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Review Article

Cyclodextrins – Development and Applications of These Versatile Oligosaccharides

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ABSTRACT. Cyclodextrins (CDs) are cyclic oligossacharides which have been known and studied for almost 130 years. This review aims to highlight the most important findings registered over this time, the physicochemical properties, preparation methods and uses of cyclodextrins, with special focus on their recently discovered applications. Due to their unique conformation, cyclodextrins are able to encapsulate a wide range of chemical entities, impacting on their solubility, bioavailability, stability, and shelf-life. Their complex formation properties together with the production from natural sources opens the door for cyclodextrins to be used in numerous and varied industries. However, the most important consumer of these versatile sugars is represented by the biomedical domain, where cyclodextrins find uses in drug formulations, delivery systems, medical textiles, implantable devices, tissue engineering, and many other connex applications. Moreover, intense research is still performed for this compounds, to develop and extend their therapeutic potential and serve as promising alternatives for treatment of severe diseases.

Keywords: cyclodextrins, inclusion complexes, biomedical applications, drug delivery, medical textiles.

INTRODUCTION

Cyclodextrins (CDs) can be defined as biodegradable cyclic oligosaccharides that naturally occur from enzymatic degradation of starch, through its bacterial digestion from various natural sources (such as potatoes, corn, rice, etc.) (Chaudhari et al., 2019; Fernández et al., 2019; Radu et al., 2016).

The history of CDs started with their incidental discovery by a French scientist, in 1891. Antoine Villiers noticed a crystalline substance in the alcohol waste remained after an experiment for producing dextrins, a substance that was produced by *Bacillus amylobacter*-digested starch (Carneiro et al., 2019; Cova et al., 2018; Shelley and Babu, 2018; Singh and Sahu, 2019). He conducted pioneering studies on the composition and chemical properties of these crystals (Gharibzahedi and Jafari, 2017) and named the compounds "cellulosing"/"cellulosine" due to their similarity with cellulose in what regards acid resistance and absence of reducing properties (Cova et al., 2018; Martin et al., 2018). Since their discovery, CDs have gained enormous research interest, being broadly scrutinized in various aspects (Gharibzahedi and Jafari, 2017). Some of the most important contributions to the development of these oligosaccharides were brought by Schardinger, who is considered to be the founder of CDs (also called "Schardinger sugars") chemistry due to its extensive studies on preparation and separation of CDs (Gharibzahedi and Jafari, 2017; Martin et al., 2018). Some other essential milestones in the evolution of CD knowledge were the discovery of their cyclic structure, assessment of their encapsulation properties, and the effects of inclusion complex formation (Fenyvesi and Szente, 2016; Leclercq, 2016a; Wimmer, 2000).

Despite being known for such a long time, the first industrial production of CDs did not happen until the 1970s, when their non-toxic character was proven, and Hungary and Japan started to synthesize them at large scales (Fenyvesi and Szente, 2016; Wimmer, 2000). 120 years after Villier's discovery, the production of CDs finally ascended with their first industrial applications in food and pharmaceutical products (Carneiro et al., 2019). Moreover, after the organization of the first symposium regarding this field, there was also published, in 1982, the first book about CDs: "Proceedings of the first international symposium on CDs", edited by Hungarian scientist J. Szetjli (Gharibzahedi and Jafari, 2017).

It was a long way from being seen as chemical curiosities to becoming available as purified pharmaceutical excipients, but CDs' journey is not complete as they are still under intense research (Loftsson and Duchene, 2007). The more recent interest in CDs has been stimulated, to a large extent, by the biotechnological breakthroughs which not only allowed for the commercial production at large scale, but also for the development of CD derivatives, with superior properties compared to the parent ones (Řezanka, 2018; Sengupta et al., 2018). Each year, almost 1000 research articles and scientific abstracts are written about CDs, especially on drug-related products. Moreover, there is an abundance of CD-including-inventions that have been recently described (Del Valle, 2004).

The aim of this review is to correlate the structure and properties of CDs to their effects on the encapsulated molecules, their release and action towards the organism, and to facilitate a better understanding of the newest biomedical applications in the field, especially concerning drug-delivery systems and medical textiles.

CHEMICAL STRUCTURE AND PROPERTIES

CDs are glucose oligomers consisting of at least 6 (α-1,4)-linked α-D-glucopyranose units, that have a truncated funnel-shaped cage structure, with a hydrophobic inner cavity and hydrophilic outer surface (Fenyvesi and Szente, 2016; Hammoud et al., 2019; Liu et al., 2019; Loftsson et al., 2005).

As it can be noticed from Figure 1, the cavity size of the CDs is dependent on the number of glucose units in the cycle (Carneiro et al., 2019). The three major CDs presented in Figure 1, α-, β-, and γ-CDs, represent the smallest members of these cyclic oligosaccharides family, consisting of 6, 7, and 8 glucose units, respectively (Fenyvesi and Szente, 2016; Liu et al., 2019). All three CDs occur naturally via enzymatic degradation of starch and have similar properties (Leclercq, 2016a; Li et al., 2014).

