Chapter

Strategies to Develop Cyclodextrin-Based Nanosponges for Smart Drug Delivery

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Abstract

In recent years, the development of various cyclodextrin (CD)-based nanosponges (NSs) has gained great importance in the controlled and-or targeted release of drugs due to their versatility and simple preparation. In this chapter, an introduction of different administration routes is explained. Further, different ways to obtain CD-NSs and their classification are shown with a brief explanation of the characterization of the inclusion complexes. Finally, illustrative examples in diverse processes or diseases will be reviewed and explained to demonstrate the potential of CD-NSs. Therefore, this division will serve to compile information on CD-NSs in recent years and to illustrate to readers how to generate and apply different derivatives of interest.

Keywords: Cyclodextrin nanosponges, drug delivery, synthesis, nanocarrier, release

1. Introduction

Society demands better treatments for each disease and therefore the industry tries to obtain them. Novel drugs with better bioactivity are researched to achieve the best result in our bodies. However, several novel drugs present problems related to their chemical properties that prevent them from being used as a pharma or nutraceutical product. The molecule can be unstable in water solution, and/or easily oxidized, and presents poor bioavailability. Different strategies might improve the current therapy. One possibility is to find a good formulation, which stabilizes the drug or carries it to the desired tissue. Moreover, the adverse effect due to the dosage can also be reduced. For this reason, a great number of carriers are been proposed to challenge the previous problems.

One of them is called cyclodextrin (CD), truncated cone-shaped oligosaccharides made up of α-(1→4) linked glucopyranoside units with six, seven and eight glucose units, α, β and γ-CD, respectively [1, 2]. A derivative called 2-Hydroxypropyl-βCD (HPβ-CD) is used as an orphan drug for Niemann Pick disease type C [3, 4]. Complexes formed of molecules and cyclodextrins (CDs) are called "inclusion complexes". Generally, CDs encapsulate poorly water-soluble compounds and hydrophobic moieties of amphiphilic molecules. Nevertheless, the

solubility of these complexes not only depends on the CD used but also on different factors such as pH or guess molecule [5–8]. The capacity of CDs to increase solubility and protect several molecules has increased their use in the pharmaceutical and food industries [1, 9, 10].

However, the improvement achieved by adding CDs is sometimes insufficient. Then, researchers developed a novel material based on these excipients baptized as Cyclodextrin-based Nanosponge (CD-NS), innovative cross-linked polymer structures with a three-dimensional network, and with a crystalline and amorphous structure, spherical and possessing good swelling properties [11]. Recent reviews [12–14] point to their wide potential and minimal toxicity [15, 16]. Some applications of these polymers include i) increasing the apparent solubility of poorly soluble drugs, ii) modulating drug release and activity, iii) protecting drugs against several agents, iv) enhancing bioactivities, v) absorbing contaminants ability, vi) delivering the drug, etc.

Cross-linking CDs brings significant benefits to CD-NSs compared with the respective native CDs. In general, CD-NSs can form complexes with a series of different molecules due to their structure. They achieve a hindered diffusion of loaded guest molecules, thus promoting slower release kinetics [17, 18]. Another important property of CD-NSs is that they can be easily recovered from aqueous media and recycled. Although they are insoluble, soluble hyperbranched NS can also be synthesized [19]. Finally, one of their principal disadvantages has been recently solved, they have been tested as a good carrier not only for small molecules but also for higher ones like proteins [20, 21].

This chapter tends to be a first step for the researcher who starts with CD-NSs: i) an introduction of the routes of administration, including advantages and disadvantages is explained, ii) an explanation about the various types of CD-NSs, including its synthesis and classification is written, iii) the different ways to characterize the inclusion complexes are reported and iv) examples of smart delivery are displayed as an encourage study to demonstrate their potential.

2. Routes of administration, advantages, and disadvantages

The choice of the route of administration is crucial as it dramatically affects drug bioavailability and thus requires specific delivery strategies. Parenteral routes include intravenous, intramuscular, and subcutaneous routes, whereas the enteral routes are the oral, sublingual, and rectal routes [22]. Others are inhalation, intranasal, etc. [23]. In this section, each route will be described briefly and special attention will be paid to the oral route, which is the most desired but, at the same time, the most challenging.

When administered via intravenous injection (IV), the drug reaches the systemic circulation directly bypassing absorption and carrying out its effect rapidly. This route is ideal for unstable or scarcely absorbed drugs (e.g. blood products), and irritating drug formulations, the administration of which via subcutaneous and intramuscular routes will be painful. It is also intended for patients who are not able to take the formulations orally, due to mental disorders, nausea, or vomiting.

Intramuscular injection (IM) can involve various muscles, including the gluteal muscle to which up to 5 ml of the formulation can be administered. Via this route, aqueous or oil-based solutions, suspensions, and emulsions are accepted. Aqueous solutions are generally absorbed in 10–30 minutes, whereas drugs insoluble at interstitial pH or suspended in oil-based solutions present a long time of absorption. Vascularisation of the muscle, the volume, and the osmolarity of the injected formulations also affect the absorption time. A depot preparation of the drug can

be given via this route with a sustained release of the drug into the bloodstream. IM injection is selected when the drug has a low oral bioavailability or when the patient is not compliant. Vaccines are also administered via this route.

