Chapter 6
Cyclodextrin-Based Polymers for Food and Pharmaceutical Applications: A Historical Review

Max Petitjean, Iñigo X. García-Zubiri, and José Ramón Isasi

Contents

Abstract The encapsulation capabilities of cyclodextrins and the controlled release of guest molecules can be modulated with the aid of the additional functionality of a polymeric macrostructure. In addition, the covalent attachment of cyclodextrin moieties to a pre-existing material is intended to immobilize them, as in the case of medical devices or packaging applications. The first references dealing with the potential use of cyclodextrin polymers as macromolecular carriers date back to the 1980s. Since then, they have been incorporated into many constructions, such as hydrogels, nanosponges, dendrimers, interpenetrating networks, molecular imprinted polymers, and other smart biomaterials.

The present chapter discusses, from a historical perspective, the evolution of the synthesis procedures to prepare covalently linked cyclodextrins, either by grafting or cross-linking mechanisms. Then, their applications in the food and pharmaceutical sectors are presented. Debittering of juices and retention of flavors were the first

M. Petitjean · J. R. Isasi (✉)
Departamento de Química, Facultad de Ciencias, Universidad de Navarra, Pamplona, Spain
e-mail: mpetitjean@alumni.unav.es; jrisasi@unav.es

I. X. García-Zubiri
Magnesitas Navarras, Zubiri, Navarra, Spain
e-mail: inigo.garcia@magnesitasnavarras.es

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proposed uses in food science, and, more recently, smart packaging using cyclodextrin polymers is being developed. In the case of the pharmaceutical and biomedical applications, numerous studies on cyclodextrin polymers are being published in the last years, mainly in drug release, but also as polymeric vectors for gene delivery as well as in the field of regenerative medicine.

Keywords History · Cyclodextrin polymers · Covalent networks · Food · Pharmacy · Drug delivery · Inclusion complexes

6.1 Introduction

In addition to their remarkable capability to establish supramolecular (host-guest) interactions by themselves because of their toroidal shape and nonpolar inside, cyclodextrins can also be covalently attached in different ways to originate more complex structures. Materials containing more than two covalently linked cyclodextrin units are known as cyclodextrin polymers. The three procedures to produce these materials are the attachment of cyclodextrins (or their derivatives) to a pre-existing polymer by grafting reactions, the cross-linking of cyclodextrins by polycondensation using multifunctional reagents, and the polymerization of cyclodextrin derivative monomers. The examples of the latter procedure are scarce in comparison with the cross-linking and grafting cases.

This chapter will cover, from a historical point of view, the synthesis and characterization of such cyclodextrin derivatives. After these new materials have been introduced, the following section will be devoted to their applications both in food chemistry and pharmaceutics and biomedicine. It needs to be mentioned that, in contrast to the enormous amount of studies on the uses of cyclodextrins in these two sectors (see Fig. 6.1), cyclodextrin polymer references are not as abundant. As a matter of fact, we will show that most of the examples found in the literature correspond to the last 10–15 years.

There are several reasons to produce cyclodextrin polymers in order to achieve new potential applications in these areas. For instance, in the case of drug delivery, which is by far the most frequently investigated subject among the biomedical applications, the complexation capabilities of cyclodextrins and the controlled release rate of the guest drugs can be modulated with the aid of the additional functionality of a polymeric macrostructure. In other cases, the covalent attachment of cyclodextrin moieties to a pre-existing structure is intended to immobilize them, as in the case of medical devices or packaging applications.

According to the previous definition of cyclodextrin polymers, this chapter will deal with those materials in which at least three cyclodextrin units are covalently attached either with each other or to a pre-existing polymer. Thus, we will not cover the functionalization of non-polymeric supports such as silica beads or inorganic nanoparticles (i.e., cyclodextrin nanocomposites). Amphiphilic cyclodextrins and star polymers with a cyclodextrin core are also very interesting macromolecular derivatives, produced by making use of the multiple hydroxyl groups that can be

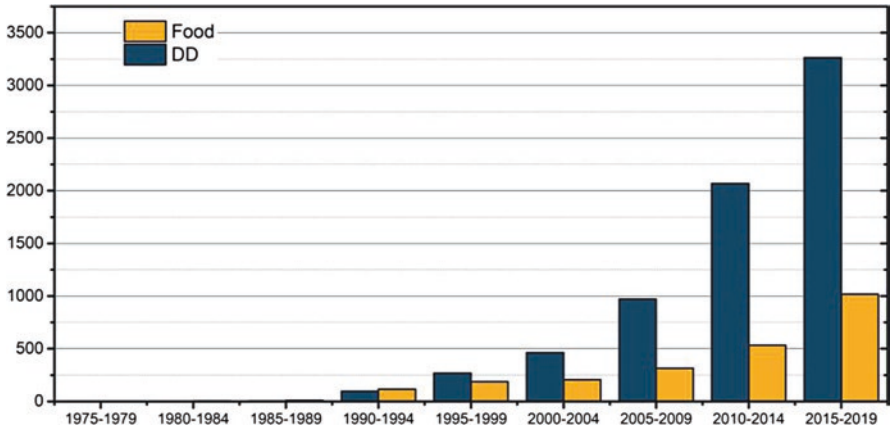

Fig. 6.1 Evolution of literature references regarding the use of cyclodextrins for food and "drug delivery" (DD) pharmaceutical applications. Although the first applications in the food sector appeared earlier, they were outnumbered by drug delivery investigations in the late 1990s. The exponential growth is still evident for both sectors

decorated with chains of different nature and lengths. In this case, we have unimeric cyclodextrins, and the host-guest interactions are not as relevant. Other remarkable materials involving cyclodextrins and polymers are polyrotaxanes. For such architectures, the threading of the cyclodextrin rings onto the polymer chains and the subsequent association among these structures yield interesting biomedical applications involving new biomaterials, such as hydrogels and scaffolds in tissue engineering. Although the functionalization of inorganic supports with cyclodextrins has been known for years and many successful results have been achieved in separation technologies, the studies on the potential applications of polyrotaxanes and amphiphilic cyclodextrins are more recent.

