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# Nanosponges for Next-Generation Drug Delivery: Mechanisms, Therapeutic Potential, and Structural Design

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## ABSTRACT

**Objective:** Reviewing the creation, composition, synthesis, characterisation, and medicinal uses of drug delivery systems based on nanosponge technology. To demonstrate how nanosponges enhance regulated drug release, bioavailability, stability, and solubility. **Methodology:** Comprehensive analysis of published studies, patents, and research data on cyclodextrin, polymeric, hybrid, mesoporous, and stimuli-responsive- nanosponges. Evaluation of synthesis approaches (solvent evaporation, melt polymerization, ultrasound, emulsion diffusion, green methods) and characterization techniques (DLS, SEM/TEM, FTIR, DSC, PXRD, EE%, release studies). Review of representative drug case studies including resveratrol, camptothecin, paclitaxel, griseofulvin, and strigolactone. **Result:** Nanosponges belong to novel drug delivery system with enhanced solubility, dissolution, stability, and drug protection due to their porous 3D network. They also possess high encapsulation efficiency (>70–90%) and sustained or controlled release mechanisms for drug delivery. Their nanoscale size (100–500 nm), stable zeta potential, reduced crystallinity, and strong drug–matrix interactions offer numerous advantages to deliver the drug molecule. Case studies reflect improved bioavailability (paclitaxel), better permeation (resveratrol), increased anticancer activity (camptothecin and strigolactone), and improved pediatric formulations (griseofulvin). Stimuli-responsive nanosponges exhibit selective drug release in tumor-like environments. **Conclusion:** Nanosponges are promising next-generation drug carriers that significantly enhance pharmaceutical performance. Moreover, their tunable structure and ability to deliver drugs in a controlled, targeted, and stable manner make them highly suitable for precision medicine. Despite challenges in scale-up, toxicity control, and regulatory approval, advancements in green synthesis, multifunctional designs, and targeted delivery continue to push this technology toward clinical translation.

**Keywords:** Nanosponges, cyclodextrin nanosponges, polymeric nanosponges, solubility, controlled release, drug delivery.

## 1. INTRODUCTION

Over the past 20 years, nanotechnology-based drug delivery has been increasingly popular, especially for enhancing the therapeutic efficacy of compounds with subpar biopharmaceutical qualities.A substantial proportion of newly developed and existing drug molecules suffer from poor aqueous solubility, low permeability, rapid degradation, and non-specific tissue distribution, all of which severely restrict their pharmacokinetic behavior and therapeutic index.[1,11] Conventional strategies—such as micronization, solid dispersions, cyclodextrin inclusion complexes, and surfactant-based systems—often fail to provide sustained improvements in solubility, stability, or bioavailability and frequently show limitations in scalability and long-term performance.[10,19] As a result, there is a growing need for carriers that can overcome these physicochemical challenges while offering controlled release, biocompatibility, and versatility across multiple dosage forms.

A new class of hyper-crosslinked, nanoporous carriers that can solve these formulation issues is called nanosponges (NSs). Initially introduced through advancements in cyclodextrin (CD) chemistry, nanosponges represent structurally unique polymeric networks that contain nano-sized cavities and interconnected pores suitable for encapsulating a wide variety of hydrophobic, hydrophilic, and amphiphilic therapeutic molecules.[6,7] Cyclodextrin-based nanosponges combine the inclusion capacity of traditional CD complexes with extended porous frameworks, enhancing drug-loading efficiency and enabling controlled or sustained release kinetics.4,5 These systems improve not only solubility but also chemical stability, protecting labile drugs from photodegradation, oxidation, or hydrolysis.[11,17]

Over time, nanosponge technology has evolved beyond classical CD-based architectures to incorporate polymeric, hybrid, mesoporous, and stimuli-responsive variants. Polymeric nanosponges derived from materials such as polycaprolactone,

hyperbranched cyclodextrin polymers, PAMAM, and chitosan enable tailored biodegradation rates, improved mechanical strength, and enhanced biocompatibility.[8,14] Stimuli-responsive nanosponges containing pH-sensitive, redox-sensitive, or enzyme-labile linkages provide on-demand release behavior, particularly beneficial in applications such as cancer therapy, where tumor microenvironments can trigger drug liberation.[20,35] Hybrid nanosponge systems incorporating metallic nanoparticles or inorganic frameworks expand their functionality to imaging, diagnostics, and combined therapeutic approaches.[5]

