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ORIGINAL RESEARCH ARTICLE

Natural and synthetic cavitands: Challenges in chemistry and pharmaceutical technology

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ABSTRACT

Supramolecular chemistry involves non-covalent interactions and specific molecular recognition of molecules/analytes by host molecules or supramolecules. These events are present in synthesis, catalysis, chiral separations, design of sensors, cell signaling processes and drug transport by carriers. The typical behavior of supramolecules is derived from their ability to build well-structured self-assembled and self-organized entities. Cavitands are a particular group of supramolecules possessing a cavity capable to include a variety of compounds thanks to host-guest non-covalent interactions developed among cavitands and analytes. Some typical cavitands are crown ethers, calixarenes, cucurbiturils, porphyrins and cyclodextrins. The two latter families are natural product cavitands that are generally considered models for molecular recognition of cations and organic and inorganic guest molecules, being attractive host molecules from the sustainability point of view. The natural cyclodextrins (α, β and γ-cd) are obtained with reasonable cost by enzymatic treatment of starch under adequate temperature conditions. They are profusely used in pharmaceutical, food and cosmetic industries due to their very low toxicity and side effects. This review is focused on the relevance andapplications of cyclodextrins in pharmaceuticaltechnology for their ability to increase solubility and stabilize drug molecules, thereby enhancing their bioavailability. The association of cyclodextrins with diverse nanostructured materials, i.e., carbon nanotubes, magnetic nanoparticles, silica and molecularly imprinted polymers, allows to synergize the properties of cyclodextrins and these nanostructured materials to reach highly specific molecular recognition of analytes. The exploitation of these benefits for analytical sample pre-treatment and chiral chromatographic separations are described. The use of cyclodextrins as mobile phases additives in hplc provides interesting results for green and sustainable chromatographic separations. Polymers incorporating cyclodextrins show exceptional adsorption properties for retaining toxic compounds and persistent organic pollutants from soils and water samples, allowing satisfactory recoveries of these environmental samples according to the stockholm convection principles.

Keywords: cavitands; cyclodextrins; drugs bioavailability; analytical chemistry; analytical sample pretreatment; chromatography; sustainable chemistry

1. Introduction

Molecular recognition is the basis of supramolecular chemistry, facilitating the selective combination of specific molecules. Pedersen, Cram and Lehn were awarded the nobel prize in chemistry in 1987 for the development of the concept of “supramolecular chemistry”, which is defined as “chemistry beyond molecules”,

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a somewhat mysterious expression because it refers to the beyond. If we consider that supramolecular chemistry deals with the study of supramolecules, we will define these as large and complex entities formed by other molecules that interact with each other through hydrogen bonds, hydrophobic interactions and coordination bonds, which, being weak, when numerous produce robust entities. This phenomenon is called the "gulliver effect", by analogy with the use of many tiny ropes to bind a giant when the protagonist is captured off the coast of lilliput. The study of non-covalent interactions and their effectiveness in the stability of macromolecular entities has been and is crucial in the various fields of chemistry[1]. The experiences of molecular recognition of cations by crown ethers, the molecular recognition between "host-guest" molecules demonstrating that certain molecules can "accommodate" others was proposed by cram and later in 1978 lehn proposed the term supramolecular chemistry. Thus, enzymes act as "host" and molecularly recognize their "guest" substrates giving rise to a specific reaction in an enzyme pocket. In 2016, sauvage, stoddardt and feringa received the nobel prize in chemistry for their work on the design and synthesis of molecular machines able to organize and self-assemble autonomously mediated by light or electrons.

The supramolecular entities possess qualities and functions that are different from the starting molecules and that respond to much more than the sum of the properties of the individual molecules. In sports terms, we can liken supramolecules to sports teams, and thus a good team is defined by the fact that it is much more than the sum of its individual components[2,3]. Supramolecular chemistry is the basis for numerous applications in synthesis, catalysis, chiral separations, sensing, signaling, drug delivery and transport. Certain supramolecules can combine and self-assemble giving rise to entities with unique geometry and topology (fullerenes, carbon nanotubes, rotaxanes and catenanes, ...) And thus a small molecule included in a nanotube such as the one formed by cyclodextrins can undergo cis-trans isomerization by absorption of energy associated with electromagnetic radiation in the 600 nm region (nir) under mild conditions that prevent its degradation by photochemical means.

2. Cavitandos

Cavitands are called the set of supramolecules that have a central cavity capable of recognizing and housing a variety of species, from cations, such as crown ethers, which are modeled on a cavitand of natural origin such as porphyrins, to the most sophisticated carbon nanotubes. Cyclodextrins[4] are also of natural origin and, using them as a model, calixarenes and cucurbiturils[5] have been designed, so called because of their pumpkin shape, which are formed by glycoluryl units linked by methylene bridges. Cyclodextrins have proven useful in the encapsulation of drugs such as camptothecin[6]. **Figure 1** shows different examples of cyclodextrin cavitands associated with polymers, forming nanosponges as well as other nanostructured materials, such as carbon nanotubes[7]. In analogy with crown ethers, azacryptands are particularly useful cavitands for anion recognition[8].

