties, uses, complexation phenomenon, approaches for making inclusion complexes, and its characterisation, advantages of inclusion complexes, mechanism of drug release, regulatory status and its applications.	Kanaka Durga Devi et al. (2010)	[83]
Basic science information and data on the development of drugs in CD-containing formulations.	Loftsson and Brewster (2010)	[128]
Critical review about experimental methods for determination of the binding constant between CD and a guest molecule.	Funasaki et al. (2008)	[10]
Historical development of CDs with emphasis on their use in pharmaceutical formulations.	Loftsson and Duchêne (2007)	[129]
CD-based pharmaceutics: past, present and future applications.	Davis and Brewster (2004)	[130]
CDs: structure, complex formation and drug solubility and non-conventional CD complexes.	Loftsson (2002)	[9]
Main impetus for the research into CD-drug combinations.	Frömming and Szejtli (1994)	[131]
Delivery release		
Application of CD nanosystems for oral drug delivery: strategies for the synthesis of these nanosystems, and their potential for the intelligent navigation of the gastrointestinal tract for optimal bioavailability and biodistribution.	Adeoye et al. (2017)	[91]
CD-mediated hierarchical self-assembly and its potential in drug delivery applications.	Antoniuk and Amiel (2016)	[132]
Supramolecular nanostructures based on CD and poly(ethylene oxide): syntheses, structural characterizations and applications for drug delivery.	Zheng and Wyman (2016)	[133]

Content	Authors	Refs.
Recent advances in drug delivery techniques utilizing CDs, and cyclic oligosaccharides consisting of α-1,4-linked α-D-glucopyranose units. Especially, drug delivery system consisting of combination systems of CDs and functional materials such as dendrimer, liposome and PEG are introduced.	Arima et al. (2015)	[134]
Relationship between CDs structure and physicochemical characteristics: self assembly and drug delivery. Importance of the nanoparticle technology preparation for the stability and application of this nanodevice.	Bonnet et al. (2015)	[135]
CD-based carriers for delivery of chemotherapeutic cytotoxic anticancer drugs.	Gidwani and Vyas (2015)	[90]
CD-based delivery systems for arthritic diseases: from development to experimental therapeutics.	Nascimento et al. (2015)	[136]
A vision for CD nanoparticles in drug delivery systems and pharmaceutical applications.	Lakkakula and Krause (2014)	[137]
CD containing biodegradable particles: from preparation to drug delivery applications.	Zafar et al. (2014)	[138]
State of the art and recent advances in the construction of CD-based assemblies and their applications for controlled drug delivery.	Zhang and Ma (2013)	[139]
CD in drug delivery: complexing agents, bioavailability and industrial applications.	Chordiya Mayur and Senthilkumaran (2012)	[86]
Recent developments of CDs in drug delivery using various routes of administration.	Laza-Knoerr et al. (2010)	[140]
Advantages of CD inclusion complexation, effects on important drug properties in formulation and applications in delivery systems (oral drug, rectal dug, nasal drug, transdermal drug, ocular drug, controlled and targeted drug, peptide and protein delivery, gene and oligonucleotide delivery, dermal and transdermal delivery, brain drug delivery or brain targetting).	Tiwari et al. (2010)	[84]
CD-based supramolecular architectures: syntheses, structures, and applications for drug and gene delivery.	Li and Loh (2008)	[141]
Applications of CDs and their derivatives in different areas of drug delivery: parenteral, oral, ophthalmic and nasal drug delivery. Other routes including dermal, rectal, sublingual and pulmonary delivery are also briefly addressed.	Rasheed et al. (2008)	[88]
Applications and comparative benefits of use of CDs and their derivatives in the design of novel delivery systems like liposomes, microspheres, microcapsules, nanoparticles, CD grafted cellulosic fabric, hydrogels, nano- sponges, beads, nanogels/nanoassemblies and CD-containing polymers.	Vyas et al. (2008)	[142]
The utility of CDs for enhancing oral bioavailability.	Carrier et al. (2007)	[143]
CDs as cosmetic delivery systems: study of ferulic acid/ CD association complexes at the light of its possible use as sunscreen.	Centini et al. (2007)	[98]
Effects of hydrophilic CDs on drug permeation through membranes and possible mechanism of action based on the current knowledge of the structural characteristics of water and the unstirred water layer juxtaposed to the membrane of interest.	Loftsson et al. (2007)	[144]

