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Review

A Review of the Application of Resorcinarenes and SBA-15 in Drug Delivery

Diana M. Galindres [1,*], Diego Cifuentes [1], Luz Elena Tinoco [1], Yesid Murillo-Acevedo [1], M. Melia Rodrigo [2], Ana C. F. Ribeiro [3] and Miguel A. Esteso [2,4,*]

[1] Grupo de Fisicoquímica y Análisis Matemático, Facultad de Ciencias y Humanidades, Fundación Universidad de América, Bogotá 111321, Colombia; diego.cifuentes@profesores.uamerica.edu.co (D.C.); luz.tinoco@profesores.uamerica.edu.co (L.E.T.); yesid.murillo@profesores.uamerica.edu.co (Y.M.-A.)
[2] Universidad de Alcalá, U.D. Química Física, 28805 Alcalá de Henares, Madrid, Spain; mmelia.rodrigo@uah.es
[3] Centro de Química, Departamento de Química, University of Coimbra, 3004-535 Coimbra, Portugal; anacfrib@ci.uc.pt
[4] Universidad Católica de Ávila, Calle Canteros s/n, 05005 Ávila, Spain
* Correspondence: diana.galindres@profesores.uamerica.edu.co (D.M.G.); mangel.esteso@ucavila.es (M.A.E.)

Abstract: Due to the diseases that people face today, scientists dedicate a part of their research to the synthesis, characterization, and study of functional compounds for controlled drug delivery. On the one hand, resorcinarenes are macrocycles obtained by condensation reactions of resorcinol and aldehyde. They include an upper and a lower rim functioning with different groups that confer solubility to the macrocycle and favor interactions with other compounds, therefore the hydroxyl groups on the upper rim improve the formation of hydrogen bonds. Additionally, resorcinarenes feature a cavity studied for forming host-guest complexes. SBA-15, on the other hand, is a mesoporous silica characterized by ordered pores in its structure and a large surface area. As a result of its properties, it has been used for several purposes, including absorbents, drug delivery, catalysis, and environmental processes. This review shows the recent advances in synthesis methods, characterization, micelle formation, interaction with other compounds, and host-guest procedures, as well as techniques for evaluating toxicity, drug retention, and their preliminary uses in pharmacology for macrocycles, such as resorcin[4]arenes and SBA-15.

Keywords: resorcin[4]arenes; SBA-15; macrocycles; pharmacology; drug delivery; mesoporous silica; adsorbents; host-guest complex

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1. Introduction

A controlled drug delivery system can be described as a therapeutic formulation [1,2], in which an active principle is delivered to specific parts of the body at a controlled rate and time [3]. It is specially designed to maintain therapeutic levels of the drug throughout the entire treatment period and not only during certain intervals of the treatment, as is regularly the case with traditional therapy where the drug is distributed through the circulatory system [4,5].

As for the use of drugs in the treatment of different diseases in humans, one of the most widely used methods is controlled delivery systems [6]. They represent a constantly growing field, in which both the demand for new therapeutic agents and the improvement of the mechanisms to administer them are increasing. Commercial presentations of drug delivery systems based on polymer technology are relatively successful, covering a wide range of applications or various application areas (for example, in the treatment of diabetes, cancer, osteoporosis, etc.) [6,7]. However, these systems tend to lose their pharmacological activity as the active principle degrades before reaching the target tissue [8].

In recent years, advances in the field of nanotechnology and supramolecular systems have led to the development of new nanostructured materials for biomedical applications [9,10]. Two approaches applied to drug delivery systems are shown in this review: The first one is supramolecular systems using synthetic macrocycles as drug reservoirs (micelles, hydrogels, vesicles, liposomes, and nanoparticles) which can respond to different stimuli to release the drug in a directed and controlled way, showing some advances in design [11–13]. They are systems based on calix[4]resorcinarenes that are considered a family of synthetic supramolecular macrocycles able to form cone-shaped structures and facilitate the formation of complexes with guest molecules [14,15]

The second one is systems based on mesoporous matrices that allow the encapsulation of the active principles, providing a longer circulation time and avoiding intoxication caused by high drug concentrations in the body. These systems have a high specific surface area, an ordered structure, and a large volume of pores, which allows a high adsorption potential and better control over the loading and release of the active principles. SBA-15 is a mesoporous material that has an ordered network of pores with homogeneous size and a large pore volume to accommodate the required amounts of drugs [16–18].

These unique properties of both calix[4]resorcinarenes and SBA-15 make these materials excellent compounds for use in controlled drug delivery systems, as summarized in Table 1:

Table 1. Summarize: Uses of Resorcin[4]arenes and SBA-15 in drug delivery.