One of the challenges today is chiral discrimination, since enantiomers have identical physical and physicochemical properties but differ in their reactivity and interaction with chiral biological entities, such as proteins (e.g., Ry and s-limonene present, respectively, in orange and lemon condition different aromas). One of the most relevant applications of cavitands is the chiral recognition of organic compounds because the spatial arrangement of the molecules leads to different affinity for the host molecules. Thus, cyclodextrins have found great utility as components of stationary or mobile phases in various analytical separation techniques (liquid, gas, supercritical fluid chromatography and capillary electrophoresis)[9,10]. Likewise, some calixarene derivatives have been successfully used for the chiral discrimination of the enantiomers of mandelic acid[11].

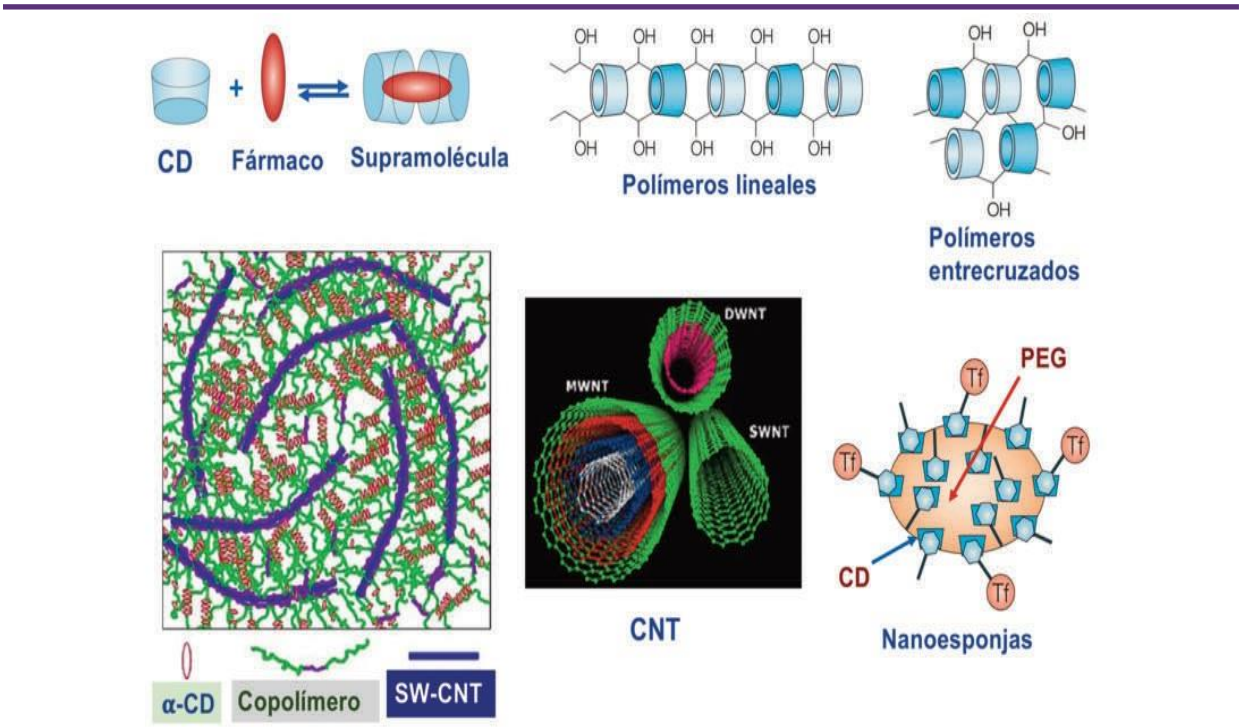

Figure 1. Encapsulation of drugs by cyclodextrins (cds). Cd polymers forming nanosponges. Symbiosis of nanostructured materials and cds. Peg: polyethylene glycol. Cnt: carbon nanotubes. Sw-cnt: coated wall carbon nanotubes. Fármaco: Drug; Supramolécula: Supramolecule; Polímeros lineales: Linear polymers; Polímeros entrecruzados: Cross-linked polymers; Copolímero: Copolymer; Nanoesponjas: Nanosponges.

3. Cyclodextrins

Cyclodextrins (cds) offer numerous advantages compared to other cavitands, as they are natural products, obtained from starch, which makes them very attractive from the point of view of sustainable chemistry. They are produced on an industrial scale through a relatively simple enzymatic process and at a reasonable price. The side or toxic effects that may occur are practically non-existent, which is why they are used in the pharmaceutical, cosmetic and food industries. They are capable of encapsulating, isolating and compartmentalizing a wide variety of compounds, since there are different sizes easily adaptable to the requirements of the compounds to be included[12–14]. All this makes them attractive in many different fields of science, from pharmaceutical technology, or chemistry, to nanotechnology.

