International Journal of Chemistry Studies
www.chemistryjournal.in
ISSN: 2581-348X
Received: 01-11-2025, Accepted: 01-12-2025, Published: 16-12-2025
Volume 9, Issue 2, 2025, Page No. 53-62

Cyclodextrin-based nanosponges: Advances in design, fabrication, and multifunctional applications in drug delivery and beyond

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Abstract
Cyclodextrin-based nanosponges (CD NSs) have emerged as an innovative class of nanoscale delivery systems with significant relevance in modern nanotechnology and nanomedicine. Their unique three-dimensional, hyper-crosslinked architecture enables the formation of stable, porous networks capable of encapsulating a wide spectrum of therapeutic molecules. Functional tunability, high inclusion capacity, and strong bioadhesive characteristics contribute to their versatility in improving drug solubility, stability, targeted delivery, and bioavailability. CD NSs also support multiple routes of administration, including oral, topical, and parenteral pathways, broadening their applicability across pharmaceutical formulations. This review provides an in-depth examination of the synthesis strategies, structural attributes, and physicochemical properties of cyclodextrin nanosponges, along with their expanding roles in therapeutic delivery. The discussion highlights recent advances, underlying mechanisms, and emerging multidisciplinary applications that position CD NSs as promising platforms for next-generation drug delivery technologies.

Keywords: Cyclodextrin, nanosponges, encapsulation, pharmaceutical, cross linking agent, targeted drug delivery

Introduction

Cyclodextrins (CDs) possess a unique amphiphilic architecture that enables the formation of hyper-crosslinked, nanoparticle-sized three-dimensional networks known as nanosponges (NS) [1]. These sponge-like structures contain a mesh of microscopic cavities capable of accommodating a wide range of compounds (Figure 1) [2]. Owing to their spherical colloidal morphology, nanosponges exhibit both inclusion and non-inclusion interactions, resulting in an exceptional ability to enhance the solubility of poorly water-soluble drugs [3]. Nanosponges not only improve solubilization but also facilitate sustained drug release and enhance bioavailability [4]. They are solid, versatile carriers that have demonstrated safety for both oral and parenteral applications [5]. Their nanoscale dimensions further support venous, pulmonary, and topical drug delivery. For oral formulations, nanosponge–drug complexes can be incorporated into matrices containing excipients, diluents, lubricants, or anti-caking agents for capsule or tablet dosage forms. For parenteral use, the complexes can be dispersed in sterile water, saline, or other aqueous media, while topical administration can be achieved by embedding them into hydrogels [6]. Overall, nanosponges encapsulate drug molecules within their nanoporous structure, making them a promising and adaptable drug-delivery platform.

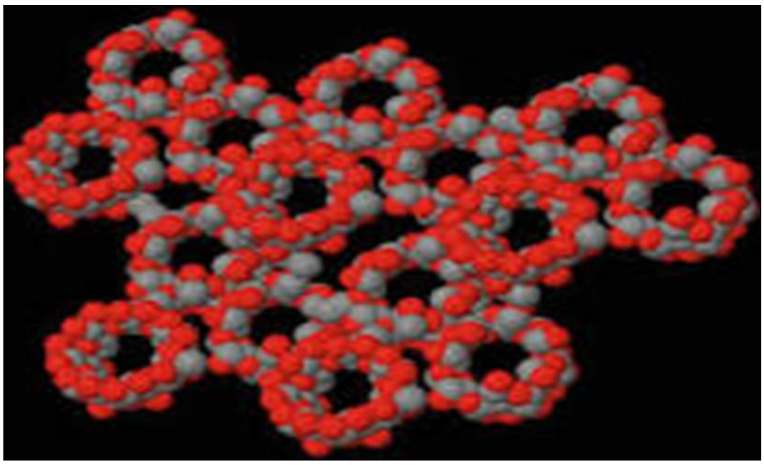

Fig 1: Cyclodextrin carbonate nanosponges' molecular structure

Nanosponges (NSs) are capable of transporting a wide variety of compounds owing to their ultra-small particulate structure, which contains nanometer-scale cavities. These porous nanoparticles can encapsulate both hydrophilic and lipophilic substances and significantly enhance the solubility of poorly water-soluble molecules. A defining characteristic of NSs is the presence of nanoscale pores, which contribute to their exceptional inclusion stability constants and high encapsulation efficiency. Cyclodextrin-based nanosponges (CDNSs) can be tailored by modifying reaction conditions during their synthesis, enabling broad applicability across scientific and technological fields such

as food, cosmetics, agriculture, chemistry, and environmental science. As an innovative colloidal drug delivery platform, CDNSs possess an average diameter of less than 1 μm—comparable to the size of a virus—and are composed of crosslinked cyclodextrin units forming hyper-reticulated, porous spherical structures [7, 8]. The most commonly used native cyclodextrins in these systems are α-, β-, and γ-cyclodextrins, which contain 6, 7, and 8 glucopyranose units, respectively. CDNSs are biodegradable, non-allergenic [9], and exhibit minimal cytotoxicity. They are also well tolerated in animal models, with mice showing good compatibility following CDNS injections. Due to their high zeta potential values (typically greater than −20 mV), most CDNS formulations form stable aqueous nanosuspensions with minimal aggregation over time. This stability offers a significant advantage in enhancing the aqueous solubility of lipophilic drugs and improving their administration in physiological fluids. Over the past decade, CDNSs have gained increasing attention not only as drug carriers but also in other applications such as pollutant removal and environmental remediation [9]. In their review, Caldera *et al* [10]. classified nanosponge drug delivery systems into four generations, summarizing their advancements and current status. The first generation comprises urethane-, carbonate-, ether-, and ester-linked NSs formed by reacting cyclodextrins with a crosslinking agent. The second generation includes polymers with specialized functional features, such as charged or fluorescent groups. The third generation consists of stimuli-responsive nanosponges that alter their behavior in response to factors such as temperature, pH, or redox changes. The fourth generation features molecularly imprinted NSs designed to exhibit selectivity toward specific guest molecules. Although nanosponges were initially employed for environmental applications, particularly in pollutant removal from water, their use has expanded significantly in recent years. They are now widely explored in pharmaceuticals, cosmetics, and analytical applications, including as components of HPLC stationary phases.

