GSC Biological and Pharmaceutical Sciences

eISSN: 2581-3250 CODEN (USA): GBPSC2

Cross Ref DOI: 10.30574/gscbps

Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

The silent revolution in drug delivery: Exploring the extraordinary potential of nanosponges in modern medicine

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GSC Biological and Pharmaceutical Sciences, 2025, 31(03), 317-329

Publication history: Received on 30 April 2025; revised on 07 June 2025; accepted on 09 June 2025

Article DOI: https://doi.org/10.30574/gscbps.2025.31.3.0223

Abstract

Nanosponges are a new class of smart drug carriers with great promise in improving drug delivery. These tiny, sponge-like particles are made by crosslinking polymers such as cyclodextrins, creating a porous structure that can hold a variety of drugs. Because of their unique design, nanosponges can carry water-soluble and fat-soluble drugs, protect sensitive drugs from breaking down, and release them slowly over time. They are stable across a wide pH and temperature range, and they reduce side effects by targeting drugs to specific sites in the body. Multiple preparation methods, including ultrasound-assisted, microwave-based, and solvent techniques, offer flexibility in design and performance. Their effectiveness is evaluated using particle size analysis, zeta potential, and spectroscopy. Applications of nanosponges include cancer therapy, antifungal treatments, protein delivery, and detoxification. Their ability to improve solubility, reduce toxicity, and allow for sustained release makes them a valuable tool in modern pharmaceutical science.

Keywords: Nanosponges; Cyclodextrines; Nanotechnology; Crosslinking agents

1. Introduction

The development of advanced drug delivery systems has significantly transformed the landscape of modern therapeutics by addressing long-standing challenges related to site-specific delivery, controlled release, and drug bioavailability. Among these innovative systems, nanotechnology stands out as a revolutionary discipline with far-reaching implications in pharmaceutical sciences. Often regarded as one of the most profound engineering milestones since the Industrial Revolution, nanotechnology involves designing, synthesizing, and manipulating materials at the nanometre scale, typically within the range of 1 to 100 nanometres to impart novel physicochemical properties and functionalities.

Nanoparticles, a nanotechnology cornerstone, are colloidal carriers ranging from 1 to 100 nm, though particles up to 1000 nm are sometimes included in drug delivery applications characterised by a substantial surface-to-volume ratio and a reactive interfacial layer. They exist in many morphologies and compositions, including polymeric nanoparticles, nanoemulsions, dendrimers, liposomes, carbon nanotubes, micelles, and more recently, nanosponges (NSs). These systems enable the encapsulation and delivery of diverse therapeutic agents, ranging from small-molecule drugs to biomacromolecules such as peptides, proteins, and nucleic acids [1].

Among these nanocarriers, nanosponges have emerged as a highly promising and versatile platform. Structurally, nanosponges are porous, three-dimensional networks formed by crosslinking cyclodextrins or other polymeric backbones with appropriate multifunctional agents [2]. This configuration yields particles with a vast surface area and

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internal cavity systems capable of entrapping a wide range of therapeutic compounds. The typical size range of nanosponges varies from 10 to 25 μm, with void spaces extending from 5 to 300 μm, offering considerable advantages in drug loading efficiency and controlled release [1].

Originally developed for topical formulations, nanosponge technology has rapidly evolved, now enabling oral, parenteral, and inhalational drug delivery routes. Their physicochemical properties, such as insolubility in both aqueous and organic media, high stability, and capacity for targeted release, make them exceptionally well-suited for modern drug delivery applications [3]. Furthermore, the use of biodegradable materials, such as polyesters, allows for sustained degradation within the physiological environment, thereby enabling precise, time-controlled release of therapeutic agents [4].

The synthetic versatility of nanosponges is further demonstrated in cyclodextrin-based systems (e.g., "As shown in Figure 1."), which are fabricated by crosslinking the hydroxyl groups of cyclodextrins with polyfunctional linkers, yielding spherical, highly stable particles [5]. These platforms have been extensively explored for the delivery of anticancer agents, antimicrobial compounds, volatile oils, and biological molecules, with encouraging results in terms of enhanced solubility, reduced toxicity, and improved pharmacokinetic profiles [3].

Given their unique architecture, multifunctionality, and adaptability, nanosponges represent a next-generation drug delivery platform with significant clinical potential. This review provides a comprehensive examination of nanosponge technology, encompassing its synthesis, structural characteristics, drug encapsulation mechanisms, and emerging therapeutic applications across various disease domains.