Subcutaneous injections can be given in the forearm or abdomen. Up to 2 ml of the formulation can be administered. Together with aqueous solutions and suspensions, adrenalin can be added to induce vasoconstriction and therefore increase the residence time of drugs (e.g. local anesthetics) or hyaluronidase to make the extracellular matrix more fluid, thus improving the absorption rate.

The absorption rate is extremely variable as it is influenced by the blood flow. Subcutaneous injections are also used for depot formulations. It is easy to administer and requires minimal skills, thus allowing self-administration. Insulin and heparin are given via this route.

Among all, oral delivery has been recognized as the most attractive route, as it is cheap, simple, accepted by patients, requires fewer sterility restrictions, and offers more possibilities in the design of the formulation (including sustained and controlled delivery) [24]. It is used for drugs with topical action in the gut and systemic effects when they reach the bloodstream. However, it is not suitable for emergencies in which an immediate effect is fundamental.

Over the past few years, many efforts have been made to develop oral delivery systems able to overcome the obstacles in the gastrointestinal tract (GI) in which the mechanism of absorption is complex with multiple levels of barriers [24].

There is a long list of variables that influence the GI absorption of drugs, which are grouped in technical challenges, physicochemical properties of the drug, and environmental factors [25].

The technical challenges concern the pharmaceutical form, i.e. liquid or solid. In solid forms, *the rate* and extent of disintegration, and dissolution of the formulation are important to a drug, and to carry out its effect, needs to be in a solution for developing the absorption.

Most drugs are absorbed in the small intestine, characterized by a large surface area of absorption and having a crucial influence on bioavailability.

The walls of the GI tract are characterized by the presence of mucus, which has been a target for drug delivery systems (DDS) capable of mucopenetration or mucoadhesion [24]. Mucopenetration consists in regulating the hydrophobicity/hydrophilicity of the carrier's matrix or combining mucolytic enzymes to promote drug penetration. On the contrary, mucoadhesive carriers, which have attracted significant attention [26–28], can adhere to mucus, thus increasing the residence time. CD NSs have proven to possess this property, making them particularly promising for oral delivery [20].

Last but not least, the first-pass effect should be borne in mind when dealing with the oral route as it is certainly a limiting factor. It refers to the metabolism (mainly in the liver) of the drug before it reaches the systemic circulation, which may lead to a drop in bioavailability [29]. For this reason, several drugs are administered via other enteral routes (e.g. rectal and sublingual).

The sublingual route offers the benefit of bypassing the first-pass effect due to the passive diffusion through the highly permeable mucosa underneath the tongue. It is simple with a low risk of infection and the effect is rapid. Nitroglycerin is administered via this route.

The rectal route exploits the highly vascularized rectal mucosa for drug absorption. The first-pass effect is partially avoided. It is indicated for patients with gastrointestinal motility problems, nausea, vomiting, and children.

Inhalation is used to obtain a rapid effect as the drug crosses the large surface area of the respiratory tract epithelium and reaches the systemic circulation. It avoids the first-pass metabolism. The particle size and morphology of the

Route of administration	Advantages	Disadvantages
Oral	• easy • safe • cheap	• not Emergency therapy • not for GI-sensitive drugs (unless they are encapsulated • first pass effect • risk of interaction with food and drugs
Sublingual	• rapid effect • suitable for emergency therapy	• uncertain dosage
Rectal	• for pediatric use • for patients with impaired GI function	• risk of irritation • unpredictable absorption
Inhalation	• rapid absorption • suitable for general anesthesia and emergency therapy	• risk of irritation • specific equipment is needed
Intravenous	• suitable for emergency therapy • adjustable • accurate dosage	• complications due to rapid onset • allergic reactions
Intramuscular	• rapid absorption • systemic administration of hydrophilic drugs • administration of sustained-release formulations	• small volumes • painful • care must be taken to avoid veins and arteries • risk of infections and abscesses
Subcutaneous	• rapid absorption • administration of sustained-release formulations	• administration of very small volumes

Table 1.
Advantages and disadvantages of the main routes of administration.

formulation inhaled are crucial. It is mainly used for the treatment of respiratory diseases. The intranasal route enables the drug to be absorbed via passive diffusion across the highly-vascularised respiratory epithelium directly into the systemic circulation. Nasal decongestants and anti-allergic drugs are administered via this route (**Table 1**).

3. Synthesis and classification of CD-NSs

The choice of appropriate synthetic conditions, allowed to obtain both water-soluble and water-insoluble polymer products, known also as CD-NSs or insoluble, and branched or soluble polymer [30–32]. The latter case allowed to overcome the limits of pristine CDs in terms of solubility in water and specific organic solvent, while the resulting formation of a three-dimensional cross-linked network was related to the presence of interstitial spaces among the monomers [33]. In this regard, the nature of the cross-linker and its amount in respect to the CD, ratio which defines the so-called cross-linking density, are presented to have a great impact on the properties and structure of the final material [34]. Also, being said interstices wider and more hydrophilic in respect to the cavities of CDs, a wider hosting capability was observed as a result.