The first references dealing with the potential use of cyclodextrin-containing covalent structures as macromolecular carriers date back to the 1980s. Since then, they have been incorporated into many constructions, such as hydrogels, nanosponges, dendrimers, interpenetrating networks, molecular imprinted polymers, or electrospinned fibers. In addition, some of these systems have proved to be responsive to stimuli, leading to the design of smart multifunctional biomaterials which can be triggered by different factors.

6.2 Cyclodextrin Polymers

6.2.1 Historical Perspective of Cyclodextrin Polymers

Following the timeline of the three main classes of cyclodextrin polymers, i.e., cross-linked networks, polymerization of cyclodextrin monomers, and grafting, the starting point belongs to those with covalent cross-linked cyclodextrin units. The

pioneering work of Solms and Egli in 1965 can be considered as the first landmark in the field of cyclodextrin polymers (Solms and Egli 1965). In that patent, the authors used epichlorohydrin as the cross-linker in an alkaline bulk reaction, and, since then, that one has been the most abundant in the literature of cyclodextrin polymers. Also in those early years, Wiedenhof et al. (1969) improved the properties of the irregular cross-linked cyclodextrin particles that were obtained in the first procedure and produced bead microparticles that, for instance, were suitable to be used in chromatographic columns.

Polyurethane-type cyclodextrin networks were prepared using diisocyanates by Buckler et al. (1969). Acid dihalides and many other potentially useful space arms, such as dihalogenated alkenes and glutaraldehyde, were also considered in the same patent. Various possible applications of those "anchored" cyclodextrins were in fact explored in that patent filing: cigarette filters, extraction of juice aromas, separation of chemicals, etc.

A few years after that, in the mid-1970s, the first cyclodextrin monomers were produced and polymerized by Furue et al. (1975). The acrylic monomers of α- and β-cyclodextrin were obtained by reacting the respective nitrophenyl esters with the natural cyclodextrins to yield water-soluble poly(acryloyl-β-cyclodextrin), with a medium molecular weight (10^4–10^5 Da). This acrylic polymer exhibited a greater catalytic effect in the hydrolysis of *p*-nitrophenyl esters due to the "cooperative effect" between two neighboring cyclodextrin moieties on a polymeric chain (Harada et al. 1977). Other polymerizable cyclodextrin monomers were obtained in the following years, but this second method to produce cyclodextrin polymers was always the least frequent (Fig. 6.2).

The third type of cyclodextrin polymers in our classification corresponds to the attachment of cyclodextrin moieties to previously existing macromolecular materials. In this case, Szetjli et al. (1979) attached cyclodextrin units to poly(vinyl

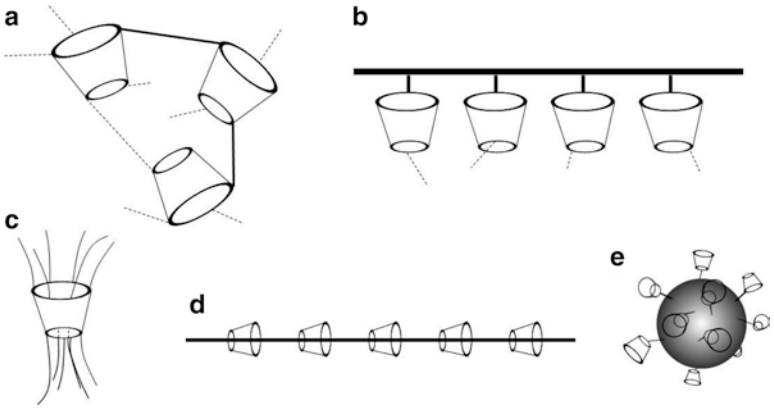

Fig. 6.2 Scheme representation of cyclodextrin-containing macromolecular systems: **(a)** cross-linked cyclodextrin polymers (more than three units); **(b)** linear polymers (either grafted-cyclodextrin polymers or monomeric cyclodextrin (co)polymers); **(c)** amphiphilic and star-like unimeric cyclodextrins; **(d)** (pseudo)polyrotaxanes; **(e)** nanocomposites and immobilized cyclodextrins

alcohol) using epichlorohydrin and epoxy ethers in the late 1970s. Poly(vinyl alcohol) was intended to provide a "skeleton" for the cyclodextrin polymer, in order to improve the mechanical properties of the resin. This procedure cannot be fully considered as a grafting modification, but it is not exactly a cross-linking process either since the cyclodextrin units are attached to a previously formed polymer. Hirayama et al. (1984) used epichlorohydrin to prepare a β-cyclodextrin/starch composite gel. The tosylation of cyclodextrins does produce reactive units that can be attached to pre-existing polymers by grafting. Thus, poly(allylamine) with cyclodextrin pendant groups was produced in the late 1980s and 1990s. In the 1990s, Pöpping and Deratani (1992) reported the production of monochlorinated cyclodextrins, and, later on, other derivatives containing heterocycles were synthesized (Reuscher et al. 1998). Earlier, in 1981, Tanaka and co-workers had immobilized derivatives of α- and β-cyclodextrin on polyurethane and also onto a polyacrylamide support after activating it with succinyl hydrazide (Tanaka et al. 1981, 1982) with the aim of obtaining stationary phases for the separation of benzene derivatives. About 20 years ago, Crini's group used cyclodextrin tosyl derivatives to produce macroporous polyamines (Crini et al. 1998a) or to modify poly(ethyleneimines) in order to coat silica beads (Crini et al. 1995). Cyclodextrin side-chain polyesters were also obtained in those years, for instance, by reacting poly(N-vinyl-2-pyrrolidone-co-maleic anhydride) with deprotonated β-cyclodextrin (Weickenmeier and Wenz 1996), and the interaction of this polymer with anionic or cationic adamantyl guests was studied. The authors also reported the synthesis of interesting associative thickeners based on the specific interaction between complementary cyclodextrin polymers and guest polymers (Weickenmeier and Wenz 1996).