The History and Evolution of Nanosponges in the Past Fifty Years

From the early days of crosslinked insoluble CD polymer research to the multifunctional polymers of today, this article gives a thorough overview of the field.

1. Insoluble Crosslinked Cyclodextrin Polymers: A History from the 1960s to the 1980s.

In 1965, Solms and Egli conducted a pioneering study on novel network polymers synthesized from cyclodextrins (CDs) crosslinked with epichlorohydrin (EPI). In their approach, CDs were dissolved in water and subsequently treated with sodium hydroxide and sodium borohydride, enabling EPI to function as the crosslinking agent. The binding properties of these newly developed materials were compared with those of EPI–dextran network polymers. The researchers observed that the polymers exhibited inclusion capabilities for iodine and several organic compounds, including benzaldehyde, butyric acid, pyridine, aniline, and both p- and o-nitrophenol. Notably, the differential inclusion behavior between o- and p-nitrophenol suggested that these materials could be applied in separation techniques based on molecular size and shape [11]. This concept was further advanced in the 1970s with the development of new stationary phases designed for the separation of mandelic acid derivatives [12] and nucleic acids [13].

2. Studies on the Properties and Uses of Polymers from the 1980s to the 1990s

During the 1980s, research shifted from merely assessing the binding capabilities of these novel cyclodextrin-based materials to a deeper investigation of their structural and functional characteristics. In 1980, studies were conducted on polyurethane–cyclodextrin (CD) network polymers and other insoluble porous polymers synthesized using crosslinkers such as 1,3-bis(isocyanatomethyl)cyclohexane, 1,3-bis(isocyanatomethyl)benzene, and hexamethylene diisocyanate (HMDI). These polymers were prepared by heating pyridine while CDs were stirred with the respective diisocyanates. Extensive characterization was undertaken to better understand the properties of these new materials. Techniques such as elemental analysis (to quantify unreacted –OH groups in CDs), thermal analysis, Brunauer–Emmett–Teller (BET) surface area measurements, and gas chromatography were employed to study the interactions between CD-based polymers and various organic compounds [14]. Additionally, researchers examined how the type and degree of crosslinking influenced the guest-binding behavior of CD polymers [15]. Crosslinkers evaluated included 1,3-butadiene diepoxide, 1,7-octadiene diepoxide, 1,2-ethanediol diglycidyl ether, 1,4-butanediol diglycidyl ether, 1,6-hexanediol diglycidyl ether, and epichlorohydrin (EPI). The potential applications of CD polymers in the food industry also began to emerge during the late 1980s and 1990s, marking an important expansion of their use beyond fundamental material studies.

3. 1999: “In the Beginning Was the Word”

Min Ma and De Quan Li used the word "nanosponge" for the first time in 1999 [16]. They reported new CD-based nanoporous polymers joined by diisocyanate linkers. The crosslinker was combined with CDs in DMF and heated for a whole day. Despite having a little surface area, these NSs demonstrated an unexpectedly high adsorption capacity, creating new opportunities in the realm of water treatment. The advantages of the purifying procedures used thus far, such as cost and adsorption capacity, have outweighed the disadvantages, which include reverse osmosis and adsorption on activated carbon, or zeolites.

4. Between 2000 and 2009: The New Millennium Brought New Uses

In the new millennium, nanosponges (NSs) opened promising avenues across emerging scientific and technological domains, while their established applications continued to remain highly relevant. Cavalli *et al*. were among the first to demonstrate that carbonate-based cyclodextrin nanosponges (CD NSs) are capable of encapsulating both hydrophilic drugs, such as doxorubicin, and lipophilic drugs, including dexamethasone and flurbiprofen, enabling prolonged drug release [17]. Carbonate CD NSs also markedly enhanced the solubility of the antifungal agent itraconazole, potentially improving its bioavailability; the incorporation of copolyvidonum and other excipients was shown to further augment therapeutic performance [18]. Toward the end of the decade, NSs found additional applications as platforms for enzyme immobilization. In particular, carbonate NSs improved the

thermostability, pH tolerance, and storage stability of immobilized catechol 1,2-dioxygenase. The enzyme-loaded NSs functioned effectively as miniature bioreactors for the environmentally friendly synthesis of cis, cis-muconic acid, a key precursor in the industrial production of adipic acid [19].