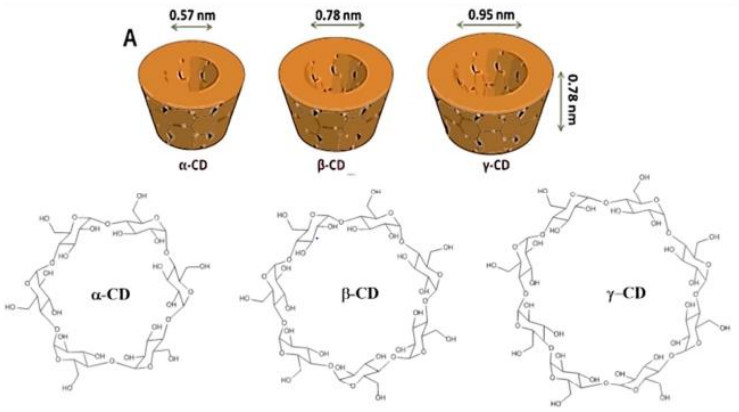

Figure 1. α-, β-, and γ-CD molecules. Reprinted from an open access source (Carneiro et al., 2019).

Aside from α-, β-, and γ-CDs, higher homologues have been described (Wimmer, 2000). Delta and nu-CDs, containing 9 and 12 glucosyl units in the ring respectively, have been isolated in small quantities, and other structures containing up to 16 glucose units in the cycle have also been reported. However, none of these compounds have gained any industrial significance yet (Hedges, 2009).

The characteristic shape (truncated cone appearance, doughnut, toroidal-, or cylinder-like shape) is given by the rigid chair conformation of the chiral glucose units and the spatial arrangement of the various functional groups (Martin et al., 2018; Szente et al., 2016). As a consequence of CDs' conformation, all the secondary -OH groups (corresponding to the carbon atoms from 2nd and 3rd positions of the glucose units) are at one of the edges of the cavity (on the wider rim), while the primary -OH groups are on the opposite end of the cavity. The hydroxyl groups from the narrow side have the ability to rotate, and hence partially block the cavity, contrary to the secondary hydroxyls which are linked through relatively rigid chains (Martin et al., 2018; Szente et al., 2016). The hydrogen bonds were noticed to have increasing strength in the following order: α-CD<β-CD<γ-CD (Leclercq, 2016b).

Due to the orientation of primary and secondary hydroxyl groups towards exterior, the outer surface has a hydrophilic character; while, due to carbon skeleton and ethereal oxygens of glucose residues, the inner side of the cavity is lipophilic, with a polarity similar to an aqueous ethanolic solution (Chaudhari et al., 2019; Fenyvesi and Szente, 2016).

The three common CDs are homogeneous, crystalline, and non-hygroscopic (Radu et al., 2016; Zafar et al., 2014). They are chiral, non-reducing oligosaccharides which, due to their natural origin, are biocompatible and accepted in biological applications (Radu et al., 2016; Wimmer, 2000). Due to the large number of hydroxyl groups found in the structure of CDs, these compounds are soluble in water (Qiu et al., 2017), and insoluble in most organic solvents, such as alcohols, ketones, ethers, chlorinated hydrocarbons, and aliphatic and aromatic hydrocarbons (Hedges, 2009; Wimmer, 2000).

Considering the properties listed in Table 1, the main feature of interest for CDs is their ability of encapsulation and formation of inclusion compounds in aqueous solutions (Giordano et al., 2001). While the cavity height is the same for all three types of native CDs, the internal diameter size varies with the number of glucose units, affecting the accommodation volume (Del Valle, 2004; Zafar et al., 2014).

Table 1. Main properties of native CDs.

PROPERTY	α-CD	β-CD	γ-CD
Number of glucopyranose units	6	7	8
Molecular weight (Da)	972	1135	1297
Solubility in water (g/L, 25 °C)	145	18.5	232
Internal diameter (nm)	0.47-0.53	0.60-0.65	0.75-0.83
Outer diameter (nm)	1.46	1.54	1.75
Height of torus (nm)	0.79	0.79	0.79

PROPERTY	α-CD	β-CD	γ-CD
Internal volume (nm³)	0.174	0.262	0.427
Number of water molecules taken by cavity	6	11	17
Crystal form (from water)	Hexagonal plates	Monoclinic parallelogram	Quadratic prisms
Crystal water, wt%	10.2	13.2-14.5	8.13-17.7
Melting range (°C)	255-260	255-265	240-245
Hydrolysis by Aspergillus oryzae α-amylase	Negligible	Slow	Rapid
Indicative price (€/g)	0.73	0.48	4.76

*The above table was adapted from literature references (Gharibzahedi and Jafari, 2017; Leclercq, 2016b; Sengupta et al., 2018; Wimmer, 2000).

The natural α-, β-, and γ-CDs are interesting hosts for complexation (Cova et al., 2018). Nevertheless, they present some limitations such as small cavity size for α-CD, poor aqueous solubility for β-CD, and low productivity for γ-CD (Leclercq, 2016a; Muankaew and Loftsson, 2018; Řezanka, 2018). In order to overcome these drawbacks, CD derivatives were synthesized through the chemical and/or enzymatical modification of parent CDs (Radu et al., 2016; Wimmer, 2000). Through chemical reactions such as amination, methylation, etherification and esterification, substituents are introduced on the "scaffolds" of the existing hydroxyl groups (Leclercq, 2016a; Radu et al., 2016; Varan et al., 2017). Depending on the substituent(s), several properties can be improved:

- increased solubility of both CDs and their inclusion complexes (Hammoud et al., 2019; Hedges, 2009; Varan et al., 2017);
- enhanced inclusion capacity (Gharibzahedi and Jafari, 2017; Szente et al., 2016);
- enhanced physical and microbiological stability (Varan et al., 2017);
- better control of chemical activity of encapsulated molecules (Varan et al., 2017);
- controlled drug delivery capacity (Cova et al., 2018; Varan et al., 2017);
- reduced/eradicated parenteral toxicity (Gharibzahedi and Jafari, 2017; Varan et al., 2017).