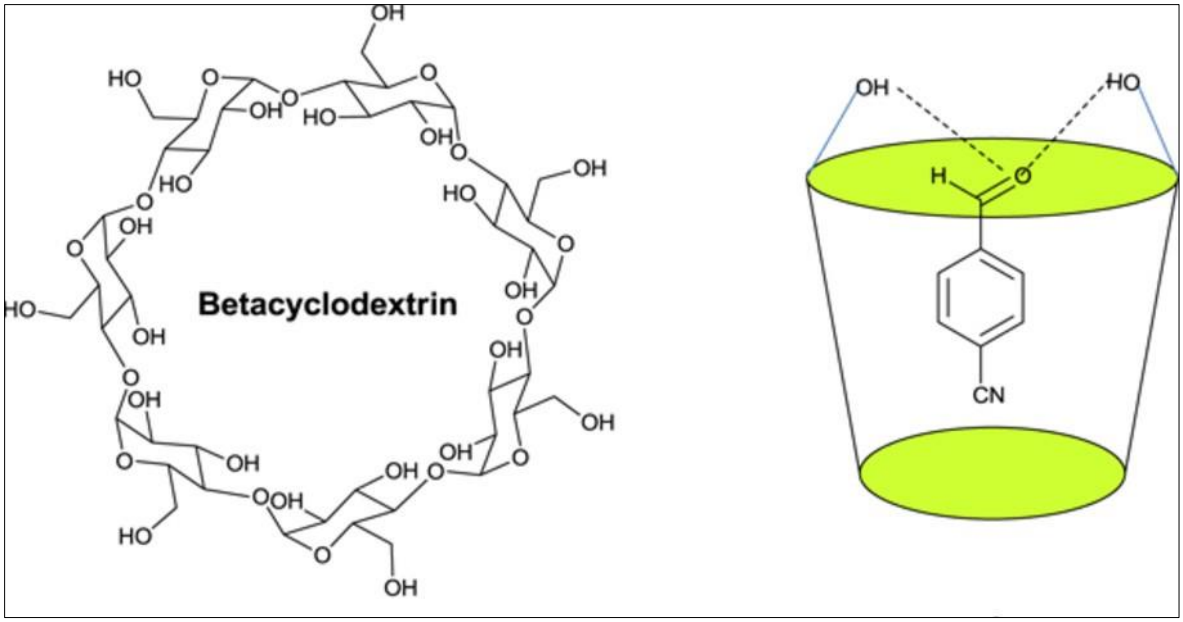

Figure 1 Structure of β-cyclodextrin and its inclusion complex

2. Types of nanosponges

Nanosponges (NS) come in many different types (e.g., "As shown in Figure 2."), and their design depends mainly on three key factors: the kind of polymer used, how much of it is added, and the method used to prepare them. These factors directly affect the final structure and function of the nanosponges. Among all types, nanosponges made from β-cyclodextrin (β-CD) are the most common and have been used in a wide range of applications. One of the reasons for their popularity is that they are relatively easy to prepare. In addition, β-CD nanosponges can be modified in different ways during or after synthesis, making it possible to adjust their properties for specific drug delivery needs [6].