5. 2010–2015: Emphasizing Nanosponges as Delivery Methods

Cavalli *et al*. (2010) specifically examined the oxygen-carrying capacity of nanosponges synthesized from α-, β-, and γ-cyclodextrins crosslinked with 1,1′-carbonyldiimidazole (CDI) [20]. Their findings demonstrated that ultrasound stimulation significantly enhanced the long-term encapsulation, storage, and controlled release of oxygen by these nanosponges—most notably by β-CD-based nanosponges—*in vitro*. Over the past several years, a wide array of NS-based drug delivery systems has been developed using different cyclodextrins and crosslinking agents. These advancements have improved drug performance by enhancing permeability, stability, sustained release, solubility, and overall bioavailability. Beyond pharmaceutical applications, cyclodextrin nanosponges have also shown promising potential in non-medical fields such as agriculture and flame retardancy. In agriculture, NSs have been employed to enhance the bioavailability and efficacy of essential nutrients, resulting in improved plant growth. For instance, Fe-loaded nanosponges promoted growth and chlorophyll recovery in tomato and sweet corn plants [21]. Additionally, nanosponges have been explored as novel flame-retardant materials due to their unique structural properties.

6. From 2016 to the Present: Current and Upcoming Developments in Nanosponges

The growing body of literature around CD-based Nanosystems (NSs) implies that they have gained traction over the past decade and have attracted attention from researchers in diverse disciplines. The ability of β-cyclodextrin/DPC NSs to encapsulate hydrophilic medications like gemcitabine as well as lipophilic medications like paclitaxel, bicalutamide, and letrozole was reviewed by Patel and colleagues (2016). Lipophilic drugs usually have a higher drug loading capacity than hydrophilic drugs because they have more lipophilic sites for drug complexation. In 2017, it was shown that β-CD/CDI NSs loaded with anti-cancer drugs erlotinib (an inhibitor of the epidermal growth-factor receptor tyrosine kinase) and camptothecin (an inhibitor of DNA Topoisomerase-I) improved oral bioavailability, solubility, and dissolution while lowering dose-related side effects [22]. In 2019, Fontana *et al*. undertook work with cyclodextrins in conjunction with calixarenes, establishing NS systems (CyCaNS) with unique columnar architectures that gave rise to pH-sensitive adsorption (of a model drug, tetracycline antibiotics) and release [23]. Coulomb interactions between the positively charged guest molecule and the average charge density on the polymeric framework—which were produced by the presence of ionizable amine or carboxylic groups through chemical post-modification—were assumed to be the cause of the material's pH-sensitive characteristics.

Fabrication Techniques Nanosponges

Cyclodextrin-based nanosponges (NSs) can be synthesized using either a solvent-based method or a melt-based technique. In both approaches, a carbonyl- or dicarboxylate-containing compound serves as the crosslinking agent, enabling the formation of nanosponge structures from any type of cyclodextrin [24]. The choice of crosslinker significantly influences key characteristics of the resulting nanoporous polymer, particularly its swellability and hydrophilic–hydrophobic balance. In the melt method, cyclodextrins and the crosslinker are fused together under controlled heating. Finely powdered reactants are placed into a 250 mL flask and heated to approximately 100 °C. The mixture is magnetically stirred and allowed to react for about five hours. Following completion of the reaction and subsequent cooling, the solid mass is crushed and thoroughly washed with appropriate solvents to remove unreacted materials and byproducts. The final product is then collected and processed further as needed (Fig. 2)., the following Figure 2 shows the techniques used to prepare nanosponges:

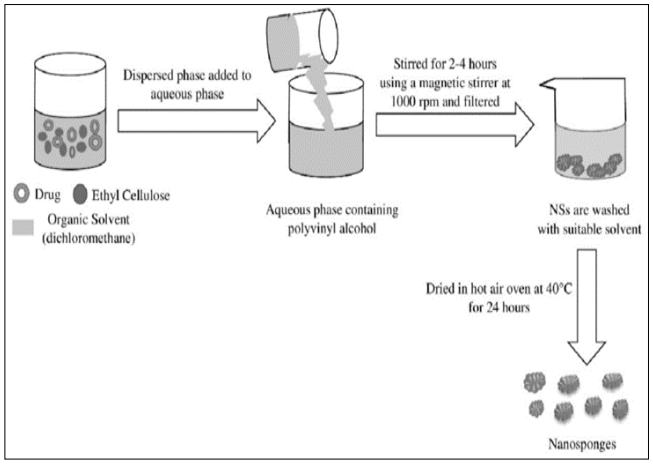

Fig 2: Illustration of the nanosponge preparation process

1. Diffusion method of emulsion solvent

First, dissolve a set amount of polyvinyl alcohol in 150 milliliters of water. Once that's ready, slowly add the mixture of drug and ethyl cellulose. You can play around with the ethyl cellulose and polyvinyl alcohol ratios to get different types of nanosponges. Mix everything at 1000 rpm for two hours. After that, filter out the nanosponges and bake them at 400 degrees Celsius for 24 hours to dry them completely [25]. Finally, place the dried nanosponges in vacuum desiccators to make sure every last bit of solvent is gone.

2. Solvent method

Start by adding a polar, protic solvent like DMSO or DMF to the polymer. Then toss in a good amount of cross-linker—aim for a molar ratio between 4 and 16. Let the reaction run anywhere from an hour to two days, keeping the temperature between 10°C [26] and the boiling point of your solvent. When it's done, collect the product using vacuum filtration. To clean things up, run a Soxhlet extraction with ethanol for a thorough wash. Once you've got your product, let the solution cool down to room temperature. Mix in a large amount of distilled water. After that, dry the product under vacuum, then grind it up in a mechanical mill until you get a nice, even powder.