Thousands of CD derivatives have been already synthesized and became available on the market, while many others are still researched for more advanced applications (Gharibzahedi and Jafari, 2017; Řezanka, 2018).

PREPARATION METHODS

As previously mentioned, CDs are produced from the enzymatic conversion of starch or starch derivatives, through the aid of CD glycosyl transferase (CGTase) (Hedges, 2009; Li et al., 2014). Various bacteria and archaea are commercially available for producing this enzyme (e.g. *Bacillus, Paenibacillus, Klebsiella, Thermoanaerobacterium, Thermoanaerobacter* species, and *Actinomycetes*) (Biwer et al., 2002; Li et al., 2014). The main drawback implied by the usage of CGTase is its poor selectivity. After this enzymatic conversion, a mixture of α-, β-, and γ-CDs is resulted, together with trace amounts of CDs having more than nine D-glucose units in the cycle. For this reason, further separation steps are required, which, depending on the process type, can be quite expensive (Li et al., 2014; Wu et al., 2012).

Generally, there are several steps to be followed when producing CDs (Wimmer, 2000):

1. Cultivation of a CGTase-producing microorganism;
2. Separation and purification of the needed enzyme;
3. Pre-hydrolysis of starch using amylases;
4. Enzymatic conversion of starch by aid of CGTase;
5. Inactivation of the enzyme by applying a heat treatment;
6. Separation of CDs from the resulted conversion mixture;
7. Purification and crystallization from water.

There can be distinguished two main types of CD production processes, namely solvent processes and non-solvent processes. On one hand, in the case of solvent processes, an organic complexing agent selectively precipitates one type of CD by directing the enzyme reaction towards the production of the CD of interest. On the other hand, the non-solvent process uses no complexing agent, leading to the production of a mixture of different CDs, which can be further separated through various techniques. Their ratio depends on the CGTase that was used and on the reaction conditions (Biwer et al., 2002; Li et al., 2014).

Solvent processes

Industrially, most CDs are produced through the solvent process. This process involves organic solvents such as toluene, ethyl alcohol or acetone, that act as complexing agents (Biwer et al., 2002). In this way, it is solved the issue

of CGTase low selectivity, as the organic precipitant directs the reaction towards formation of only one CD type (Hedges, 2009).

The process starts with starch liquefaction of 20-30% concentration. Native starch is gelatinized by aid of several cleavage factors, such as heat (70°C), stable α-amylase, acids, or mechanical disintegration of thermostable CGTase (Biwer et al., 2002; Wu et al., 2012). At industrial level, the liquefaction step is carried out using jet-cooking (Biwer et al., 2002).

Then, after the resulted starch solution is cooled down to meet the enzyme reaction temperature, CGTase and organic complexing agents are added (Biwer et al., 2002; Wu et al., 2012). Enzymatic degradation occurs and, through the cleavage of starch chains and joining of the ends, cyclization takes place leading to the production of CDs (out of which only the desired type of CD forms a complex with the solvent and precipitates) (Biwer et al., 2002; Hedges, 2009).

After the reaction is complete, CD-agent complex is easily separated either by centrifugation or filtration. The separated complex is washed, then suspended in water and cleaved through heat treatment. Steam distillation or liquid-liquid extraction follows, in order to separate the complexing agent from the product. Further on, the product solution is concentrated by vacuum distillation. In the crystallization step, CD is precipitated, filtered, washed, and dried. The downstream process only separates the CDs from the rest of the reaction solution but does not separate different CDs from each other. Thus, the choice of an appropriate enzyme and complexing agent determines the selectivity of CD formation and recovery (Biwer et al., 2002).

Non-solvent processes

A process is considered non-solvent when the enzymatic degradation of starch takes place in a completely aqueous environment (Hedges, 2009). Because no complexing agent is added, the non-solvent process is economically and industrially suitable only for the production of β-CD. This happens due to the lower solubility of this CD compared with that of the other natural CDs that result in the reaction (Biwer et al., 2002; Wimmer, 2000; Zafar et al., 2014).

Similar to the solvent process, β-CD production begins with starch liquefaction stage, followed by enzymatic conversion. At the end of the reaction, the enzyme is inactivated, the pH is reduced, and glucoamylase is added to the solution in order to convert the unreacted starch or other non-cyclic dextrin byproducts into glucose or maltose (process called saccharification). It is important that these impurities are removed not to affect the further purification steps. Then, the solution is cleared by aid of activated carbon, filtered, and concentrated under pressure. After crystallization and recrystallization, the precipitated β-CD is isolated, washed, centrifuged, and dried. The rest of the solution is not thrown away either. As it consists of edible substances (glucose, maltose, and α- and γ-CD), it is concentrated to a syrup and it can be used as a food additive (Biwer et al., 2002; Wimmer, 2000).

INCLUSION COMPLEXES

The common feature of all CDs, and their most notable one, is their ability to form inclusion complexes (also found in literature as "host-guest complexes", "adducts", or "clathrates") with a wide range of molecules and ions, both in the solid state (crystalline substances) and in solution. What makes CDs suitable for encapsulating guest molecules is their toroidal-shaped nanodimensional cavity. Inside their hydrophobic cavities, drug molecules of low aqueous solubility and appropriate size can be accommodated either partially, or totally, generating the "inclusion complex" (Figure 2) (Del Valle, 2004; Martin et al., 2018; Řezanka, 2019; Sengupta et al., 2018; Wimmer, 2000).