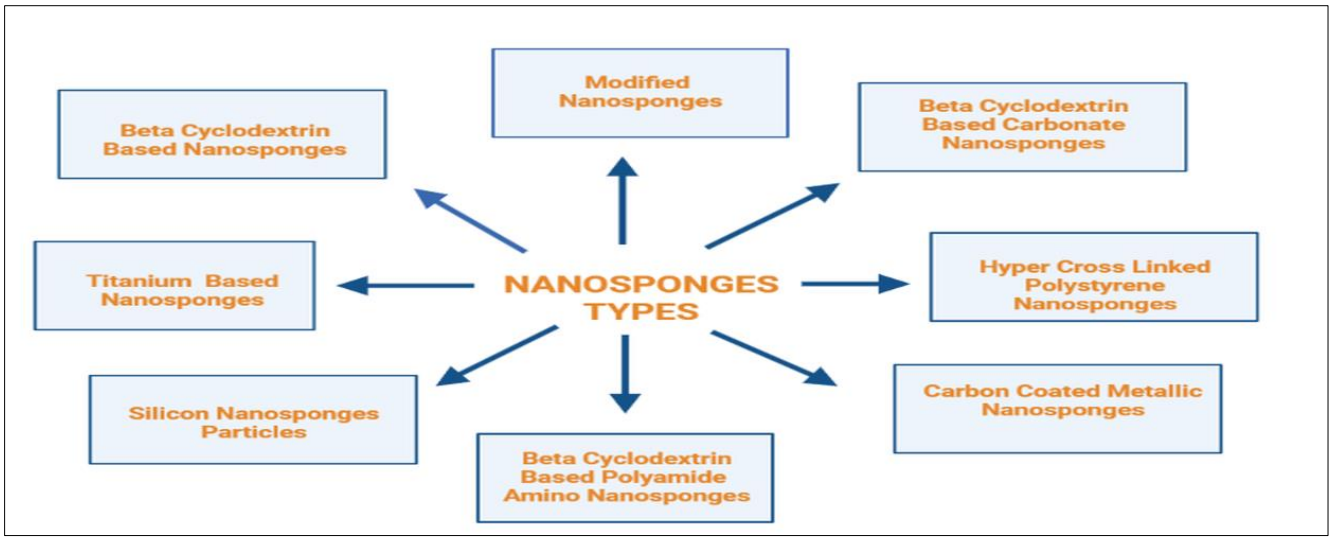

Figure 2 Composition-based classification of nanosponges

3. Salient features of nanosponges

Nanosponges exhibit a range of distinctive physicochemical properties that make them highly versatile for pharmaceutical applications. Their particle size and polarity can be finely tuned by adjusting the ratio of polymer to crosslinking agents during synthesis, allowing for the customization of nanocarriers tailored to specific drug delivery needs. Typically measuring less than 1 µm, nanosponges can exist in crystalline or paracrystalline forms. The crystalline nature is particularly important, as the structural order directly affects drug encapsulation efficiency by influencing the molecular stacking within the nanosponge matrix [7].

One of the most significant advantages of nanosponges is their adaptability to encapsulate a wide spectrum of pharmaceutical compounds, owing to their tunable polarity. They are especially valued for their ability to prolong drug release for up to 24 hours, encapsulate immiscible liquids, reduce irritation, and improve formulation flexibility and stability. Although they are primarily used for delivering small drug molecules, they have also demonstrated potential for accommodating macromolecules and oligonucleotides, thereby expanding their application scope [8].

In terms of physical robustness, nanosponges exhibit excellent thermal stability, tolerating temperatures up to 130°C, and maintain structural integrity across a broad pH range (1 to 11). Additionally, their biocompatibility, biodegradability, and non-toxic profile further enhance their appeal as next-generation drug delivery systems [9].

4. Advantages [10-12]

- Nanosponges effectively mask the unpleasant taste of drugs in oral and buccal delivery.
- They reduce irritation and toxicity by encapsulating harmful excipients.
- Nanosponges enhance the solubility of poorly water-soluble drugs.
- They can carry both hydrophilic and lipophilic drugs.
- Their porous structure prevents microbial contamination, offering self-sterilising properties.
- Nanosponges provide sustained drug release for up to 24 hours.
- They improve patient compliance by reducing dosing frequency.
- Their manufacturing process is scalable for commercial production.
- Nanosponges are biocompatible, non-toxic, and safe for therapeutic use.
- They remain stable across a wide pH range and high temperatures (up to 130°C).
- Nanosponges can neutralise toxins and aid in systemic detoxification.

5. Disadvantages [1,13]

- Nanosponges are highly effective at encapsulating small pharmacological compounds.
- The degree of crosslinking directly affects drug loading capacity by controlling internal cavity space.

- Inadequate crosslinking can lead to dosage dumping due to premature disintegration.
- Nanosponges are ideal for trapping low-molecular-weight drugs within their confined cavities.
- Their ability to encapsulate large or bulky molecules is limited.

6. Mechanism of drug release from nanosponges

Nanosponges are three-dimensional structures made of cross-linked polymers. The amount of cross-linking polymer added to the formulation affects both the entrapment and solubilizing effectiveness of nanosponges. The toroidal form of nanosponges allows them to have a hollow inside the structure that can hold a variety of medicinal compounds. Because of this sort of structure, they can operate as drug carriers for a variety of medications; as long as the active ingredient is compatible with the geometry and polarity of the cavity, the drug will be released at the intended spot. The structure of the nanosponge plays an important role in determining when these active chemicals will be released, and it may be adjusted to meet medication release requirements. Several ligands or carriers can also be bonded to the surface of the nanosponge to direct molecules to specific places in the body [14].

7. Materials used for the preparation of Nanosponges

A variety of compounds have been effectively utilised in the synthesis of nanosponges, with their selection largely influenced by the intended type of nanosponge and the required degree of crosslinking. The extent of crosslinking, governed by the amount of crosslinking agent used, is a key factor that impacts both the drug loading efficiency and the release profile. As such, the materials chosen during formulation play a pivotal role in defining the overall functionality of the nanosponge system. Below are some of the commonly applied compounds in nanosponge fabrication.

7.1. Polymers and Copolymers in Nanosponges

The type of polymer used in nanosponge formulation significantly affects drug loading, release, and stability. Cyclodextrins and their derivatives are widely used due to their ability to host both hydrophilic and hydrophobic drugs within their cavity structure. Studies have shown enhanced solubility and drug delivery using β-cyclodextrin-based nanosponges for compounds like ferulic acid, temoporfin, and neuropeptide Y. Other polymers, such as ethyl cellulose and copolymers like PLGA (Poly(lactic-co-glycolic acid)) and PEG (Polyethylene glycol), have been employed to improve targeted delivery, bioadhesion, and drug encapsulation efficiency. The choice and ratio of polymers and copolymers are critical in optimising nanosponge performance.