The inherent adaptability of nanosponge materials has led to their investigation across numerous administration routes including oral, topical, transdermal, ophthalmic, parenteral, buccal, and mucosal deliveries.[3,17] Their ability to enhance solubility, prolong release, improve membrane permeation, reduce irritation, and provide site-specific targeting makes them a versatile platform in modern pharmaceutics. Additionally, nanosponge systems have been explored for the delivery of anticancer agents, anti-inflammatory drugs, antifungals, antioxidants, antibiotics, and even biomacromolecules, demonstrating broad compatibility and high therapeutic potential.[14,15]

Given this expanding landscape, the present review aims to consolidate current scientific knowledge on nanosponge engineering, with emphasis on their structural design, mechanisms of drug loading and release, synthesis methodologies, characterization strategies, and pharmaceutical applications. By integrating findings from key studies, including cyclodextrin-based, polymeric, and stimuli-responsive nanosponge systems, this work underscores the growing significance of nanosponges as next-generation drug carriers capable of meeting unmet formulation challenges.[1,17]

## 2. Evolution of Nanosponge Technology

Advances in supramolecular host-guest complexation and cyclodextrin (CD) chemistry are directly linked to the development of nanosponge technology. The capacity of cyclodextrins, cyclic oligosaccharides made of α-1,4-linked glucopyranose units, to encapsulate hydrophobic molecules inside their lipophilic cavities has long been known. Six Traditional CD inclusion complexes, however, frequently have poor structural stability, a restricted loading capacity, and only slight increases in solubility for many active medicinal compounds. In order to address these drawbacks, scientists worked to develop more resilient, porous structures that might greatly increase surface area and molecular entrapment efficiency while maintaining the inclusion capabilities of CDs.

A major breakthrough came when Trotta and colleagues developed the first crosslinked cyclodextrin-based polymer networks, later termed as “nanosponges” by using organic carbonates such as diphenyl carbonate (DPC) and carbonyl diimidazole (CDI) as crosslinking agents.[6] This innovation transformed simple CD complexes into three-dimensional, hyper-crosslinked matrices containing interconnected nanopores. These early β-CD nanosponges demonstrated markedly improved solubilization and sustained release of poorly soluble drugs such as camptothecin and griseofulvin, establishing the foundation for nanosponge-based drug delivery.[11]

The second stage of evolution involved optimization of crosslinking chemistry. Alternative linkers including pyromellitic dianhydride (PMDA), carbonyldiimidazole, and various dianhydrides were introduced to modulate the rigidity, porosity, and physicochemical behavior of nanosponges.[5] By adjusting the crosslinker ratio, researchers achieved finer control over swelling behavior, drug diffusion rates, and mechanical stability. During this period, synthesis routes also diversified: solvent-free melt polymerization emerged as a greener technique, while ultrasound-assisted synthesis enhanced nucleation and reduced particle size distribution.[10]

The evolution of nanosponge platforms later expanded beyond cyclodextrin frameworks. Polymeric nanosponges composed of polyesters, polycaprolactone, polyamidoamines, and hyperbranched CD polymers were developed to improve biodegradability, achieve extended release kinetics, and overcome drug compatibility limitations seen with pure CD matrices.[8,14] These polymeric scaffolds allowed for greater flexibility in tailoring degradation profiles, thermal resistance, and mechanical properties, opening avenues for transdermal, topical, and oral dosage forms.

Nanosponge research advanced toward stimuliresponsive systems as interest in precision medicine grew. Redox-sensitive, enzyme-cleavable, and pH-responsive nanosponges were engineered using dynamic covalent linkages designed to respond to pathological microenvironments such as cancer tissues or inflamed sites.[20,35] These “smart” nanosponges release their payload selectively in response to intracellular glutathione levels, acidic tumor conditions, or enzyme overexpression, thereby improving targeting efficiency and minimizing systemic toxicity.

Nanosponge applications have been further expanded by developments in hybrid material science. Inorganic–organic nanosponge hybrids incorporating metallic nanoparticles, silica, magnetic nanostructures, or gold nanorods were developed for theranostic purposes, combining imaging, diagnostics, and therapy into a single platform.[5] These multifunctional constructs offer controlled drug release alongside photothermal, photodynamic, or imaging functionalities.