3. Synthesis using ultrasound assistance

Hit the mixture with some sonication—no solvent needed—and the polymers and cross-linkers jump into action,

forming nanosponges. They come out round and pretty consistent in size, always under 5 microns [27]. For the cross-linker, it's either diphenyl carbonate or pyromellitic anhydride. After purification, just keep the nanosponges at 25 °C.

Cyclodextrin based nanosponges

Cyclodextrins are a group of ring-shaped sugar molecules called cyclic oligosaccharides. They form when cyclodextrin-glycosyl transferase (CGT) breaks down starch and creates these circular sugar chains. People usually call these cyclic oligosaccharides simply CDs [28]. To make CDs, you start by mixing the polymer and a cross-linker in a flask. Heat the flask up to 90°C, then place it in an ultrasonic water bath and let it sonicate for five hours. After that, crush the solid in a mortar, and use ethanol soxhlet extraction to wash away any leftover polymer or impurities. CDs are built from anhydrous α-D-glucopyranoside units (AGU) [29], each connected by an α-1,4 bond. CDs don't reduce other substances, they're crystalline, and they dissolve in water. The number of AGU units usually sits at six, seven, or eight, which gives you α-, β-, and γ-CD, in that order [30]. Each type forms a hollow, cone-shaped cylinder, typically about 5–10 x 10–10 meters wide and 7.9–8 x 10–10 meters deep. The size of the hollow space depends on how many glucose units are involved. You can check out the specific structural details for α-, β-, and γ-CD in Table I.

Table 1: Physicochemical characteristics of α-, β-, and γ-cyclodextrins relevant to nanosponge formation

Characteristics	α -CD	β -CD	γ - CD
Molar mass (g mol–1)	972	1135	1297
Depth-height cone (10–10 m)	7.9-8	7.9-8	7.9-8
Internal diameter (10–10 m)	4.9	6.2	7.9
External diameter (10–10 m)	14.6	15.4	17.5
Cavity volume	174	262	472
Water solubility (g per 100 cm3) at25°C	14.5	1.85	23.2
Crystal water (m, %)	10.2	13.2-14.5	8.13-17

Cyclodextrins, or CDs, have got this cylindrical shape with a hollow center, and their structure gives them polar features, higher electron density, and strong Lewis base behavior. Thanks to this cage-like setup, CDs can actually trap other molecules—if the size and polarity fit—inside their cavities when they're in water. You can see some examples of this in Table I. Here's the cool part: the main reason these complexes form isn't because of covalent bonds. Instead, it's the release of water molecules from inside the CD that drives the process. Those water molecules are packed with energy, so when they leave, it makes the whole thing more stable. People have also figured out that if you treat CDs on their secondary face with C6 aliphatic esters, you can make them into nanospheres and nanocapsules using nanoprecipitation [31]. But, studying CD complexes isn't always straightforward. Sometimes the drug doesn't dissolve well, or the drug/CD complex just isn't stable enough, so you don't get the solubilizing effect you want. That's where nanosponges come in. They help tackle these problems. Out of the natural CDs—α, β, and γ—β-cyclodextrins stand out. They're the best at forming stable complexes and work great as crosslinking agents for making nano-sponge systems. Their structure lets drugs slip inside the cage and hang around in a controlled way, thanks to their extensive internal network.

Nanosponges' characterization

Nanosponges are defined by the following factors in order to investigate how they interact with loaded pharmaceuticals and to comprehend the synthesis, production, and design process.

1. Phase solubility

To figure out phase solubility constants, you start by mixing extra amounts of the drug with the right solvents until you hit saturation. Then, you add blank nanosponges to these saturated solutions at different ratios—like 1:1, 1:2, 1:3, and so on [32]. This whole process helps show how nanosponges affect how well the drug dissolves. As you increase the amount of nanosponges, more of the drug interacts with them. You keep going until everything balances out. To plot the drug concentration against the nanosponges concentration, the Higuchi and Connors method is used to make sense of the curve [33]. The stability constant you get from this tells you just how strong the drug-nanosponge connection is. Basically, when drugs mix with nanosponges, they can dissolve better and faster than on their own. So, for drugs that barely dissolve in water—like steroids, anti-inflammatories, or some cancer medications—nanosponges really boost their solubility.

2. Porosity

The porosity of the nanosponges is measured using a helium pycnometer because helium gas can flow through both intra- and inter-particular channels in materials. The actual volume of the material is calculated using the helium displacement method [34]. Because of their porous nature, nanosponges are more permeable than the parent polymer that created the system. The percentage of porosity can be computed as follows:

% Porosity = Bulk volume - True volume / Bulk volume × 100

3. Sem and Tem

These instruments help us figure out the size and shape of the particles. With SEM, you hit the particles with a focused electron beam, making them conductive while they sit in a vacuum. ESEM works when you need to look at wet samples, so it's handy in those situations. If you want to see what particles look like when they're floating in liquid, you use TEM. Ansari and his team actually used both TEM and SEM to study prepared nanosponges [35]. Their TEM results showed these nanosponges are pretty regular—round and uniform in size. Even after loading the drug into the nanosponges, their size and shape stayed the same.