So far, we have presented some examples of cyclodextrin polymers produced during the first years after the first announcement of this particular type of cyclodextrin derivatives. A more comprehensive collection can be found, for instance, in the review of cyclodextrin-containing adsorbents by Crini and Morcellet (2002). In the last two decades, more complex cyclodextrin polymer structures have been produced, namely, interpenetrated networks, molecular imprinted polymers, dendrimers, nanogels, polymer assemblies, and nanocomposites. The following subsection will be devoted to describe in detail each of these types of structures, with some examples found in the literature of the evolution of the synthetic procedures and the characterization techniques employed to analyze them, irrespective of their potential applications in food and pharmacy, separation technologies, chemical recognition, or other areas. The especial cases of the feasible uses of these materials in these two sectors will be the goal of the last section of this chapter.

6.2.2 Covalent and Supramolecular Architectures

Cyclodextrin Cross-Linked in Covalent Networks

Cyclodextrin cross-linked with epichlorohydrin polymers, the most abundant in the literature, were also the first type known, synthesized by Solms and Egli (1965). Epichlorohydrin is one of the oldest and most widely used cross-linking agents in

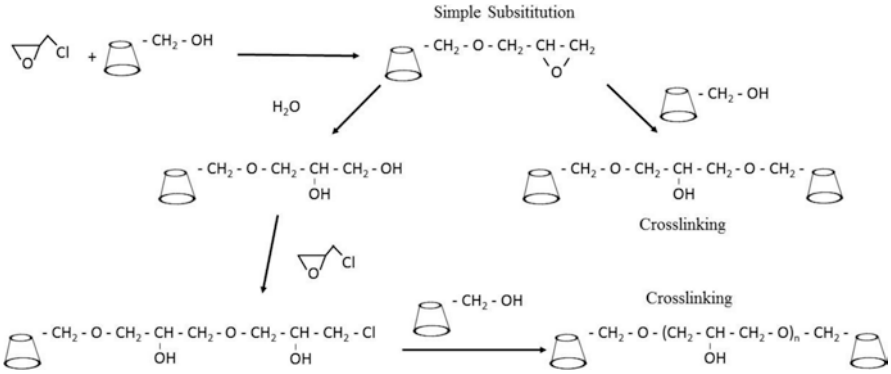

Fig. 6.3 Synthesis of cyclodextrin polymers using epichlorohydrin as a cross-linking agent. The self-polymerization of epichlorohydrin creates cross-linked bridges of variable lengths between cyclodextrin units. A 3D network is produced because of the high functionality (hydroxyl groups) of the cyclodextrin moieties

polymer synthesis. Its two reactive functional groups (epoxide group and a chlorine atom) can react with the cyclodextrin hydroxyls to yield ether linking units. In addition, epichlorohydrin can easily react with itself due to the inductive effect of chlorine. Thus, in the synthesis of these cyclodextrin polymers, several possible reactions can take place, as shown in Fig. 6.3 (where only the reactions of the primary hydroxyls of cyclodextrins have been considered).

The reaction of saccharides such as glucose with epichlorohydrin is well-known (Dumitriu 1996) and proceeds with the initial opening of the epoxy ring by a nucleophilic attack and the subsequent displacement of chlorine. Unlike other epoxides, epichlorohydrin does not yield a hydroxide as a product of a simple substitution by reacting with the cyclodextrin molecule, but it is instead capable of forming an epoxide adduct that can either react with another cyclodextrin molecule or to yield the hydroxyl product. The primary product of the reaction of β-cyclodextrin with epichlorohydrin in alkaline media is a heterogeneous mixture of several ethers, of low molecular weight and viscosity, soluble in water. In this reaction, the self-polymerization of epichlorohydrin, which is favored at high temperatures, can also occur (Renard et al. 1997). The cross-linking reaction of cyclodextrin is relatively slow, so it is feasible to control the degree of polymerization. The final product is a material where there are two structural units: cross-linked cyclodextrin units and self-polymerized epichlorohydrin units. Both structural units possess hydroxyalkyl and ether groups, which makes hard to find differences that permit their correct characterization.

The bulk synthesis procedure of Solms and Egli (1965), already mentioned in the previous section, produced irregular polymer particles. A few years after that, Wiedenhof et al. (1969) proposed a two-phase emulsion polymerization with controlled stirring, in which the cyclodextrin dissolved in water is dispersed in a nonpolar organic solvent containing a nonionic surfactant and the cross-linker. In this way, the insoluble cyclodextrin polymer resins are obtained as uniform microspheres

(beads) with better physicochemical properties: they are easily swollen, being insoluble in water and organic solvents, and stable in alkaline solutions.

These networks become insoluble provided that the "gel point" has been reached during the cross-linking process, and, because of their hydrophilic character, they will have the ability to absorb high amounts of water. They can be considered, therefore, as hydrogels. Obviously, the presence of cyclodextrin units in these hydrogels makes them capable of forming inclusion complexes with suitable host molecules. Nevertheless, the structure of the polymer network needs now to be taken into account, looking at other factors that influence the diffusion of molecules. In order for the sorbate molecules to be trapped by the polymer, they must interact with the cyclodextrin cavity and/or with the polymer network. Therefore, the amount of cyclodextrin in the polymer, the amount and type of cross-linker used, the swelling capacity (a consequence of the latter), and the possible further chemical modifications thereof need to be considered. These cyclodextrin polymers, in addition to the "rigid" cavities of the cyclodextrin moieties, have other cavities constituted by the cross-linking bridges between the cyclodextrin units (secondary cavities). Those additional cavities can be considered more flexible than those of cyclodextrin, at least when the cross-linker is the self-polymerizable epichlorohydrin molecule. Sorption in these polymers takes place then by inclusion in the cyclodextrin cavities or by specific interactions in the secondary ones. In addition, the cross-linker tails are also capable of interacting with the sorbate molecules. As potential drug delivery devices, cyclodextrin-epichlorohydrin hydrogels made with a controlled geometry are useful to obtain kinetic parameters by fitting experimental data to mathematical models suitable for drug release and to obtain diffusion coefficients according to the contact surface of the polymeric matrix (Machín et al. 2012).