Active Principle/ Disorder	Carrier	Functional Group *	Topic.	Author/Year
Hyperglycemia Insulin	Resorcinarene	Sulfonyl Diazonium	Thermodynamics Solubilities in water Insulin fibrillation Nanotransporters Nanocapsules.	Galindres Jimenez et al., 2019. Han, Tian, et al., 2017. Maldonado et al., 2017. Ziganshina et al., 2019.
Antibiotic Doxorubicin Clarithromycin Chloramphenicol Amoxicillin	Resorcinarene	Guanidine Acylhidrazone N-methyl-glucamine Ethylene glycol N-alkyl, N-Aryl	Micelles Nanotransporters	Albayati et al., 2019. Ali et al., 2020. Pang et al., 2013 Sergeeva et al., 2020. Sevimli & Yılmaz, 2012. Shumatbaeva et al., 2019–2020.
	SBA-15	Amine Polyethyleneimine	Adsorption/Desorption	
Anti-inflammatory IndomethacinI buprofen Naproxen	Resorcinarene	PEG N-alkyl, N-aryl Ethylene glycol	Micelles Nanocarriers Dendrimers	Gao et al., 2014. Ahmadi et al., 2014. Pedro-Hernández et al., 2017. Shumatbaeva et al., 2019. Malfait et al., 2020.
	SBA-15	Amine	Adsorption/Desorption	
Anticancer Chlorambucil Gemcitabine	Resorcinarene	Polyamidoamine	Dendrimers	Mendoza-Cardozo et al., 2019. Raval et al., 2021. Sevimli & Yılmaz, 2012.
	SBA-15	Amine	Adsorption/Desorption	

* It refers to the functional group used in the synthesis of Resorcinarene or the SBA-15 material.

2. Synthesis of calix[4]resorcinarenes and Porous Materials (SBA15)

2.1. Synthesis of calix[4]resorcinarenes

Controlled drug delivery is a technique that aims to achieve optimal therapeutic effects by delivering a drug into the body in a controlled and precise manner[1]. The approach of this management system comprises three main actions: (1) choice of the route of administration and improvement of absorption, (2) controlled release of the formulation, and (3) orientation toward the site of action [19]. According to these approaches, the encapsulation of the different active principles inside protective structures is a very attractive alternative. These systems seek, among others, to reduce possible physicochemical or enzymatic alterations of the active compound. They also aim to increase the bioavailability of the active compound and reduce the undesirable side effects of its non-specific distribution [20].

Pharmaceutical formulations of active ingredients with low or no aqueous solubility often have poor bioavailability when administered into the body and therefore low efficacy. Among the compounds that appear as suitable vehicles for the administration of drugs with

low solubility are the calix[4]resorcinarenes [21], These and their water-soluble derivatives show good biocompatibility and no cytotoxicity, aspects relevant to their application in any practical drug delivery system [22].

The synthesis of calix[4]resorcinarenes usually involves condensation of either aliphatic or aromatic aldehydes with resorcinol (Figure 1); the reaction is catalyzed by an acid and is carried out using ethanol as solvent [23,24].

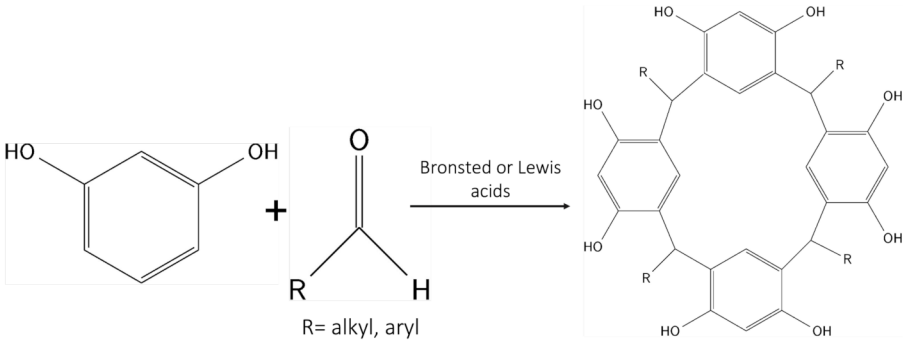

Figure 1. The condensation reaction between resorcinol and aldehyde.

The ability of calix[4]resorcinarenes to form host-guest complexes is based on their structure. These molecules consist of four phenolic residues linked to methylene groups, allowing the conformation of five structures (Figure 2), the most common of which is the crown conformation used for host-guest processes [21].

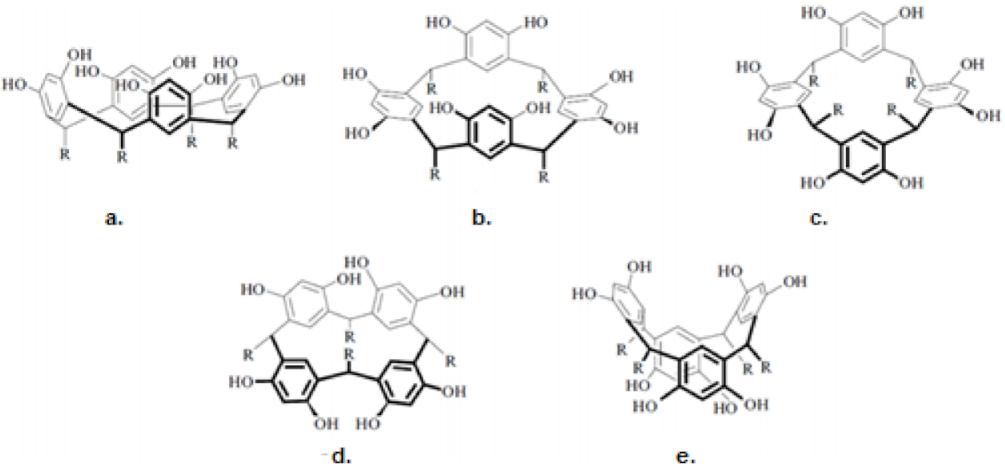

Figure 2. Conformations of calix[4]resorcinarenes: (**a**). Crown; (**b**). Boat; (**c**). Chair; (**d**). Diamond; (**e**). Saddle.