Content	Authors	Refs.
Interesting findings and applications of CDs and their derivatives in different areas of drug delivery, particularly in protein and peptide drug delivery and gene delivery. Applications in the design of various novel delivery systems like liposomes, microspheres, microcapsules, and nanoparticles.	Challa et al. (2005)	[89]
CDs in drug delivery. Pharmaceutical products worldwide containing drug/CD complexes on the market.	Loftsson et al. (2005)	[145]
Recent findings and applications of both unmodified and modified CDs for in vivo drug delivery. Use of CDs for parenteral, oral, ophthalmic, and nasal drug delivery. Other routes including dermal, rectal, and pulmonary delivery are also briefly addressed.	Rajewski and Stella (1996)	[54]
Carrier		
Potential therapeutic application of dendrimer/CD conjugates with targeting ligands as advanced carriers for gene and oligonucleotide drugs.	Arima et al. (2017)	[146]
Drug carrier systems based on CD supramolecular assemblies and polymers: present and perspectives.	González-Gaitano et al. (2017)	[147]
CD-based polymeric nanoparticles as efficient carriers for anticancer drugs.	Duchêne et al. (2016)	[148]
Potential use of chemically modified CDs as high-performance drug carriers in drug delivery systems with emphasis on the more recent developments.	Rasheed et al. (2008)	[88]
CD drug carrier systems: characteristics, improvements of drug properties by CD complexation and CD-based drug delivery systems.	Uekama et al. (1998)	[149]
Solubilization and permeation		
CDs in pharmaceutical formulations: solubilization, binding constant, and complexation efficiency.	Jambhekar and Breen (2016)	[18]
Use of CDs as complexing agents to enhance the solubility of poorly soluble drugs and issues associated with developing and commercializing poorly water soluble drugs.	Chaudhary and Patel (2014)	[16]
Pharmaceutical applications of CDs: effects on drug permeation through biological membranes.	Loftsson and Brewster (2011)	[150]
General background to the use of CD as solubilizers as well as highlight kinetic and thermodynamic tools and parameters useful in the study of drug solubilization by CDs.	Brewster and Loftsson (2007)	[15]
CDs as solubilizers as well as highlight kinetic and thermodynamic tools and parameters useful in the study of drug solubilization	Loftsson and Brewster (1996)	[19]
Protein		
Use of CDs and their derivatives as antiaggregant agents in a number of proteins and some multimeric enzymes.	Oliveri and Vecchio (2016)	[151]
CD-based multivalent glycodisplays: covalent and supramolecular conjugates to assess carbohydrate–protein interactions.	Martínez et al. (2013)	[152]
CD interactions with protein-like structures in order to describe their possible applications in the formulation of pharmaceutical proteins.	Varca et al. (2010)	[153]

Content	Authors	Refs.
Encapsulation		
Encapsulation of CD/drug inclusion complex into conventional, deformable and double loaded liposomes: characteristics of these systems and advantages and disadvantages of each one.	Gharib et al. (2015)	[154]
Encapsulation of biocides by CDs: toward synergistic effects against pathogens.	Nardello-Rataj and Leclercq (2014)	[34]
Use of CDs as encapsulating agents for bioactive plant molecules in the pharmaceutical field.	Pinho et al. (2014)	[35]
Excipients		
Background review for CDs used as excipients.	EMA/CHMP/333892/ (2013)	[155]
CDs as functional excipients: methods to enhance complexation efficiency.	Loftsson and Brewster (2012)	[156]
Formulations		
CDs in pharmaceutical formulations: structure and physicochemical properties, formation of complexes, and types of complex.	Jambhekar and Breen (2016)	[17]
Evaluation of CDs drug complexes in pharmaceutical formulation: preparation of sodium valproate phenytoin sodium/ β-CD inclusion complex in a trial to stabilize the drug against moisture absorption and forming non-hygroscopic powders and preparation of phenytoin sodium/β-CD inclusion complex in a trial to stabilize the drug against moisture absorption and mask its bitter taste.	Akasha et al. (2014)	[157]
CDs in topical drug formulations: drug delivery from aqueous CD solutions by diffusion and membrane controlled.	Loftsson and Masson, (2001)	[158]
Miscellaneous		
Types of fluorophores which have been used for CD tagging: synthetic strategies used for the conjugation and pharmaceutical applications of these 'visualized' macrocycles including their use in photodynamic therapy.	Benkovics et al. (2017)	[159]
CDs' legacy as complexing agents and future prospects of this class of chemical entities in pharmaceutics as new active pharmaceutical ingredients.	di Cagno and Pio (2017)	[160]
Use of CD in the different routes of drug administration.	Shimpi et al. (2005)	[161]
Recent findings on the safety profiles of three natural CDs and several chemically modified CDs: stability against non-enzymatic and enzymatic degradations in various body fluids and tissue homogenates and their pharmacokinetics via parenteral, oral, transmucosal, and dermal routes of administration.	Irie and Hekama (1997)	[162]
Pharmacology		
Production, physiochemical properties, pharmacokinetics, toxicity and applications of γ-CD and its derivatives.	Saokham et al. (2017)	[15]
Interactions between CDs and cellular components: medical applications.	Leclercq (2016)	[163]
Inclusion of terpenes in CDs: preparation, characterization and pharmacological approaches.	Lima et al. (2016)	[164]