7.2. Crosslinking agent

The choice of crosslinking agents is fundamental in determining the effectiveness of nanosponge formulations, as they directly affect drug loading, release behaviour, and stability. Crosslinkers such as carboxylic acid dianhydrides, carbonyl diimidazoles, and glutaraldehyde help manipulate important properties like swelling, hydrophilicity, and hydrophobicity, allowing for the design of nanosponges with tailored characteristics for specific drug delivery needs. The concentration of the crosslinker plays a crucial role in optimising the drug encapsulation and controlling the release rate. For example, using carbonyl diimidazole with cyclodextrin enhanced the solubility and stability of resveratrol, while the amount of diphenyl carbonate used with cyclodextrins influenced the particle size and drug release profile of quercitrin. Moreover, combining cyclodextrin-calixarene copolymers with triazole as a linker has been shown to improve the delivery of bioactive compounds. In conclusion, adjusting the type and amount of crosslinking agent is essential for fine-tuning nanosponge formulations to achieve optimal drug delivery outcomes.

7.3. Drug Substance

When selecting a drug for nanosponge formulation, certain characteristics are essential. The drug should typically have a molecular weight between 100 and 400 Da and a solubility of less than 10 mg/ml in water. Its melting point should be below 250°C, ensuring it remains stable during formulation. Additionally, the drug should have fewer than five condensed rings in its molecular structure, which aids in optimising its incorporation into nanosponges for effective delivery. These factors are crucial for ensuring the drug's compatibility and performance within the nanosponge system [15].

8. Method of preparation of Nanosponges

8.1. Emulsion Solvent Diffusion Technique

The emulsion solvent diffusion technique is a widely employed method for fabricating nanosponges, utilising both organic and aqueous phases. In this approach, the drug and ethyl cellulose are dissolved in 20 mL of dichloromethane to form the organic (dispersed) phase. Simultaneously, a measured quantity of polyvinyl alcohol (PVA) is dissolved in 150 mL of distilled water to create the aqueous (continuous) phase.

The organic solution is then slowly introduced into the aqueous phase under vigorous stirring at 1000 rpm for 2 hours, enabling the formation of a fine emulsion. During this process, the diffusion and gradual evaporation of the organic solvent promote the self-assembly of nanosponges. The formed nanosponges are separated via filtration, followed by drying in a hot air oven at 40 °C for 24 hours. The final product is stored in a desiccator to eliminate any residual solvents and maintain stability [16].

8.2. Solvent Method

This method utilizes polar aprotic solvents, such as dimethylformamide (DMF) and dimethyl sulfoxide (DMSO), to facilitate the synthesis process. The polymer was introduced into the solvent mixture and thoroughly stirred to ensure uniform distribution. The optimal ratio of crosslinker to polymer was determined to be 8:2, and this specific ratio was applied to the mixture. The reaction was then conducted for 48 hours, with temperatures maintained between 10°C and the reflux temperature of the solvent. Following the reaction, the solution was allowed to cool to room temperature. To isolate the product, an excess of bi-distilled water was added to the cooled solution, and the resulting mixture was filtered under vacuum to recover the nanosponges [17].

8.3. Ultrasound-Assisted Method

The ultrasound-assisted synthesis technique utilizes an ultrasonic bath to facilitate the polymer crosslinking process, eliminating the need for solvents. The polymer and crosslinker are combined in an appropriate molar ratio and placed in a flask. During the sonication process, the flask is immersed in an ultrasonic bath maintained at 90°C for 5 hours. After sonication, the temperature of the mixture is gradually reduced, and the resulting solid is separated and washed with excess water to remove unreacted polymers and reagents. The purified material is then subjected to Soxhlet extraction with ethyl alcohol. The nanosponges are filtered, vacuum-dried, and prepared for further drug-loading applications [18].

8.4. Bubble Electrospinning

A conventional and typical electrospinning arrangement comprises basically of a syringe, a syringe pump, as specified in numerous publications, a high-voltage power source, and a grounded collector. However, one of the key restrictions that restricts their applicability is the volume of nanofiber production. In bubble electrospinning, polyvinyl alcohol may also be utilized as a polymer. The polymer (10%) solution was organized by adding distilled water to it, and it was then heated at 80-90°C for 2 hours to form a single-phase mixture. It was then left to attain room temperature with the polymer solution before being employed to manufacture nanoporous fibers [19].

8.5. Synthesis Using Microwave Radiation

Microwave-assisted synthesis presents an efficient method for the preparation of cyclodextrin (CD) nanosponges (NSs), significantly reducing reaction time. This technique enhances the crystallinity of the resulting nanosponges, producing a more uniform particle size distribution. Compared to traditional heating methods, microwave irradiation reduces reaction time by a factor of four while achieving consistent crystallinity. A study compared microwave-assisted heating to conventional methods for synthesizing CD-based nanosponges. Their findings indicated that microwave-assisted synthesis enhanced the drug retention capacity of the model compound. High-resolution transmission electron microscopy (HR-TEM) analysis demonstrated that the nanosponges produced through microwave radiation were highly crystalline, with a uniform size distribution and an increased level of structural complexity. The primary advantage of microwave-assisted synthesis lies in its ability to deliver energy directly to the targeted molecules, thereby reducing energy waste typically associated with heating container walls or solvents. As a result, the reaction progresses more efficiently to completion [1].