Compared to other macromolecular systems that have been studied for drug delivery, the systems like calix[4]resorcinarenes have fewer reports in terms of biomedical applications, due to their hydrophobic properties [9]. In an attempt to solve this problem, novel alternatives arise in the synthesis of calix[4]resorcinarenes that favor the hydrophilic characteristics and increase the solubility of these compounds in water. Functionalization by aromatic nucleophilic substitution in position 2 of the aromatic rings or by nucleonic substitution on the hydroxyl groups [25], opens the possibility of generating functionalized calix[4]resorcinarenes systems with groups that allow them to improve their solubility. The interactions with other molecules, selective complexation, the ability to react with various molecules, the tendency to form self-associations, and surface activity, have been studied [26].

N-methyl-D-glucamine-resorcin[4]arene, a derivative with higher water solubility than its precursor, can be obtained by a Mannich reaction between decylresorcin[4]arene

and N-methyl-D-glucamine. The synthesized compound showed antimicrobial activity only against Gram-positive bacteria. Evaluating its cytotoxic effect on human erythrocytes, it is found that this macrocycle does not cause complete hemolysis, unlike other derivatives of the calixarenes family [27].

Methyl (C1), pentyl (C5), and undecyl (C11) were used as systemic substituents on each ring of the functionalized amido(dimethyl)amino-calix[4]resorcinarene as they act as reducing and stabilizing agents in the synthesis of colloidal gold nanoparticles with spherical shape (4–8 nm). In the synthesis of nanoparticles, increasing the concentration of the macrocycle in the solution and using macrocycles with functional groups with greater hydrophobicity leads to a decrease in the size of the particles formed. The synthesized particles tend to form a macrocycle bilayer on the surface, which gives stability and greater water solubility to the colloidal system. The binding capacity of colloidal systems with a non-steroidal anti-inflammatory molecule (Naproxen) was studied. Modifying gold nanoparticles with macrocycles results in a significant increase in the drug's binding properties, with aggregations between 85% and 98%. [26].

2.2. Synthesis of SBA-15

A cooperative self-assembly process is used for the synthesis of SBA-15. For this purpose, a non-ionic triblock copolymer (Pluronic P123) is used as a template, which consists of ethylene oxide (EO) and propylene oxide (PO). On the other hand, tetramethoxysilane (TMOS) or tetraethoxysilane (TEOS) are used as silica sources. The hydrophobic part is made of propylene oxide, while the hydrophilic part is made of ethylene oxide. The process occurs in an acidic medium in two steps: (1) the formation of micelles with hydrophobic groups inward and hydrophilic groups outward; (2) the interaction between water molecules and alkylene oxides as a result of hydrogen bonds [28,29].

A review of the synthesis procedure for this mesoporous compound can be found in the literature [30]. Briefly, this synthesis involves the following steps: (a) the initial solution is heated at 30–40 °C for 20–24 h; (b) then the temperature is raised to 80–120 °C for 24–48 h; (c) at room temperature overnight, the solid obtained is filtered, washed and dried; (d) next, the solid is dried at 80 °C for 5–6 h, and (e) finally, the sample is calcined at 550 °C for 4–6 h. The calcination process is key because it removes the template (Figure 3). Likewise, depending on the synthesis conditions, the size of the mesoporous can vary (from 5 to 30 nm) as well as their morphology, hexagonal or cubic (a low EO: PO ratio favors hexagonal morphology) [28]. As a result, the porous solid obtained will have different properties related to a high surface area and mechanical and chemical resistance.

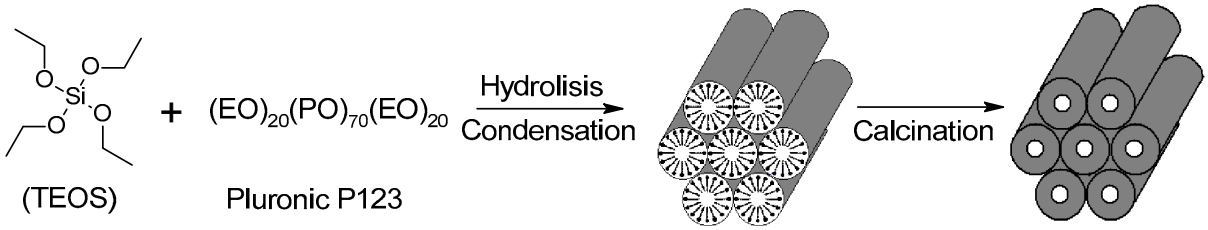

Figure 3. General scheme for the preparation of SBA-15.