4. Differential scanning calorimetry (DSC)

Thermoanalytical methods helps to detect the drug changes before the entire drug delivery system breaks down from

heat. These tests show if the drug melts, evaporates, decomposes, oxidizes, or shifts between different crystal forms—basically, all the ways it can interact with other materials. When you look at a thermogram from DTA or DSC, you check for things like peaks moving, new ones popping up, or old ones fading away [36]. These changes say a lot about what's happening inside the material. If the drug spreads out evenly in the polymer, the DSC thermogram reflects that. You can also spot inclusion complexes by looking at weight loss on the graph. When the DSC thermogram no longer shows the drug's melting peak, it means the drug isn't in its usual crystalline state anymore—it's mixed in with the NS structure [37]. That missing peak backs up the idea that the drug and NS are interacting. So, both the changes in weight and the altered thermogram point to the formation of these inclusion complexes.

5. Thermogravimetric analysis (TGA)

These investigations aim to really get how these particles act when it comes to crystals, melting, and holding up under heat [38]. Trotta and the team found that β-CD breaks down all at once when you put it in a nitrogen atmosphere. What's left is a carbon-rich residue that sticks around and only slowly breaks down as the temperature climbs. If you heat that char in air below 600 °C, it turns into volatile compounds. What's left below 800 °C is a stable, ceramic-like residue. During charring, as the cyclodextrin rings break open, you get more unsaturated, carbonyl, and aromatic structures, while glycoside and hydroxyl groups disappear—pretty much the same chemical changes you see in cellulose. Nanosponges act in a similar way. No matter which atmosphere you use, they form a stable char at 800 °C and lose the most weight at 320 °C when they break down completely.

Elements that influence the development of nanosponges

Hydrophilic and hydrophobic materials are encapsulated in nanosponges, which function as three-dimensional networks. A variety of characteristics are addressed below that impact the formulation of nanosponges using different techniques.

1. Crosslinkers and polymer types

The type of polymer employed in the composition of nanosponges determines how efficient they are. Three-dimensional (3D) structures are created from nanoporous molecular structures using efficient crosslinkers. Depending on the degree of crosslinking, target molecules may become entangled in hydrophilic or hydrophobic sections. The insoluble or soluble nature of the nanosponges in water depends on the type of crosslinkers used [39]. Epichlorohydrin can be crosslinked to create hydrophilic nanosponges, which can enhance drug absorption across biological membranes and serve as an effective drug carrier. Hydrophobic nanosponges can be made with crosslinkers like diphenylcarbonate, pyromellitic anhydride, and diisocyanates to distribute hydrophilic drugs, like proteins and peptides, over a long period of time.

2. Drug and medium type for interaction

The formulation of nanosponges can be affected by the type of drug to be loaded, the solvents used, and the type of crosslinker and polymer used. For drug molecules to adequately encapsulate in nanocavities, they must possess certain advancing properties. To effectively encapsulate medications in nanocavities, molecules should have a molecular weight between 100 and 400 Da**,** a melting point below 250^{o}C, fewer than five condensed rings, and a water solubility of less than 10 mg/ml [40]. Typically, substances that have a higher melting point normally become unstable in order to hold stable complexes with drugs. Temperature variations also impact a complex's stability constant. An increase in temperature has an inverse relation with stability constant. As temperature increases there are fewer contact forces between the drug and the nanosponge, which will decrease the apparent size of stability constant. This provides insight into how stability should be considered in the formulation of a nanosponges. Drug loading will be impacted by the drug's high melting point. Organic solvents can liberate organic molecules trapped in the nanosponges, and vice versa, by employing a hydrophilic medium to release organic guest molecules into hydrophobic cavities. This indicates that the targeted molecule's interactions with the Nanosponge cavity are also malleable based on the medium that has been formulated.

3. Temperature

The drug-nanosponge complexation may be impacted by temperature variations. The apparent stability constant of the drug/nanosponge complex typically decreases with increasing temperature. This could be explained by a decrease in the drug/nanosponge contact forces, such as van der Waal and hydrophobic forces.

Application of nanosponges

As Table 2 shows, nanosponges can contain a wide range of drugs. They are also sufficiently adaptable and biocompatible to be utilized as excipients in the production of tablets, capsules, pellets, granules, suspensions, solid dispersions, and topical dosage forms. Chemical, physical, and thermal stability can be improved, longer release and reduced irritation can be achieved, and product performance and appearance can be improved with nanosponges.

Table 2: Drugs formulated using cyclodextrin-based nanosponges and their associated therapeutic advantages.

Drug	Medicinal action	Transport of Nanosponges	Features	Route of Administration
Itraconazole	Antifungal	β-CD, copolyvidonum	Improved solubility of the medication	Oral, topical
Dexamethasone	Reducing inflammation	β-CD, diphenylcarbonate	Improved solubility of the medication	Oral, parenteral
Flurbiprofen	Reducing inflammation	β-CD, diphenylcarbonate	Continuous release of drugs	Oral,
Doxorubicin	Antineoplastic	β-CD, diphenylcarbonate	Continuous release of drugs	parenteral
Nelfinavir mesylate	Antiviral	β-CD, diphenylcarbonate	Improved solubility of the medication	Oral,
Gamma-oryizanol	Antioxidant	β-CD, diphenylcarbonate	Improved permeability, stability, and solubility	Topical
Fluorouracile	Antineoplastic	β-CD,	Improved solubility of the medication	intravenously, topical

Tamoxifen	Antiestrogen	β-CD, carbonyldiimidazole	Improved solubility and bioavailability	Oral,
Resveratrol	Antioxidant	β-CD, carbonyldiimidazol	Improved stability and penetration,	Oral, topical
Curcumin	Antineoplastic	β-CD, dimethylcarbonate	Increased solubilization and activity	intravenously,

Drug delivery using nanosponges

Nanosponges' minuscule porosity structure allows them to transfer the medication, which is insoluble in water. Solubility and permeability are essential for medication nanosponges to dissolve more quickly. β-cyclodextrine-based nanosponges are said to be three to five times more effective at delivering the medication to the desired location. Usually made of solid substances, nanosponges are available in parent, topical, oral, and inhalation dosage forms. To make the nanosponges complexes suitable for oral administration as tablets and capsules, they are dissolved with a suitable excipient, such as lubricants, diluents, or anti-cracking agents [41]. A number of characteristics of nanosponges improve product performance and aesthetics, including regulated and prolonged release, reduced skin irritation, improved solubility, and increased product flexibility.