4. Cyclodextrins in pharmaceutical technology

One of the most representative aspects of the use of cyclodextrins in the industry is their application in pharmaceutical technology to improve the solubility and stability of drugs, which directly leads to an improvement in their efficacy through an increase in bioavailability because they are capable of transferring the drugs to their site of action without alterations, which leads to an increase in the plasma concentrations of the active principles[4,15,16]. The monograph corresponding to the β-cd is part of pharmacopoeias such as the european, united states and japanese pharmacopoeias. **Tables 1** and **2** show, by way of example, some of the active principles that are formulated with various cds to improve their technological and biopharmaceutical properties. Many active ingredients have reduced pharmacological effectiveness due to poor chemical or photochemical stability[17]. The inclusion in the cyclodextrin cavities isolates some molecules from others and individualizes them, thus preventing certain undesired reactions and achieving an improvement in the stability of the active ingredients.

Table 1. Active ingredients formulated with cyclodextrins and listed in various pharmacopoeias.

Drug/pharmacological group	Cyclodextrin
Barbiturates	B-cyclodextrin .
Vitamin d3	B-cyclodextrin .
Digitalis glycosides	Γ-cyclodextrin .
Spironolactone	B-cyclodextrin and γ-cyclodextrin.
Diazepam	Γ-cyclodextrin .
Acetohexamide	B-cyclodextrin .
Ketoprofen	Trimethyl-β-cyclodextrin and β-cyclodextrin
Phenytoin	B-cyclodextrin .
Flurbiprofen	B-cyclodextrin .
Hydrocortisone	2-hydroxypropyl-β-cyclodextrin

Table 2. Improved drug stability as a consequence of the inclusion of cyclodextrins (cds) in the cavities. The percentage of unchanged active ingredient after irradiation time is shown (in parentheses). Comparison of the percentages of active ingredients included in cds in relation to the free drug.

Active ingredient	Without cd	B-cd	Dimethyl-β-cd	Trimethyl-β-cd
Nifedipine (6 h)	71.1	56.0	74.2	59.0
Hydrochlorothiazide (6 h)	62.0	79.0	44.2	38.0
Pyridoxine hydrochloride (6 h)	37.4	74.3	79.2	88.0
Furosemide (2 h)	68.1	87.2	98.0	99.2
Clofibrate (6 h)	74.0	88.2	97.3	80.0
Retinyl acetate (80 min)	42.0	67.0	45.0	64.1
Retinoic acid (60 min)	31.8	44.3	54.6	65.8*
Nitroglycerin (8 h)	99.0	99.0	99.2	99.0

*corresponds to 2-hydroxypropyl-β-cd instead of trimethyl β-cd.

This is the case of retinoids, compounds susceptible to photochemical isomerization. Our group has shown that, both in the case of retinal and retinoic acid, there is a very beneficial effect on the stabilization of the biologically active forms, the all-trans isomers. The all-trans derivatives see very difficult isomerization by irradiation, when they are included in β-cd and its derivatives 2-hydroxypropyl-β-cd (hp β-cd), 2,3 di-o-methyl-β-cd (dmβ-cd) and 2,3,6-tri-o-methyl-β-cd (tm β-cd). Thus while after 60 minutes of irradiation in ethanol of the all-trans retinoic acid is transformed into the different cisderivatives leaving only 31% active form, for retinoic acid including hp β-cd it remains as all-trans form with a percentage of 68% (**Figure 2**). All the cyclodextrins studied provide significant protection, so that irradiation does not transform even 50% of the all-trans isomer[18].