3.1 General synthesis protocol

The most common method announced for the synthesis of CD based polymers, is characterized by employing a suitable solvent which could be either organic solvent or, in specific cases water, for the dissolution of the CDs. Afterwards, under continuous stirring, the chosen linking agent is added to the solution. Nevertheless, when required, the introduction of a catalyst occurs before the linking agent, and in specific cases, an increase in temperature is necessary to start the cross-linking reactions. The use of an ultrasound bath instead of stirring was also considered [35]. Eventually, either a sol–gel process or a precipitation polymerization can be observed, leading to the formation of a monolithic block or a precipitate, respectively. Also, in those cases in which the cross-linker is in the liquid form, and able to solubilize the CD, a melt polymerization can be performed [36, 37].

Once the synthesis is completed, the solvent, the catalyst, eventual unreacted monomers, and by-products are removed from the synthesized product by purification with water or other volatile solvents. In the end, a dry solid powder is collected [37–39]. Another well-known approach to synthesize CD-NSs is achieved through simple dehydration reactions. In this case, the CDs and the cross-linker, which is usually an acid bearing two or more carboxylic groups, are solubilized in water. After the addition of a suitable catalyst, the solution is heated to remove the water introduced as solvent as well as the water released as a by-product of the cross-linking condensation reaction. Moreover, the use of vacuum together with the temperature allows to shift the equilibrium of the reaction toward the products [40, 41]. Besides, less used synthetic routes report the use of interfacial or radical polymerization. In the first case, two immiscible phases such as a water solution of CD and a chlorinated solvent solution containing the chosen cross-linker, are mixed and stirred vigorously. The cross-linking occurs rapidly at the interface of the immiscible phases, and a precipitate is obtained [39]. While in the second case, a multistep procedure involving also preliminary derivatization of CD was displayed [42].

3.2 General classification

In general, based on the technological evolution of these materials, CD-NSs can be classified into four generations, considering their chemical composition and properties [19]. The first generation comprises all those NSs synthesized by a simple one-step reaction of CDs with a cross-linker. This generation was further divided into sub-categories according to the chemical nature of the linking molecules adopted for the synthesis. In this frame, carbonate, ester, ether, and urethane types are the most reported. These specific types of NSs will be described in more detail in the following paragraphs. Subsequently, the introduction of specific functions such as charge or luminescence to the final polymer structure defined the second generation of NSs. These materials displayed more complex polymer architectures achieved either via pre- or post-synthesis functionalization. In the first case, the introduced functions were limited to the surface of the polymer, whereas in the second case a more homogeneous distribution was observed. Referring to the division into generations, the 3rd generation deals with stimuli-responsive NSs, able to modulate their behavior (for example increasing/decreasing a drug release) according to the external environment.

3.2.1 CD-based polyurethane NSs

Urethane, or carbamate, CD-NSs are synthesized by reacting CDs (or a different dextrin) with a suitable diisocyanate as, for example, hexamethylene diisocyanate (HDI), toluene–2,4-diisocyanate (TDI). The reaction scheme is reported below

(**Figure 1**, inset a). The resulting NSs are usually characterized by a rigid structure and a negligible swelling in water (in comparison with other CD-NSs), and organic solvent and high resistance to chemical degradation. Carbamate CD-NSs, were originally developed by Li and Ma for the treatment of wastewaters, as an alternative for activated carbon. They demonstrated with NSs remarkable performances in the removal of organic molecules such as p-nitrophenol reducing concentration of waste from 10^{-7}–10^{-9} M to ppt level. The surface area was usually lower than activated carbon, (1–2 m^2/g, two orders of magnitude) but it is supposed that organic molecules can be adsorbed, diffuse through the surface, and be absorbed inside the bulk of NSs [43].

The good affinity of organic molecules showed for pollutants [44], is also demonstrated by the application of urethane NSs in the complexation with biologically relevant compounds, such as bilirubin or amino acids. In 2006, Tang et al. evaluated the difference in absorption of aromatic amino acids and branched-chain amino acids: the absorption of branched-chain amino acids was negligible whereas NSs absorbed 24% of the aromatic amino acids.

In previous works the same polymer was tested for the absorption of bilirubin, reducing the initial concentration of bilirubin (40 mg/l) up to 92.6% after the addition of the NS [45].

3.2.2 CD-based polycarbonate NSs

Polycarbonate CD-NSs are usually synthesized using active difunctional carbonyl compounds such as 1,1′-carbonyldiimidazole, triphosgene, and diphenylcarbonate (**Figure 1**, inset b). Since the resulting CD NSs present carbonate bonds between CD monomers, these NSs present short cross-linking bridges and, consequentially, a reduced swelling ability (if compared to CD- based polyesters NSs, for example) and good stability to acidic solutions. The affinity to organic molecules and the surface area are comparable to carbamate NS [46]. The ability of β-CD carbonate NS to remove from wastewater chlorinated persistent organic pollutants (also known as POP) was investigated by Trotta and Cavalli in 2009 [47]: the absorption efficiency was higher than the average of activated carbon. For the specific case of hexachlorobenzene the NS was capable of removing around 99.5% of the pollutant.

