RESEARCH
www.commprac.com
ISSN 1462 2815

EXPLORING THE VERSATILE WORLD OF CYCLODEXTRIN NANOSPONGE: SYNTHESIS, CHARACTERIZATION, AND APPLICATIONS

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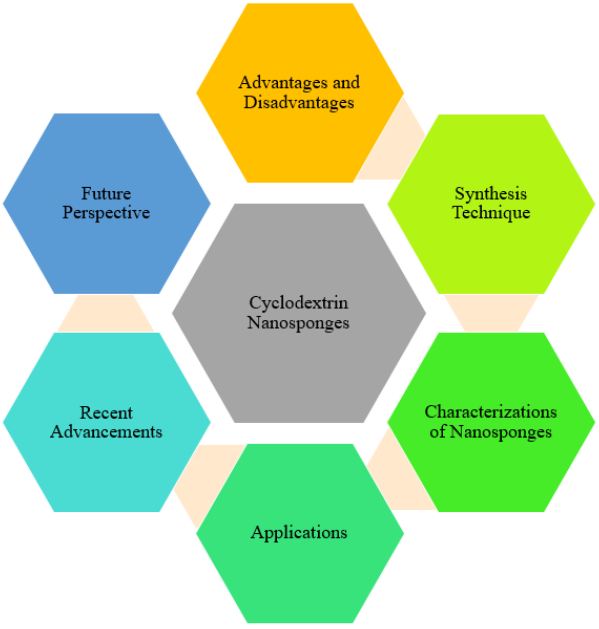
DOI: 10.5281/zenodo.12723560

Abstract

This study explores the potential of cyclodextrin-based nanosponges (CDNS) for enhancing drug delivery systems. Cyclodextrins are known for their ability to encapsulate guest molecules, enhancing the solubility and stability of poorly water-soluble drugs. The study focuses on preparations, characterization, and applications of nanosponges. These nanosponges exhibit significant advantages, improving drug solubility, controlled drug release, biocompatibility, and low toxicity. The study also highlights the novel applications of CDNS in areas such as cancer therapy, gene therapy, antimicrobials, and biosensors. Analytical techniques like FTIR, PXRD, and thermal analysis are employed to characterize the nanosponges and confirm the formation of the inclusion complex. The findings demonstrate the CDNS offers a promising platform for advanced drug delivery, with potential applications extending beyond pharmaceuticals to environmental sectors.

Keywords: Cyclodextrin, Nanosponge, Applications, Characterizations, Recent Advancements.

Graphical Abstract



1. INTRODUCTION

Cyclodextrins (CDs) have been the subject of investigation for more than a century and are extensively utilized in pharmaceuticals due to their ability to encapsulate or adhere to guest molecules within their central cavity [1]. Presently, CDs are widely employed in the food industry, textiles, personal care products, and various cosmetics, in addition to certain medical applications [2]. These remarkable molecules possess an intriguing amphiphilic structure, consisting of natural oligosaccharides created by α-(1,4)-linked glucopyranose units [3]. The initial 3 members of CDs, labeled as α-, β-, or γ-cyclodextrin, contain 6, 7, or 8 glucopyranose units, correspondingly. With their glucopyranose units adopting a chair conformation, CDs take on the truncated cone & torus shape, featuring a hydrophobic cavity [4]. Their Lewis base nature enables the creation of host−guest supramolecular structures, while the hydroxyl groups positioned at the cavity at both ends result in a hydrophilic outer surface, facilitating interaction with the polar compounds as well as enhancing water solubility [5,6]. The inner cavity is lined with skeletal C-H groups as well as ethereal oxygen from the residue of glucose, providing lipophilic properties. The hydroxyl groups of the sugar units in CDs are positioned in a way that the secondary hydroxyl group is at the broader edge and the primary ones are at narrow edges, making the outer surface hydrophilic [7]. The ability of glucose units to rotate around glycosidic linkage bonds can lead to dynamic rearrangement, affecting the optical activity along with cyclodextrins binding properties through an 'induced fit' mechanism [8].

Cyclodextrins exhibit a lower octanol/water partition coefficient (log Po/w almost ranging from −3 to 0) and possess numerous hydrogen donors and acceptors. These attributes prevent cyclodextrins from permeating biological membranes [9]. They are generally recognized as safe (GRAS) by the FDA, as toxicity researchers have demonstrated their oral administration to be non-toxic because of the minimal absorption from the gastrointestinal tract [10]. The technique of cyclodextrin complexation is primarily utilized to modify drug solubility, leading to a significant alteration in solubility when the drug forms a complex with cyclodextrin [11]. Cyclodextrin can form complexes with drugs in both solid and solution states, provided the guests are steric-compatible and fulfill polarity requirements [12]. The inclusion complex involves cyclodextrin's internal hydrophobic cavity acting as the host along with the hydrophobic moiety serving as the guest. The cavity allows for the partial or complete encapsulation of a hydrophobic component of appropriate dimensions. Within an aqueous solution, the hydrophobic part displaces water inside the hydrophobic cavity, leading to the creation of the host-guest complex [13]. The cyclodextrin hydrophobic part needs to have an appropriate structure to enter the cyclodextrin cavity and create an inclusion complex [14].