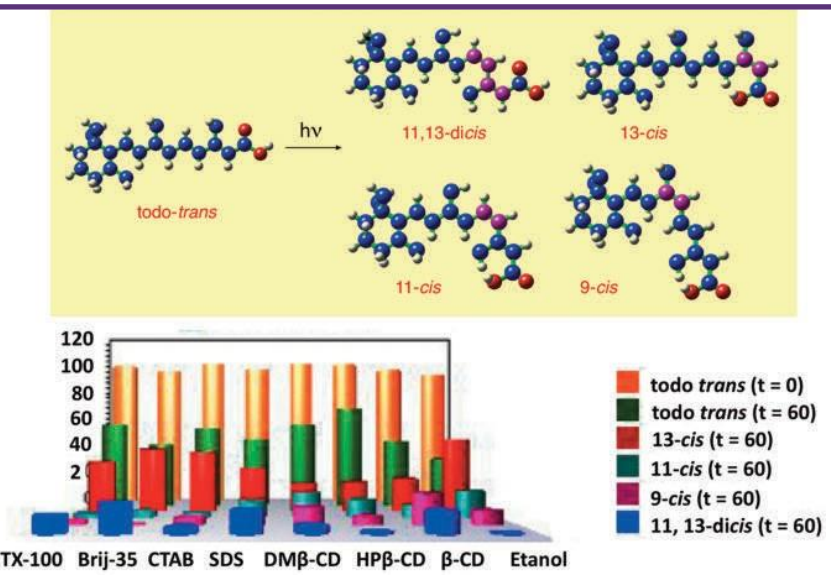

Figure 2. Stabilization of drugs by nanoencapsulation in cds. Variation of the ratio of all-trans-retinoic acid before and after photochemical isomerization. Percentage of retinoic acid isomers produced after 60 min of irradiation in different environments: ethanol, surfactants (triton x-100, brij-35, ctab and sds) and cyclodextrins. Quantification was carried out by hplc-uv[18]. Etanol: Ethanol; todo trans: all trans.

Cyclodextrins have good water solubility thanks to the hydrophilic groups on the outside; however, the inside of the cavity is hydrophobic, thus allowing drugs with low water solubility to be accommodated. Therefore, the inclusion of drugs with increased solubility leads to better distribution and bioavailability of the active ingredients. In this sense, cyclodextrins chemically modified with methyl and hydroxypropyl groups are also available that contribute to increase water solubility with respect to natural cds, and in this aspect, the degree of substitution plays an important role in the increase of water solubility as well as in the increase in size of the cd cavity[19]. Among the examples of solubility enhancement we will comment on our own experience with improved solubilization of the topoisomerase inhibitor antitumor drugs, camptothecin and luotonin a. Both experience considerable increase in solubility. Both experience a considerable increase in water solubility in the presence of β-cd and hp β-cd. One of the luotonin a derivatives, more hydrophobic due to the nature of the substituents, has an even greater enhancement in solubility. The methodology developed for these solubility assays are in accordance with established principles of sustainable chemistry and furthermore it was confirmed by mass spectrometry that the majority complexes are of 1:1 stoichiometry (**Figure 3**) for both cpt and luotonin a[20].

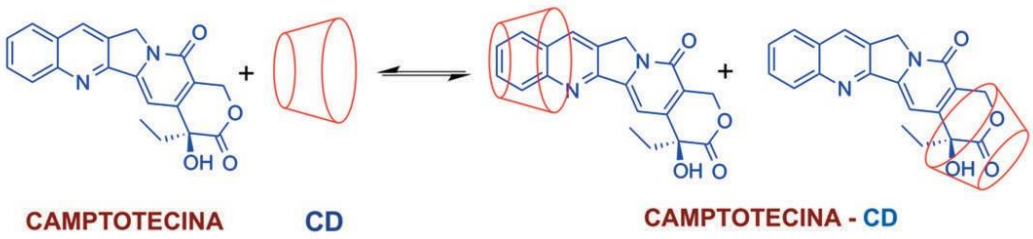

Figure 3. Inclusion complexes of the antitumor camptothecin and modified β-cd (20). Camptotecina: Camptotecin.

5. Cyclodextrins and analytical pretreatment

The sample pretreatment stage is still the most laborious and the most difficult in terms of automation and reproducibility. The choice of a sample preparation and treatment procedure is crucial for the reliability of the analysis results[21–23].

The materials that integrate extractant support to retain analytes can be grouped into three main groups:

1) nanostructured materials, including carbon nanotubes and magnetic nanoparticles.
2) adsorbent materials based on molecular recognition, among which printed polymers and immunosorbents stand out.
3) organic metal-composite networks, a type of hybrid material consisting of organic and inorganic elements with high porosity and adjustable polarity[24].

Thanks to the highly selective molecular recognition of the cyclodextrin cavities towards very diverse analytes, these cavitands have been successfully employed through the functionalization of the adsorbent surface with cds in such a way that they retain certain compounds separating them from the rest of the sample components.

Among the different analytical methodologies for the pre-concentration, clean-up and purification of analytes, solid-phase extraction (spe) stands out for its efficiency and robustness. In the 1990s, solid-phase microextraction techniques (spme) were developed with the main objective of reducing time and solvent consumption while maintaining extraction efficiency[25]. Although the configurations and disposition of the extractant materials in both analytical methodologies are very varied, being out of this context due to their extension; however, we will focus on some general aspects common to both methodologies.

5.1. Purification and extraction using cyclodextrin polymers

These methodologies are based on the preparation of nanosponges consisting of cds and designed with the purpose of retaining compounds or analytes. The polymerization of cds is one of the first resources for the efficient extraction of multiple analytes. The extraction efficiency is a function of the stability of the complexes formed as well as the loading capacity of the support materials used.

Nanosponges (**Figure 1**) are a new class of polymers with a high number of hyper cross-linked bonds formed from colloidal structures that house cavitands with cavities of a few nanometers in internal diameter[26,27]. Cyclodextrins are one of the cavitands used with great success in the synthesis of nanosponges because of their efficiency in the extraction of numerous analytes and in drug delivery[28].