Content	Authors	Refs.
Self-assembly of CDs and their complexes in aqueous solutions.	Ryzhakov et al. (2016)	[48]
Diagnostic utility of flow cytometry and improvement of rocuronium-induced anaphylaxis with the use of sugammadex.	Takazawa et al. (2016)	[165]
Sugammadex for reversal of rocuronium-induced neuromuscular blockade in pediatric patients: a systematic review and meta-analysis.	Won et al. (2016)	[166]
Improving the therapeutic response of analgesic drugs by CDs.	De Oliveira et al. (2015)	[167]
Types of CDs, and their efficacy, physicochemical properties and transformation into nanoparticles with interesting in vitro and in vivo applications.	Lakkakula and Krause (2014)	[137]
Potential therapeutic use of CDs and CD nanoparticles in neurodegenerative diseases, stroke, neuroinfections and brain tumors.	Vecsernyés et al. (2014)	[168]
Basic and clinical pharmacology of sulfobutylether-β-CD.	Loftsson and Brewster (2010)	[128]
Basic and clinical pharmacology of sulfobutylether-β-CD.	Luke et al. (2010)	[169]
CD introduction to anesthesia practice: form, function, and application.	Welliver (2007)	[170]
Findings on the safety profiles of three natural CDs and several chemically modified.	Irie and Uekama (1997)	[162]
Medical and biomedical		
Key features of the CDs therapeutic discovery. Application of computational chemistry approaches such as QSAR/QSPR, molecular docking, and molecular/quantum mechanics for modeling of CD-drug system.	Abdolmaleki et al. (2017)	[171]
Recent development of copolymeric delivery system for anticancer agents based on CD derivatives.	Feng et al. (2016)	[172]
General features and applications of CDs and their interactions with isolated biomolecules leading to the formation of inclusion or exclusion complexes: potential medical applications.	Leclercq (2016)	[163]
Data on the general properties and complexing ability of CDs and assessment methods (phase solubility, DSC tests and X-ray diffraction, FTIR spectra).	Radu et al. (2016)	[173]
CD interactions with protein-like structures: possible applications in the formulation of pharmaceutical proteins.	Vecsernyés et al. (2014)	[168]
Amphiphilic CDs and their applications: preparation of nanoparticles based on amphiphilic CDs for biomedical applications.	Parrot-Lopez et al. (2010)	[174]
A supramolecular approach to medicinal chemistry: essential roles played by intermolecular forces in mediating the interactions between chemical molecules and biological systems.	Smith (2005)	[175]
Medicinal applications of CDs: improvement of drug properties, use of drug/CD complexes, CDs in tabletting and direct treatment with CDs.	Szejtli (1994)	[176]
Environmental Chemistry and Applications		
Nanosponge CD polyurethanes and their modification with nanomaterials for the removal of pollutants from waste water.	Leudjo Taka et al. (2017)	[177]