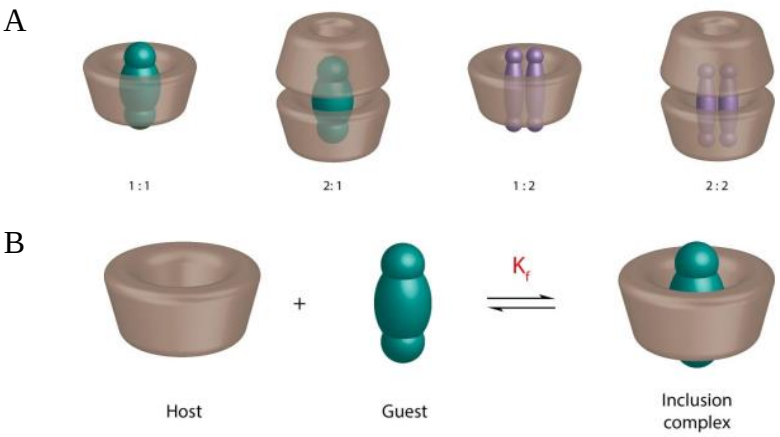

Figure 2. Schematic representation of: A – main stoichiometries of the inclusion complexes and B – formation of an inclusion complex. Reprinted from an open access source (Kfoury et al., 2018).

The dimensional fit between the volume of the cavity and the size of the accommodated entities is of great importance for the stability of the complex. Because CDs are unstable as such, the formation of clathrates helps creating more stable aqueous compounds, without implying any cleavage or formation of covalent bonds (Niculescu et al., 2016; Zafar et al., 2014). The better the complementarity between the guest and the CD cavity, the stronger the final complex (Crini et al., 2018b; Řezanka, 2019).

In what concerns the polarity of encapsulated molecules, the lipophilicity of the cavity favorizes the complexation with lipophilic entities or lipophilic parts of amphiphilic molecules, with either linear or cross-linked structures (Liu et al., 2019; Radu et al., 2016). Due to the unique conformation of CDs, they can entrap one or more drug molecules within one, two, or even three cavities, but the host : guest ratio is usually 1 : 1 (Crini et al., 2018b; Qiu et al., 2017).

The process of forming inclusion complexes with CDs as hosts is based on the intricate interaction of several factors, each playing an important role in this activity (Singh and Sahu, 2019). Adduct formation result from a dynamic association/dissociation equilibrium between free guest molecules, un-complexed CDs, and the complex (Muankaew and Loftsson, 2018; Zafar et al., 2014). The direction of this reversible process is determined by the Kf constant (formation/stability constant) – the higher the Kf value, the more stable is the complex, and hence less prone to dissociation (Crini et al., 2018b).

There are several forces which influence the complex formation, such as release of high-energy water molecules, complementary interactions (van der Waals forces, hydrogen bonds, electrostatic interactions, hydrophobic interactions,, etc.) and release of conformational strain (Crini et al., 2018b; Leclercq, 2016a; Řezanka, 2018). However, the main driving force is considered to be the hydrophobic effect (release of enthalpy-rich water molecules present in the cavity), making the process to be considered entropy-driven (Del Valle, 2004; Leclercq, 2016b).

Inclusion complexes are of great interest due to their impact on the physicochemical properties of the encapsulated molecules (Qiu et al., 2017). The effects of CDs upon the complexed substances are as follows:

- altered apparent solubility of the molecule (improved aqueous solubility) (Carneiro et al., 2019; Del Valle, 2004; Dos Santos Lima et al., 2019; Wimmer, 2000);
- stabilization against light, heat, and oxidizing conditions (Del Valle, 2004; Qiu et al., 2017; Wimmer, 2000);
- improved bioavailability (Carneiro et al., 2019; Dos Santos Lima et al., 2019; Qiu et al., 2017; Wimmer, 2000);
- reduction of volatility (Del Valle, 2004; Wimmer, 2000);
- prolongation of the shelf-life of drugs (Carneiro et al., 2019; Muankaew and Loftsson, 2018);
- controlled release (modified drug delivery site and/or time profile) (Carneiro et al., 2019; Wimmer, 2000);
- enhanced drug permeation (Muankaew and Loftsson, 2018);
- reduction (or elimination) of unpleasant taste and odor (Qiu et al., 2017; Wimmer, 2000);
- reduction of irritation (Qiu et al., 2017);
- prevention of drug-drug or drug-excipient interaction (Carneiro et al., 2019);
- conversion of liquid drugs into powders (Carneiro et al., 2019; Qiu et al., 2017).

BIOMEDICAL APPLICATIONS

As the number of possible applications seems to be unlimited, the research and market interest in native CDs and their derivatives continues to grow. The patents on CDs are counted by thousands due to their versatility. CDs find use in various domains such as pharmaceutical, medical, biomedical, and biotechnological industries, computer-aided drug-design, drug and gene delivery, food industry, cosmetics, chemical synthesis and analysis, agriculture, environmental protection technologies, textile industry, and many other industrial applications (Carneiro et al., 2019; Leclercq, 2016b; Martin et al., 2018; Niculescu et al., 2016; Pereva et al., 2016).

Out of the many domains in which CDs are useful, the first global consumer of such substances is the pharmaceutical industry, both natural and chemically modified CD derivatives emerging as attractive vehicles for encapsulation and delivery of a wide range of hydrophobic drugs (Leclercq, 2016b; Sengupta et al., 2018). Due to their unique characteristics regarding drug release ability, stimuli-responsiveness and mechanical properties, CDs are perceived as "dream molecules" for the development of applications in biomedicine and nanomedicine (such as medications, nanocarrier systems, innovative biosensors for identification of biological targets, molecular diagnosis, medical imaging, and tissue engineering) (Carneiro et al., 2019; Crini et al., 2018a; Flores et al., 2017).