5.2. Purification and extraction using nanostructured materials involving cyclodextrins

A procedure widely used for its simplicity is the use of magnetic particles. These ferric oxide particles can be functionalized by means of a suitable treatment (propylethylsiloxane), leaving a dense core of magnetite covered by a silica surface functionalized with amino groups to which the cyclodextrins will be bonded in the next step of the synthesis. The functionalized particles coated with cds are suspended in the aqueous medium to which the biological sample to be analyzed (blood, plasma, urine, etc.). Is added, so that only those analytes that are suitable for their size and polarity are included in the cds. After the necessary time has elapsed, a magnetic field is applied in such a way that all the magnetic particles, together with the extracted analytes, go to the bottom of the beaker and can be easily separated from the rest of the sample (**Figure 4A**).

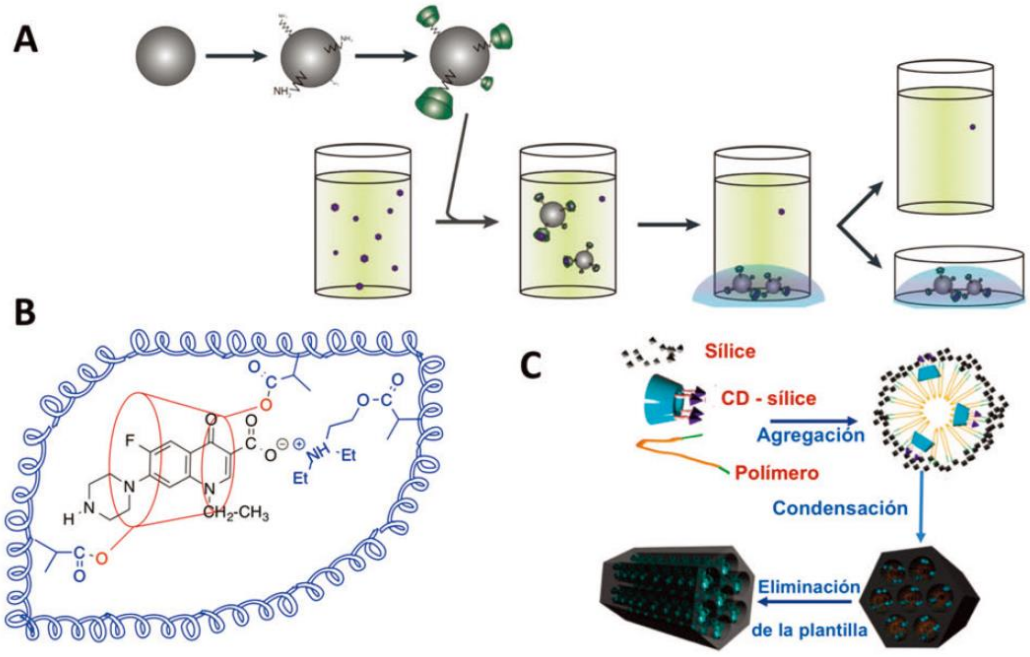

Figure 4. Cds as a basis for analytical sample pretreatment systems: **(A)** magnetic nanoparticles modified with cds for efficient and selective extraction of analytes in biological samples; **(B)** printed polymers using cds for selective extraction of antibiotics (quinolones); **(C)** printed polymers using cds and other nanostructured materials with high extraction capacity. Sílice: Silica; Agregacion: Aggregation; Polímero: Polymer; Condensacíon: Condensation; Eliminación: Disposal; de la plantilla: of the staff

The use of magnetic nanoparticles has several advantages over traditional extraction methods, as the synthesis and functionalization of magnetic particles is relatively inexpensive. The magnetite and iron oxides used to obtain the central core is inexpensive and commercially available, and the porous material (silica) that is often used to coat the magnetic particles is also inexpensive. The separation of the magnetic particles that have trapped the active ingredients is simple, and requires no instrumentation, simply applying a magnetic field to attract the particles to the bottom, so the separation is fast and efficient. Moreover, the extraction efficiency of the target compounds by the cyclodextrins is high, obtaining a high extraction efficiency.

This procedure has been successfully used for the extraction of benzodiazepines from blood samples[29] and 5-hydroxy-3-indolacetic acid as a tumor biomarker in urine samples[30].