All things considered, nanosponge technology has developed from basic cyclodextrin inclusion complexes to complex nanostructured carriers that can transport drugs in a controlled, targeted, and environmentally sensitive manner. This development—from traditional CD nanosponges to polymeric, hybrid and stimuli-sensitive systems—emphasizes the adaptability and quickly growing significance of nanosponge platforms in contemporary pharmaceutics.[3,17]

**3. Structural Design and Chemistry of Nanosponges**

The structural design of nanosponges is fundamentally based on the formation of a three-dimensional, hyper-crosslinked polymeric architecture that provides both internal cavities and external porous surfaces suitable for drug encapsulation. At the core of most nanosponge systems lies a network of crosslinked building blocks—either cyclodextrins (CDs) or polymeric materials—that create nanoscale voids capable of hosting a wide range of therapeutic agents.[6,7] These voids arise from the controlled crosslinking of functional groups on CDs or polymer backbones, resulting in a stable, sponge-like matrix with high surface area and tunable physicochemical properties.

In cyclodextrin-based nanosponges, each CD molecule retains its intrinsic hydrophobic cavity, which enables classic host–guest inclusion of hydrophobic or moderately hydrophilic molecules. However, upon crosslinking with agents such as diphenyl carbonate (DPC), carbonyl diimidazole (CDI), or pyromellitic dianhydride (PMDA), additional interstitial nanopores are formed throughout the network.[5,6] This dual-porosity system significantly enhances drug-loading capacity compared to conventional CD complexes. The internal CD cavity can encapsulate small, lipophilic portions of drug molecules, while the outer porous matrix provides adsorption sites, hydrogen bonding interactions, and electrostatic binding opportunities.[4] This unique structural integration explains why CD nanosponges can load drugs that do not typically form stable inclusion complexes with native CDs.

The crosslinker selection and ratio have a significant impact on the chemical and physical characteristics of nanosponges. Carbonate-type crosslinkers (DPC, CDI) tend to create flexible, elastic networks with moderate porosity, whereas highly rigid linkers such as PMDA generate stiff, densely crosslinked structures with reduced swelling capacity but enhanced stability.[5,7] An increase in crosslink density generally reduces pore size and matrix flexibility; however, it can also slow drug release and enhance mechanical stability. On the other hand, higher swelling, quicker release, and more water molecule transport through the nanosponge matrix are made possible by lower crosslinking levels.

Thus, optimizing the degree of crosslinking is essential for tailoring nanosponge performance based on drug properties and the intended route of administration (e.g., topical vs. oral).[4]

Beyond cyclodextrin systems, polymeric nanosponges utilize materials such as polycaprolactone (PCL), chitosan, polyesters, polyamidoamine dendrimers, and hyperbranched cyclodextrin polymers to create structurally diverse nanosponge architectures.[8,14] Polymeric nanosponges offer advantages in biodegradability, thermal stability, and mechanical flexibility, making them suitable for sustained-release formulations and biomedical applications. The polymer chains provide abundant functional groups (–COOH, –OH, –$NH_2$) that can interact with drug molecules via hydrogen bonding, van der Waals forces, or ionic interactions, enhancing encapsulation efficiency.[15] The polymer backbone also enables precise control over degradation rates, which is particularly beneficial for long-acting or implantable delivery systems.

Drug release behavior, cellular interaction, and nanosponge stability are all significantly influenced by surface chemistry. Modifying surfaces with functional groups such as carboxyl, amine, or hydroxyl groups can significantly influence zeta potential, mucoadhesive properties, and dispersibility in aqueous media.[17] For example, chitosan-coated nanosponges exhibit increased cationic charge, enhancing interactions with negatively charged mucosal surfaces and improving cellular uptake. Polyethylene glycol (PEG) grafting, on the other hand, enhances stealth characteristics, minimizing opsonization and prolonging circulation time in systemic applications.[14]

Hybrid nanosponge systems combine organic polymer networks with inorganic components such as gold nanoparticles, silica, or iron oxide. These hybrid constructs provide additional functional properties—such as magnetic responsiveness, enhanced imaging contrast, or photothermal activity—while maintaining the inherent drug-loading benefits of nanosponge structures.[5] The integration of inorganic materials into the nanosponge matrix occurs via in situ growth or physical entrapment, resulting in multifunctional carriers suitable for theranostic applications.