Drug delivery systems

For a drug to be delivered to the targeted cell, it has to be water-soluble enough to travel through aqueous media and reach the cellular membrane, but hydrophobic enough to cross this barrier and pass inside the cell (Del Valle,

2004; Dos Passos Menezes et al., 2019). Through their ability of enhancing the solubility of poorly water-soluble drugs by encapsulating them in the bucket-shaped cavity, CDs can be used for constructing different structural architectures for optimum drug loading and superior biofunctionalities (Adeoye and Cabral-Marques, 2017; Muankaew and Loftsson, 2018; Shelley and Babu, 2018).

As the pharmacological action depends on the amount of drug reaching the target site, the increased bioavailability effect CDs have over the guest molecules represents a great opportunity for dosage optimization (Del Valle, 2004; Dos Passos Menezes et al., 2019). Therefore, including pharmacological compounds (with anti-inflammatory, antinociceptive, anticancer, antiviral, antioxidant, antidiabetic, or cardioprotective activities) inside CDs protects the drug until meeting specific receptors at the action site, in order not to be degraded by enzymes in the path or accumulate in non-target tissues (Dos Passos Menezes et al., 2019; Dos Santos Lima et al., 2019).

Consequently, CD-based nanosystems can improve drug release profiles, increasing the efficacy of the therapy while minimizing the side effects of the drug treatment (Dos Passos Menezes et al., 2019).

Oral drug delivery

Oral administration of drugs is considered to be one of the most important due to a series of advantages it provides: dosing flexibility, possibility of self-administration, convenience in chronic therapy, and wide patient acceptability. Regardless, there are several aspects to be achieved in an ideal oral nanosystem, such as high drug loading, ensuring controlled/targeted drug release, optimizing gastric solubility and/or intestinal permeability (depending on the preferred level for drug absorption), reducing side effects, and preventing the pre-systemic inactivation of the active pharmaceutical ingredients (APIs) (Adeoye and Cabral-Marques, 2017). To overcome these challenges, CDs serve as an excellent vehicle (Sharma and Baldi, 2016). Their versatility allows creating constructions that are drug-specific and able to modulate physicochemical properties and pharmacokinetic parameters. CDs deliver drugs at the surface of the gastrointestinal tract without being absorbed (they leave the body unmetabolized), they achieve sustained or site-specific drug release, leading to a positive effect on treatment outcomes (Adeoye and Cabral-Marques, 2017; Sharma and Baldi, 2016; Shelley and Babu, 2018). In addition, due to the sweet taste and taste masking properties, CDs can be applied for encapsulating bitter, bad smelling, or even irritating substances, protecting the gastric mucosa against their potentially harmful action (Del Valle, 2004; Shelley and Babu, 2018).

Ocular drug delivery

There is a major challenge to design ophthalmic formulations because of several restrictions that are encountered: complex anatomical barriers and defense mechanisms, rapid drainage, and applicability difficulties. For the API to have the proper therapeutic effects, it must be dissolved in the lacrimal fluid and pass the tear film barrier. This aqueous environment represents a challenge for lipophilic molecules which require the application of solubility enhancer additives. One of the most useful such additives are CDs, which were shown not only to increase water solubility, aqueous stability, and bioavailability of the delivered ophthalmic drug, but also to reduce the irritation occurring as a side-effect in this type of administration. Moreover, the formed complexes between CDs and APIs can be adjusted to increase the residence time via addition of mucoadhesive polymers, hence leading to higher therapeutic efficacy (Bíró and Aigner, 2019; Sharma and Baldi, 2016).

Magnetically guided systems

Some of the promising nanotools that have become more and more common in biomedical applications are magnetic nanoparticles (MNPs), in general, and superparamagnetic iron oxide nanoparticles (SPIONs), in particular. What makes them so appealing for use in imaging and drug/gene delivery are the advantageous properties they exhibit, such as low toxicity, narrow size distribution, high colloidal stability, high specific surface area, and, most important, superparamagnetism (easily magnetized when an external magnetic field is applied, reverting back to their demagnetized nature once the magnetic field is removed). Therefore, MNPs are easy to be separated, removed, and recovered, and they are also capable of localizing the targeted site within the organism, as a response to the magnetic field applied from the exterior of the body (Jeon et al., 2016; Shelley and Babu, 2018). By conjugation with CDs, MNP-CD nanosystems can reach the desired spot for liberating the carried substances (Shelley and Babu, 2018), and CDs can also serve as coatings for MNPs, improving their biocompatibility (Agotegaray et al., 2020). As an example of such application is a system that uses multivalent host-guest interactions between polymerized β-CD conjugate (pCD) and polymerized paclitaxel conjugate (pPTX), integrated with SPIONs. This nanoassembly retains the magnetic properties of the MNPs, while enhancing the magnetic-guided drug delivery. The designed pPTX/CD-SPION provides the possibility of guiding the delivery even to the tumors deep inside the body, and it shows enhanced anticancer effects both *in vivo* and *in vitro* (Jeon et al., 2016).

Vesicle-CDs systems

CDs can be also associated with other particles with carrying abilities, such as micelles, vesicles, and polymers, in order to form complex biocompatible systems for drug delivery purposes (Adeoye and Cabral-Marques, 2017; Fernández et al., 2019). Out of the combination possibilities, the most commonly used are the vesicle-CD systems

(especially with liposomes) for encapsulating, transporting, and delivering pharmaceutical substances. These generated nanosystems combine the benefits of the two components, preventing the downsides of each part: the solubility and stability of the drugs is increased, while they are transported and released in a prolonged circulating time (Fernández et al., 2019; Qiu et al., 2017). Such drug/CD/liposome constructions are of importance in the delivery of anti-cancer and anti-inflammatory drugs, both for mucosal and subcutaneous administration routes (Dos Passos Menezes et al., 2019).