1.1. *Advantages of Nanosponge*

The benefits of nanosponge technology include:

a) It significantly improves the solubility of poorly water-soluble drugs by forming inclusion complexes, thus enhancing their bioavailability [15].

b) They protect encapsulated drugs from degradation caused by environmental factors such as light, heat, and pH changes [16].

c) It can be engineered to release drugs in a controlled manner, extending the therapeutic effect and reducing dosing frequency [16].

d) They are known for their biocompatibility and low toxicity, making CDNS safe for use in medical and pharmaceutical applications [17].

e) They are non-immunogenic and can be safely metabolized by the body [18].

f) They can trap and remove contaminations [19].

g) They are used to stabilize active ingredients in the cosmetics and food industries [20].

1.2. *Disadvantages of Nanosponge*

The drawbacks of nanosponge technology are as follows: [21,22]

a) Nanosponges are limited to small molecules.

b) Reliance solely on loading.

2. TYPES OF NANOSPONGES

The interaction among 2 cyclodextrin molecules depends primarily on the crosslinker's type and characteristics used. Various NSs (NanoSponges) with different linkages are created depending on the specific crosslinker utilized.

2.1. Carbonate Nanosponges

In this scenario, active carbonyl compounds like carbonyl diimidazole, diphenyl carbonate, and trifosgene are utilized as crosslinkers. These compounds form carbonate bonds among 2 cyclodextrin monomers, causing the creation of carbonate NSs. The processing can be conducted either through the melt approach or solvent technique, at temperatures ranging from 80 to 100°C or at room temp, with or without the presence of a solvent. Carbonate cyclodextrin-based nanosponges are characterized by their notable polarity and adaptable cavity sizes.

Carbonate NSs could be produced in an amorphous state using the solvent approach or in a semi-crystalline state using the melt method, depending on the reaction conditions. Carbonate NSs are widely employed for encapsulating various “drug molecules like doxorubicin, flurbiprofen, dexamethasone, paclitaxel, cilostazol, camptothecin, progesterone, resveratrol, 5-fluorouracil, oxcarbazepine, nelfinavir mesylate, itraconazole, and tamoxifen, among others.

These nanosponges enhance the wetting along with the solubility properties of poorly water-soluble drugs”. Moreover, NSs of carbonate have minimal impact on the water surface tension and are non-hygroscopic, thus retaining their crystalline structure during moisture absorption and desorption [18].

Depending on their level of crystallinity, these nanosponges derived from carbonate cyclodextrin can improve solubility. For instance, amorphous nanosponges doubled the solubility of acyclovir, a commonly used antiviral medication, while crystalline nanosponges quadrupled the solubility of dexamethasone, a prominent anticancer drug [23].

2.2. Carbamate Nanosponges

Cyclodextrins are mixed with DMF solution and then “reacted with diisocyanates like hexamethylene diisocyanate (HDI) and toluene-2,4-diisocyanate (TDI) in a nitrogen atmosphere at the temp of 70 ℃ for 16–24 hours. After the reaction, any leftover DMF is” thoroughly eliminated by rinsing with the acetone, leading to the crosslinked

polymer powder creation. These NSs have an affinity for organic molecules and are primarily utilized for water purification purposes. For instance, nitrophenol can be effectively separated even at very low concentrations from its solution of water using these NSs. The NSs can typically adsorb organic molecules at a capacity ranging from 20 -40mg per cm3. NSs can eliminate around 84percent “of dissolved organic carbon from the wastewater [24]. Nanosponges are used to remove unwanted compounds from the water, like 2-methylisoborneol and geosmin, by utilizing cyclodextrin-based carbamate NSs [25].

Tang et al. investigated cyclodextrin-based carbamate NSs for their ability to adsorb aromatic amino acids, specifically L-phenylalanine, L-tryptophane, and L-tyrosine from a PBS. The adsorption effectiveness of these aromatic amino acids on cyclodextrin-based carbamate NSs followed the order: L-tryptophane > L-phenylalanine > L-tyrosine [26]”.

2.3. Polyamidoamine Nanosponges

NSs are usually created through a reaction carried out “in water. The β-CD polymerization with the acetic acid 2,20-bis(acrylamide) takes place over 94 hours at room temperature. Subsequently, the CD undergoes swelling in water, a behavior dependent on pH, and possesses both acidic as well as basic residues. Upon contact with the water, the polymer instantly forms a translucent gel, which was confirmed to remain stable for up to 72 hours in bio-relevant media through time-dependent swelling research.