3. Resorcinarenes and their Applications in Drug Delivery

Supramolecular chemistry is a discipline of chemistry that studies the interactions between molecules from which the formation of intermolecular bonds is derived and consequently the formation of supramolecular aggregates. It studies the chemical, physicochemical and biological properties of these species that possess non-covalent intermolecular forces [31]. Among the compounds of interest are the resorcin[4]arenes, which have a cavity, an upper rim, and a lower rim. These macrocycles can be functionalized: the lower rim with hydrocarbon chains, which allow the hydrophobicity of the macrocycle to vary, and the upper rim, with various functional groups, such as the sulfonate group, the amino

group, and others that give them the property of being soluble in water, which is necessary for processes related to drug delivery [32–34].

Studies have been carried out on the thermodynamic properties of resorcin[4]arenes showing the behavior of these macrocycles in solution. Diazoted resorcin[4]arene has been characterized and synthesized by spectroscopic techniques [35]. The viscosities and densities of their solutions in dimethyl sulfoxide (DMSO) were measured at temperatures ranging from 293.15 K to 313.15 K, in a concentration range of (0.0058 to 0.023) (mol kg^{-1}).

Based on these data, thermodynamic functions are considered, which contribute to understanding intermolecular interactions in solution. For example, the study of viscosities suggests the existence of strong solute-solvent interactions, while that of volumes indicates the presence of strong solute-solute interactions. On the other hand, sulfonated resorcin[4]arenes have been synthesized and studies on their mutual diffusion coefficients and molar ionic conductivities in aqueous solution at 298.15 K, at concentrations lower than 0.010 mol dm^{-3} have been reported. The results are discussed in terms of interactions in solution, the effect of the length of the chain located at the lower rim of the resorcin[4]arene, and the hydrodynamic radii as compared between the two techniques [36]. The diffusion coefficients of bovine serum albumin in water and in the presence of sulfonated resorcin[4]arenes were also evaluated; the values obtained from the diffusion coefficients were analyzed in terms of interactions and as the presence of resorcin[4]arene favors the interaction between protein and water; the salting-in effect was also evaluated [37]. The transport properties were used to model diffusion in pharmaceutical and medical applications.

Water-soluble resorcinarenes have been shown to be non-toxic and exhibit proper biocompatibility, and biodegradability, making them important and useful molecules for drug delivery processes [38–40]. Menon et al. conducted studies on inclusion complexes of sulphonatocalix[4]resorcinarene and mycophenolate mofetil, *in vitro* tests performed on animals, showing no toxic effects of the complex and monitoring their weight, respiratory system, circulation, and sleep. Mycophenolate mofetil was found to have an oral LD50 of 352 mg kg^{-1} in rats, 1000 mg kg^{-1} in mice, and 6000 mg kg^{-1} in rabbits, but complex formation with resorcinarene does not cause mortality up to 2200 mg kg^{-1} [41].

Dawn et al. performed *in vitro* cytotoxicity assays of calixarenes functionalized with different groups and a metallosupramolecular complex, cell viability studies were performed using CellTiter-Glo cell and MTT. The compound efficacy was evaluated in rat C6G cells and human HEK293 cells, with toxicity varying from low to moderate. This study shows that the CC50 values indicate that the presence of phosphonate groups and the suppression of the coordination capacity reduce the cytotoxicity of macrocycles, therefore it is evident that the use of calixarenes or resorcinarenes as drug carriers is appropriate [42].

Several studies have shown that a variety of molecular hosts are accommodated in resorcinarene cavitands. These are versatile molecular hosts that even manage to temporarily isolate them from their environment [43]. Water-soluble cavitands synthesized by adding polar groups at the upper rim or at the lower rim have been studied. These compounds have shown a great ability to accept guests in aqueous solutions and have also been shown to act as hosts when used in micelles and lipid bilayers.

Insulin is a hormone released by the pancreas due to the presence of glucose in the blood. This hormone ensures that glucose enters the cells to be used as an energy source. However, when insulin does not work properly, glucose accumulates in the blood and causes various diseases [44,45]. For this reason, some authors have dedicated their studies to evaluating compounds that can serve as insulin transporters in the body [46,47]. Xu Han et al. investigated the role of resorcinarenes in inhibiting or promoting Insulin Fibrillation. In this study, modified resorcinarenes with a sulfonate group at the upper rim and with modifications of hydrocarbon chains at the lower rim were used to analyze the effect of the presence of these resorcinarenes in the insulin fibrillation process through experimental and computational studies. ThT assay, CD spectra, and AFM images were carried out experimentally. Among the results obtained, it is highlighted that the presence of the hydrocarbon chain of the resorcinarene effectively inhibits insulin fibrillation; these

results are promising for possible therapeutic strategies. The experimental conditions used by the authors were: Thioflavin T (ThT) fluorescence intensity at 485 nm as a function of incubation time at 65 °C in 0.1 M NaCl; fibrillation kinetics of 0.2 mg / mL human insulin; pH 1.6 with the ratio of insulin and resorcinarene at 1: 0, 1: 0.02, 1: 0.05, 1: 0.1 and 1: 0.2, respectively [48].