8.6. Quasi-emulsion solvent technique

The NSs were organized in various amounts using the polymer. The inner stage is prepared with Eudragit RS 100 before being put in a dissolvable stage. The medication employed elicited a reaction and degraded at 35°C under ultrasonication. This internal process, which is employed in the exterior phase and contains polyvinyl alcohol, acts as an emulsifier. At room temperature, the mix is blended at 1000-2000 rpm for 3 hours before drying for 12 hours in an air-warmed oven at 40°C [20].

8.7. Polymerization Method

Polymerization procedures are commonly utilized to create nanosponges by using the development of a three-dimensional cross-linked polymer network. These approaches usually include the use of monomers, crosslinkers, and initiators to create nanosponges with specific characteristics. The polymerization process causes the construction of a reservoir-type structure that opens at the surface via pores. A non-polar drug solution is prepared in the monomer, which is then mixed with an aqueous phase containing surfactant and dispersant to enhance suspension. Polymerization occurs once a suspension with distinct droplets of the required size is formed, by activating the monomers either by catalysis or higher temperature [21].

8.8. Melt Method

In the melt method, the polymer and crosslinking agent are directly melted together without the use of a solvent. The ingredients are thoroughly mixed and homogenised under heat, initiating the crosslinking reaction. Once the reaction is complete, the solidified mass is repeatedly washed with an appropriate solvent to remove any unreacted polymer and crosslinker residues. This purification step isolates the final product in the form of nanosponges. The resulting blank nanosponges can then be used for drug loading by incorporating active pharmaceutical ingredients through various encapsulation techniques. This method is simple, solvent-free, and suitable for heat-stable materials [22].

9. Factors influencing Nanosponges

9.1. Depending on the properties of the polymer and crosslinker employed

Crosslinkers help to form a 3D structure of NSs. The degree of crosslinker utilized helps to determine drug entrapment and determines organ targeting. The kind of crosslinker utilized impacts whether the NS is soluble in water or other solvents. The usage of epichlorohydrin as a crosslinker is intended to produce hydrophilic NSs. The advantage of utilizing hydrophilic NSs in drug delivery is that they enhance drug absorption through biological membranes and are a valuable transporter for pharmaceuticals to produce instant release formulations. Water-hating NSs are made with DPC, pyromellitic anhydride (PVA), diisocyanates, and carbonyl imidazoles as crosslinks. Hydrophobic NSs are utilized as a transporter in a constant release drug delivery system for water-loving pharmaceuticals, including peptides and proteins.

9.2. Influence of Temperature on Complexation Behaviour

Temperature fluctuations significantly impact the interaction between nanosponges and the encapsulated drug molecules. An increase in temperature tends to weaken the stability of the drug–nanosponges complex by lowering the stability constant. This reduction occurs due to the diminished strength of non-covalent interactions, such as Van der Waals forces and hydrophobic (water-repelling) interactions, which are essential for maintaining drug binding within the nanosponge matrix. As the temperature rises, these interactions become less effective, potentially leading to a decline in drug-loading efficiency and complex stability. Therefore, understanding and optimizing temperature conditions is crucial to preserving the structural integrity and therapeutic performance of the nanosponge–drug complexes [23].

9.3. Degree of Substitution

The degree of substitution refers to the number and type of functional groups attached to the cyclodextrin molecule and plays a vital role in shaping the properties of nanosponges. These substitutions influence how effectively cyclodextrins interact with crosslinkers, directly affecting the formation of various nanosponge types, such as cyclodextrin-carbonate nanosponges. An increased number of substituents typically leads to a higher degree of crosslinking, resulting in a more porous, mesh-like structure that enhances drug encapsulation and release performance.

In addition to the number of substituents, their position on the cyclodextrin ring and the method of synthesis also impact the final product. For example, cyclodextrins with the same degree of substitution may exhibit different properties if

produced under different conditions, as the functional groups may occupy different locations. This positional variation can alter the physicochemical characteristics, such as solubility, stability, and complexation ability. Thus, the degree of substitution is a key determinant in the quality and functionality of nanosponges and must be carefully controlled during formulation to ensure optimal performance [8].

9.4. Type of Drug and Medium Used for Interaction

The efficiency of nanosponge formulation is strongly influenced by the characteristics of the drug and the medium used during preparation. To be effectively encapsulated, a drug should have a molecular weight between 100 and 100 - 400 Da, a melting point below 250°C, water solubility under 10 mg/mL, and contain fewer than five condensed rings. Drugs with higher melting points often face stability issues when incorporated into nanosponges, as elevated temperatures weaken the interaction between the drug and the nanosponge, leading to reduced complex stability. Thus, maintaining an optimal temperature during preparation is essential for ensuring efficient drug loading.