Content	Authors	Refs.
Progress in the immobilization of β-CD and their application in adsorption of environmental pollutants.	Han et al. (2016)	[178]
Interactions of CDs and their derivatives with toxic organophosphorus compounds.	Letort et al. (2016)	[179]
CD inclusion of four phenylurea herbicides: determination of complex stoichiometries and stability constants using solution ^{1}H NMR spectroscopy.	Smith et al. (2010)	[69]
Fluorescence spectroscopy as a tool to study the properties of CD host-guest complexes. Overview of recent studies concerned with exploiting the properties of CDs and their inclusion complexes to study energy transfer through the use of photochemical antennas and the development of chemical and environmental sensors.	Fakayode et al. (2007)	[27]
Synthesis and applications of adsorbents containing CDs in the field of chromatographic separations and in waste water treatment.	Crini and Morcellet (2002)	[180]
Personal care and toiletry		
CDs as cosmetic delivery system: study of ferulic acid/CD association complexes.	Centini et al. (2007)	[98]
Inclusion complex formation of CD with its guest and their applications in foods and flavors, personal care and toiletry, environment protection, pharmaceuticals among others.	Cheirsilp and Rakmai (2016)	[42]
Possible applications of CDs in cosmetic products and some examples of their present uses.	Buschmann and Schollmeyer (2002)	[99]
Industrial applications		
Enabling technologies and green processes in CD chemistry: microwaves, ultrasound and ball mills have become irreplaceable tools in the synthesis of CD derivatives. Examples of sonochemical selective modification of native α-, β- and γ-CDs including heterogeneous phase Pd- and Cu-catalysed hydrogenations and couplings.	Cravotto et al. (2016)	[181]
Major fields of enzyme application and overview on previous protein engineering studies wherein natural enzymes were modified to meet the operational conditions required for industrial application.	Jemli et al. (2016)	[24]
Applications of CDs in medical textiles: general data properties and complexing ability of CDs and assessment methods (phase solubility, DSC tests and X-ray diffraction, FTIR spectra, analytical method).	Radu et al. (2016)	[173]
Applications of CDs in various industrial products, technologies, analytical and chemical processes and recent industrial advancements.	Sharma and Baldi (2016)	[182]
General features of β-CD and their applications in the textile industry: attachment technique of β-CD to the textile's surface.	Bhaskara-Amrit et al. (2011)	[183]
CDs in pharmaceutics, cosmetics, and biomedicine: current and future industrial applications.	Bilensoy (2011)	[184]
Role of CDs in the textile chemical technology: remove the surfactants from the material or to inactivate them in liquid phase, to intensify the enzyme processes or as balancers in dyeing with reactive pigments.	Grigoriu and Popescu (2011)	[185]
Amphiphilic CDs and their applications. Preparation of nanoparticles based on amphiphilic CDs for biomedical applications.	Parrot-Lopez et al. (2010)	[174]

Content	Authors	Refs.
Applications of CDs in pharmaceuticals with a major emphasis on drug delivery systems. Utility in a variety of foods, flavors cosmetics, packaging and textiles.	Singh et al. (2002)	[186]
Applications of CDs in pharmaceuticals, foods and flavours, cosmetics, chemical industry, agricultural industry and adhesives, coatings and other polymers.	Arenskötter et al. (2001)	[187]
Industrial applications of CDs. Production and analysis of complexes.	Hedges (1998)	[188]
Utilization of CDs in industrial products and processes: (i) textiles, fibers and papers; (ii) foods and cosmetics; (iii) plastics and rubber; (iv) photographic and recording materials; (v) biotechnology and (vi) environmental protection.	Szejtli (1997)	[189]
Overview about industrial uses of CDs and their derivatives.	Duchêne and Wouessidjewe (1992)	[190]
CD inclusion compounds in research and industry: production of pharmaceuticals, pesticides, foodstuffs, and toilet articles among others.	Saenger (1980)	[191]
Nano		
General overview of CDs and pharmaceutical nanotechnology in oral delivery systems. Strategies for the synthesis of these nanosystems, and their potential for the intelligent navigation of the gastrointestinal tract for optimal bioavailability and biodistribution.	Adeoye and Cabral-Marques (2017)	[91]
Nanosponge CD polyurethanes and their modification with nanomaterials for the removal of pollutants from waste water.	Leudjo et al. (2017)	[177]
CD-based supramolecular host–guest interactions for engineering supramolecular nanoparticles: biomedical applications.	Mejia-Ariza et al. (2017)	[192]
CD-based polymeric nanoparticles as efficient carriers for anticancer drugs.	Duchene et al. (2016)	[148]
CD-based nanosponges: a versatile platform for cancer nanotherapeutics development.	Swanimathan et al. (2016)	[193]
Supramolecular nanostructures based on CD and poly(ethylene oxide): syntheses, structural characterizations and applications for drug delivery.	Zheng and Wyman (2016)	[133]
Nano-sized CD-based molecularly imprinted polymer adsorbents for perfluorinated compounds.	Karoyo and Wilson (2015)	[194]
Overall view of the diversity of designs of CD-based supramolecular nanosystems with a special focus on the advances materialized in the last five years, including clinical trials.	Simoes et al. (2015)	[195]
Recent advances in the construction of nanoassemblies driven by CD-based inclusion complexation and their application in biomedical and biomimetic fields.	Kang et al. (2014)	[196]
A vision for CD nanoparticles in drug delivery systems and pharmaceutical applications.	Lakkakula and Krause (2014)	[137]
Approaches tested to synthesize nano- to macro-size covalently cross-linked CD networks: (i) direct cross-linking through condensation with di- or multifunctional reagents, (ii) copolymerization of CD derivatives with acrylic/vinyl monomers, and (iii) grafting of CDs to preformed medical devices.	Concheiro and Alvarez-Lorenzo (2013)	[197]