5.3. Purification and extraction using printed polymers

The idea of trapping compounds in a complementary and empty matrix was proposed by wulff and sarhan in 1972, but it was not until the 1990s that sellergren described the potential of these materials as adsorbents for spe and began to use them by synthesizing adsorbent materials based on this idea[21,31]. If we think that in a fossil we can identify a plant species, because only it is capable of leaving that fingerprint, we have a good simile to imagine the good selectivity of this type of materials aimed at the molecular recognition of specific analytes. Taking as a template the target compound to be analyzed, it will be bound by non-covalent interactions (dipole-dipole, hydrogen bonds, electrostatic interactions, ...). To a minimum of three functional monomers capable of molecularly recognizing key points in the target compound. After a polymerization process in which cross-linked bonds are formed, a solid adsorbent matrix is obtained from which, with a suitable washing procedure, the target compound that has acted as a template is extracted. This leaves the printed polymer free and available to recognize and trap the analyte molecules analogous to the template and present in the test samples. Printed polymers have advantages over other adsorbent materials, such as their selectivity and robustness accompanied by high chemical and thermal stability. These characteristics are not found in adsorbents based on proteins, antibodies and nucleic acids, which, although they have high selectivity,

are nevertheless quite labile[24].

An imprinted polymer employing β-cd for the extraction of fluoroquinolone-derived antibiotics (norfloxacin) from water samples is presented in **Figure 4B**[32]. Printed polymers involving cyclodextrins as an essential part of the extractant template possess high selectivity and high extraction yield compared to other materials and have been successfully employed in the extraction of pharmaceuticals, pesticides, hormones, and plastics additives among other examples[33]. A summary of examples of solid-phase extractions and solid-phase micro-extractions using adsorbent materials with cds, either in the form of magnetic particles, nanostructured materials or printed polymers, is given in **Table 3**.

Table 3. Examples of the use of polymers and nanostructured materials using cyclodextrins for analytical pretreatment of samples.

Analito	Matrix/sample	Nanostructured polymer/material	Cyclodextrin	Removal technique	Reference
Benzodiazepines	Plasma and whole blood	Magnetic fe3o4 particles, conjugated to 3-aminopropyltriethoxysilane, to bind β-cd	*B-cd*	Solid phase extraction (spe)	29
5-hydroxy-3-indole acetic acid	Fortified urine samples	Magnetic particles, silica-coated with subsequent β-cd binding.	*B-cd*	Solid phase extraction (spe)	30
Sulfonamides	Meat products	Magnetic fe2o3 particles, coated with au functionalized to bind β-cd via thiol groups.	*B-cd*	Solid phase extraction (spe) coupled to hplc	36
Malachite green, violet crystal	Water, textile industry waste	Magnetic fe3o4 particles coated with functionalized sio2 and bonded to the β-cd ester.	*B-cd*	Solid phase extraction (spe) and hplc-uv	37
Insecticides derived from benzoylurea	Honey	Atapulgite (magnesium aluminosilicate) modified with β-cd	*B-cd*	Solid phase microextraction (spme)	38
Polycyclic aromatic hydrocarbons (pah)	River waters	*B-cd* bonded to carbon nanotubes attached to magnetic iron oxide nanoparticles.	*B-cd*	Solid phase microextraction (spme)	39
Phytohormones	Tomato varieties	*B-cd* supported by dispersion over reduced graphene oxide and fe3o4	*B-cd*	Solid phase extraction (spe) coupled to hplc	40
Bright blue	Carbonated beverages, juices, chewing gum, chewing gum, etc.	Polymer of β-cd by reaction with epichlorohydrin.	*B-cd*	Solid phase extraction (spe)	41
Phenolic compounds	River water, sea water, waste water, domestic water	*B-cd* bonded to native silica	*B-cd*	Solid phase extraction (spe) coupled to liquid phase micro extraction (lpme)	42
Organic micropollutants	Water samples	Porous polymer of β-cd copolymerized with bifunctional catechols and aliphatic alkoxides.	*B-cd*	-	43
Bilirubin	Human serum	Printed polymer based on hexane1,6-diisocyanate	*B-cd*	Printed polymers (mip) for solid phase extraction (spe)	44
Phthalate	Plastics	Allyl-β-cd and methacrylic acid	*B-cd*	Printed polymers (mip)	45
Pyrethroid insecticides	Food and water	2,4-di-isocyanate toluene	*B-cd*	Printed polymers (mip)	46
Dichlorophenol		Methacrylic acid functionalized with β-cd and trimethylolpropane trimethacrylate.	*B-cd*	Printed polymers (mip)	47

6. Cyclodextrins in chromatographic separations

The possibilities of chemical substitution of the primary and secondary hydroxyls of cyclodextrins as well as the use of natural β- and γ-cyclodextrin derivatives as starting cavitands provide a high capacity for molecular recognition that is remarkably selective and accommodating or modifiable depending on the characteristics of the analytes to be separated[34].

Substitution with different functional groups, either polar or of low polarity, allows multiple intermolecular interactions of electrostatic type, ionic pairs, dipole-dipole, hydrogen bridges or $\pi\pi$-stacking[35].