Albumin, a protein” with approximately 90 percent encapsulation effectiveness, was utilized in the research, and in vitro investigations of the release of the drug indicated the potential for modulating protein release for up to 24 hours. Additionally, the product stability has been assessed using “sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS PAGE), confirming the” formulation stability, which remained stable for several months [27].

2.4. Modified Nanosponges

Modifying the reaction parameters allows for the customization of carbonate NSs to suit specific applications. A fluorescent variant is produced by the reacting carbonate NSs using fluorescein isothiocyanate at a temp of 90°C for several hours in the solvent DMSO.

These fluorescent NSs have proven to be useful in cancer treatment. Carboxylated NSs could be created utilizing cyclic organic anhydrides like maleic anhydride or succinic anhydride [23,27].

These NSs can interact with biologically relevant carriers like proteins, chitosan, or biotin, potentially providing targeted delivery to specific receptors for particular compounds of the drug. Additionally, PXRD analysis revealed the amorphous characteristics of these NSs.

They are non-cytotoxic and non-hemolytic. The carrier systems involving carboxylated NSs appear promising and protected for the delivery of drugs, as demonstrated in the anticancer agent camptothecin delivery [28,29].

3. THE TECHNIQUE USED IN THE SYNTHESIS OF CYCLODEXTRIN NANOSPONGES

The primary approaches utilized for the preparation of cyclodextrin nanosponges include:

3.1. Hot Melting Procedure

This straightforward, solvent-free, and reproducible method relies on combining cyclodextrin (CD) with a carbonyl linker, typically diphenyl carbonate being the most commonly employed. Typically, the mixture is homogenized at temperatures ranging from 90 to 130°C for a minimum of 5 hours to ensure thorough crosslinking [30]. Additional crosslinking may necessitate longer incubation periods [31]. Upon reaction completion, a fine, uniform powder is produced [32,33]. This powder is then subjected to repeated washing with water and/or acetone. Often, it undergoes Soxhlet extraction with ethanol & acetone and may undergo an additional wash with a solution of NaOH [34]. Water helps remove excess CD, while ethanol/acetone assists in eliminating any unreacted crosslinker and also with any other impurities like imidazole & phenol that may form when using DPC or CDI linkers. The ion of phenoxide produced from the phenol is usually soluble in the water. Rinsing with a base like NaOH guarantees thorough impurity elimination. Its absence could be verified through ferric salt, UV-vis spectroscopy, or HPLC analysis [35,36].

3.2. Solvent Condensation Method

This method entails “dissolving CD (cyclodextrin) & crosslinker in a suitable solvent, which can include petroleum-based polar aprotic solvents like DMSO, DMF, pyridine, or butanone, [37] or environmentally friendly solvents such as water, aqueous solutions, or deep natural eutectic solvents (NADES) to enhance sustainability [38]. If required, a catalyst may be incorporated to expedite the reaction [39]. Typically, an excess of the crosslinking agent is utilized, with CD: Crosslinker molar” ratios ranging from 1:2 to 1:16 [40]. Following the reaction, nanosponges recovery which might include precipitation by utilizing acetone, water, ethyl acetate, or other suitable solvents [41–43].

3.3. Interfacial Condensation Method

In this approach, cyclodextrin is fully dissolved in an alkaline aqueous solution with a pH exceeding 10, while the crosslinking agent is dissolved in an organic solvent like chloroform, butanone, or methylene chloride [44,45].

3.4. Emulsion Solvent Diffusion Method

This technique depends on emulsification and consists of two separate phases that do not mix. The internal phase has been created by slowly adding the crosslinker while continuously stirring it into a solution that includes cyclodextrin “and an inclusion analyte dissolved in a polar aprotic solvent, generally DMF. The outer phase consists of an aqueous solution whereas the inner phase has been added slowly with strong stirring at room temp. The suspension” is freeze-dried to obtain the cyclodextrin nanosponges [46].

3.5. Ultrasound-Assisted Synthesis

By employing ultrasonic vibration, it becomes feasible to induce crosslinking between cyclodextrin and a suitable linker at specific molar ratios, all without the need for

solvents, thus establishing an environmentally conscious process [47]. This technique yields spherical particles with consistent sizes. Sonication proves beneficial for both the melting and solvent condensation methods [48].

3.6. Microwave-Assisted Synthesis

Conventional as well as ultrasound heating approaches often result in uneven transformations due to thermal gradients, leading to longer reaction times and challenges in scalability. In contrast, microwave irradiation accelerates reactions by four times compared to the melting approach, offering greater reproducibility and scalability because of its uniform as well as controlled heating [49]. Consequently, microwave synthesis enables the production of highly crystalline cyclodextrin nanosponges (CDNSs) with a narrow size of the particle distribution by reacting cyclodextrin with a suitable crosslinker, typically diphenyl carbonate (DPC), in polar aprotic solvents like DMF [37,47]. Solvent condensation synthesis can be carried out by utilizing MW-irradiation and tin octanoate catalyst to enhance the reaction among βCD as well as HDI crosslinker in DMF solvent at the temp of 80°C for the time of 30 mins [50].