The choice of medium also plays a key role. In aqueous environments, hydrophobic cavities within the nanosponge are more likely to capture organic drug molecules, enhancing encapsulation. Conversely, using organic solvents can disrupt these interactions and may lead to premature drug release. Therefore, both the physical properties of the drug and the type of solvent must be carefully considered to achieve a stable and effective nanosponge-based delivery system [16].

10. Evaluation studies

10.1. Determination of particle size

The size of the nanoparticles is an important component to consider while optimizing nanosponges. A medication's particle size may influence both its release and solubility. Particle size can be determined using a Zeta sizer or a laser light diffractometer. Plotting the total percentage of drug release from nanosponges of varied particle sizes over time can be used to investigate how particle size influences drug release. Nanoparticles ranging in size from 10 to 25 nm are more suited for topical medicine administration since larger particles may feel gritty [24].

10.2. Resiliency (viscoelastic properties)

Sponge resiliency can be adjusted to provide softer or harder beadlets for certain formulations. Increased crosslinking slows down the rate of release. As a result, sponge resiliency will be evaluated and adjusted based on the requirements, taking into account release as a function of cross-linking over time. The toughness (viscoelastic properties) of NSs may be adjusted to produce softer or firmer beadlets according to the final product needs. An increase in crosslinking gradually decreases the release rate. As a result, by taking into account the release pattern as a function of crosslinking with time, sponge resilience may be investigated and modified as needed [25,26].

10.3. Zeta potential determination

Zeta potential is a measure of the surface charge of particles suspended in a liquid, and it plays a vital role in evaluating the physical stability of nanosponge dispersions. It describes the potential difference between the surrounding liquid and the stationary layer attached to the particle surface. When particles carry a strong surface charge, they repel each other, preventing clumping and leading to a more stable system. Zeta potential can be measured using instruments such as a Zetasizer, which uses an electric field to detect how quickly the particles move. A higher zeta potential—whether positive or negative usually means better stability of the nanosponge suspension [27].

10.4. Microscopic characterization

High-resolution imaging techniques like Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) are commonly used to assess the structural features of nanosponges and their drug-loaded counterparts. These methods provide insight into particle shape, surface texture, and internal architecture. Differences observed between pure drug particles and the nanosponge-drug formulations, particularly in surface form or crystallinity, can suggest successful formation of inclusion complexes. Such structural changes are often captured after formulation using co-precipitation or similar preparation methods, offering visual confirmation of nanosponge integration and drug encapsulation [28].

10.5. Solubility Evaluation of Nanosponge Complexes

Solubility enhancement is one of the primary advantages offered by nanosponge-based drug delivery systems. Inclusion complex formation between the drug and the nanosponge matrix is frequently employed to improve the aqueous

solubility and overall bioavailability of poorly water-soluble drugs. This process is typically analyzed using phase solubility studies, wherein the relationship between the concentration of the drug and the carrier is plotted to determine the extent and nature of the interaction. A linear or non-linear solubility curve provides insights into the stoichiometry and stability of the formed complexes.

Moreover, these studies assist in examining how the solubility profile of a drug varies under different pH conditions and in the presence of various solvents or excipients. Factors such as temperature, ionic strength, and the presence of surfactants can also significantly influence the solubilization efficiency. Understanding these parameters is essential for optimizing nanosponge formulations and achieving consistent drug release profiles in both in vitro and in vivo settings [29].

10.6. Swell Index

The Brunauer–Emmett–Teller NS test was carried out using the N_2 adsorption micro-metric ASAP analyzer. Before conducting the investigation, the samples were pre-heated at 120°C for 2 hours. At the optimal temperature and after reaching equilibrium, a consistent amount of dehydrated NS sample (Wd) was added to the bath. The outside surface was then dehydrated and measured using filter paper (Wh). The technique was repeated three times, and the average Wh value was determined [30].

Swelling ratio = Wh/Wd

10.7. Dissolution Test

The release of drugs from nanosponges can be evaluated using the USP XXIII dissolution apparatus. This system includes a rotating stainless steel basket with a mesh size of 5 µm, operating at 150 rpm. The test is carried out under sink conditions to ensure proper drug solubility throughout the process. At specific time intervals, small samples are withdrawn from the dissolution medium. These are then analyzed using spectrophotometry to measure the amount of drug released over time [31].

10.8. Stability studies

The NSs were studied for stability under accelerated circumstances and during photodegradation trials. The formulation is evaluated for three months each year. The changes in appearance, size, and physical attributes are evaluated to determine the drug's qualities. The photodegradation analysis is conducted for 1 hour under a UV light while stirring in the dark. The NSs are 10cm from the light. The material is extracted using HPLC and evaluated [32].