6.1. Cyclodextrins in chiral separations

Chiral chromatographic separations are one of the challenges of analytical chromatography for the resolution of chiral mixtures in the pharmaceutical, biotechnological and food industries. Chiral separations by liquid chromatography have increased exponentially due to their robustness as an analytical technique and their wide application in quantitative analysis. They are also used with great success in large-scale and intermediate-scale preparative separations in industry. The immobilization of different cyclodextrin derivatives on the surface of silica particles[36] through ether, urea or amino bonds gives rise to chiral stationary phases (**Figure 5**) that exhibit very high enantioselectivity and adequate chemical stability[37,38].

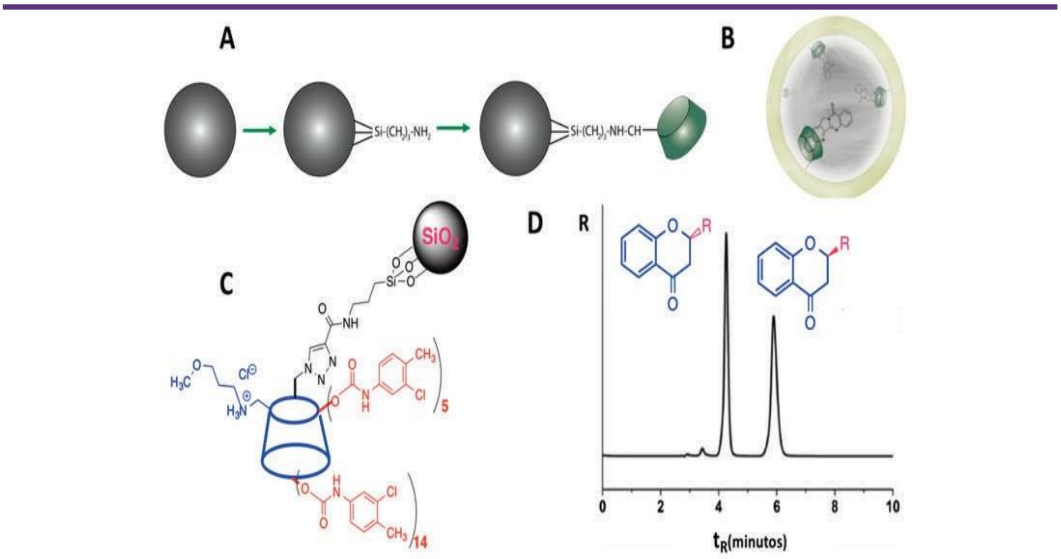

Figure 5. Chiral stationary phases (csp) for analyte separation by liquid chromatography (hplc). **(A)** surface modification reactions of silica incorporating cds on its surface; **(B)** schematic of analyte retention by cyclodextrins inside a chiral chromatographic column; **(C)** silica particles incorporating chemically modified cyclodextrins to increase the enantioselectivity of the separation; **(D)** chromatogram showing the chiral resolution of flavanones r: detector response; tr: retention time[35,38].

An alternative to chiral stationary phases, which is widely used and very useful, is the use of non-chiral stationary phases, i.e., conventional stationary phases analogous to those used in routine separations, combined with mobile phases incorporating cyclodextrins as additives in the mobile phases to achieve chiral discrimination. Both natural and chemically modified cyclodextrins are used in this mode of chiral separation. Thus sulfobutylether-β-cyclodextrin, in which the oh of positions 2, 3 and 6 are substituted, known by the trade name captisol®, is widely used in the pharmaceutical industry for the purification of chiral analytes, but they have also been used in the separation of peptides and proteins[39], 2-hydroxypropyl-β-cyclodextrin provides very good enantio-resolution in the case of so-called "designer drugs" such as β-keto-phenethylamines and cathinones derivatives with β-keto-phenethylamines structure[40]. The effect of native β-cyclodextrin and dimethyl-β-cyclodextrin, allows the chiral separation of about thirty compounds, however the best resolution

is achieved in the presence of 2-hydroxypropyl-β-cyclodextrin at 20 mm concentration in the mobile phase. The results are compared with those obtained under analogous conditions in capillary electrophoresis separation. The influence of the chemical nature and concentration of cyclodextrin is also key to achieving chiral separation targets in 10 mandelic acid derivatives[41].

6.2. Cyclodextrins in chemically sustainable separations

Liquid chromatography is a robust technique widely used in industry, with one hplc unit generating around 500 mL of potentially environmentally harmful waste per day. In the last 20 years there has been a growing interest in the search for sustainable analytical methodologies, among which the use of environmentally friendly solvents is a growing trend[42,43]. The use of cyclodextrins as additives in mobile phases in chromatography reduces the proportion of organic solvent in the mobile phase while increasing efficiency and resolution. The combination of a methylsilane-type stationary phase (c1) with ethanol and cyclodextrins in the mobile phase allows a 50%–70% reduction in the proportion of organic solvent in the mobile phase compared to other separation methodologies that do not use cyclodextrins in the mobile phases (**Figure 6**)[44].