All things considered, the chemistry and structural layout of nanosponges depend on precisely planned interactions between surface functions, crosslinkers, and core monomers. Researchers can create adaptable nanosponge platforms for a variety of pharmaceutical applications by fine-tuning porosity, mechanical strength, stability, and drug-carrier interactions.[3,17]

## 4. Synthesis Techniques

A variety of chemical and physicochemical techniques are used in the manufacture of nanosponges in order to create hyper-crosslinked, porous nanoscale structures with adjustable surface chemistry and drug-loading capacities. Nanosponge shape, particle size, porosity, crosslink density, and overall efficacy in drug delivery applications are all strongly impacted by the synthesis technique selection. Early developments focused mainly on cyclodextrin-based nanosponges, but subsequent advancements have expanded synthesis strategies to include polymeric, hybrid, and green technologies.[6,10]

### 4.1. Solvent Evaporation and Melt Polymerization

Solvent evaporation is one of the earliest and most widely used methods for preparing cyclodextrin nanosponges. In this method, β-cyclodextrin and a crosslinker such as diphenyl carbonate (DPC) or carbonyl diimidazole (CDI) are dissolved in an appropriate organic solvent and subjected to heating to initiate crosslinking.[6] As the solvent evaporates, polymerization proceeds, resulting in the formation of a solid nanosponge mass, which is later pulverized, washed, and dried. This technique offers good control over crosslinking efficiency but requires careful solvent removal to avoid residual toxicity.[7]

Melt polymerization was later introduced as a greener alternative. In this solvent-free method, cyclodextrin and crosslinker are heated above the melting point of the crosslinker, allowing polymerization to occur without the use of organic solvents.[4] Melt methods minimize environmental impact and reduce purification requirements, but high processing temperatures may limit their use with thermolabile drugs.

### 4.2. Ultrasound-Assisted Synthesis

Acoustic cavitation is used in ultrasound-assisted techniques to speed up crosslinking reactions and decrease particle size. Intense local heat and pressure are produced by the quick collapse of cavitation bubbles, improving mixture homogeneity and encouraging effective polymerization. According to Swaminathan et al. (2010), compared to traditional techniques, ultrasound-assisted synthesis resulted in cyclodextrin nanosponges with better shape, smaller size distributions, and higher entrapment efficiencies. This technique is especially useful for producing nanosponges with smaller particle sizes and more uniform porosity.[10]

### 4.3. Emulsion Solvent Diffusion

This method involves emulsifying a polymer-drug solution in a volatile organic solvent into an aqueous phase that contains stabilizers such polyvinyl alcohol (PVA). Upon diffusion and evaporation of the organic solvent, the polymer precipitates, forming porous nanosponge-like particles.[8] This method is advantageous for encapsulating heat-sensitive drugs and allows fine control over particle size through adjustment of emulsification speed, solvent ratio, and surfactant concentration.[14]

### 4.4. Free-Radical Polymerization

Stimuli-responsive nanosponge systems are frequently synthesized via free-radical polymerization. When a crosslinker is present, monomers like acrylates, methacrylates, or vinyl derivatives polymerize to create networks that resemble nanoscale gels. 3 It is possible to directly insert functional groups into the polymer backbone that can react to internal or external stimuli, such as pH, redox conditions, or enzyme activity. Redox-labile disulfide linkers and acid-sensitive bonds have been utilized to develop nanosponges capable of selective drug release in cancer or inflamed tissues.[20,35] Free-radical polymerization thus provides exceptional versatility in designing environmentally responsive nanosponge platforms.

### 4.5. Green and Hybrid Synthesis

The use of green synthesis techniques has been spurred by growing environmental concerns. These include the use of biodegradable crosslinkers such as citric acid, water-based reaction media, or non-toxic solvents to produce safer nanosponge systems.[4] Hyperbranched cyclodextrin polymers synthesized using citric acid demonstrate excellent biocompatibility and reduced risk of residual toxicity.