3.7. Mechanochemical Synthesis

Mechanochemistry provides a different approach to trigger the reaction between CD and crosslinker by directly absorbing mechanical energy to activate chemical bonds [51]. Usually, this activation takes place between solid materials or reactants solidified in ball mills, either without solvents or reducing their use as much as possible. This contrasts with conventional methods that heavily rely on solvents, primarily derived from fossil fuels. Mechanosynthesis offers a sustainable approach by promoting efficient transport of mass and dispersion of energy by effective solid-state grinding. Acetone and ethanol are commonly used in purifying cyclodextrin nanosponges (CDNSs), but they are more volatile than higher “boiling point polar aprotic solvents like DMF or DMSO, which require complex recycling procedures. Despite its advantages, using ball mills poses challenges such as scalability issues, imprecise temperature control (although the temperature typically does not exceed 72°C in CDNS synthesis), and the utilization of the closed containers, which prolong the time of polycondensation reaction” by preventing water elimination at the time of the batch procedure. These limitations could be addressed by employing twin-screw extruder reactors, enabling precise temperature control and facilitating scalability by transitioning from batch to continuous processing methods [52].

3.8. Chain-Growth Polycondensation Method

The “conventional step-growth procedures rely on a polycondensation reaction where monomers react with each other, followed by the incorporation of a new monomer into the growing polymer chain, with both functional groups exhibiting identical reactivity. However, there exists the possibility to transition to a chain-growth polycondensation approach, especially when the group of reactive at the end of the polymer chain”, created through reaction with a monomer, remains stable and exhibits higher reactivity compared to the monomer itself [53]. Consequently, an initiator could be introduced to facilitate polymer growth by generating highly reactive sites at the chain ends, thereby enabling easy attachment of new monomers and subsequent chain elongation. In this process, “monomers do not interact with each other but selectively bond by the reactive terminals, resulting in cyclodextrin nanosponges (CDNSs) with reduced polydispersity. A chain-growth approach involves utilizing βCD alongside a monomer

of acrylic acid in the existence of ammonium persulfate as an initiator & MBA as a crosslinking agent [54]".

4. CHARACTERIZATION OF NANOSPONGES

4.1. Microscopy Studies

Transmission "Electron Microscopy (TEM) as well as Scanning Electron Microscopy (SEM) are utilized to analyze the morphological characteristics, like shape & size, of the active ingredient, carriers (nanosponges), and the resulting complex (drug/ NSs complex). The differences in the crystallization state between the product as well as raw materials, found through an electron microscope, indicate the inclusion of complex formation [22,55].

4.2. Particle Size Determination and Zeta Potential

Determining the size of the particle is a crucial factor in optimizing nanosponges, as it directly impacts the drug's release and solubility. Zeta potential, which measures surface charge, serves as an indicator of the NS's colloidal stability. Zeta potential values exceeding +25mV or falling below -25mV usually indicate higher stability levels [22,55].

4.3. Drug Loading and Entrapment Efficiency

The "excess drug solution is mixed with a water dispersion of CDNSs in the drug loading experiment. The mixture is stirred for a set amount of time at room temp., then filtered, and the NS sample is freeze-dried. The lyophilized product is analyzed to quantify the amount of the drug that exists in the systems. The drug-loaded NSs have been then dispersed in a solvent where the drug" is soluble for experiments evaluating entrapment efficiency. Sonication is used to break down the complex, allowing the drug contained in the nanosponges to dissolve in a solvent. The concentration of the drug is measured by utilizing analytical approaches like UV-visible spectrophotometry and HPLC [56]. You can determine the entrapment efficiency by using the formula given [57].

%Drug entrapment efficiency = Drug Encapsulated/Drug Total × 100

4.4. Porosity

Porosity indicates the degree of nanochannels as well as nanocavities formed within the NSs. The porosity is investigated using a helium pycnometer because helium gas could permeate the inter- and intra-particle channels of the material. The material's actual volume is determined based on the amount of helium displaced. The percentage of porosity is calculated using the provided formula [58].

% "Porosity (E) = Bulk volume − True volume/Bulk volume × 100"

4.5. Average Diameter and Polydispersity

A size particle analyzer utilizes DLS, also known as photon correlation spectroscopy (PCS), to establish the average diameter and polydispersity [59]. DLS/PCS correlates variations in scattered light intensity to the size of a particle through the auto-correlation function [60]. This method assumes all particles are spherical, measuring their hydrodynamic diameter. By factoring in efficient viscosity, the dispersing medium refractive index, and temp., DLS/PCS provides the size of particle information, considering multiple variables. However, to ensure comprehensive analysis, it is

advisable to complement these measurements with qualitative assessments by utilizing approaches like SEM, TEM, or ESEM, which allows for the examination of the size of particles and morphology by dispersing the sample in the water or any other appropriate solvents [56].