10.9. Infrared (IR) Spectroscopy

Infrared spectroscopy is a valuable analytical tool used to study interactions between drug molecules and nanosponges in the solid state. When a drug forms an inclusion complex with nanosponges, characteristic shifts in the IR spectral bands may occur, especially if only a portion of the molecule is involved in the interaction. These changes often indicate weak interactions, typically involving less than 25% bond strength, suggesting partial inclusion. IR analysis is particularly useful for compounds containing functional groups like carbonyl or sulfonyl moieties. Moreover, IR spectra can provide insights into hydrogen bonding, as the presence of such interactions usually results in band broadening and a shift to lower wavenumbers due to stretching vibrations.

10.10. X-ray Diffractometry and Single-Crystal X-ray Structural Analysis

X-ray powder diffractometry is a key technique for identifying the formation of solid-state inclusion complexes involving nanosponges. Unlike solid materials, liquids and uncomplexed nanosponges typically lack distinct diffraction patterns. When a drug in solid form is combined with a nanosponge, the resulting diffraction profile may differ from that of the pure drug or a simple physical mixture. While physical mixtures display a combination of diffraction peaks from both components, true inclusion complexes often exhibit entirely new diffraction patterns, reflecting the formation of a unique crystalline or semi-crystalline phase. These changes in the diffractogram provide evidence for complexation and structural transformation. Additionally, single-crystal X-ray diffraction allows for detailed structural analysis, offering precise information on the spatial arrangement and molecular interactions between the nanosponge framework (host) and the encapsulated drug (guest). This method is highly effective in confirming the formation and configuration of inclusion complexes at the atomic level [33].

10.11. Compatibility Evaluation via Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) is widely used to investigate potential interactions between active pharmaceutical ingredients and nanosponge carriers. For this analysis, about 5 mg of the drug is placed into a sealed aluminum pan and gradually heated at a rate of 15 °C per minute. The heating process is conducted in a nitrogen atmosphere, typically covering a temperature range from 25 °C to 430 °C. Any noticeable alterations in thermal behavior, such as the appearance, shift, or disappearance of melting peaks, can suggest a physicochemical interaction between the drug and the polymer, indicating whether the components are thermally compatible [34].

11. Nanosponges Applications

11.1. Harvesting Rare Blood Cancer Markers Using Nanosponges

Nanosponges (NSs) functionalized with specific bait molecules can selectively capture particular blood protein families, protecting them from enzymatic degradation in the bloodstream. This unique capability makes NSs an effective tool for isolating and harvesting rare cancer biomarkers, offering a promising approach for the detection and study of blood cancers [35].

11.2. Enhancement of solubility

Nanosponges (NSs) have also been utilised to enhance the solubility and dissolution rate of poorly water-soluble drugs, thereby contributing to a controlled release profile. However, molecular size and shape are significant limiting factors that influence the formation and stability of inclusion complexes with NSs and may not be universally suitable for all drug molecules. For instance, cefpodoxime proxetil-loaded nanosponges have been developed to improve the drug's dissolution rate [36].

11.3. Nanosponges for Cancer Treatment

Due to their poor solubility, many anticancer drugs present significant challenges in pharmaceutical formulation and delivery. Recent studies suggest that nanosponge complexes are up to three times more effective in inhibiting tumour growth compared to conventional direct drug injections. These nanosponges encapsulate the anticancer drug and display targeting peptides on their surface, which bind selectively to receptors expressed on radiation-damaged tumour cells. Upon contact, the nanosponges adhere to the tumour cell surface and facilitate controlled release of the encapsulated drug. This targeted delivery approach enhances therapeutic efficacy while minimising systemic side effects by concentrating the drug at the site of action [37].

11.4. Nanosponges for Protein Delivery

The protein encapsulation potential of β-cyclodextrin-based nanosponges was evaluated using bovine serum albumin (BSA) as a model protein. Since BSA in solution is prone to instability, it is typically stored in a lyophilized form. However, lyophilization can lead to protein denaturation, affecting its native structure. A major challenge in protein formulation is preserving the protein's structural integrity during processing and ensuring its stability during long-term storage. Cyclodextrin-based nanosponges have shown promise in enhancing the stability of proteins like BSA, offering improved protection during administration. Additionally, nanosponges have been applied to the immobilization of enzymes, the encapsulation of proteins, and controlled drug delivery, further highlighting their versatility in biomedical applications [38].

11.5. Nanosponges as Absorbents for Toxin Removal from the Bloodstream

Nanosponges function as effective absorbents, capable of capturing and removing toxic substances from the bloodstream. Instead of relying on traditional antidotes, nanosponges can be introduced directly into the blood, where they selectively absorb poisons. Their structure allows them to mimic red blood cells, which deceives the toxins into interacting with them, ultimately leading to the absorption of these harmful molecules. The capacity of each nanosponge to absorb toxins is dependent on the type and concentration of the poison present in the bloodstream [39].