In the same way, Sergeeva et al. reported the study of sulfonated resorcinarenes as insulin transporters and their release in the presence of glucose, Resorcinarenes were described as nanocarriers consisting of a polymer sphere containing sulfonated resorcinarene molecules linked by phenylboronate bridges, with insulin encapsulated in the cavity. It was found that depending on the glucose concentration, the nanocarrier also acts; for example, at a low glucose level (5 mM), insulin release is no more than 10%, but an increase in glucose concentration up to 10 mM leads to nanocarrier dissociation and the subsequent massive insulin release. Dialysate composition, particles stability, and insulin retention ability were evaluated by NMR. The amount of unencapsulated insulin was calculated from the ratio of the integral of the standard insulin solution (0.35 mg) in 0.04% DMF to the integral of the insulin signals at 3.47–3.55 ppm and the DMF signal at 7.92. On the other hand, the amount of encapsulated insulin was calculated as the difference between the amounts of total and non-encapsulated insulin. In this study, the behavior with different concentrations of glucose was also evaluated by NMR using the UV-Vis technique, complemented by insulin absorption studies. In the two previous studies, an important factor mentioned is that resorcinarenes are not toxic. In addition, because they possess a cavity, they can effectively encapsulate other molecules such as insulin and depending on the groups with which they are functionalized, they can become very soluble in water and in blood plasma at normal pH levels [49].

Proteins tend to be structurally damaged during extraction and purification processes. For this reason, studies have focused on systems designed to improve protein stability [50–52]. Resorcin[4]arenes have been used not only for insulin fibrillation but also for inhibition of Aβ-fibrillation. Studies were performed using techniques such as ThT assays, atomic force microscopy, circular dichroism, and complementing the experimental measurements with computational methods. Among the main findings, it was found that they are compounds with low toxicity and that in addition to blocking Aβ aggregation, it delays the formation of toxic species [53].

Zoledronate is a drug that belongs to the bisphosphonate group and is used to treat osteoporosis. Nine macrocycles based on calix[4]arenes and calix[4]resorcinarenes were studied as hosts for the zoledronate molecule by *ab initio* density functional theory calculations for the energies of eighteen host-slave complexes and for the structures. Phosphonated and sulfonated calix[4]arenes and calix[4]resorcinarenes were used, and the geometry of the internal cavities was considered and compared with those of the host-guest complexes. Calculations of the binding energy in the gaseous and aqueous states, and the limiting molecular orbitals including HOMO and LUMO were made for the quantitative evaluation of the formations of the host-guest complexes, showing that they are stable in aqueous solutions, while in the gaseous state some are stable but others are not. The norm-conserving pseudo-potential pseudo-atomic orbital method was adopted with the standard DZP basis sets and the BLYP + vdW (Grimme) GGA functional. According to the obtained results, calix[4]resorcinarenes allow a better host-guest coupling than calix[4]arenes due to the hydrogen bonds formed with the top edge OH groups, while sulfonate-calix[4]arenes are the most appropriate host for ZOD guest on 1:1 stoichiometry [54].

In water and in dodecyl phosphocholine (DPC) micelles, Javor et al. studied the host capacity of molecules containing water-soluble resorcinarenes and a guanidine group at the lower rim, using NMR spectroscopy techniques. Initially, the cavitand synthesis was carried out and later the authors simulated both molecular dynamics and optimization programming using the PM3 semiempirical method in the Spartan 04 software, converted to GROMOS (gmx53a6 force field) topology through the Topolbuild 1.3 program. Here, the

spontaneous incorporation of the cavitand into the micelle is evidenced, thus evaluating their behavior as carriers of biological compounds and their future applications [43].

New molecules of calix[4]resorcinarenes and methoxy-PEG (mPEG) conjugated through acylhydrazone bonds were synthesized. The effect of these compounds on the formation of supramolecular drug delivery systems was studied. The calix[4]resorcinarenes were synthesized in boat and chair conformations to obtain amphiphilic conjugates as supramolecular nanocontainers and dendrimeric. The structures of the conjugates were worked from 1H, 13C, FT-IR spectroscopy and NMR, Maldi-TOF mass spectroscopy, and SLS method. The cytotoxicity of the compounds and the ability to encapsulate drugs such as Dox and Methylene Blue were evaluated and *in vitro* studies with M-Hela cells and Chang liver cells were carried out. The results show that the Dox-conjugate has a better effect against tumor cells than that of the free drug. Studies confirmed the hemolysis test with the lowest hemotoxicity of the conjugates: only 2.2% of cells stain in the presence of 9 $mg \cdot mL^{-1}$ of C11-mPEG and 8.7% in the presence of 4.5 $mg \cdot mL^{-1}$ of C1Ph-mPEG [55].

Doxorubicin (DOX) is a well-known drug that has antimitotic and antiproliferative activity. Sergeeva et al. synthesized a polymeric nanocarrier for the doxorubicin delivery: basically, consists of N-methyl-glucamine resorcinarenes covalently bound to phenylboronic acid. The nanocarrier was found to be non-toxic and hemolytically inactive in the concentration range in which the authors worked. In addition, it was concluded that the nanocarrier is stable at normal pH but hydrolyzes at pH below 6. Studies used techniques such as TEM, NMR, fluorescence, and cytotoxicity, finding that the nanocarrier favors its penetration into the cancer cells and increases the cytotoxicity of DOX towards cells [56].