4.6. Water Uptake and Swelling Studies

A water absorption, as well as swelling investigation, is conducted for the swellable polymer-based NS. This is achieved by immersing the NS directly in the water. The swelling index and water absorption are calculated using the provided “equations [58].

Percent swelling = $S_t/S_0 \times 100$

Where S_t = cylinder marking at a specified time point after soaking

S_0 = initial cylinder marking before soaking.

Percent water uptake = $M_t/M_0 \times 100$

Where, M_t = hydrogel mass after a specific time

M_0 = dry polymer initial mass”.

4.7. Moisture Analysis

Dynamic vapor sorption research can confirm the non-hygroscopic characteristics of NSs along with their ability to maintain their crystalline structure while absorbing and desorbing moisture [61].

4.8. Saturation State Interaction

UV spectroscopy is employed to investigate the interaction between saturated solutions. Fixed drug concentrations are combined with incrementally rising concentrations of nanosponge solutions. The mixtures are then left to stand overnight. Drug loading is established by scanning the formulation in the range of UV & examining any change in the peak of absorbance (λmax) in spectra in comparison to pure drugs [62].

4.9. Phase Solubility Studies

The phase solubility study, as described by Higuchi & Connors, is commonly employed to examine inclusion complexation and assess the impact of NSs on the solubility of the drug. Phase solubility diagrams are utilized to evaluate the extent of drug complexation with nanosponges [8]. The phase solubility constant is determined by saturating suitable solvents with excess drugs. Various concentrations of blank nanosponges are then introduced to the saturated drug solution, leading to gradual drug-nanosponge interactions with increasing nanosponge concentration. This process continues until equilibrium is reached. A graph has been plotted to depict the concentration of NS against the concentration of the drug, categorized according to Higuchi & Connors's classification [7]. The resulting stability constant value indicates the level of interaction between nanosponges and the drug. Enhanced rate of dissolution, as well as poorly water-soluble drug solubility, are observed as the interaction between drugs and nanosponges intensifies [58].

4.10. In Vitro Release Studies

The drug release pattern from nanosponges is assessed through an in vitro release research. This involves employing a multi-compartment rotating cell, where the donor

compartment contains “an aqueous dispersion of NSs loaded with the drug, while the receptor compartment holds phosphate buffer at the desired pH”. The compartments are divided by a hydrophilic dialysis membrane. The receptor buffer is entirely replaced by the fresh buffer at set intervals. The drug released quantity is then determined using an appropriate analytical technique, allowing calculation of the drug release percentage [58].

4.11. Fourier Transform-Infrared Spectroscopy (FTIR)

FTIR serves as a crucial tool for structural analysis, particularly in detecting functional groups. During polymerization reactions, monomers combine to form polymers, and the characteristic peaks of functional groups in FTIR spectra indicate this process. Spectra in the range of 4000–650 cm−1 are typically examined for the polymer, drug, blank NS, drug-polymer physical mixture, and drug-loaded NSs to identify potential interactions. This technique also reveals the hydrophobic & hydrophilic regions of the nanosponges. The absence of certain functional group peaks, particularly in the hydrophobic drugs case, suggests their encapsulation within the cyclodextrin/NS cavity [62].

4.12. Powder X-ray Diffraction (PXRD)

Chemical decomposition along with the complexation analysis are performed utilizing PXRD. The diffraction pattern alters when the drug interacts with cyclodextrin/NS, leading to a modification in the drug's crystalline structure. The sample's PXRD pattern is analyzed using the scattering angle [63]. Complex formation is identified by peak growth, the emergence or disappearance of the new peak, and the relocation of specific peaks. Powder X-ray diffractometry enables the inclusion complexes detection in the solid state. As liquids lack a diffraction pattern, the newly formed substance's pattern notably differs from that of uncomplexed NSs, indicating complex formation. A comparison is conducted among the expected complex diffractogram along with the drug mixture as well as molecules of polymer for solid drug samples. Single crystal X-ray evaluation can be utilized to identify the intricate inclusion structure, enabling the observation of interactions among the host as well as guest molecules and the establishment of accurate geometrical relationships [58].

4.13. Thermal Analysis

Thermoanalytical approaches like DSC, DTA, and TGA are highly significant for determining parameters like degree of crystallinity (Xc), crystallization temperatures (Tc), melting temperature (Tm), and the thermal as well as thermal-oxidative stability of drugs & drug-NS complexes [64]. DTA and DSC are examined for any shifting, broadening, or appearance/disappearance of peaks, which can indicate drug molecular dispersion in the polymer. Weight loss variations can indicate the inclusion complexes formation. Thermal analysis is essential for evaluating the characteristics, behavior, and crystalline structure of NS [38].