CD-based metal-organic frameworks

A novel class of hybrid materials for biomedical purposes became of interest: metal-organic frameworks (MOFs). Composed of inorganic centers (metal ions) and organic coordinating linkers (polyfunctional organic acids), MOFs are highly porous, crystalline frameworks, with high surface area and tunable pore size, shape, and functionality. These features make MOFs suitable for a wide range of applications, such as catalysis, separation, gas storage, but once their toxicity is reduced, they can also serve in drug delivery applications. For this improvement are responsible, once again, CDs. γ-CD was shown to increase the biocompatibility, while also maintaining the porous framework in the crystalline state. Anti-inflammatory drugs can be entrapped within γ-CD-MOFs, which due to the remarkable loading ability and controlled release, are of great importance particularly for colon-specific drug delivery systems (Abuçafy et al., 2018; Emam, 2019).

Drug-eluting stents

It was noticed that surface grafting or thermo-fixation of CDs on medical devices (such as catheters, prosthesis, grafts, stents, implants) is also possible and beneficial for patients. The new generation of drug-eluting stents is of special attention in this matter. These stents incorporate biocompatible and bioresorbable CD-based polymers onto classic metallic devices (Crini et al., 2018b). Several layers form the stent coating, which in the order of their application onto the platform are as follows: polydopamine (strong adhesive polymer), CD (fixed by in situ polycondensation with citric acid), and an amine-rich polymer (stabilizer for the anionic CD layer) (Crini et al., 2018a).

Hydrogels

Hydrogels are one of the most promising platforms for wound dressings, delivery systems and medical devices (Gupta et al., 2020; Jeong et al., 2018). Being exceptionally patient-friendly, hydrogels promote healing by maintaining a moist environment at the wound site (donate moisture in the case of dry wounds and absorb water or biological fluids in excess in the case of exudative wounds). Moreover, they reduce pain through their cooling effect, allow gas exchange and can be loaded with antimicrobials and healing agents (Gupta et al., 2019; Moradi et al., 2020). However, the main limitation of hydrogels is their incompatibility with lipophilic substances, showing decreased loading strength and less control over the release mechanism of such drugs. To overcome these drawbacks, incorporation of CD molecules in the hydrogels' hydrophilic network was approached (Jeong et al., 2018; Larrañeta et al., 2019; Malik et al., 2017). Such CD-based hydrogels find applications in contact lenses, as they offer extended drug release and longer residence time in the tear film than traditional eye drops (Chaudhari et al., 2019; Larrañeta et al., 2019). A particular case of such materials is represented by chitosan grafted with β-CD which exhibits mucoadhesive and controlled release properties (Malik et al., 2017). Another possibility is to incorporate CD derivatives inside hydrogels, in order to form inclusion complexes with hydrophobic drugs. One such example is the complexation of curcumin (substance with wound healing ability, less likely than antibiotics to develop resistant strains) within hydroxypropyl-β-CD (HPβCD) for enhancing the healing properties, physical performance, and cytocompatibility of the platform (Gupta et al., 2019; Kaolaor et al., 2019). Carboxymethyl cellulose (CMC)-based hydrogels can also benefit from the additivation with CDs. CMC matrixes have lower mechanical strength than simple cellulose-based hydrogels, but, through the integration of carboxymethyl-β-CDs, the strength is increased while also preserving the efficient drug release properties and good swelling capacity (Jeong et al., 2018). One drug that can be included in such structures is acyclovir, an antiviral substance used for treating herpes viral infections. This application helps reducing the frequency of administering the treatment and decreasing unwanted effects by providing an efficient and desirable drug release profile (Malik et al., 2017).

Nanosponges

In recent years, nanosponges were researched and developed as novel 3D hyper cross-linked polymer-based colloidal structures (Cova et al., 2018; Crini et al., 2018b; Sherje et al., 2017). CDs can be employed for creating such tiny mesh-like structures, in which, due to the high porosity, a wide range of substances can be encapsulated. As nanocarriers, they have an exceptional drug loading and the delivery can be designed to selectively release the complexed drugs. CD-based nanosponges (CD-NSs) have the advantageous ability to include both hydrophobic and hydrophilic drug molecules, due to the internal hydrophobic cavities and external hydrophilic network spaces, respectively (Adeoye and Cabral-Marques, 2017; Dos Passos Menezes et al., 2019; Sherje et al., 2017). β-CD-NSs, in particular, have been shown to enhance solubility, increase chemical stability, improve drug permeability, modulate

drug delivery through changes in the dissolution and pharmacokinetic profiles, protect APIs from physicochemical degradation, and reduce their toxicity (Adeoye and Cabral-Marques, 2017; Crini et al., 2018b; Deshmukh et al., 2016). Some substances that can be impregnated onto such sponges are lysozyme (an enzyme with antimicrobial action), calcium (released at a controlled rate for 24 hours to prevent its depletion), melatonin (transdermal controlled release), and anticancer drugs (treatment of prostate cancers) (Deshmukh et al., 2016; Dos Passos Menezes et al., 2019; Mihailiasa et al., 2016). Owing to their biocompatibility, versatility, and possibility for targeted delivery, CD-NSs can constitute a whole new approach on cancer treatment. They could be employed in imaging, diagnosis, and treatment per se with minimal leaking during the sustained delivery, increased biodistribution, and cellular trafficking of chemotherapeutics (Dos Passos Menezes et al., 2019; Sherje et al., 2017).