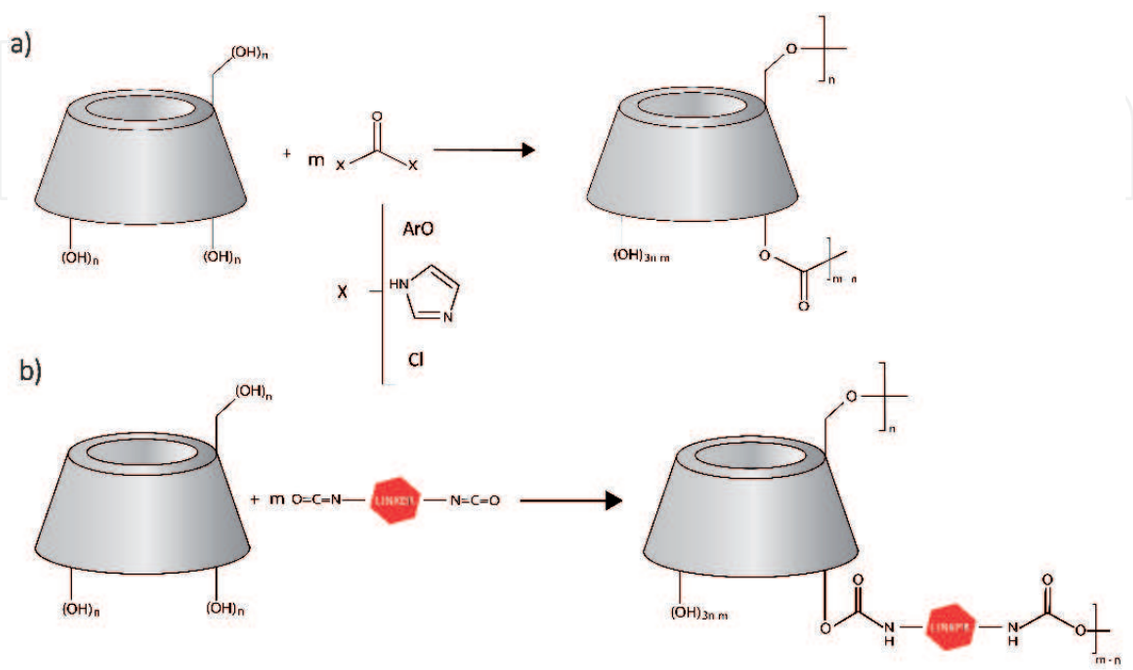

Figure 1.
Schematic synthesis of a) CD-based polyurethane NSs and b) CD-based polycarbonate NSs.

An interesting method to evaluate the degree of cross-linking of carbonate β-CD NSs, employing infrared and Raman spectroscopy, was described by Castiglione et al. [48]. Data from spectroscopic analysis and chemical computation demonstrated a correlation between the intensity of carbonyl absorption peak and the degree of cross-linking: the degree of cross-linking increased with the amount of cross-linker, in total agreement with the stoichiometry. Dealing with sugar-based predominantly amorphous materials, the reported method represents a valid and advantageous alternative to x-ray. The crosslinking density or the amount of crosslinker, strongly influences the stiffness and elastic properties of the NSs. Rossi et al. demonstrated in their study that the mechanical features of the NSs can be easily tuned by changing the molar ratio CD/cross-linker, on the other hand, the CD used for the synthesis does not affect the mechanical properties of the final NS [34, 49].

3.2.3 CD-based polyester NSs

Ester CD-based NSs are synthesized using dianhydrides or di/polycarboxylic acids, such as pyromellitic dianhydride (PMDA), ethylenediamine- tetraacetic dianhydride (EDTA dianhydride), butanetetracarboxylic dianhydride, citric acid [46, 50].

Dissimilarly from polycarbonate and polyurethane NSs, polyester NSs are generally able to absorb remarkable amounts of water (up to 25 times/g dry sample), and form stable hydrogels. Similarly as seen before with mechanical properties, the swelling capability of the CD-NSs is generally dependent on the degree of cross-linking. The swelling capability is usually inversely proportional to the density of cross-linking: the lower the degree of cross-linking, the higher the water uptake. The structure of the material dramatically influences chemical stability. Ester NSs are subjected to hydrolysis in aqueous media more easily than polycarbonate and polyurethane NSs. The structure is remarkably interesting because of the presence of free carboxyl groups in their chemical structure, moieties that can be exploited for the absorption of cations, using the material as an ionic exchange resin.

There are in literature many examples of the formation of complexes with a metal cation. The metal ions complexation ability of pyromellitic NSs is studied by Berto et al. in for different metal cations, such as Al^{3+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+} and Pd^{2+}.

In most cases, pyromellitic NSs were found to be capable of absorbing more than 70% of the tested cation [51].

A similar test of removing heavy metals from wastewaters, crosslinking also CDs with citric acid, is performed by Rubin Pedrazzo et al. in 2019 [52]. At a metal concentration of 500 ppm, the pyromellitic NSs (substituted before absorption with Na^{+}) exhibited a higher retention capacity than the citrate NSs. At lower metal concentrations ($\leq$ 50 ppm) both the citrate and the pyromellitic NSs showed high retention capacities (up to 94% of the total amount of metal). While in the presence of interfering sea water salts, the citrate NSs were able to selectively adsorb a significantly higher amount of heavy metals than the pyromellitic NSs.