Mendoza-Cardozo et al. used four resorcinarene-polyamidoamine (PAMAM) conjugates of chlorambucil dendrimers with different groups at the lower part of the macrocycle; the dendritic arms of different lengths generated good stability of the chemical bond between the carrier and the drug. The anticancer activity of resorcinarene conjugates with chlorambucil was tested. *in vitro* tests were performed against six human cancer cell lines: U-251, PC3, K-562, HCT-15, MCF-7, and SKLU-1. Studies conducted with K-562, human chronic myelogenous leukemia cells showed that chlorambucil was less effective than the conjugate as an antiproliferative agent [57].

Calix[4]resorcinarene nanovesicles with a diameter of 210 nm were synthesized. The macrocycles were characterized by techniques such as Dynamic Light Scattering (DLS), Fourier Transform Infrared Spectroscopy (FTIR), Mass Spectroscopy, Differential Scanning Calorimetry (DSC), and X-Ray Diffraction (XRD). The results show that in the presence of chloroform, the synthesized macrocycles exhibit good monodispersity of drug and calixars and show a loading capacity of 85%. The spherical shape of the vesicle was verified using techniques such as atomic force microscopy, which leads to a good release of the drug. *In vitro* tests and hemolysis, tests were carried out, finding results that can be extrapolated to a potential application as a drug transporter against cancer [58].

Resorcinarene-centered amphiphilic eight-armed star block copolymers (SPCL-b-PEG) were synthesized. The compounds were obtained with a defined architecture and controlled molecular weight. Their suitability as nanocarriers for indomethacin and other drugs was evaluated as they self-assembled in the form of micelles. A strong hydrophobic interaction between the drugs and the PCL blocks was found, showing a high efficiency to encapsulate the drug. The macrocycles were synthesized by a series of reactions and characterized by H-NMR; subsequently, their micellization capacity and the critical micellar concentration were investigated. Controlled release and drug loading were evaluated, finding that encapsulation efficiency decreased from 88.1% to 57.3% and drug loading content increased from 8.8% to 17.2% when the theoretical indomethacin loading increased from 10.0% to 30.0% [59].

The synthesis of multi-tailed resorcinarene (MTR) was performed through two reactions, the first was the reaction by O-alkylation of 4-hydroxybenzaldehyde and the second was the condensation with resorcinol. The macrocycle was characterized by ^{1}H-NMR, mass spectrometry, and FT-IR. From the studies, the self-assembly and aggregation be-

havior of the amphiphilic macrocycle in an aqueous medium, and the vesicles in terms of morphology and critical micellar concentration (CMC), CMC values of 0.055 mM and niosomal vesicles with an average diameter of 210 ± 2 nm were determined. Hydrophobic drugs such as clarithromycin were loaded due to the ability of the MTR to self-assemble. Drug entrapment efficiency of 65.12 ± 3.31% and maximum drug release after 8 h were observed [33].

Resorcinarene-derived macrocycles were synthesized to evaluate the efficacy of quercetin; the biocompatibility was assessed by hemolysis and cytotoxicity tests. The critical concentration of association (CCA) of cynnarene-based macrocycle (Benzyloxy Macrocycle, BM) was determined by using a UV-Vis spectrophotometer. Quercetin-loaded vesicles revealed a size of approximately 225.5 ± 16.31 nm with 88 ± 1.52% QRT encapsulation [60].

At the lower edge of the macrocycle, ibuprofen conjugates were synthesized with resorcinarene dendrimers with aliphatic and aromatic substituents. Cellular internalization of the resorcinarene-PAMAM-ibuprofen dendrimers was evaluated by clathrin-mediated endocytosis. In this work, the authors found that the length of the dendritic branches and their chemical structure directly influenced the hydrolysis of the drug-conjugated dendrimers. It is proved that the synthesized compounds have high potential anticancer activity, especially in the presence of 8- and 16-residue substitutions of ibuprofen in the dendritic branches compared with the effect of ibuprofen alone, this was proved by biological activity assays [61].

The synthesis and characterization of the new conjugate of tetraphenylenexypentylcalix[4]resorcinarene and methoxy-poly(ethylene glycol) was carried out. The formation of micelles in an aqueous solution was studied. The presence of phenylene-oxy-groups in the hydrophobic core of the micelles promotes the encapsulation of drugs such as naproxen, ibuprofen, and doxorubicin; the values of encapsulation effectiveness were 39.8%, 26.7% and 28.9%, respectively [62].

4. Inclusion Complexes Based on SBA-15 and Their Applications in Drug Delivery

The controlled drug delivery process is associated with the adsorption process, in which the drug is preferentially adsorbed in the porosity and rather than on the surface. Surface adsorption requires examining different variables of the medium, such as pH changes to prevent crystallization. As a result, it is determined that the concentration of the drug has a fast adsorption kinetic and that a short time interval is needed for the desorption kinetics to be released in the intended organ [63].