4.14. Raman Spectroscopy

Raman spectroscopy proves highly valuable in molecular analysis due to its sensitivity to confirmation, molecular environment, and intermolecular reactions, as reflected in the wavenumber, intensity, and width of Raman peaks. It facilitates the examination of CD-NS upon transitioning from a dry to a swollen state, providing insights into the state of water as well as dissolved solute within the nanoporous NS structure. Of particular importance is the assessment of diffusion dynamics from a gelled condition.

Analysis of decoupled vibration modes C-H & O-H groups against a bulk water background allows for the investigation of hydration dynamics [65].

4.15. NMR Spectroscopy

Nuclear magnetic resonance (NMR) approaches, including 1H NMR, 13C “NMR, 2D-NMR (ROESEY and COESEY), and higher-resolution magic angle spinning (HR-MAS) NMR, have” emerged as important tools for examining the CD cross-linked polymers structure [66]. These NMR methods are also applicable for assessing the molecular structure, evaluating the cyclodextrin molecular mobilities within the nanosponge framework, and investigating interactions in complex drug-polymer systems. Changes in chemical values in NMR experiments suggest proton exchange among the reacting species, validating the creation of NSs. Crini et al. were the 1st to utilize HRMAS spectra for analyzing insoluble beta-CD polymers. Their work indicates that this NMR technique is useful for characterizing cross-linked materials with restricted movement and for identifying polymeric structures [67].

4.16. Stability Studies

To ensure the stability of drug products, it is imperative to conduct stability studies according to the guidelines outlined by the International Council for Harmonisation (ICH). Nanosponges have undergone stability assessments, including enhanced stability studies “and exposure to UV lamps. Shende et al. performed accelerated stability research on calcium NSs in a stability chamber kept at 25°C/60percent RH. The NSs have been created by combining beta-Cyclodextrin with 1,1’-carbonyldiimidazole as a cross-linker”. Over a period of 3 months, samples from the stability study were periodically evaluated for size, physical appearance, and drug properties, and have been observed to remain stable. There were no significant alterations observed in these parameters during the 3-month evaluation period [68]. The study examined “the photo-degradation of resveratrol-loaded dimethyl formamide cross-linked” NSs complexes by exposing the formulation to UV light at a distance of 10cm for 1 hour. The study indicated that the complex of the nanosponge & drug exhibited greater photostability compared to the plain drug [56].

5. APPLICATIONS OF NANOSPONGES

5.1. Oral Delivery of Drugs

Nanosponges are designed to enhance the solubility and achieve the desired release profiles of hydrophobic drugs classified under BCS class II. Their high surface area and microchannels enable the entrapment of drug molecules within their pores, facilitating improved solubilization efficiency [69].

5.2. Topical Delivery Systems

Nanosponges present a promising alternative for topical drug delivery compared to conventional methods, offering uniform and sustained drug release while reducing skin irritation and maintaining effectiveness. These nanoparticulate systems allow for the suspension or encapsulation of various substances, which can then be incorporated into different final products such as creams, tablets, capsules, or liquids. Drugs belonging to classes like antifungals, antibiotics, and local anesthetics can be effectively created using topical NSs. Examples include itraconazole nitrate, ketoconazole, voriconazole, miconazole nitrate, among others [69,70].

5.3. Protein Delivery

β-CD-based NSs maintain the original structure as well as improve the protein's stability by enclosing them in expandable CD-based poly(amidoamine) NSs. β-CD was complexed with BSA. The swellable nanosponges NS 10 & NS 11 were created by cross-linking β-CD with 2,2-bis(acryl amidoacetic acid) or a short polyamidoamine chain derived from 2,2-bis(acryl amidoacetic acid) and 2-methylpiperazine. The reduction of PAA-NS into nanosuspension was achieved using a high-pressure homogenization technique. These swellable cyclodextrin-based nanosponges were observed to be highly responsive to changes in the pH of the surrounding medium [71].

5.4. Sustained Delivery System

The sustained-release formulation is formulated to enhance the dosing schedule by ensuring continuous drug delivery throughout the entire dosing period, thereby reducing the need for frequent dosing and enhancing patient adherence. By employing appropriate polymers as well as crosslinking agents, the drug release kinetics from the NSs could be modified to prolong the release period. Additionally, nanosponges contribute to extending and preserving the release of volatile compounds like essential oils after encapsulation [69].

5.5. Antiviral Application

Nanosponges are efficient carriers for delivering antiviral medications or smaller interfering RNA (siRNA) to the nasal epithelia as well as lungs, targeting viruses that cause respiratory tract infections (RTIs) like influenza virus, rhinovirus, and respiratory syncytial virus. They have been utilized to target HBV, HSV, and HIV. For instance, carboxylated nanosponges have shown a loading capacity of 60% w/w for Acyclovir. Furthermore, in vitro studies have demonstrated a sustained release profile and enhanced antiviral efficacy against HSV compared to the pure drug in cell culture [27,70]. Silencing RNAs can be used with nanostructured β-CDNSs as an alternative method for antiviral purposes, protecting delicate molecules such as proteins or peptides. The NSs imitate along with compete cell-surface receptors that viruses use to attach to cells [72].