For ester NSs, similar studies of the correlation of cross-linking degree with properties are performed. Surprisingly, the highest cross-linking degree was observed in the sample prepared using the molar ratio 1: 6, CD: PMDA [53].

Higher contents of cross-linker, molar ratios like 1:8 and 1:10, led to a decrease of the degree of cross-linking; this is possibly related to the steric hindrance generated by the pyromellitic units linked to CDs. Interestingly, by working under limited dilution conditions during the reaction and with an even lower CD/cross-linker ratio (e.g., 1:2 molar ratio), it is possible to obtain a hyperbranched water-soluble polymer [54]. As already described for carbonate NSs,

Raman and Brillouin scattering experiments permitted Rossi et al. to evaluate a relationship between the mechanical characteristics of the polyester pyromellitic β-CD NS and the molar ratios CD/cross-linker: as seen before, stiffness and elasticity of the polymeric structure can be tuned by varying the amount of cross-linker [49].

4. Inclusion complex preparation and analysis

4.1 Preparation of inclusion complexes

Once the CD-NS is ready, the inclusion complex can be obtained by several procedures [55] as its summarized in **Figure 2**. Firstly, it is performed the classical mixing of drug and CD-NS in a solvent, commonly water for 24 h to form the complexes. In this procedure, we should consider the insoluble or soluble nature of our complexes. Depending on this, the desire fraction is purified. Using kneading, the drug and the CD-NS are mixed in a mortar with an appropriate quantity of water or another solvent to form the complexes. At this point, other additional techniques are used to form the powder: The solvent can be removed using lyophilization, co-evaporation, or spray-drying procedures.

4.2 Analysis of inclusion complexes

Different techniques can be employed to characterize not only inclusion complexes but also CD-NS. For information purposes, we will name some of them and briefly explain their possibilities [56, 57]:

4.2.1 Ultraviolet/visible spectroscopy

UV–vis is a simple, easy, and fast method for studying the host-guest complexation when its formation changes any particularity of the spectrum of a guest molecule or to check the solubilization efficacy [14, 16, 58, 59].

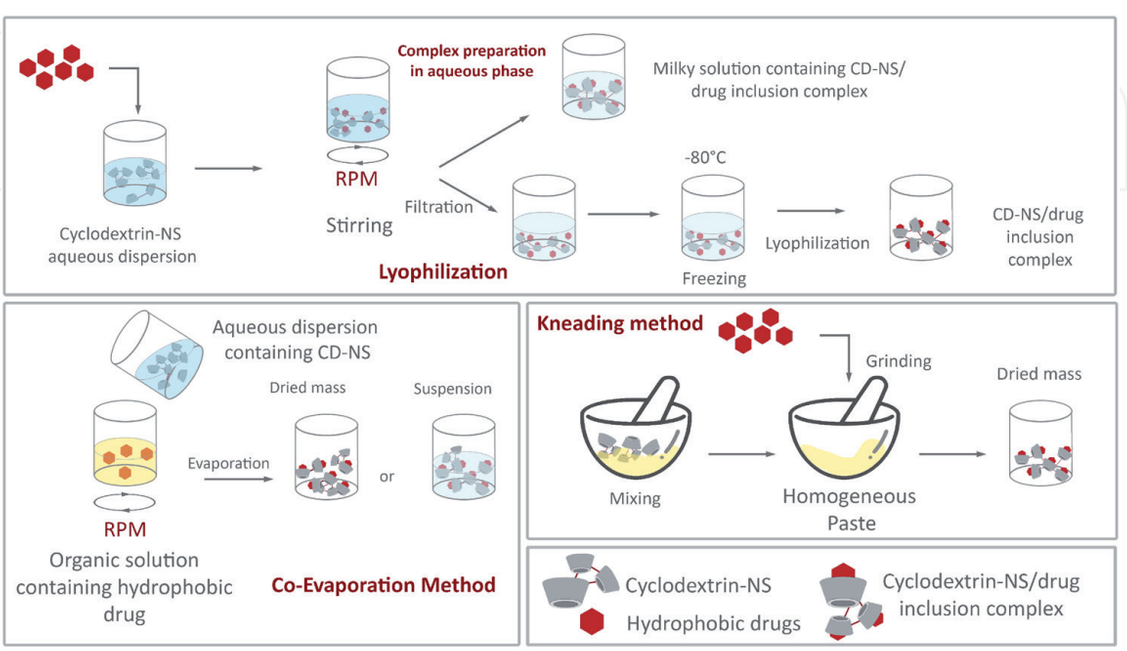

Figure 2.
Different methods to prepare inclusion complexes.

4.2.2 Fourier-transform infra-red (FTIR)

This technique is usually used in solid complexes, generally in the range of 400–4000 cm^{-1}, although it depends on the studied drug [58, 60]. Changes in the characteristics bands of the guest molecule or shifts in the wavenumber can indicate the formation of the complex. In addition, the same principle can be used to follow the CD-NS synthesis.

4.2.3 Nuclear magnetic resonance (NMR) spectroscopy

NMR is one of the most useful procedures to obtain complete analytical information of the CD-NS and the complex formed. An alteration in the chemical shift of the protons occurs when the drug enters the CD-NS providing specific information about the orientation of the guest molecule inside the cavity.