Table 3: Class II drugs (Biopharmaceutical Classification System) commonly targeted for nanosponge-mediated solubility enhancement.

Category/Class	Examples
Antihypertensive drugs	Felodipine, Nicardipine, Nifedipine, Nisoldipine
Antiarrhythmic agents	Amiodarone hydrochloride
Antibiotics	Azithromycin, Ciprofloxacin, Erythromycin,
Anticonvulsants	Carbamazepine, Clonazepam, Felbamate, Oxycarbazepine, Primidone
Antifungal agents	Econazole nitrate, Griseofulvin, Itraconazole
Antineoplastic agents	Camptothecin, Docetaxel, Etoposide, Exemestane, Flutamide, Irinotecan,
Antipsychotic drugs	Chlorpromazine Hydrochloride
Cardiac drugs	Carvedilol, Digoxin, Talinolol
Diuretics	Chlorthalidone, Spironolactone
Immunosupressants	Cyclosporine, Sirolimus, Tacrolimus
Gastroprokinetic agent	Cisapride

1. Pharmaceutical Applications

As drug carriers in many pharmaceutical formulations, CD-based NS are innovative systems that appear to hold promise. Drug-CNS interactions, molecular-level encapsulation, and other adjustments with the appropriate CDs help to overcome issues with permeability and solubility, among other things, and promote safer and more effective drug delivery [42]. BCS (Biopharmaceutical Classification System) and volatile oils and chemicals are also encapsulated with the help of NS. Through adsorption, NS nanopores trap flavors and odors, disguising the disagreeable tastes and smells of many organic molecules. They also offer a way to turn liquids into solid powders. Numerous researchers have cited the use of C-based NS to remove organic contaminants and oil spills from water. According to numerous previous researches, β-C based NS effectively distributes drugs to target locations three to five times more efficiently than direct injection. Hydrogels and other topical dosage forms work well for topical delivery, as do simple dispersions of the complex prepared in saline, sterile water, or other aqueous solutions for parenteral administration.

1.1 Modulating drug release

Most traditional commercial distribution methods have frequent administration as their main disadvantage. However, a drug that has been incorporated into the nanosponge structure may be kept and administered gradually over time. Hydrophilic CDNS can act as a powerful drug carrier in rapid release formulations and alter the rate of drug release to improve drug absorption through biological barriers. Hydrophobic CD NS have the potential to function as prolonged release vehicles for water-soluble medications, such as protein and peptide medicines [43]. In addition, nanosponges can be utilized to transport medications, such as the anticancer medication doxorubicin, and they may shield the medication from harm. When the pH is raised to 7.4, the medicine releases more quickly, but at pH 1.1, it releases very slowly.

1.2 Effective delivery carriers

Cyclodextrin nanosponges have been utilized to deliver anticancer medications like tamoxifen, camptothecin, and paclitaxel, which have poor or nonexistent water solubility and hence pose bioavailability issues. In order to examine the antiproliferative activity of the medicines, they were integrated into nanosponges and tested on a variety of cell lines. The effect of complexes was higher than that of the medication by itself. Loading paclitaxel into nanosponges increased its mean absolute bioavailability, which was found to be 2.5 times greater than that of the drug in its simple form [44] Effective therapy requires the application of high doses of active drugs because econazole nitrate does not significantly adsorb when applied topically.

2. Nanosponges as biocatalysts carrier

The transport of proteins, enzymes, vaccines, and antibodies is accomplished using nanosponges. Many industrial processes that rely on chemical transformation have operational issues. The downstream process frequently necessitates high pressures and temperatures, requiring a significant amount of energy and cooling water, and non-specific reactions result in low yields. These enzymes are very selective, act more quickly, and function in mild reaction circumstances. They help the environment by using less energy and producing less pollution. Enzymes are now more stable, economical, and specific thanks to advancements in genetic engineering, and their industrial

uses are growing daily. Enzymes that are useful in industry include ligninase, which breaks down lignin; alpha amylase, trypsin, cellulose, and pectinase; and lipase, which is used in the detergent industry and in the creation of biodiesel, among others. The catalytic activity of the enzyme is mostly dependent on the active site's proper orientation. Additionally, proteins, peptides, enzymes, and their derivatives have applications in biology and medicine. Gene therapy uses DNA and oligonucleotides, while type I mucopolysaccharidosis and cancer can be cured with proteolytic enzymes. The stability, economy, and specificity of enzymes have improved due to advancements in genetic engineering, and their industrial uses are growing daily. Enzymes that are useful in industry include lipase, cellulose, pectinase, ligninase, alpha amylase, and trypsin. Lipase is used in the production of biodiesel and in the detergent industry. The enzyme's catalytic activity is mostly determined by the active site's proper orientation [45]. Proteins, peptides, enzymes, and their derivatives can also be used in the biological and medical domains. To increase protein stability, cyclodextrin-based swellable poly (amidoamine) nanosponges are used to encapsulate proteins like BSA (Bovine Serum Albumin)

3. Nanosponges as a barrier against deterioration or light

As a natural antioxidant, gamma-oryzanol, a ferulic acid ester combination, has garnered a lot of attention lately. Usually, it is utilized as a sunscreen in the cosmetics business as well as to stabilize raw ingredients used in cooking and medicine. There are limitations to its utilization because of its high instability and photodegradation. Gamma-oryzanol exhibited strong defense against photodegradation [46] when enclosed in nanosponges.