Content	Authors	Refs.
Development of nanosponges as drug delivery systems, with special reference to CD based nanosponges.	Tejashri et al. (2013)	[92]
Preparation, characterization and advantages for pharmaceutical and biomedical applications of CD-based nanogels.	Moya-Ortega et al. (2012)	[198]
Formation and applications of CD nanoaggregates induced by guest molecules, the concerned thermodynamics behind the process and the effect of concentration of the guest molecules on the morphology of the aggregates.	Purkayastha et al. (2012)	[199]
Approaches employed in delivering drugs to the central nervous system. Changes in blood-brain barrier function in several neurological disorders.	Martín-Banderas et al. (2011)	[200]
Fabrication technologies of supramolecular systems including nanoplatforms and hydrogels as well as their applications in nanomedicine and pharmaceutical sciences.	Zhang and Ma (2013)	[139]
Classification, physicochemical properties, efficacy and safety of nanoparticles prepared from different amphiphilic CDs are discussed in light of the current literature work with in vitro and in vivo findings.	Bilensoy and Hincal (2009)	[201]
Analytical and physicochemical applications		
Reviews		
Classical and modern instrumental analytical methods suitable for identification, characterization and determination of CDs themselves, CDs in finished products or even in biological samples.	Szente et al. (2016)	[2]
CDs in in sample preparation, sensitivity and selectivity improvement, enantio-separation, creating single-molecule sensors, and automatizing DNA sequencing.	Szente and Szeman (2013)	[28]
CDs: from molecular recognition to CDs as enzyme models. Reactivity and chemistry, chromatography, X-ray, NMR plus other physicochemical methods, as well as model calculations, rotaxane and catenane structures, and applications in the pharmaceutical industry are overviewed.	Dodziuk (2006)	[202]
Use of CDs in major areas of analytical chemistry such as chromatography, electrophoresis, spectroscopy, electrochemistry and as analytical sensors.	Mosinger et al. (2001)	[203]
Role of CDs in three of the major areas of modern instrumental analysis: separations, spectroscopy and electrochemical analysis.	Armstrong (1998)	[204]
Chirality		
CD-functionalized monolithic capillary columns: preparation and chiral applications.	Adly et al. (2016)	[205]
Recent developments in CD functionalized monolithic columns for the enantioseparation of chiral drugs.	Guo et al. (2016)	[206]
Advances on the use of CDs in the chiral analysis of drugs by capillary electrophoresis.	Saz and Marina (2016)	[80]

Content	Authors	Refs.
Recent contributions to the understanding of the binding mechanism between chiral selectors and selectands in analytical enantioseparations including polysaccharide derivatives, CDs, cyclofructans, macrocyclic glycopeptides, proteins, brush-type selectors, ion-exchangers, polymers, crown ethers, ligand-exchangers, molecular micelles, ionic liquids, metal-organic frameworks and nucleotide-derived selectors.	Scriba (2016)	[77]
Development of cationic CDs for chiral separation. Update of the research endeavors of synthetic and analytical chemists in evaluating enantioselectivity of cationic CDs using different analytical methods and the study of the chiral recognition mechanism.	Zhou and Scriba (2016)	[75]
Advances in enantiomeric resolution on monolithic chiral stationary phases in liquid chromatography and electrochromatography.	Al-Othman et al. (2014)	[207]
Recent examples of mechanistic aspects of capillary enantioseparations with regard to mathematical modeling of enantioseparations, investigations of the analyte-complex structures as well as new chiral selectors and applications of chiral analyses by CE and CEC.	Jac and Scriba (2013)	[208]
Review of the latest advances in developing modified CDs as chiral selectors for various chromatographic and electromigration techniques.	Tang et al. (2013)	[76]
Chiral analysis of amphetamines, methadone and metabolites in biological samples by electrodriven methods.	Mandrioli et al. (2011)	[209]
The growth and applications of CDs as chiral discriminator.	Pathak and Pathak (2008)	[210]
CDs in capillary electrophoresis enantioseparations: recent developments and applications.	Scriba (2008)	[90]
Separation of enantiomeric barbiturates by capillary electrophoresis using a CD containing run buffer: a laboratory experiments for degree students.	Contradi et al. (1997)	[82]
Complexes characterization		
Physicochemical characterization of CD-drug interactions in the solid state and the effect of water on these interactions.	Ogawa and Takahashi (2015)	[52]
Analytical techniques for characterization of CD complexes in the solid state.	Mura (2015)	[51]
Analytical tools which can be employed for the characterization of drug-CD inclusion complexes in solution, with emphasis on their respective potential merits, disadvantages and limits.	Mura (2014)	[47]
Surfactant-CD host-guest association: fundamentals, drawbacks and advantages of techniques commonly used to obtain insights on the structural and bulk solutions changes resulting from host-guest association mechanism, and corresponding methods for binding quantification.	Valente and Söderman (2014)	[30]
CD inclusion complexes probed by NMR techniques.	Pessine et al. (2012)	[45]
A literature review of CD inclusion complexes characterization: X-ray diffraction, infrared spectroscopy and nuclear magnetic resonance.	Takahashi et al. (2012)	[211]