6. RECENT ADVANCES OF CYCLODEXTRIN NANOSPONGES

Cyclodextrin nanosponges (CDNS) have generated significant attention in recent years for their potential in anti-cancer therapy and environmental applications. These innovative materials, derived from cyclodextrin, possess a unique three-dimensional network structure, enabling them to encapsulate various therapeutic agents effectively. Some of the cyclodextrin nanosponges draw attention to recent research and studies.

6.1. Anti-cancer Therapy

The study demonstrated that cross-linking beta-cyclodextrin significantly enhances the complexation efficiency and solubilization of curcumin, making it a promising strategy for formulating poorly soluble active ingredients. Curcumin complexes formed with cross-linked beta-cyclodextrin nanosponges in a 20% ethanolic solution exhibited greater stability and solubility compared to those formed with non-cross-linked beta-cyclodextrin. However, the study also found that increasing the amount of cross-linker beyond a 1:4 molar ratio of beta-cyclodextrin to diphenyl carbonate negatively

impacted the complexation efficiency and solubilization effect, indicating an optimal cross-linker concentration is crucial for maximizing the benefits of this formulation [73].

The study shows that PMDA (pyromellitic dianhydride) and CDI (carbonyl diimidazole) nanosponges polymeric particles effectively deliver Nisin Z, a peptide drug, showing significant uptake and higher toxicity against MCF-7 and HT-29 cancer cell lines compared to free Nisin Z, as evidenced by MTT and LDH assays. Nisin Z encapsulated in NSs was particularly more effective against HT-29 cells, likely due to the activation of an apoptotic pathway. Additionally, the stability of Nisin Z in the presence of CD-NSs complexes was enhanced, as demonstrated by pepsin degradation studies and release profile, indicating that CD-NSs complexes hold promise for delivering protein drugs with low stability in the gastrointestinal tract. These results indicated that nanosponges might be good candidates to protect peptides and deliver drugs against intestinal cancer [74].

The study demonstrated that beta-cyclodextrins cross-linked with diphenyl carbonate significantly improve the bioavailability and anticancer efficacy of fisetin, particularly when coated with the active targeting ligand lactoferrin (LF-FS-NS). The optimized LF-FS-NS formulation enhanced fisetin bioavailability through both oral and IP routes and significantly increased its effectiveness against breast cancer, as evidenced by cellular and molecular studies on MDA-MB-231 cells and Ehrlich ascites tumor models. The actively targeted LF-FS-NS formulation showed superior anticancer effects compared to fisetin suspension, indicating that LF-FS-NS represents a versatile and potent strategy for targeted nano therapy in delivering fisetin and potentially other phytomedicines for breast cancer treatment [75].

The study demonstrated the effectiveness of PMDA-NS, a stimuli-sensitive nanoparticle, for targeting cancer cells. By utilizing a polymer that reacts with glutathione (GSH), more prevalent in chemoresistant tumor cells, they successfully designed a system that releases doxorubicin in response to GSH levels. This controlled release mechanism showed prolonged drug release proportional to GSH concentration, especially effective against colon, hepatocyte, and ovarian tumor cells. These findings suggested that PMDA-NS could offer a promising approach for targeted cancer therapy, potentially minimizing side effects and optimizing therapeutic outcomes [76].

6.2. Environmental Application

Cyclodextrin-based nanosponges demonstrate promising potential as effective adsorbents for the removal of emerging pollutants, exemplified by the successful purification of treated water contaminated with Ciprofloxacin within the framework of European Project Life “Clean up”. The batch adsorption process exhibited rapid removal of Ciprofloxacin, achieving 90% removal efficiency within minutes with a maximum adsorption capacity of 2 mg/g. It demonstrated recyclability with effective desorption using 0.1 M NaCl, ensuring sustainable reuse while minimizing environmental impact. Furthermore, the versatility of CDNSs was demonstrated by their successful removal of other contaminants like Diclofenac, Carbendazim, Furosemide, and Sulfamethoxazole, both individually and in a complex mixture, showcasing their potential for practical applications in real-world water treatment scenarios [77].

In another study, CDNSs specifically CDHD6 and CDHD12 synthesized using diamines with 6 and 12 methylene groups respectively, demonstrate significant

potential as effective adsorbents for the removal of 2,4-D from aqueous solutions. Physio-chemical characterization revealed that CDHD12, with its longer linker chain, exhibits a more compact structure and higher thermal stability, likely due to enhanced hydrophobic interactions. The environmentally friendly alkali desorption strategy developed enables the recycling and reusability of these adsorbents, enhancing their cost-effectiveness and sustainability for the management of agricultural wastewater contaminated with phenoxy herbicides. The CDNSs represent a promising class of materials for efficient water treatment applications, combining favorable adsorption properties with environmental compatibility [78].