3.2 Nanosponges for treating cancer

The distribution of anticancer medications is among the most difficult within the pharmaceutical field due to their code splendid solubility. Researchers from Vanderbilt University have created nanosponges that are meant to be used with tumors and as a way to deliver anticancer drugs. According to thier research, this delivery system is three or five times greater than that of giving the medication directly to a tumor. Once the tiny nanosponges are loaded with medicine, a targeting peptide is released that binds to the radiation-induced tumor cell surface receptors. When the nanosponges stick to the surface of the tumor cells they encounter, they will release their medication. At the same dosage, a targeted medication delivery system offers more beneficial treatment with fewer side effects.

4. Remediation of the Environment

When used in environmental remediation, CDNSs' three-dimensional structure offers a number of benefits, as evidenced by their comparable pollutant removal percentages to activated carbon (AC). It's also been shown that a variety of synthetic parameters influence the material's physico-chemical characteristics and, consequently, the effectiveness of pollutant removal. These components include solvents, aliphatic or aromatic linkers, and the molar ratio of crosslinkers to CDs. EPI is one of the aliphatic linkers most frequently used for CD coupling in environmental remediation, along with citric acid, HDI, and EDTA. Aromatic linkers include TDI and tetrafluorotephtalonitrile (TFP).

5. Heavy Metals

Due to their ease of absorption by living things, which causes bioaugmentation and bioaccumulation, heavy metals are one of the main pollutant classes on Earth. Furthermore, mental impairment, liver and kidney issues, dementia, and allergic reactions can all result from exposure to heavy metals in particular [47]. Both aliphatic and aromatic crosslinker-based CDNSs have been used to synthesize and assess heavy metals such as Cu (II), Zn (II), Pb (II), Cd (II), Ni (II), Co (II), Hg (II), Fe (III), Cr (III), and As (V). Both EDTA and citric acid [48] are crucial crosslinkers for aliphatic-based CDNSs because they develop highly crosslinked materials and have a lot of carboxylic acid groups available, which greatly expands the number of active sites for interaction with metal ions. These substances can also sorb substances that change in pH. Nevertheless, as the number of sorption/desorption cycles increases, its removal efficiency falls [49]. The sorption process of pure βCD-EDTA is facilitated by an acidic pH, which removes over 90% of Pb (II), Ni (II), Cu (II), Co (II), Hg (II), and Cr (III) in about one minute. Likewise, the removal of Pb (II), Cu (II), and Cd (II) was investigated using methacrylic-βCD with 1–vinylimidazole (VI) (MCD:VI) and NSs of βCD and TFP [49]. When considering the substantial amount of heavy metals absorbed per gram of material, βCD: TFP has the largest active surface area (Pb (II): 196.4 mg g−1, Cu (II): 164.4 mg g−1, and Cd (II): 136.4 mgg−1).

6. Dyes

Many industries, most of which are in the consumable manufacturing business, for example, paper, textiles, and inks, use dyes. The textile industry accounts for possibly the largest use of water in terms of the sheer volume as well as the quality of water; it is also a major source of environmental pollution via its use of dyes. Also, it is difficult to remove dyes from wastewaters, as they are usually chemicals soluble in water. The dyes methylene blue (MB), safranin O (SF), and crystal violet (CV) were removed using βCD: EDTA. The MB results showed a more than 90% elimination efficiency. Zhao *et al*. (2015) demonstrate how the interaction of dye molecules with carboxylate groups in EDTA is essential. A variety of dye intermediates and benzene derived dyes were investigated using two specific linkers: 4,4′ bis(chloromethyl)-1,1′-biphenyl (FPS) for βBCD and 4,4′ bis(chloromethyl)-1,1′-biphenyl (CMP) for βCD. βCD: FPS achieved ≥80% and ≥99% removal efficiency for 2-naphthol elimination in batch and flow-through sorption studies, respectively [50]. Many other aromatic compounds have been or are being studied with respect to their potential to adsorb on βCD:CMP that included nitrobenzene, 2-nitrophenol, 2-nitroaniline, 4-nitroaniline, and 2-chloroaniline.