Among the most frequently used non-epoxide cross-linkers are diisocyanates, first introduced by Buckler and co-workers (1969), as mentioned above. Dihalogenated acid dihalides or dihalogenated dicarboxylic acids of different sizes have also been used as space arms (Buckler et al. 1969; Zemel and Koch 1990), besides other agents such as dihalogenated alkenes or, more recently, maleic anhydride (Girek et al. 2000). Shono's group prepared insoluble porous polymers with a high cyclodextrin content, polymerizing α- and β-cyclodextrin with diisocyanates as cross-linking agents in pyridine or dimethylformamide, and studied their capability to absorb aromatic derivatives (Mizobuchi et al. 1980; Tanaka et al. 1981). Since those initial investigations, the most commonly used diisocyanates to produce cyclodextrin polymers are hexamethylene diisocyanate and toluene diisocyanate. After those, other groups also prepared cyclodextrin polymers with these same cross-linkers and certain properties, and applications have been studied thereof: stationary phases in chromatography (Lee et al. 2002), artificial cholesterol receptors (Asanuma et al. 1998), solid phase for the extraction, and subsequent analysis of carcinogenic aromatic compounds (Bhaskar et al. 2004). Ma's group, which also used these two diisocyanates, postulated the presence of interconnected nanoporosity in these polymers (Li and Ma 1999; Ma and Li 1999), which increases the apparent inclusion constant with respect to other cyclodextrin polymers such as those cross-linked with epichlorohydrin. The use of difunctional cross-linkers with longer

spacers between their two reactive groups can lead to macromolecular networks with increased porosity, which are also more flexible and less compact. In these networks, smaller molecules can increase their diffusion rates, and bulkier substances may also become entrapped (Mocanu et al. 2001).

Even though the clean polymer resulting from the synthesis using toxic reagents, such as acid dichlorides, epichlorohydrin, or diisocyanates, should be harmless, the use of nontoxic cross-linkers like the polycarboxylic acids is also feasible. Martel's group described the synthesis of soluble and insoluble polymers (Martel et al. 2005) and the production of cotton-bound cyclodextrin using these cross-linkers (Martel et al. 2002).

Several parameters are of great interest when characterizing these materials: cyclodextrin and cross-linker amounts and ratios, water contents (intrinsic moisture of the polymer), the water sorption capacity (swelling processes), the particles size and shape and their porosity, e.g., for suspension of polymerized beads, and, obviously, the sorption capacity of organic molecules of interest. In the last years of the past century, a comprehensive bibliography concerning the synthesis and sorption studies for cyclodextrin polymers could be gathered, but, in contrast, not much information on their characterization was available at that time. The analysis of cyclodextrin polymers cross-linked with epichlorohydrin is complicated when it comes to infrared or Raman spectroscopic techniques (Crini et al. 2000) because, as mentioned above, both the cross-linked cyclodextrin units and the self-polymerized epichlorohydrin possess hydroxyalkyl and ether groups. Nevertheless, the interpretation of the infrared spectra of starch cross-linked with epichlorohydrin was resolved at that time (Dumoulin et al. 1998; Delval et al. 2004).

While the spectroscopic characterization of cyclodextrin-epichlorohydrin polymers is not easy, that of cyclodextrin polymers cross-linked with diisocyanates seemed to be simpler. Qualitative characterizations by infrared spectroscopy (Li and Ma 1999; Bhaskar et al. 2004) or Raman (Lee et al. 2002) were attempted, and the successful quantitative analysis was achieved, thanks to the intense carbonyl band of the cross-linker (García-Zubiri 2005). Thermal and thermogravimetric analysis were also used in most of those studies, as well as nuclear magnetic resonance spectroscopy (Asanuma et al. 1998; Lee et al. 2002). For polymers with other cross-linkers, such as maleic anhydride, there were also some nuclear magnetic resonance results of interest (Girek et al. 2000).

As for the cyclodextrin content of the polymer, the most common procedures used already in the 1990s were the colorimetric methods using chlorotetrazolium blue (Crini et al. 1995, 1998b; Janus et al. 1999) or iodometry (Renard et al. 1997) and phenolphthalein (Mäkelä et al. 1987). For soluble cyclodextrin polymers, proton nuclear magnetic spectroscopy could be used (Renard et al. 1997), and for the insoluble resins, ^{1}H or ^{13}C solid-state nuclear magnetic resonance were employed (Crini et al. 1998b, 2000). Thus, the β-cyclodextrin-epichlorohydrin (or, rather, 2-hydroxypropyl ether) ratio can be determined because the signal corresponding to the hydrogen atoms in the 2-hydroxypropyl ether segments is displaced below the two wide peaks of the glucopyranose units.

Another technique used to determine the cyclodextrin content in the polymers is CHN elemental analysis. This method is especially useful and simple for polymers cross-linked with diisocyanates, since the nitrogen content is directly proportional to the amount of cross-linker in the polymer (Lee et al. 2002). Nevertheless, it must be used with great care in the case of cyclodextrin-epichlorohydrin polymers due to the similar elemental composition of both constituents (Romo et al. 2006).

Other Novel Cyclodextrin Polymers

The reticulated cyclodextrins, also known as nanosponges, have evolved into more complex structures in the last 10–20 years. Four generations of nanosponges can be defined, according to the classification by Trotta's group (Caldera et al. 2017). First of all, a reticulation reaction using a simple molecule such as epichlorohydrin gave us the first generation of "nanosponges." Besides those ether linkages, ester, carbonate, and urethane are the main connectors investigated in the literature. The decoration of those primary nanosponges using a cross-linker plus a special functional group produced the second generation. If this extra space arm or the added functions react to external stimuli (such as temperature or pH), allowing the nanosponges to change their shape, swelling behavior, or sorption/release capabilities, then the new "smart material" synthesized is said to belong to the third generation. Finally, a fourth generation of nanosponges is feasible by creating molecular imprinting polymers using a template, in order to improve the selectivity of the matrix toward such molecules (Caldera et al. 2017).