Medical textiles

Starting from 1941, people realized that textiles could act as protectors against bacteria and disease spreading by developing and incorporating biofunctional fibers. (Celebioglu et al., 2019; Cova et al., 2018; Emam, 2019). Regardless of their early beginnings, such advanced materials are still of great interest nowadays and under intense research for improvements and new applications (Leclercq, 2016b). Smart textiles can be used for wound management, providing protection to the damaged tissue while speeding the natural healing processes (Flores et al., 2017). The microbial burden is reduced in order to prevent infections of the wounded area and avoid cross-contamination between patients (Reddersen et al., 2016). Moreover, the combination between conventional textiles and performant drug delivery systems results in fabrics with transdermal drug release ability (Cova et al., 2018; Mihailiasa et al., 2016).

CDs have drawn the attention for improving the efficiency and obtaining of new functionalities of medical textiles (Leclercq, 2016b; Sharma and Baldi, 2016). CDs can be attached in several methods onto the fabric, such as grafting, surface coating, dyeing, impregnation, printing, spraying, padding, or foam finishing (Leclercq, 2016b; Radu et al., 2016; Singh and Sahu, 2019). They were proposed for large scale development of such materials, conferring functional properties such as UV protection, antimicrobial, antifungal, and antibacterial activity, aroma delivery, insecticide delivery, and dyeing (Cova et al., 2018; Crini et al., 2018b; Singh and Sahu, 2019).

In what concerns the substrates for CD-attachment, the preferred ones are cellulose-based fibers (Mihailiasa et al., 2016). Functionalization of cellulose is of growing interest due to the chirality, biodegradability, broad chemical modification capacity, and ability to arrange in versatile semi-crystalline fibers (Emam, 2019). The purest form of cellulose available in nature is cotton which, owing to its good absorbency and softness, makes a comfortable textile support for patients with skin diseases (Mihailiasa et al., 2016; Radu et al., 2016). In order to serve as a drug delivery material, it is important to attach the CDs covalently to the surface of cellulose, so that the hydrophobic cavities remain accessible to the guest molecules (Cova et al., 2018). For instance, monochlorotriazmyl-β-CD reacts with hydroxyl groups from cellulose and form permanent bonds between the fibers and exterior surface of CDs (Leclercq, 2016b; Radu et al., 2016).

Contrastingly, CDs were successfully grafted on synthetic fibers as well, by using citric acid as crosslinking agent. It is quite common and easy to perform this process on polyester or polyamide, in order to obtain biofunctional materials (Leclercq, 2016b). However, for synthetic supports it is preferred to include the antibacterial agents prior to the extrusion of the polymer spun mass (Radu et al., 2016). An example of such textile would be a blend of viscose/polyester additivated with β-CD which leads to an increase in the material's hydrophilicity and healing properties (El Ghoul et al., 2017).

Moreover, CDs are applied for functionalization of both textiles that can be included inside the body and textiles that come in contact only with the outside surface of the dermis. Hence, they are called implant materials when used for operating at a systemic level (as specific devices such as vascular prostheses, suture threads, stents, or substitutes for tendons) and medical textiles when used on the surface of the body (in knitted, woven, and non-woven structures such as wound dressings, pajamas, tracksuits, caps, socks, gloves, elbow and knee pads, or underwear) (Emam, 2019; Radu et al., 2016; Radu et al., 2017; Reddersen et al., 2016). Therefore, medical textiles find applications in maintaining a good hygiene and health state, but are also used for surgical and therapeutic purposes (Emam, 2019).

The working principle of these textiles is based on the interface created between the material, drug, and skin, where the transfer vehicle is represented by "*perspiratio insensibilis*". In other words, the physiological perspiration is diffused through the skin, forcing the drug to leave the CD's cavity and transfer itself to the epidermis. The quantity of drug applied is equivalent to the therapeutic dose, with the advantage that the treatment becomes effortless in this way (as the drugs are released even if the patient is unaware of it) (Radu et al., 2016; Radu et al., 2017). Due to the release mechanisms of these textiles, they can be also used for diagnostics purposes, by encapsulating substances present in the patient's sweat within CD cavities (Emam, 2019).

The medication included in CD medical textiles is usually intended for treating allergies, infectious dermatitis and burns, and also chronic conditions (psoriasis, venous failure, and skin cancer) (Radu et al., 2017). Studies were performed on inclusion of several antiseptics (chlorhexidine diacetate, iodine, and polyhexanide) and there were reported better skin compatibility, higher antimicrobial activity, and enhanced storage stability (Reddersen et al.,

2016). Other researchers investigated methylene blue as a drug model and assessed the release kinetics through sustained release in water (El Ghoul et al., 2017). Silver nanoparticles or other types of noble metal nanocrystals can also be included to act against the growth of *Escherichia coli* and *Staphylococcus aureus* over 24 hours treatment (Celebioglu et al., 2019). Because insects are common vectors for a plethora of diseases (e.g. yellow fever, dengue fever, malaria), including insecticides in CD-containing textiles can be a promising protection approach (Leclercq, 2016b).

Research started recently being focused also on a technology mixing cosmetics and textiles. Cosmetotextiles are products that ensure the controlled release of cosmetic products, being at the borderline of medical applications (Crini et al., 2018b; Leclercq, 2016b). The encapsulated products (usually natural hydrophobic substances having skin benefits) gradually perfume, moisturize, slim, refresh, relax, and protect against UV radiation, ensuring an occlusive layer onto the epidermis (Azizi et al., 2019; Leclercq, 2016b).