Ahmadi et al. reported that modification of the surface of SBA-15 with amino groups results in a decrease in the rate of drug delivery but also significantly increases the interaction with the functional carboxyl group of ibuprofen. In this study, SBA-15 modified with (3-aminopropyl)triethoxysilane is used for the transport of ibuprofen. Using techniques such as X-ray diffraction (XRD), scanning electron microscopy (SEM), N_2 adsorption-desorption isotherm, thermogravimetric analysis (TGA), differential thermal analysis and Fourier Transform Infrared Spectroscopy (FTIR), SBA-15-NH_2 was saturated with ibuprofen in n-hexane solution at different times, temperatures, ibuprofen/silica ratios and stirring rates. In this sense, the optimal experimental conditions were found to be 40 °C, 35 h, with a drug/SBA-15 ratio of 50:100 and a stirring speed of 100 rpm. The interaction between the amino groups of SBA-15-NH_2 and the carboxyl groups of ibuprofen considerably increases the drug concentration on the surface, so the functionalization of mesoporous materials with amino groups has a high impact on both drug transport and adsorption process. Based on the results of this study, we conclude that ibuprofen is transported more efficiently on the modified surface of SBA-15 with SBA-15 amino groups; however, this implies a decreased release rate [64].

The effect of modifying the surface of SBA-15 with amino groups, to be used as an adsorbent for an antibiotic such as chloramphenicol in aqueous solution, was studied using a post-synthesis procedure. Experiments were conducted analyzing variables such as contact time (0–72 h), mass (10–120 mg), and initial concentration (10–120 mg·L^{-1}) to

determine the effects of the different variables on the efficiency of the adsorption process. Characterization techniques such as SEM, BET surface area, FTIR, TGA and XRD, show that the obtained materials correspond to SBA-15 and NH_2-SBA-15. The results found allowed to obtain an adsorption capacity of 51% for a concentration higher than 20 $mg \cdot L^{-1}$. On the other hand, the drug release results show an optimal time of half an hour, with a value of 41.35%. Thus, it can also be deduced that the adsorption capacity is directly proportional to both the NH_2-SBA-15 dose and the contact time but inversely proportional to the initial concentration [65].

Bahrami et al. reported that the release of gemcitabine (a drug used for cancer treatment) depends on pH; this was in the case of the modified samples containing NH_2 groups. The obtained results show a promising future in terms of applications of mesoporous materials in anticancer drug delivery systems. They worked with NH_2-SBA-15, $N(OH)_2$-SBA-15, and 3N-SBA-15 functionalized with APTES, HAPS, and AEPS, respectively. Characterization techniques such as TGA, N_2 adsorption/desorption, SEM, TEM, small angle X-ray scattering (SAXS), elemental analysis, UV spectroscopies, and FTIR were used. It was concluded that the formation of carriers that interact better with the drug may be due to surface modification. Furthermore, the type and number of alkoxysilane groups affect the adsorption of gemcitabine on the modified samples. The maximum amount of adsorbed drug (21.65 wt%) is related to the concentration of APTES on the surface of NH_2-SBA-15 (2.64 $mmol \cdot g^{-1}$). It can be concluded that a modification of the surface chemistry of SBA-15 makes the modified SBA-15 nanorods suitable carriers for gemcitabine [16].

Mesoporous silica SBA-15 was evaluated as a carrier for the transport of the cytotoxic natural product emodin (EO). A dose-dependent decrease in cell viability is shown, strictly related to an increasing amount of EO in SBA-15 up to 27% EO. On the other hand, a constant activity was observed at 32% and 36% EO in SBA-15.

The proportion of SBA-15 and EO was varied (SBA-15, always 100 mg; EO: 20, 30, 40, 50 or 60 mg; SBA-15 | EO1 → SBA-15 | EO5, respectively) obtaining materials with different concentrations. The EO content in SBA-15 for these materials ranged from 8.1 to 36.4 % with an efficiency of 88.2–95.6% (in contrast to SBA-15 | EO where only 0.7% EO was found in mesoporous silica nanoparticles (MSN)).

SBA-15 | EOn (n = 1 to 5) was characterized by nitrogen adsorption-desorption isotherms, energy dispersive X-ray spectroscopy (EDX), SEM, TEM, IR spectroscopy, and SAXS. SBA-15 was activated under the following conditions (vacuum, 150 °C, 16 h) and used to obtain different amounts of EO. First, EO loading (ratio: SBA-15, 100 mg; EO, 10 mg) was performed at room temperature (→ SBA-15 | EO1) and at 60 °C (→ SBA-15 | EO1a), to check the temperature dependence of the concentration efficiency in SBA-15. High and comparable drug concentration efficiency in SBA-15 was demonstrated in the cases studied under the specified conditions (at room temperature: 88.2%; at 60 °C: 90.4%).

Accordingly, the authors determined that a porous material such as SBA-15 enhances the activity of EO *in vitro*, and even protects the active compound from spontaneous inactivation by light or from degradation by gastric pH, where extremely acidic conditions prevail [66].