Content	Authors	Refs.
A literature review of CD inclusion complexes characterization: differential scanning calorimetry and thermogravimetry.	Takahashi et al. (2012)	[68]
A bilogarithmic method for the spectrophotometric evaluation of stability constants of 1:1 weak complexes from mole ratio data.	Boccio et al. (2006)	[212]
NMR studies of CDs and CD complexes. Comprehensive overview about the most important approaches to structural problems with CDs, mainly in solution.	Schneider et al. (1998)	[213]
The stability of CD complexes in solution: binding equilibria and kinetics, strengths and structures of CD complexes, the sources of CD complex stability and prediction of CD complex stability.	Connors (1997)	[46]
Separation Methods		
State-of-the-art applications of CDs as functional monomers in molecular imprinting techniques.	Lay et al. (2016)	[214]
CDs in capillary electrophoresis: recent contributions, practical uses (e.g. solute-CD binding constant estimation and further potentials), developments and applications (mainly chiral and achiral analysis).	Escuder-Gilabert et al. (2014)	[79]
Recent developments and new trends.		
Separation processes in the presence of CDs using molecular imprinting technology and ionic liquid cooperating approach.	Zhang et al. (2011)	[59]
Role of CDs in chromatography. Influence of The formation the physicochemical parameters of the guest molecule (adsorption capacity, polarity, hydrophobicity, etc.).	Cserhat and Forgaes (2003)	[71]
Summary of the information concerning the synthesis of materials containing CDs and general overview of the different possible applications of CDs as sorbents in the field of separation techniques.	Crini and Morcellet (2002)	[180]
CDs as a versatile tool in separation science. The techniques examined include gel electrophoresis, isotachophoresis, isoelectric focusing, preparative scale electrophoretic techniques, thin-layer chromatography, electrochemically modulated liquid chromatography, use of monolithic media in liquid chromatography, microdialysis, separation on hollow fibers, foam flotation enrichment, solid- and liquid-phase extractions, countercurrent chromatography, separation through liquid and composite membranes, and CD applications in molecularly imprinted polymers.	Schneiderman and Stalcup (2000)	[61]
Utilization of CDs and their derivatives in gas-liquid and gas-solid-, gel-, inclusion-, thin-layer-, affinity-, and high performance liquid chromatography.	Szejtli (1987)	[215]
Applications of CDs in chromatographic separations and purification methods.	Hinze (1981)	[73]
Spectrofluorometric Methods		
Spectrofluorometric analytical applications of CDs based on host-inclusion complex.	Elbashir et al. (2014)	[64]
Room temperature phosphorescence in CDs: analytical applications.	Muñoz de la Peña et al. (2000)	[66]

Content	Authors	Refs.
Electrochemical Methods		
Advantages and detecting mechanism of electrochemical sensors based on CDs functionalized materials, and recent advances for CDs-based materials (including CDs/carbon nanotubes, CDs/graphene, CDs/conducting polymers and other CDs-based nanomaterials) in electrochemical sensing.	Zhu et al. (2016)	[70]
Substrate/analyte solubilization and stabilization to the development of CD based sensors and detectors.	Szente and Szejtli (1998)	[216]
State of the art of the electrochemistry of α-, β-, and γ-CDs and CD inclusion complexes and their polarographic and voltammetric assay.	Bersier et al. (1991)	[71]
Enzyme—Biomimetic-Bioactive assemblies recognition		
General overview of three different categories of CD-based artificial enzymes including metal free CD-based artificial enzymes, CD-based artificial metalloenzymes and CD-based artificial enzymes with computational design, focusing on their rate acceleration factor.	Aghahosseini and Ramazani (2016)	[21]
Major fields of enzyme application and overview on previous protein engineering studies wherein natural enzymes were modified to meet the operational conditions required for industrial application.	Jemli et al. (2016)	[24]
Macromolecules based on recognition between CD and guest molecules: synthesis, properties and functions.	Liu et al. (2015)	[217]
Representative contributions in the construction and the structural characteristics of CD-based supramolecular assemblies and their interactions with biologically important substrates.	Chen and Liu (2010)	[218]
New chemistry based on the principles used by Nature: biomimetic chemistry.	Breslow (2009)	[23]
Literature overview on reactions in which CDs bind substrates and then either catalyze their reactions or mimic a step in an enzymatic catalytic sequence.	Breslow and Dong (1998)	[22]
Adjusting the lock and adjusting the key in CD chemistry. An introduction in biomimetic chemistry.	Breslow (1980)	[219]
Miscellaneous		
Functioning via host–guest interactions: achievement of selective molecular adhesion, self-healing, toughness, and actuation properties. These functions have been achieved by reversible bond formation with CDs.	Takachima and Harada (2017)	[29]
Qualitative and quantitative analysis of research outputs on molecular modeling in CDs.	Zhao et al. (2017)	[220]
Supramolecular polymer assembly in aqueous solution arising from CD host-guest complexation. Effects of such complexation on properties at the molecular and macroscopic levels.	Wang et al. (2016)	[32]
Superstructures with CDs: chemistry and applications.	Wenz and Monflier (2016)	[221]