4.2.4 Thermogravimetric analysis (TGA)

TGA determines the changes of weight to temperature increases. The comparison of the weight loss profile of pure components, physical mixture, and the complex shows differences correlatives to the complex formation. A stage on TGA around 300°C is found in CD-NS due to CD decomposition [59].

4.2.5 Differential scanning calorimetry (DSC)

It can provide detailed information about their physical and energetic properties. The comparison of the thermal curves of single components, their physical mixture, and the presumed inclusion compound ought to provide insight into modifications and interactions due to the formation of the inclusion complex. The change that occurs in the fusion point of the guest molecule is usually hiding by the complex formation, while it remains in the physical mixture. This, and several modifications in the shape and temperature peak of the CD dehydration and/or with the disappearance of the drug melting peak among others, are proves of the complexation.

5. Applications in smart drug delivery

5.1 Improving solubility and controlled release of drugs

5.1.1 CD-based polyurethane NSs

Another study showed the capability of CD polyurethane to reduce the levels of natural product contaminants, particularly, Ochratoxin A (OTA) from spiked solutions between 1 and 10 μgL-1 [61]. Following the attracted considerable interest that these polymers have shown in their use for water purification systems [62] and drug delivery [63], there were further done several chemical modifications on the CD NSs. Even though the modified CD NSs were used to enhance the properties and usefulness of CD NSs, their characterization at the molecular level remained a challenge. Therefore, a study described the structural characterization at the molecular level of both, native CD nanosponge polyurethanes and bionanosponge polyurethane cyclodextrin nanocomposite (pMWCNT-CD/Ag-TiO2) showing a great antibacterial and antifungal activity. The greatest antimicrobial activities were in the case of the developed polyurethane nanocomposite (pMWCNT-CD/

Ag-TiO2). Consequently, it was concluded that this developed synthesis can be considered an active antimicrobial compound [64]. Another potential application of CD polyurethane polymer is as immobilization supports in enzyme catalysis. The lipase was immobilized into the aforementioned polymers via physisorption. It is observed an improvement in the stability and catalytic activity of lipase, knowing that the enzymes are generally unstable, insoluble in organic solvents, and sensitive. Accordingly, this study presented the chance to prepare immobilized biocatalysts with tunable catalytic activities attributed to the alteration of reaction conditions [65]. Further research was focused on the novel polyurethanes containing simultaneously β-cyclodextrin (β-CD), β-glycerophosphate groups, and hexamethylene-diisocyanate (HDI). This polymer developed was used to complex the delivering therapeutic agents such as antibiotic ciprofloxacin. It was observed an improvement of the drug release in the case of the drug-polymers complexation than that of the free drug [63].

5.1.2 CD-based polycarbonate NSs

CD-based polycarbonate NSs synthesized using carbonyldiimidazole (CDI) showed antimicrobial activity against various microorganisms such as *E. coli*, *S. aureus*, *P. aeruginosa*, *S. typhi*, *C. albicans*, and Clostridia, when compared with Ciprofloxacin that was used as a standard drug. The formulations were prepared by polymer condensation, and interfacial phenomenon, and were effective for 6 months at a condition of 40°C and 75% of relative humidity [66]. This type of CD NSs was further used to deliver and increase the activity of several anticancer drugs such as paclitaxel [67], bortezomib [68], flutamide [69], tamoxifen [70], etc. Following their high potential to entrap a variety of molecules, the β-CD/CDI NSs were also used to deliver and improve the solubility and dissolution of paliperidone, an antipsychotic drug for the treatment of schizophrenia [71]. Further, rilpivirine is used for the treatment of HIV infection but has low aqueous solubility. Therefore, the β-CD/CDI NSs presented a strategy to improve this drawback and also the bioavailability and dissolution rate [72]. The antioxidant activity of kynurenic acid, an endogenous substance, was improved by loading it in β-CD/CDI NSs. The higher antioxidant activity was observed because of the increment in solubilization of kynurenic acid [60]. CD-based polycarbonate NSs synthesized using diphenyl carbonate (DPC) were used to overcome the poor solubility and stability of Babchi oil that is known for possessing numerous activities such as antifungal, antibacterial, antiviral, antitumor, antioxidant, etc. [73]. Further, the bioactive properties of the piperine, an alkaloid with anti-microbial, anti-inflammatory, anti-cancer properties, etc., were protected by the β-CD/DPC NSs [74]. This type of NSs exhibited complexing ability toward nifedipine, as an oral calcium channel blocking agent that is used to treat angina pectoris and hypertension. It was observed an improvement in the oral solubility of nifedipine after its incorporation into NSs [75].

5.1.3 CD-based polyester NSs

CD-based Ester NSs synthesized with pyromellitic dianhydride (PMDA) are well known for delivering, enhancing solubility, and preventing the degradation of various drugs such as Curcumin [76], Insulin [20], Resveratrol [77], Erlotinib hydrochloride [78], among others. Ethylenediaminetetraacetic dianhydride (EDTA) is another cross-linker to synthesize ester CD NSs. Based on HRMAS probe-heads in a high-resolution NMR spectrometer on the transport properties of Ibuprofen sodium salt (IP), it was found that these NSs can be utilized for the rational design of smart systems for drug delivery and controlled release [79]. The

various applications of CD-based polyester NSs ranging from the environment to pharmacy, chemistry, agriculture, gene delivery, cosmetics, biocatalysis, brought to a detailed study on their cross-linking density. Being a very challenging task, it presented the effect of cross-linking density on β-CD NSs physicochemical properties. Flory-Rehner theory and rheology enabled the authors to understand the correlation between the structural features of NSs and their physicochemical properties, which is a key requirement for future applications [34].