From a historical point of view, the last three classes can be considered as those of the present days, although some of these new attractive features of novel cyclodextrin nanosponges have been known for a couple of decades. Thus, molecular imprinted polymers using cyclodextrin moieties were already produced in the late 1990s (Piletsky et al. 1998). Stimuli-responsive polymers based on cyclodextrins were prepared in 1995 using the ubiquitous N-isopropylacrylamide monomer (Nozaki et al. 1995). Interpenetrated networks containing cyclodextrins also appeared at that time (Sreenivasan 1997). Fenyvesi et al. (1996) encapsulated several cationic disinfectant agents, in chemically modified (carboxymethylated) nanosponges, based on cyclodextrin linked to polyvinyl alcohol, to be used in the prolonged treatment of wounds.

Nanogels combine the advantages of hydrogels and nanoparticles into a single carrier that can be tailored for specific therapeutic molecules, such as low molecular weight drugs, peptides, or proteins, and target them to specific tissues or cells (Moya-Ortega et al. 2012). Liu et al. (2004) prepared cyclodextrin microgels, including one interpenetrated network, by inverse-emulsion polymerization. About 10 years ago, nanoparticles with differing charge densities were synthesized by a one-step condensation polymerization of β-cyclodextrin, choline chloride, and epichlorohydrin by Gil et al. (2009). The top-down approach can break bigger networks into the nanoscale size by using ultrasounds (Swaminathan et al. 2010). The water-in-oil emulsion method has been thoroughly employed in the last decade to

produce cyclodextrin nanogels, but their direct synthesis by polymerization of cyclodextrin monomers is more rare (Moya-Ortega et al. 2012).

Another interesting method of producing nanogels was designed by Gref et al. (2006) and consists on supramolecular nanoassemblies between a cyclodextrin-epichlorohydrin polymer and an alkyl-grafted dextran. Other potential uses of cyclodextrins as "smart" components of polymer nanoparticles were reviewed by Gref and Duchêne (2012), including nanoparticles made of cyclodextrin-based copolymers using various polyesters and polypeptides prepared in the 2000s. In the field of drug delivery, cyclodextrins had already been added in their monomeric form to improve the drug-loading capacity of polymeric nanoparticles, but the use of cyclodextrin polymers opened new perspectives. Thus, a variety of cyclodextrin-based architectures (linear, dendrimers, stars, polyrotaxanes) were used in the preparation of polycomplexes for gene delivery (Mellet et al. 2011). In 1997, β-cyclodextrin was attached to dendrimer poly(ethyleneimines) (Suh et al. 1997). Two years later, linear cationic alternate copolymers capable of binding deoxyribonucleic acid with transfection efficiency were prepared by the group of Mark E. Davis (Gonzalez et al. 1999). Later on, Choi et al. (2005) prepared polyplexes grafting cyclodextrin to poly-L-lysine instead of using poly(ethyleneimine). Besides the aforementioned cyclodextrin-coated dendrimers, cyclodextrin-centered dendrimers (i.e., star-shaped), polyrotaxanes, and polycationic amphiphilic cyclodextrins also present many interesting capabilities in the field of gene delivery, but, as mentioned above, those architectures are not the subject of this review.

Electrospun nanofibers have been used as drug delivery materials due to their high specific area, and, obviously, various formulations including cyclodextrins have been tested in the last 5 years (Costoya et al. 2017). Cyclodextrin polymers have been also explored as components of electrospun nanofibers very recently, firstly by mixing cyclodextrin-epichlorohydrin polymers with poly(methacrylic acid) inter-cross-linked at high temperature to render them insoluble in water (Oliveira et al. 2015). Nevertheless, the design of electrospinnable cyclodextrin polymers should be still improved.

6.3 Applications in the Food and Pharmaceutical Areas

6.3.1 Cyclodextrin Polymers in Food Science

In the food industry, cyclodextrins have been studied for different applications as sorption/release agents or, more recently, for packaging purposes. Many of these involve the use single cyclodextrins incorporated into different types of products as fibers (Celebioglu et al. 2018) or films (Plackett et al. 2006). Cross-linked cyclodextrins were firstly proposed for food-related applications as early as the 1960s with the patent of Bucker et al. One of the possible applications of those novel materials was related to their suitability as agents for concentration of organic molecules such

as flavors or aromas in the food industry (Buckler et al. 1969). As explained above, in order to form the cyclodextrin polymers, reagents that possess two or more functions capable of reacting with hydroxyl groups are needed to form an insoluble resin that can be used as a sorbent matrix.

Some years after the abovementioned patent was filed, a cyclodextrin polymer made with epichlorohydrin was developed to reduce the bitterness of fruit juices (Shaw et al. 1984). The purpose of that investigation was to improve the taste of orange or grapefruit juices using α- or β-cyclodextrin polymers as sorbents to form a complex with limonin, narangin, and nomilin, three natural bitter components. Their results were conclusive showing a good absorption of the bitter molecules and a taste preference of the new bitterless juice over the control juice, without absorbing other flavor or valuable components such as ascorbic acid, and with the possibility to regenerate the cyclodextrin polymer sorbent. A couple of years after that, the selectivity of these cyclodextrin polymers was tested (Shaw and Buslig 1986), using γ-cyclodextrin polymer as well, with other juice containing the same bitter components and also caffeine, and proved that cyclodextrin polymers do not complex with the latter. In the same research paper, they studied the importance of the cross-linking agent used to prepare the cyclodextrin polymers. Their study concluded that naringin removal was more effective when using β-cyclodextrin polymer resins, compared to α- and γ-cyclodextrin polymers or a standard Amberlite XAD-4 resin, which did remove caffeine or limonin in turn.