Other applications

Encapsulation of essential oils

Besides their fragrant properties, essential oils also exhibit various biological properties, such as antimicrobial, anticancer, anti-obesity, or anti-inflammatory activities. However, they present some disadvantages which restrict their applications; they are insoluble in aqueous media, highly volatile, and degrade under the action of environmental factors (Kfoury et al., 2019). In order to protect essential oils against external factors, but also to ensure a lengthier release, different encapsulation systems can be employed (Radu et al., 2017). CDs represent an excellent candidate for improving the solubility of essential oils, suppressing their volatility and increasing the bioavailability (Moradi et al., 2020). The release is delayed and has a controlled rate, taking place only when the specific humidity and temperature conditions are met (Kfoury et al., 2018). An important biomedical application of such kind consists in forming inclusion complexes between CD and thymol (the most effective component of thyme oil), the latter having inhibiting properties over both Gram-positive and Gram-negative bacteria, such as *Escherichia coli, Bacillus subtilis, Klebsiella pneumonia,* and *Staphylococcus aureus* (Moradi et al., 2020).

Tissue engineering

In order to develop more and more performant biomaterials for tissue engineering, special attention has to be given to increasing the bioavailability of biomolecular cues (e.g. growth factors) to promote desired cell responses (Grier et al., 2018). The CD tissue engineering applications that are already under development are joint or bone trauma and arthritis (Braga, 2019). β-CD is used to bind growth factors (transforming growth factor β-TGF-β1 and bone morphogenic proteins - BMP-2) from solution prior to cell-seeding, as a way to stimulate mesenchymal stem cells (MSC) differentiation with lineage guidance. By incorporating these complexes within a collagen-glycosaminoglycan scaffold, they can help generate new bone and cartilage, by driving MSCs towards osteo-chondral differentiation and proliferation (Braga, 2019; Grier et al., 2018).

Electrochemical sensors

The continuous progress in electrochemistry led to the development of enzyme-based biosensors, which can detect metabolites (e.g. glucose, lactate) and drugs. Because the enzymatic activity lowers in time once attached on the electrode surfaces, the performance of the biosensors decreases as well. This issue can be solved by including the needed enzymes inside the cavities of CDs and ensuring in this manner the stability of the sensors for a longer time. Due to the size match between its inner volume and targeting diagnostic-molecules, β-CD is most commonly used to provide selectivity to future electrochemical sensing-devices. Further research upon employing also chemical modifications on the CD surface leaves the door open for numerous applications in diagnostics, life science, and biology (Casulli et al., 2019).

Active ingredients

If it is already clear by now that CDs can form useful complexes, it is also important to mention that these oligosaccharides represent also active ingredients in pharmaceutical formulations. They can be included as such, in order to further capture guest molecules from inside the body, hence treating several illnesses (Braga, 2019; Crini et al., 2018b; Fernández et al., 2019). The internal biomolecules to which CDs can bind are the following (in increasing order of strength): carbohydrates, nucleic acids, proteins, and lipids. For this reason, most of the investigations involve the extraction of lipids from plasma membrane. Removing cholesterol from patients suffering from cardiovascular diseases by employing this non-toxic and non-invasive tools represent a promising method for fighting against the morbidity and mortality associated with these conditions (Leclercq, 2016a). Moreover, CDs are able to sequester cholesterol from the membranes of any virus of lipophilic nature (Braga, 2019). This activity can be manifested against influenza virus, human immunodeficiency virus (HIV), murine corona virus, poliovirus, human T cell leukemia virus (HTLV-1), Newcastle virus, varicella-zoster, hepatitis B virus, bluetongue virus, and many others (Leclercq, 2016a). As an example, sulfonated CDs were reported to diminish the infectivity of HIV and block the *in vitro* replication. Another useful derivative with antiviral activity is hydroxypropyl-β-CD, which can remove cholesterol molecules from

both host cells' membrane and viral particles. In this two-fold mechanism, host cell are rendered less susceptible for viral infection, while viruses are disrupted (Braga, 2019). HP-β-CD can also inhibit the growth of leukemic cells, through cell-cycle arrest and apoptosis (Qiu et al., 2017). Moreover, CD-mediated cholesterol modulations can change the activity of certain proteins from the epithelial cells membrane in the blood brain barrier. Extensive research of this aspect can result into improvement of therapies for numerous pathologies, such as stroke, cerebral hypoxia and ischemia, epilepsy, central nervous system infections, Alzheimer, Parkinson, and Huntington diseases, and brain tumors (Crini et al., 2018b).

CONCLUSIONS

In conclusion, due to their versatility, unique structure, and properties, CDs have gained great research and commercial interest over the past 120 years. Taking into account all the evidence presented in this review, it is clear that CD-inclusion complexes have enormous potential, especially in the pharmaceutical domain, as they provide new and useful properties related to the possibility of non-covalent binding. Great progress has been noticed in developing CD-based drug delivery systems, with enhanced efficacy for oral, ocular, transdermal, and mucoadhesive administration routes. Moreover, in association with metallic particles and/or devices, these systems benefit from synergic effects: increased biocompatibility and guided delivery. Including CDs as part of different systems (micelles, vesicles, polymers, and solids), as well as improving their characteristics through different chemical modifications are still under research and development, resulting in thousands of articles and patent applications. However, in most of the studies toxicity tests tend to lack. This aspect should be thoroughly investigated in the future, in order to avoid potential complications in clinical trials. In what concerns the imminent perspectives of research, CDs might represent a key element in finding treatment against the new strain of coronavirus. Being already proven to have anti-viral activity, CDs should be included in such pharmaceutical formulations and tested as soon as possible.

CONFLICTS OF INTEREST

The author declares no conflict of interest.

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