5.2 Last generations of NSs for selected target drug delivery

Stimuli-responsive NSs represent the third generation, polymers that have been designed to modulate their behavior according to the surrounding environment. In this case, changes in the chemical structure of the material were reported to be triggered by pH, temperature gradients, or oxidative/reducing conditions. This feature was exploited for studying the targeted release of drugs, changes in color, and permeability. The use of glutathione (GSH) bioresponsive CD-NS was proposed as the system to deliver anticancer drugs or bioactive compounds [80–83]. This is because GSH is 100 to 1000 times higher inside cells than that in the extracellular fluids and circulation. Indeed, in cancer cells, this concentration is almost higher being a good system for target drug delivery [84]. Different drugs such as doxorubicin [81] or bioactive compounds such as resveratrol [82] were tested showing a well-targeted drug delivery, and therefore is considered a promising therapy. In addition, the linkage of cholesterol was proposed as a good procedure for increase the targeted drug delivery of doxorubicin-loaded CD-NS [85].

Lastly, molecularly imprinted cyclodextrin-based polymers (**Figure 3**) define the fourth generation of NSs. Molecular imprinting represents a specific approach of inducing molecular recognition features to a three-dimensional polymer. This property can be achieved as a result of the presence of a template molecule introduced during synthesis. The template molecule after being removed from the polymer matrix leaves size-complementary vacancies, enabling the network to display high selectivity and affinity toward the chosen template. Eventually, molecularly

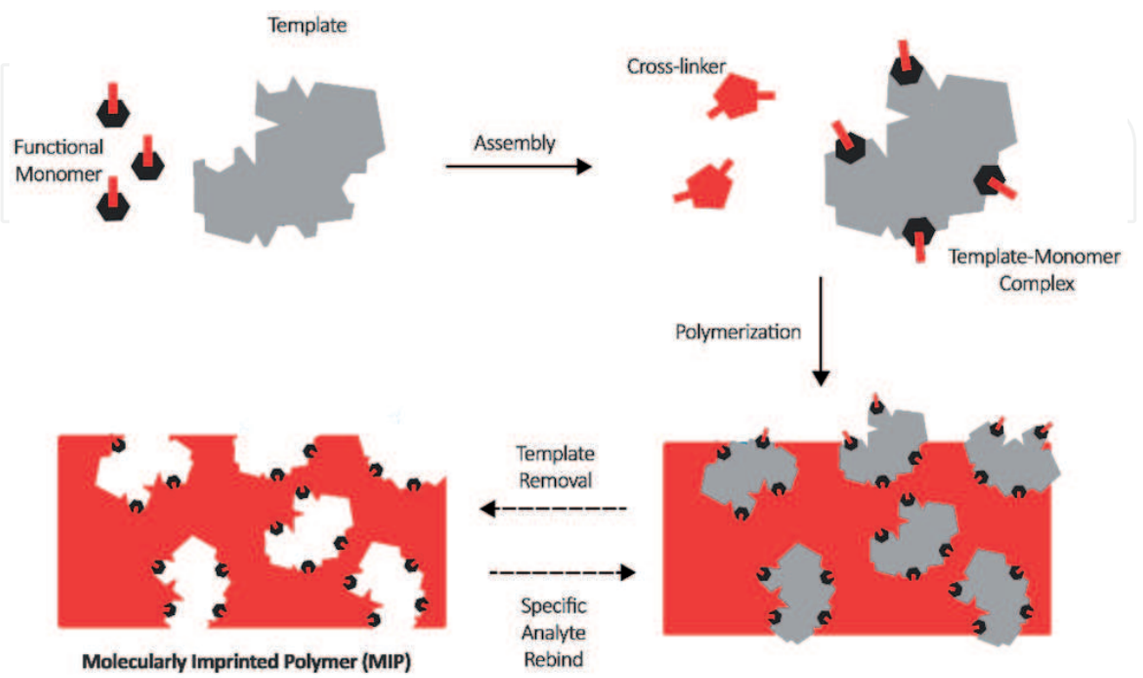

Figure 3.
Schematic synthesis of molecularly imprinted NSs.