Two decades later, β- or γ-cyclodextrin were linked to chitosan through succinyl or maleyl bridges to improve the sorption of bitter compounds (Binello et al. 2004). This bitter-masking potential was measured by analyzing the bitterness of different solutions composed of either a single model molecule (caffeine) or natural extracts. Pure chitosan possesses a good sorption capacity of bitter compounds, better than those of the α-, β-, or γ-cyclodextrin monomers. However, the chitosan β-cyclodextrin adducts improve the bitter-masking power in all cases. Besides the batch procedures, Wagner Jr. et al. (1988) reported, also in the 1980s, on the result of a pilot-plant fluidized-bed procedure, where the β-cyclodextrin polymer was regenerated over 20 times without apparent loss of capacity. The debittering of other juices has also been reported later on (Szejtli and Szente 2005).

In the last decade, another area of application searched in food science and cosmetics is the retention of fragrance or aroma molecules. For example, the encapsulation of two molecules (linalool and camphor) composing *Lavandula angustifolia* essential oil using cross-linked cyclodextrin-epichlorohydrin polymers and their subsequent liberation was studied using a static headspace gas chromatography technique both in gaseous and aqueous phases and compared to those of the parent and derivative cyclodextrins (Ciobanu et al. 2012). Cyclodextrin polymers present different retention profiles depending on cyclodextrin/cross-linker ratios, the phase, and the volatile compound.

In 2009, cyclodextrin polymers were used in solid-phase extractions to determine additives in food (Li et al. 2009). Epichlorohydrin was used to cross-link β-cyclodextrin with soluble starch to evaluate the content of brilliant blue in food. The detection is feasible between 0 and 12 ppm. As solid-phase extraction research

continues, molecular imprinted cyclodextrin polymers also arrived in this field. As in the previous example, the determination of dyes in food is in order. For instance, monomeric cyclodextrin reacts with maleic acid, and then, in presence of a template, such as Congo red, the polymerization takes place with N,N′-methylenebisacrylamide as the cross-linker (Liu et al. 2015). Thanks to this type of synthesis procedures, the molecular imprinted cyclodextrin polymer shows a high selectivity and a remarkable sorption power for its target. Also in recent years, cyclodextrin polymers have been prepared with some especial characteristics. A few examples are a cyclodextrin polymer with a higher specific area (Li et al. 2018), grafted onto metallic graphene (Li et al. 2016a), added to ionic liquids (Feng et al. 2015), or imprinted on carbon nanotubes (Liang et al. 2019). Many of these new materials are designed in order to be used in solid-phase extractions, and the main interests are their capabilities for the removal and/or the determination of organic molecules present in food.

Among their many possible applications, cyclodextrin monomers are also common for food packaging, and they began to be exploited for that purpose since the end of the past century (Szente and Fenyvesi 2018). In those first uses, cyclodextrins are present in a polymer network but without being cross-linked to it. The first reported use of a cyclodextrin polymer in packaging dates back from a decade ago. At that time, β-cyclodextrin and polyvinyl alcohol were cross-linked with glyoxal, following different procedures, to remove an undesirable product in food such as cholesterol (López-De-Dicastillo et al. 2011).

On the other hand, active films are designed to liberate chemicals encapsulated in them. In this case, cyclodextrin units are, for instance, grafted onto a modified polyamide, both by a non-covalent and a covalent cross-linking; in the presence of a template, two different synthetic polymers mixed produced a film capable to release chemicals using UV stimuli (Tan et al. 2016). One of the most sought characteristics for a packaging film is its antibacterial power. In order to achieve this potential, it is also feasible to integrate ZnO nanoparticles into polymer films (Andrade-Del Olmo et al. 2019). In this investigation, anionic cyclodextrin is added with chitosan layer by layer onto a poly-L-lactic acid-ZnO film to provide it the antibacterial ZnO properties but also with the ability to release carvacrol, plus the hydrophobicity from poly-L-lactic acid and the biodegradability provided by all the polymeric components. Another path to create an antibacterial film is to cross-link a sorbate/cyclodextrin complex, such that with sodium benzoate (Yang et al. 2019). By a green synthesis procedure, xylan, hydroxyethyl cellulose, and the complexed cyclodextrin molecules are cross-linked using citric acid. The resulting film possesses the desired mechanical properties, besides a low oxygen permeability and good antibacterial properties.

6.3.2 Cyclodextrin Polymers in Drug Delivery

The first reviewing of the potential applications of cyclodextrin polymers in the pharmaceutical industry was written by Fenyvesi (1988), and it was mainly based on cyclodextrin cross-linked with epichlorohydrin. The soluble cyclodextrin-epichlorohydrin

polymers were used for promoting the solubilization of several drugs. The first bioavailability study using a soluble cyclodextrin polymer was reported in the mid-1980s (Uekama et al. 1985). The absorption-promoting effect of the soluble cyclodextrin polymer on the sublingual route was also demonstrated in the case of steroids (Pitha et al. 1986). Karadake et al. (1982) showed that the drug release was retarded and the stability against oxidation and degradation was greatly increased when penicillin complexed with soluble cyclodextrin polymer was microencapsulated. In those years, the safety of these new materials was obviously a concern, so its innocuity was checked. Practically no hemolytic effects were observed when compared to natural or methylated cyclodextrins.

On the other hand, some applications of the insoluble cross-linked cyclodextrin polymer were also investigated. For instance, its effect on wound healing was tried on tissues of rats (Felméray et al. 1996). In addition, the cyclodextrin-epichlorohydrin sorption capabilities were tested for the removal of phenylalanine from a protein hydrolysate in order to make it digestible for children suffering from phenylketonuria (Specht et al. 1981). Also at that time, the effectiveness of a cyclodextrin polymer as a tablet disintegrant was studied in direct compression systems (Fenyvesi et al. 1984).