Content	Authors	Refs.
Synthesis of CD half-channels derived by per-functionalization of the CD primary positions and their activity as channels assessed by the bilayer clamp technique.	Chui and Fyles (2014)	[222]
Construction of supramolecular structures of CDs with some polymers (polyrotaxanes) and formation of supramolecular oligomers and polymers formed by CD derivatives.	Harada et al. (2009)	[223]
Systematic analysis of methods that are available for modification of CDs. The focus is on methods for transformation where the number and the exact positions of modifications are ascertained and pure compounds with unambiguous structures are obtained.	Khan et al. (1998)	[224]
Applications of computational chemistry to the study of CDs: molecular modeling, structural features of CDs, dynamical aspects of CD structure and computational studies of host–guest complexation.	Lipkowitz (1998)	[225]
CD-based catenanes and rotaxanes.	Nepogodiev et al. (1998)	[226, 227]
Organic reactions mediated by CDs: effect in solid CD complexes.	Takahashi (1998)	[228]

Table 1. Selected papers on food, pharmaceutical, pharmacology, cosmetic, industrial, and analytical applications of cyclodextrins (CDs).

the number of papers cited by journal for the most cited journal (number of references ≥2) appears. Emphasis is stressed on reviews and taking into account the high number of references available, the authors apologize for those they may have overlooked or inadvertently omitted.

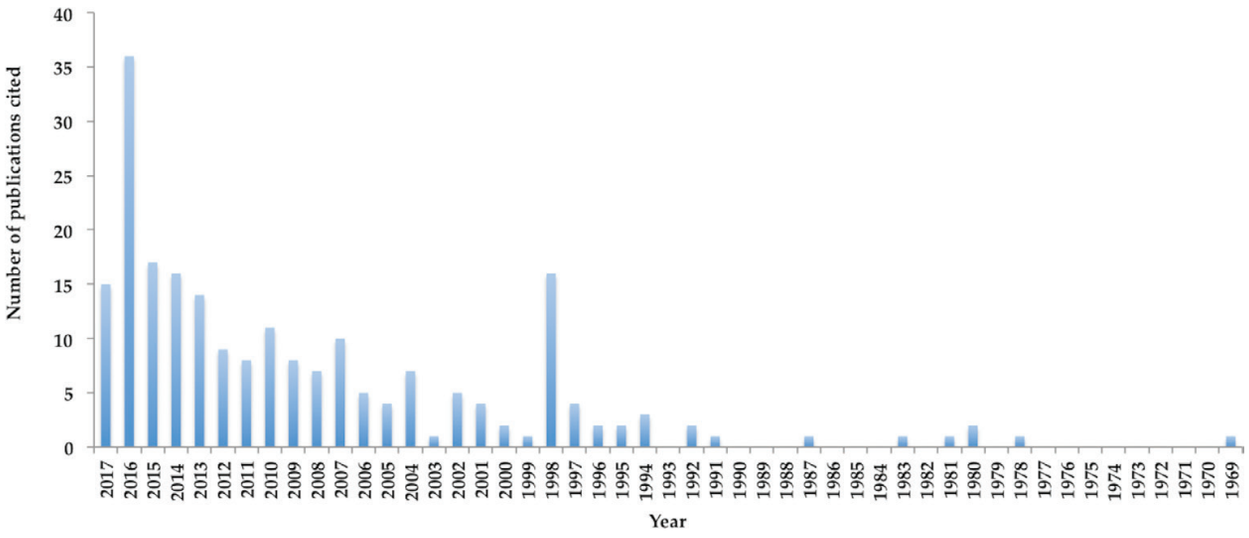

Figure 5. Number of publications cited per year.