6.3. Oxygen Therapy

In recent years, heart failure has become more common worldwide, often caused by a myocardial infarction (MI) followed by ischemia and reperfusion. The use of PMDA-NS to improve oxygen transport in cardiovascular disease treatments. These nanosponges were saturated with pure oxygen and tested for compatibility with red blood cells, showing minimal hemolysis and confirming their biocompatibility. The study demonstrated that the oxygen stored in nanosponges was released slowly and steadily. When tested in an ischemic buffer and a special medium with H9c2 cardiomyoblast cells, the oxygen concentration remained stable. The cross-linked polymers in the nanosponges were crucial for storing and releasing oxygen. This nanotechnology approach is beneficial for treating acute myocardial infarction, as the oxygen nanosponges protect cardiomyoblast cells under both normal and H/R conditions. This method of using oxygen-filled nanosponges can help reduce damage during surgeries or reperfusion treatments, offering a promising strategy for improving outcomes in heart failure and myocardial infarction patients [79].

6.4. Biosensors

Researchers developed a new way to enhance signals in tests used to monitor celiac patient's adherence to a gluten-free diet. They created nanosponges to improve colorimetric and electrochemical assays. These nanosponges were modified to attach antibodies to their surface and encapsulate horseradish peroxide particles. The effectiveness of this complex was tested using a Sandwich format, where gliadin (an antigen) was immobilized, and anti-gliadin antibodies labeled with horseradish peroxide were captured. The studies showed that these nano bioconjugates could be used to create extremely sensitive biosensors. Through this innovative approach using nanosponges can significantly enhance the sensitivity of tests for monitoring celiac disease, potentially leading to better patient management [80].

In another study, the researcher developed a method to estimate glucose levels using non-molecular imprinted polymer (NIP) and molecular imprinted polymer (MIP) nanosponges. They used D-glucose-6-phosphate as a template for creating MIP. The study found that MIP had a much better ability to bind glucose compared to NIP. Therefore, MIP was chosen for further studies on estimating blood glucose levels in rats. The rats were divided into three groups: a control group receiving distilled water, a group given an aqueous glucose solution, and a group given MIP followed by glucose. Blood tests showed no changes in glucose levels in the third group, indicating that MIP effectively bound the glucose. MIP shows a greater affinity for glucose than NIP due to its larger surface area, which allows better diffusion of glucose into the formed cavities, thus showing promise for use in monitoring blood glucose [81].

7. FUTURE PERSPECTIVE

Cyclodextrin nanosponges (CDNS) represent a promising advancement in nanotechnology and pharmaceuticals, offering numerous potential future applications due to their unique properties. These include enhanced drug delivery systems, where nanosponges can be engineered for targeted delivery and personalized medicine. In cancer therapy, they offer a way to deliver chemotherapeutic agents directly to cancer cells, and future developments might incorporate multiple drugs for combination therapy or enhance immunotherapy. For gene therapy, CDNS can deliver genetic material, with potential applications in Clustered regularly interspaced palindromic repeats (CRISPR) delivery and RNAi therapy. They also have promising antimicrobial and antiviral applications, such as nanosponge-based coatings for medical devices and broad-spectrum antimicrobials. Beyond medicine, CDNS can aid environmental remediation by purifying water and treating industrial waste. In cosmetic and personal care, nanosponges can improve the delivery and efficacy of active ingredients, and in biosensors and diagnostics, they can enhance disease detection and environmental monitoring. Despite their potential, challenges such as safety, scalability, and regulatory approval need to be addressed for widespread adoption. Continued research and development in these areas will be crucial for translating the potential of CDNS from laboratory successes to real-world applications across various fields.

8. CONCLUSION

Cyclodextrin nanosponges have proven to be a highly effective platform for enhancing the delivery and efficacy of hydrophobic drugs through solubility, stability, bioavailability, and therapeutic outcomes. The study demonstrates the successful application of CDNSs in forming inclusion complexes, which significantly enhance the pharmacokinetic profiles of therapeutic agents. Additionally, CDNSs offer substantial environmental benefits, particularly in the adsorption and removal of water contaminants, highlighting their potential for sustainable environmental management. The biocompatibility and low toxicity of CDNSs make them promising candidates for diverse biomedical applications, including drug delivery systems and biosensors. This review supports further exploration and development of CDNSs to drive innovations in pharmaceutical and environmental technologies.

Declarations

Ethics Approval: Not applicable

Competing Interests: Not applicable

Funding: Not applicable

Availability of Data and Material: Not applicable

Author's Contributions: The manuscript is written by Mukul Nishad while the manuscript study conception and design is contributed by Sushma Verma. The data collection and data interpretation/analysis are done by Arvind Kumar and MVNL Chaitanya respectively.

Acknowledgments: Not applicable

Grants: Not applicable

Funds: Not applicable

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