Those first attempts to show their capabilities in the sorption and release of aromatic model molecules pointed to the use of cyclodextrin polymers as controlled release agents (Friedman et al. 1989). Specifically, the release of cetylpyridinium chloride (an antimicrobial agent) and iodine, using cyclodextrin polymers, was patented in the late 1980s (Friedman 1988; Szejtli et al. 1988). An earlier example of a cyclodextrin polymer as a macromolecular carrier in the field of antitumor chemotherapy was published also in the mid-1980s (Kaji et al. 1985). In that work, a bifunctional delivery system composed of mixed micelles and a complex between the drug (1-hexylcarbamoyl-5-fluorouracil) and cyclodextrin polymer was tested.

The following decade showed only a few other distinct examples of the applicability of cyclodextrin polymers in the field of drug delivery. Thus, drugs complexed in cyclodextrin polymers were entrapped into liposomes. The latter present some problems in the accommodation of water-insoluble drugs in their lipid bilayers, so the new formulation using cyclodextrin polymer could circumvent such limitations (McCormack and Gregoriadis 1994). On the other hand, the need to prepare degradable materials for medical applications, including drug delivery, associating networks using cyclodextrin-epichlorohydrin polymers and degradable copolyesters containing adamantyl groups were tested and were shown to be pH sensitive (Cammas et al. 1999).

Cyclodextrin-based nanosponges, prepared by cross-linking reactions using either condensation or interfacial polymerization reactions, are biocompatible nanoporous nanoparticles. They have been designed in the last years to increase the dissolution rate, the solubility, and stability of drugs, to prolong the release time, and also applied in semisolid formulations for skin delivery (Ansari et al. 2011; Shende et al. 2013; Conte et al. 2014).

As mentioned above, cyclodextrin moieties can be incorporated to pre-existing polymeric materials via grafting reactions. In most of the drug delivery applications, cyclodextrins are attached to polysaccharides (Luzardo-Alvarez et al. 2014), such as

chitosan, for which the adsorption and release of a model drug (ketoprofen) were evaluated some time ago (Prabaharan and Mano 2005). Although cyclodextrin adds new drug inclusional properties to the polycationic polymer, a decrease in mucoadhesion of cyclodextrin-chitosan was observed, an effect attributed to the increase in the chain compaction caused by the cyclodextrin grafting (Venter et al. 2006). More recently, cellulosic substrates (uncoated and crepe paper and a medical bandage) were grafted by a cyclodextrin polymer to sustain the release of antibacterial agents (Cusola et al. 2013). Besides those polysaccharides, other materials such as poly(hydroxyethylmethacrylate) have also been grafted with β-cyclodextrin for its application in soft contact lenses conservation liquids and to sustain drug delivery in the lacrimal fluid (dos Santos et al. 2009). The use of some cyclodextrin polymers for therapeutics delivery was patented in 2013 (Cheng et al. 2013).

In the turn of the century, a new class of polymers for the delivery of macromolecular therapeutics arose (Gonzalez et al. 1999). Polymeric vectors for gene delivery and gene therapy, in contrast to viral vectors, avoid an immune response, and, in addition, they are capable of carrying nucleic acids of virtually any size. Thus, cationic cyclodextrin polymers used to bind deoxyribonucleic acid showed comparable or even better results to those obtained for polyethyleneimine. Thus, low molecular weight poly(ethylenimine) cross-linked by (2-hydroxypropyl)-β-cyclodextrin or (2-hydroxypropyl)-γ-cyclodextrin demonstrated its lower cytotoxicity and higher transfection efficiency for the delivery of plasmid deoxyribonucleic acid compared with those of poly(ethylenimine) (Huang et al. 2006). Another significant achievement has been, for instance, the use of a specific functional group such as folic acid grafted to poly(ethyleneimine)-cyclodextrin carriers, to target the tumor cells (Yao et al. 2009). Intranasal mRNA vaccination with the aid of a cationic cyclodextrin-poly(ethyleneimine) conjugate, capable of overcoming the nasal epithelial barrier, has also been recently proposed (Li et al. 2016b).

Drug release behavior can be modulated with the aid of stimuli-responsive polymers. Among them, poly(N-isopropylamide) has attracted much attention in the recent past because of its sharp and somewhat tuneable phase transition close to 32 °C, ideal for injectable clinical applications. Moreover, the design of interpenetrated networks permits to combine the temperature responsiveness of poly(N-isopropylamide) gels with the inclusional capabilities of cyclodextrin networks. For instance, a semi-interpenetrated network was prepared incorporating a water-soluble cyclodextrin-epichlorohydrin polymer into the poly(N-isopropylamide) hydrogel to find that the release rate of the model drug (ibuprofen) from the β-cyclodextrin containing gel was slower and the release time was greatly prolonged (Zhang et al. 2005). Another semi-interpenetrated network was prepared by the radical polymerization and cross-linking of N-isopropylacrylamide in the presence of β-cyclodextrin-grafted polyethylenimine. The propranolol release rate from the semi-interpenetrated network matrix was retarded because of the formation of complexes between the drug and the β-cyclodextrin moieties, and the release kinetics could be tuned by controlling the environmental temperature (Zhang et al. 2008). Interpenetrated

networks can also be used to develop new selective and synergistic sorption capacities for specific purposes such as a combined drug release (Fujiyoshi et al. 2019).

A remarkable pH-responsive behavior can be achieved using acrylic acid containing polymers. Thus, highly hydrophilic pH-sensitive networks which load large amounts of hydrophobic drugs with sustained release capabilities were prepared over 10 years ago by the copolymerization of cyclodextrin with acrylic monomers (Siemoneit et al. 2006). Other examples have been reported in the recent literature: highly pH-dependent swelling in graft cyclodextrin/acrylic acid copolymers for the delivery of ketoprofen (Wang et al. 2009) or mucoadhesive hydrogels by the cross-linking of poly(acrylic acid) with cyclodextrins for the controlled release of diflunisal and fluconazole (Kutyła et al. 2013). A biocompatible system based on guar gum, poly(acrylic acid) and β-cyclodextrin using a nontoxic cross-linker, and tetraethyl orthosilicate, for intestinal delivery of dexamethasone, has also been reported (Das and Subuddhi 2015).