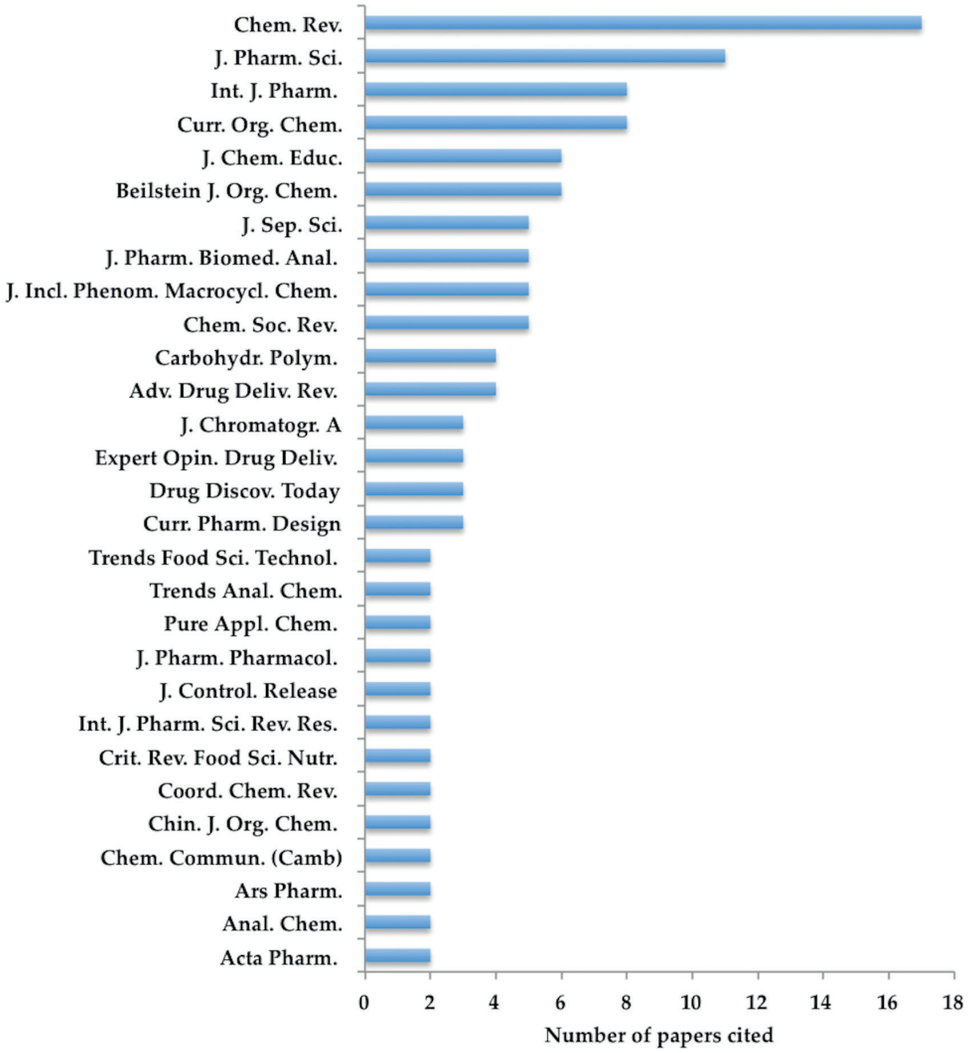

Figure 6. Number of papers cited by journal.

5. Conclusion

Currently, there are a large number of drugs with poor solubility, bioavailability, permeability issues, undesirable properties as taste and odor, and irritation potential, and CDs can become an useful tool for optimizing drugs problematic [84]. Additionally, new uses of cyclodextrins are being explored, in different fields as nanoparticles, liposome and microsphere. The ability of making inclusion complexes with drugs makes CDs have a great future, as reflected by the rising number of publications and patents having been filed. Some researchers also believe that there will be more a still wider use for CDs as the knowledge about their properties increase [7]. The studies of CD-based nanosystems have recently increased, as they become platforms providing pharmacokinetic and formulation design efficiency without posing security problems [91]. CDs are also generating interest for gene therapy and exploration of non-viral methods,

probably for the difficulties in viral gene delivery [7]. A new area which is going to increase, is the study of the effects of the environment in the reactivity between CD-guest molecules [115]. The creation of new types of CD is going to enhance due to the wide range of possibilities in the treatments of atherosclerosis, cancer, and degenerative brain disease that are considered lethal disease [160]. CDs will surprise us in the future with not predictable uses [184].

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