In Malfait et al., a mill-based loading method (MAL) is used to concentrate a poorly water-soluble drug (ibuprofen, IBP) in the solid state within the SBA-15 matrix. From the resulting TGA, Raman, differential scanning calorimetry analysis, and X-ray diffraction it appears that the crystallites are surrounded by a liquid monolayer and located in the core of the channel. It is also evident from the study that the decrease in melting temperature of the confined crystallites is affected by the pore diameter and not by the size of the crystallites along the channel direction, which are regularly larger than the pore diameter. DSC experiments showed that these crystallites coexist with amorphous PPI located in the core of the channel and surrounded by an amorphous surface-interacting layer, with a thickness approximately equal to one molecule of ibuprofen (∼1 nm). As described, very high solubility and fast release from SBA-15 (9 nm) matrices for amorphous PPI can be achieved from PPI confinement. The PPI release can be prolonged by slightly manipulation

of the physical state; for example, maintaining high solubility of the amorphous state while inducing lean crystallization [67].

Pang et al. use folic acid (FA) ligands conjugated to poly(ethylene imine) (PEI) modified with SBA-15 (PEI/SBA-15) particles via an amide reaction, resulting in FA/PEI/SBA-15 particles. An anticancer drug called doxorubicin hydrochloride (DOX) is transported. PEI/SBA-15 particles show higher cytotoxicity compared to FA/PEI/SBA-15 particles, while the latter loaded with DOX show much higher inhibition in two types of cancer cells studied (HeLa cells and A549 cells). It follows that when the current anti-cancer drug carriers (FA /PEI/SBA-15 particles loaded with DOX) mediated by the FA receptor are used, excellent cellular uptake is observed, which is evident from both flow cytometry analysis and fluorescence microscopy. From toxicity tests, it can be inferred that the DOX-loaded FA /PEI/SBA-15 particles show better anticancer activity than pure DOX and DOX-loaded SBA-15 particles due to their higher FA receptor-mediated cellular uptake. Therefore, this work demonstrates that DOX-loaded FA/PEI/SBA-15 particles may have great potential in delivering anticancer drugs for cancer therapy [68].

SBA-15 particles surface functionalized and hydrothermally synthesized by the post-grafting synthesis method with (3-aminopropyl)triethoxysilane served as carriers for a drug delivery system named amoxicillin [38]. The transport of amoxicillin was analyzed by FITR, SAXS, N_2 adsorption/desorption analysis, TEM, solid-state silicon angle nuclear magnetic resonance (Si-MAS-NMR), high-performance liquid chromatography (HPLC), TGA, elemental analysis and ultraviolet (UV) spectroscopy. According to the obtained results, it is deduced that it is possible to incorporate a slightly higher amount of amoxicillin inside the mesoporous particles of SBA-15. The amount of incorporated amoxicillin decreases or increases depending on the concentration and type of alkoxysilane, so that a permanent release of amoxicillin is possible. Finally, it can be concluded that the similarity of the release profiles suggests that functionalization has no effect on the release of amoxicillin [69].

In some studies, silica nanoparticles were found to be biocompatible and degrade in the body. *In vitro* studies demonstrated low toxicity at low concentrations. For example, the experiments conducted show low toxicity with low doses of SBA with particle sizes of 1 and 2 μm [70].

On the other hand, the mesoporous silica types SBA-15 and SBA-16 were used in combination with antigens against respiratory infections in pigs. However, the results showed a greater efficiency of SBA-15 compared to SBA-16, which is due to the structural difference between these two silicas. This implies that a higher percentage of antigen adsorption in SBA-15 reduces the disease and lung damage caused by M. hyopneumoniae [70]. The SBA-15 has been used in the oral administration of hepatitis B to achieve a high response compared to intravenous administration of the antigen. On the contrary, SBA-15 has been used in the oral administration of hepatitis B, with a stronger response compared to intravenous administration to release the antigen [71].

The process used in the controlled delivery of drugs is associated with the adsorption process, in which the drug is preferentially adsorbed in the porosity and not on the surface. In the case of the surface adsorption process, different variables of the medium must be analyzed, such as changes in pH to avoid crystallization, since within the general objective it is found that the concentration of the drug has a fast adsorption kinetics and its time that the desorption kinetics that can be released in the desired organ, in a short time interval [63].

5. Conclusions and Outlook

In the last decades, the use of macrocycles in drug delivery has increased due to their properties and characteristics that allow them to intervene in host-guest processes, self-assembly, and micelle formation. This review shows studies about the synthesis and characterization of compounds such as resorcin[4]arenes and SBA-15.

The simulation of the interactions of macrocycles such as resorcin[4]arenes and SBA-15 was analyzed, showing the different types of relationships in solution, the effect of the

solvent, the solvation processes, and the interactions generated with other compounds such as various drugs. A comparison of the structures of resorcin[4]arenes and SBA-15 reveals the presence of aromatic and hydroxyl groups in resorcin[4]arenes modified with different functional groups, allowing them to increase their solubility and interact with compounds of biological interest.

Moreover, *in vitro* tests with resorcin[4]arenes and SBA-15 indicated that these compounds do not demonstrate cytotoxicity. For this reason, these compounds have been tested in cancer cells, obtaining adequate cellular uptake; the absence of damage in blood cells stands out. In addition, the formation of complexes between these hosts and various drugs has a positive effect on the bioavailability of these drugs, compared to the levels they exhibit freely. These results represent a breakthrough for applications in medicine and pharmacology. In the near future, the goal will be to obtain experimental results for the application of these materials *in vivo*.

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