In the last decade, triple-response (pH, temperature, and glucose) semi-interpenetrated hydrogels were prepared by polymerization in the presence of the magnetite (Fe_3O_4) nanoparticles, a cyclodextrin-epichlorohydrin polymer, and a cross-linker (Huang et al. 2012). These targeting hydrogels could control the release of quercetin by adjusting both the pH value and glucose concentration of the release media. More recently, a carboxymethyl-β-cyclodextrin polymer was grafted on the surface of chitosan-coated magnetite NPs by an emulsion chemical cross-linking method (Ding et al. 2015). The loading and release of 5-fluorouracil from these magnetic composites showed that these were promising targeted anticancer drug carriers for tumor therapies.

Finally, cyclodextrin polymers have also recently found applications in the field of regenerative medicine (Alvarez-Lorenzo et al. 2017). Bone and cartilage diseases are each day more challenging because of the increasing number of people affected. Vascular polyester and polyamide prostheses can be coated with grafted cyclodextrins that can be loaded with an antibiotic in order to reduce the risk of postoperative infections (Blanchemain et al. 2005). Polyvinylidene difluoride membranes can also be grafted with cyclodextrins to improve the capture and subsequent release of antiseptic agents (Tabary et al. 2007). Polyamide inguinal meshes (El Ghoul et al. 2008) or polypropylene abdominal wall implants for the prolonged delivery of ciprofloxacin (Laurent et al. 2011) have been prepared using citric acid as a cross-linker. Hydroxyapatite used in bone implants can also be functionalized with a cyclodextrin polymer for loading antibiotics (Hoang Thi et al. 2010; Taha et al. 2014). Recently, injectable hydrogels of polyelectrolyte complexes between chitosan and cyclodextrin polymers (both soluble and insoluble) have been rheologically tested to select those with a better performance in biomedical applications (Palomino-Durand et al. 2019).

As in the case of "monomeric" (both natural and derivative) cyclodextrins, an increasing number of publications can be found in the recent literature concerning cyclodextrin polymers. As Table 6.1 shows, many reviews have been published in the last 5 years, and the interested reader is referred to them to acquire a better idea of the goals this field of research is heading and the paths, or approaches, taken. In

Table 6.1 Recent reviews (2015–2019) on the applications of cyclodextrins and cyclodextrin polymers in pharmacy and biomedicine

Reference	Review title
Simões et al. (2015)	Supramolecular cyclodextrin-based drug nanocarriers
Osmani et al. (2015)	Cyclodextrin-based nanosponges: impending carters in drug delivery and nanotherapeutics
Wei and Yu (2015)	Cyclodextrin-functionalized polymers as drug carriers for cancer therapy
Gidwani and Vyas (2015)	A comprehensive review on cyclodextrin-based carriers for delivery of chemotherapeutic cytotoxic anticancer drugs
Gonzalez-Gaitano et al. (2016)	Drug carrier systems based on cyclodextrin supramolecular assemblies and polymers: present and perspectives
Mejia-Ariza et al. (2017)	Cyclodextrin-based supramolecular nanoparticles for biomedical applications
Peng et al. (2017)	Polymeric nanocarriers based on cyclodextrins for drug delivery: host-guest interaction as stimuli-responsive linker
Adeoye and Cabral-Marques (2017)	Cyclodextrin nanosystems in oral drug delivery: a mini review
Alvarez-Lorenzo et al. (2017)	Cyclodextrins as versatile building blocks for regenerative medicine
Topuz and Uyar (2019)	Electrospinning of cyclodextrin functional nanofibers for drug delivery applications
Yao et al. (2019)	Cyclodextrin-based polymer materials: from controlled synthesis to applications
Zhang et al. (2019)	Cyclodextrin-based delivery systems for cancer treatment

addition to the reported references, some other recent reviews on new materials for pharmaceutical and biomedical applications also include a section on cyclodextrin-based systems (Larrañeta et al. 2018; Levack et al. 2018; Solanki et al. 2018).

6.4 Conclusion

Carbohydrates molecules, one of the most abundant products in nature, are present in animals, plants, bacteria, or fungi. These molecules show an enormous diversity: starch, cellulose, alginate, guar gum and other hydrocolloids, chitin and chondroitin, etc. Some of them can be easily modified, such as chitin into chitosan, in order to achieve improved characteristics to make them suitable for biomedical of food-related applications. Cyclodextrins, these peculiar cyclic oligosaccharides of bacterial origin, have been also applied in these fields. It was soon realized that, because of its encapsulation capabilities, immobilized cyclodextrins could be used in the food industry to improve taste, extract some nutrients or flavors, or, more recently, as constituents of the smart packaging of comestible products. The capabilities of the parent and modified cyclodextrins as carriers of substances of low solubility, such as most drugs, were exploited for

pharmaceutical applications as well. Exploring cyclodextrin polymers in drug delivery was not immediate because of the obvious concerns on biocompatibility and toxicity of those new materials.

The challenges cyclodextrin polymers face today mostly have to do with safety and cost, if their promising features, conscientiously proven in the thousands of investigations published so far, are expected to cross the bridge between academia and industry. Even though many of the raw cross-linking agents needed to prepare these cyclodextrin polymers are toxic, once the product is finished, it can be considered "clean." This new material obviously needs yet to be tested following the protocols applicable in each case, depending on their uses.

In many pharmaceutical applications, the final cost of the produced carriers will not be a concern if they are designed as "high-tech" smart gels or vectors suitable for some particular purposes. On the other hand, for food-related applications, cost is a major concern. For instance, a higher efficiency in the removal of a certain bitter agent will not justify the replacement of a low-cost sorbent with a somewhat lower performance.

Finally, among the features required for the new cyclodextrin polymers to be designed in the near future, sustainability is a must. The new materials, especially those designed for large-scale applications, need to be as "green" as possible. Natural cyclodextrins themselves do fulfil this criterion, and polymers made from them should also be produced by means of the new ways of doing chemistry in the twenty-first century.

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