7. Sensors

Cyclodextrin-based materials employ host-guest complexation or molecular assembly with fluorescent/luminescent probe molecules to activate or deactivate fluorescence, making them suitable for both direct and indirect sensor applications. Two fluorescent ligands, tetrakis (4-hydroxyphenyl) ethane (TPE) and 4,4′-diisocyanato–3,3′-dimethyl biphenyl (IMP), can cross-link βCD to create a fluorescent probe based on cyclodextrin. Turn-off detection of trinitrophenol and nitrobenzene was accomplished with the fluorescent βCD-polymer. These

aromatic compounds have the potential to pollute the environment and endanger human health when used in the production of dyes and insecticides [51]. βCD: PMA was created as a fluorescent probe with a molar ratio of 1:7 mol/mol and an emission wavelength of 423 nm. The polymer's size distribution is heterogeneous and its polydispersity index is high. It has strong diclofenac selectivity in tablets and aqueous solution (LOD 0.92 µM); the presence of other medications has no discernible effect on its value, most likely due to diclofenac's greater hydrophobicity [52]

8. Catalysts

The high active surface area and numerous accessible active sites of porous polymeric materials, also known as CD nanosponges, make them promising candidates for use as heterogeneous catalysts. An intriguing illustration is βCD: CDI, which exhibits metal-free catalytic activity in a one-pot condensation reaction of three constituents (amines, methylene compounds, and aromatic aldehydes) for the creation of organic scaffolds that contain nitrogen. According to Sabzi and Kiasat (2018), βCD: CDI has an active surface area of 11 $m^2g{-}1$ and the nanoporous structure shows a diameter of 5 nm. The authors mention that pyranopyrazole derivatives and spiro [indoline–3,4′–pyrano(2,3–c) pyrazole] can be synthesized using βCD: EPI (i.e., βCD: epichlorohydrin) (which has surface area of 11 $m^2g{-}1$ and a pore diameter of 5 nm) via a solvent-free reaction with four components. However, they go on to state that the reaction only proceeds with a high yield at 100 °C. In a different study, a heteropolyacid referred to as DPC (which has a surface area of $3m^2g{-}1$ with a pore size of 14 nm) was immobilized onto βCD, in order to catalyze the synthesis of xanthenes with good yields (87-95%), at reflux temperatures, and in short reaction times (Sadjadi *et al*. 2017b). At 80 °C, good yields were observed in the absence of solvent. A stable porous composite with a surface area of 11 $m^2g{-}1$ was produced by covalently bonded amino-βCD NSs.In the Biginelli reaction, βCD:CS was employed as a metal-free catalyst to produce octahydroquinazolinone and dihydropyrimidinone in water. The composite exhibits remarkable catalytic activity at 25°C with yields of up to 100% when treated with ultrasonic assistance. A yield drops of roughly 10% was seen when the composite was reused after five cycles (Sadjadi and Koohestani, 2021a).

Conclusion

Cyclodextrin-based nanosponges represent a highly adaptable class of multifunctional, hyper-crosslinked polymeric carriers capable of encapsulating both hydrophilic and lipophilic compounds through inclusion and non-inclusion mechanisms. Their versatility enables safe and effective drug delivery via oral, topical, and parenteral routes, while also offering controlled release, enhanced stability, and reduced toxicity. The structural rigidity imparted by extensive crosslinking supports supramolecular host–guest interactions and enables the development of specialized systems, including matrices exhibiting Aggregation-Induced Emission (AIE). The potential to integrate biodegradable and bioabsorbable components further strengthens their suitability for biomedical use. Although significant progress has been made, deeper investigation is required to fully understand the *in vivo* behavior, long-term safety, and biological fate of these nanoscale carriers. The tunability and functional flexibility of cyclodextrin nanosponges make them promising candidates for future advances in drug delivery, catalysis, sensing, and environmental remediation. Continued research is expected to unlock new applications and optimize their performance across diverse scientific and industrial domains.

Future Perspectives

In the widest range of fields, cyclodextrin nanosponges are still in their infancy stages of widespread use. Their use in the biomedical and pharmaceutical sectors is the basis for many of the studies that are currently being discussed in the literature. However, relevant studies on the application of nanosponges in water and, to a lesser extent, soil restoration have been included in recent publications. A notable study on CDNSs' ability to remove chlorinated disinfection by-products (DBPs) was conducted in 2007 (Mhlanga *et al*., 2007) [53]. NSs should be created for this reason since the European Community has prioritized this issue after fifteen years. Insecticides, antibiotics, and antidepressants are among the other pollutants whose molecular structures suggest that CDNSs may have a high removal efficiency. Cyclodextrins are stiffened by hypercrosslinking, which limits the degree of freedom of guest molecules interacting with NSs through supramolecular host-guest interactions. When creating matrices for aggregation-induced emission, this phenomenon is helpful (Hong *et al*., 2009) [54]. Chromophore aggregation is generally assumed to result in a dampening of light. Aggregation-Induced Emission, on the other hand, is the opposite effect of some compounds. The limitation of intramolecular rotation (RIR) could be the cause of this. CDNSs appear to be possible matrices that support the RIR mechanism and, thus, cause the chromophores to emit light. This phenomenon may have an impact on fields like sensors and optoelectronics. We also consider the application of NSs to heterogeneous catalysis to be in its early stages. Because they require the use of chiral metal complexes, hazardous organic solvents, and homogeneous catalysis techniques, the majority of current asymmetric synthesis methods are not sustainable. However, using heterogeneous matrices for enantiomeric discrimination that have a high density of hydrophobic voids could be a useful substitute. Additionally, metallic nanoparticles can be added to CDNSs to modify them, enabling the creation of organometallic heterogeneous catalysts that are more sustainable. It should be noted that the writers have tried some of these ideas and opinions, and the findings are preliminary. " In spite of this, we are convinced that CDNSs, either alone or in conjunction with other polymers, hold significant potential for a number of as-yet-undiscovered applications outside their primary utility.

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