Drug	Nanocarrier prepared	Outcome	References
Controlled Drug Delivery			
CD-based Polyurethane NSs			
Erythromycin, vancomycin, and rifampicin	βCD/HDI	*Long-term sustained release of antibiotics.*	[89]
Mitomycin C	ϒCD/HDI	*Prolonged anti-proliferative drug release.*	[90]
CD-based Polycarbonate NSs			
Curcumin	βCD/DMC	*Increased anti-cancer drug solubility, and prolonged release.*	[91]
Norfloxacin	βCD/DPC	*Enhanced anti-bacterial drug permeability.*	[92]
Tamoxifen	βCD/CDI	*Increased anti-cancer drug solubility, and bioavailability.*	[93]
Resveratrol	βCD/CDI	*Increased the permeation, stability, and cytotoxicity against cancer*	[94]
Camptothecin	βCD/DPC	*Increased anti-cancer drug stability, and prolonged release.*	[95]
Acyclovir	βCD/CDI	*Enhanced anti-viral drug loading, and prolonged release.*	[96]
Telmisartan	βCD/DPC	*Enhanced anti-hypertensive drug solubility, improved bioavailability, and prolonged release.*	[97]
Babchi Oil	βCD/DPC	*Enhanced anti-bacterial essential oil solubility, photo-stability, and safety.*	[98]
Rilpivirine	βCD/CDI; PMDA; DPC	*Enhanced anti-viral drug solubility, and bioavailability.*	[99, 100]
Paclitaxel	βCD/CDI	*Enhanced anti-cancer drug solubility, and pharmacological effect.*	[101]
Sulfamethoxazole	βCD/CDI	*Enhanced anti-bacterial drug solubility.*	[102]
Quercetin	βCD/DPC	*Enhanced anti-oxidative drug dissolution, and prolonged release.*	[103]
Melatonin	βCD/CDI	*Controlled drug release through skin.*	[104]
Kynurenic acid	βCD/CDI	*Enhanced anti-oxidant potential of kynurenic acid.*	[105]
D-Limonene	βCD/DPC	*Enhanced anti-bacterial potential of the drug.*	[106]
Azelaic acid	βCD/DPC	*Enhanced drug solubility, and its depigmenting action on the skin via antioxidant, and antityrosinase effect.*	[107]
Chrysin	βCD/DPC	*Enhanced drug solubility, in-vitro antioxidant, and antitumoral activity.*	[108]
Paliperidone	βCD/CDI	*Enhanced antipsychotic drug solubility.*	[109]

Drug	Nanocarrier prepared	Outcome	References
Ferulic acid	βCD/DPC	*Enhanced drug solubility, and bioavailability for the local therapy of vessels wall.*	[110]
Flutamide	βCD/CDI	*Enhanced anti-cancer drug dissolution rate.*	[111]
Griseofulvin	βCD/DPC	*Enhanced antifungal oral drug bioavailability, and improved dissolution rate.*	[112]
CD-based Polyester NSs			
Insulin	βCD/PMDA	*Enhanced anti-diabetic drug stability, and prolonged release.*	[113]
Imiquimod	βCD/PMDA	*Enhanced drug aqueous solubility, and skin permeation capability.*	[114]
Acetyl salicylic acid	βCD/PMDA	*Enhanced anti-inflammatory drug stability, and prolonged release.*	[115]
Doxorubicin	βCD/PMDA	*Improved anti-cancer effectiveness.*	[116]
Meloxicam	βCD/PMDA	*Increased anti-inflammatory drug solubility, and wettability.*	[117]
Targeted Drug Delivery			
DB103 - [2-(3, 4-dimethoxyphenyl)-3-phenyl-4H-pyrido]	βCD/DPC	*Enhanced drug solubility, and bioavailability for the local therapy of vessels wall.*	[118]
L-DOPA	βCD/CDI; PMDA (Molecularly imprinted cyclodextrin-based polymers)	*Enhanced drug solubility, and prolonged release.*	[119]
Doxorubicin	Tripeptide glutathione (GSH) nanosponge (NS)	*Enhanced antioxidant potential, and it is useful in targeting chemo-resistant tumors.*	[120]
Strigolactones	GSH/pH-NS	*Enhanced anticancer activity.*	[121]
Erlotinib hydrochloride (ETB)	GSH-NS	*Exhibited excellent drug uptake, extended drug release, in-vivo antitumor efficacy, and biodistribution.*	[122]

βCD, Beta Cyclodextrin; ϒCD, Gama Cyclodextrin; HDI, Hexamethylene diisocyanate; CDI, Carbonyldiimidazole; DMC, Dimethyl Carbonate; DPC, Diphenyl carbonate; PMDA, Pyromellitic Dianhydride.

Table 2.
The use of cyclodextrin based nanosponges in drug delivery.

imprinted CD-NSs are studied as suitable material to develop biosensors, drug delivery systems, catalysts, or synthetic antibody mimics [86–88]. A good example of this application is the L-Dopa as a novel possibility to treat Parkinson's Disease. The molecularly imprinted CD-NSs showed a slower and more prolonged release profile than the non-imprinted NSs, indicating the good capacity to better complex L-Dopa than non-imprinted NS. The use of CDs in controlled and targeted drug delivery is shown in **Table 2**.

6. Conclusions

CD-NSs are demonstrated to be safe, cheap, and biocompatible polymers. Consequently, several authors are focused on this field recently achieving novel applications. This chapter summarized the general information that will guide the advanced research to investigate the CD-NSs. Information about the routes of administration, synthesis protocols, recommendations, classifications, and applications of the novel synthesized materials, with special attention to targeted drug delivery, are mostly collected. It is shown the ability of CD-NSs to entrap drugs and to control their release from the matrix which can be modulated by different physicochemical agents.

As a remark, CD-NS is a good promise to improve the current problems in drug formulations and open novel strategies for drug delivery that identify the light in the future.

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Conflict of interest

The authors declare no conflict of interest.

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