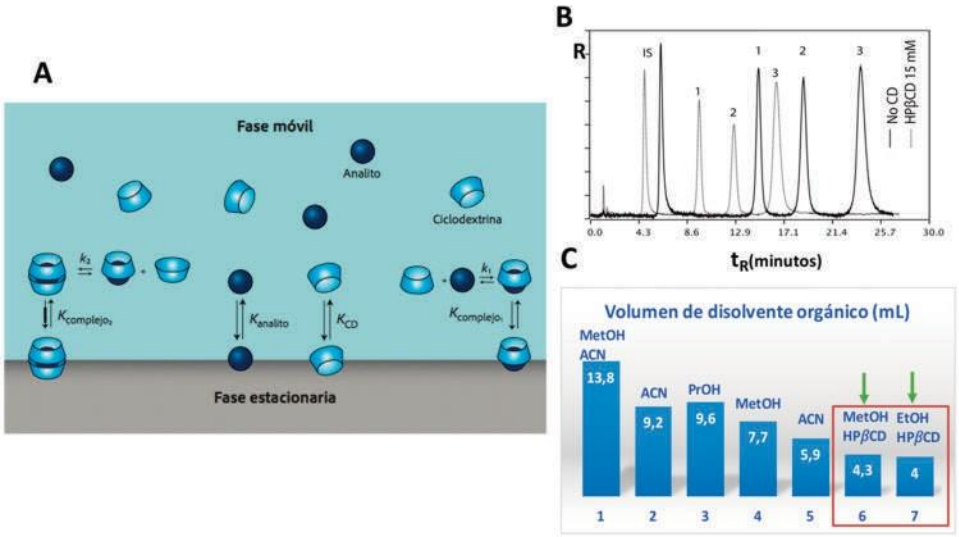

Figure 6. Cyclodextrins as mobile phase modifiers in liquid chromatography (hplc). **(A)** distribution equilibria in the presence of cds **(B)** chromatogram showing the improvement in separation efficiency in the presence of 2-hydroxypropyl-β-cd. R: detector response; tr: retention time; is: internal standard; 1: norharmane; 2: harmane; 3: harmine. **(C)** reduction in the proportion of organic solvents in mobile phases incorporating cyclodextrins. Volume of organic solvent consumed in the chromatographic separation according to the separation procedure[44].

The introduction of cyclodextrins as modifiers in mobile phases (mobile phase additives, mpa) involves the introduction of a secondary equilibrium to the main equilibrium in chromatography, i.e., the distribution equilibrium of the analytes between the stationary phase and the mobile phase. The inclusion of the analytes in the cavities of the cyclodextrins causes a significant decrease in retention times[45] and in the retention factors of the analytes and this is due to the increase in the solubility of the analytes in the mobile phases and also increases the resolution and efficiency of the separation and with significant advantages from the point of view of sustainability[46].

7. Cyclodextrins in environmental remediation

On 23 May 2001, 179 countries ratified the agreements known as the "stockholm accords". These agreements commit to the gradual elimination of the so-called "persistent organic pollutants" (pops). These agreements came into force in 2004 and this has led to a growing interest in the search for environmentally friendly ways of eliminating all these types of compounds. In this sense, the synthesis of adsorbent polymers based on cyclodextrins for the capture of different materials present in the environment is very attractive and notoriously successful[47]. The high specific surface area as well as the remarkable porosity of cyclodextrin-based polymers make them extremely useful adsorbent materials in the recovery and treatment of water and soil to avoid the presence of harmful residues in them[48]. For this reason, they are used with great success in water purification plants[49] to capture a wide variety of contaminants such as drugs[50,51], dyes[52,53] and persistent volatile pollutants[54,55]. Its use in the uptake of heavy metals has also been described[56,57]. Different methodologies have been implemented for the destruction and elimination of pollutants present in the environment, among the most successful and effective are oxidation and photocatalysis techniques; however, methodologies based on adsorption processes are very advantageous due to their low cost, ease of operation and high efficiency. It is in this scenario of adsorption methodologies where cyclodextrins, their polymers, nanosponges and their associations with other adsorbent materials (carbon nanotubes and silica) are extremely attractive and have a promising future.

8. Conclusions

The role of cyclodextrins has been reviewed in different aspects such as pharmaceutical technology, analytical chemistry, either in the pre-analytical stage or in the analytical stage itself, and more specifically in chromatography determinations. The role of cyclodextrins as essential adsorbent elements for environmental remediation by capturing the compounds responsible for environmental pollution is particularly significant. We have focused on the analytical applications of cyclodextrins because they have been the subject of our research work for almost 30 years. Their uniqueness as highly selective cavitands able to capture and discriminate chiral compounds, and to differentiate between chemically and structurally related analogues confers them unique properties and applications. In addition, they are relatively easy to produce from natural sources and are totally sustainable because they are natural compounds.

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Conflict of interest

The authors declare no conflict of interest.

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