11.6. The Role of Nanosponges in Treating Fungal Infections

Fungal infections, particularly those affecting the skin, are a significant global health concern. Topical therapies offer several advantages for treating cutaneous infections, such as the ability to deliver medication directly to the site of infection while minimizing systemic side effects. Econazole nitrate, an imidazole antifungal agent, is commonly used for treating conditions like athlete's foot, ringworm, tinea versicolor, jock itch, and vaginal thrush. Available in various formulations, including creams, ointments, lotions, and solutions, econazole nitrate typically has poor skin absorption.

Effective treatment requires high drug concentrations to achieve therapeutic levels. To address this challenge, econazole nitrate-loaded nanosponges were developed using the emulsion solvent technique. These nanosponges were incorporated into a hydrogel formulation to provide sustained, controlled release of the drug for improved therapeutic outcomes [40,41].

11.7. Nanosponges as a Sustained Drug Delivery System

Nanosponges offer a promising solution for the sustained release of acyclovir, an antiviral commonly used to treat herpes simplex virus infections. Due to its slow, inconsistent, and incomplete absorption in the gastrointestinal tract, acyclovir's bioavailability can be unpredictable. However, the in vitro release profiles of acyclovir from various types of nanosponges demonstrate a prolonged release of the drug. For example, after 3 hours, approximately 22% of the acyclovir was released from carb-nanosponges, while 70% was released from other types of nanosponges. Importantly, no initial burst release was observed, indicating that the drug was not merely adsorbed on the surface of the nanosponges but was gradually released over time.

11.8. Nanosponges as Protective Agents Against Light and Degradation

Gamma-oryzanol, a natural antioxidant and a combination of ferulic acid, is widely used in stabilizing food and pharmaceutical materials. However, its application is often limited due to its susceptibility to light-induced degradation. Encapsulation of gamma-oryzanol in nanosponges effectively shields it from light exposure, enhancing its stability and prolonging its effectiveness.

11.9. Nanosponges as Carriers for Biocatalysts

Nanosponges can serve as versatile carriers for various biocatalysts, including enzymes, vaccines, proteins, and antibodies, making them useful in diagnostic applications. Cyclodextrin-based nanosponges are particularly efficient at adsorbing and encapsulating proteins and other macromolecules, providing controlled and protected delivery for therapeutic and diagnostic purposes [3].

12. Future Prospects

The future of nanosponges in pharmaceutical science appears highly promising due to their versatility and adaptability. Ongoing research focuses on enhancing their ability to deliver drugs precisely at targeted sites, improving treatment outcomes, and minimizing side effects. Innovations such as environment-responsive nanosponges triggered by pH, enzymes, or temperature are under development to achieve controlled and on-demand drug release. Additionally, their role in personalised medicine, gene therapy, and protein protection is gaining interest. Beyond healthcare, nanosponges may also find applications in environmental cleanup and cosmetic formulations. As technology progresses, nanosponges will likely become key components in advanced therapeutic and diagnostic systems.

Abbreviations

- BSA – Bovine Serum Albumin
- CD – Cyclodextrin
- DMF – Dimethylformamide
- DMSO – Dimethyl Sulfoxide
- DPC – Diphenyl Carbonate
- DSC – Differential Scanning Calorimetry
- FTIR – Fourier Transform Infrared Spectroscopy
- HR-TEM – High-Resolution Transmission Electron Microscopy
- HPLC – High-Performance Liquid Chromatography
- IR – Infrared
- NS / NSs – Nanosponge / Nanosponges
- PEG – Polyethylene Glycol
- PVA – Polyvinyl Alcohol
- PLGA – Poly(lactic-co-glycolic acid)
- rpm – Rotations per Minute
- SEM – Scanning Electron Microscopy
- TEM – Transmission Electron Microscopy
- UV – Ultraviolet
- USP – United States Pharmacopeia

- XRD – X-ray Diffraction
- ASAP – Accelerated Surface Area and Porosimetry (context: ASAP analyzer)
- µm – Micrometer
- nm – Nanometer
- pH – Potential of Hydrogen

13. Conclusion

Nanosponges have opened a new chapter in drug delivery science, offering a smart and flexible approach to solving long-standing pharmaceutical challenges. Their sponge-like design, with countless tiny pores, allows them to trap drugs securely and release them precisely where and when they are needed. This not only boosts the effectiveness of treatment but also minimises side effects and improves patient comfort.

What makes nanosponges truly remarkable is their adaptability. By adjusting the type of polymer and method of preparation, these carriers can be customised for a wide range of drugs and medical uses, from cancer therapy to protein protection and detoxification.

As research continues, nanosponges are poised to become key tools in creating safer, more targeted, and more efficient drug delivery systems. Their future lies in innovation and improving real lives through better medicines.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interest related to this review article.

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