Inorganic elements like magnetic oxides, silica nanoparticles, or gold nanorods are incorporated into organic nanosponge matrices in hybrid nanosponge systems. These materials are typically synthesized through in situ growth of inorganic nanoparticles within the crosslinked polymer network or via blending during polymerization.[5] Hybrid nanosponges combine the drug-loading advantages of organic carriers with functionalities such as imaging capability, photothermal activity, or magnetic responsiveness, broadening their applications in theranostics.

**5. Characterization of Nanosponges**

To comprehend nanosponges' physicochemical characteristics, structural integrity, drug-loading behavior, and appropriateness for pharmaceutical applications, a thorough characterisation is necessary. Because nanosponges possess complex porous morphologies and diverse surface chemistries, multiple analytical techniques are required to evaluate key parameters such as particle size, surface charge, morphology, crystallinity, thermal behavior, molecular interactions, and release kinetics.[4,10]

5.1. Particle Size and Polydispersity Index (PDI)

Dynamic Light Scattering (DLS) is the most widely used technique to determine particle size and polydispersity index. Nanosponge formulations typically fall in the range of 100–500 nm, although the size may vary depending on crosslink density, synthesis method, and polymer composition.[22,23] A PDI value below 0.3 indicates uniform size distribution and high colloidal stability. Particle size greatly influences drug loading, permeation, and biodistribution, making DLS a critical tool during nanosponge optimization.[8]

5.2. Zeta Potential Measurements

Zeta potential provides insights into the surface charge and colloidal stability of nanosponge dispersions. Particles with zeta potential values greater than |±15–20| mV exhibit better electrostatic repulsion, preventing aggregation.[21] Cyclodextrin nanosponges often exhibit negative charges due to carboxyl or hydroxyl groups, while polymeric or chitosan-coated nanosponges may display positive surface potentials.[17] Zeta potential also influences mucoadhesion, cellular uptake, and in vivo circulation behavior.

5.3. Morphological Characterization (SEM, TEM, AFM)

Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) offer comprehensive insights into the surface texture, pore architecture, and morphology of nanosponge.

These techniques typically reveal highly porous, sponge-like structures with rough surfaces, confirming successful crosslinking and nanoscaleporosity.[14] AFM may also be used to analyze surface roughness, topography, and mechanical stiffness. Morphological characterization is critical for validating the nanosponge's internal porous framework, which directly affects drug entrapment and release characteristics.

5.4. Fourier-Transform Infrared Spectroscopy (FTIR)

FTIR identifies chemical functional groups and possible interactions between the drug and nanosponge matrix. Shifts in characteristic absorption peaks, disappearance of drug-specific bands, or broadening of functional-group peaks indicate successful drug encapsulation and non-covalent interactions such as hydrogen bonding or van der Waals forces.[11] FTIR also confirms successful crosslinking by comparing spectra of native cyclodextrin or polymers with functionalized nanosponge structures.

5.5. Differential Scanning Calorimetry (DSC) and Thermal Analysis

Thermal transitions including melting point, glass transition temperature, and enthalpy changes are analyzed using DSC. Drug-loaded nanosponges often show disappearance or broad reduction of drug melting peaks, indicating amorphization or molecular-level dispersion within the nanosponge.[10]

Thermogravimetric Analysis (TGA) may also be employed to study thermal stability, decomposition behavior, and moisture content, particularly for polymeric nanosponge systems.

5.6. Powder X-Ray Diffraction (PXRD)

PXRD reveals the crystalline or amorphous nature of drugs and nanosponge matrices. Sharp diffraction peaks of crystalline drugs often disappear or diminish after encapsulation, demonstrating successful conversion into amorphous or molecularly dispersed forms.[4] This enhancement in amorphization directly contributes to improved solubility and dissolution of poorly soluble drugs.

5.7. Entrapment Efficiency (EE%) and Drug Loading

Entrapment efficiency is typically determined by separating unencapsulated drug from the nanosponge—commonly via centrifugation or filtration—and quantifying it using HPLC or UV–Vis spectroscopy.[22,23] Nanosponge formulations often exhibit EE% values ranging from 50–90%, depending on molecular size, hydrophobicity, crosslinker ratio, and loading method.[8]

5.8. *In-Vitro* Drug Release Studies

Drug-release behavior is commonly studied using dialysis bag methods, Franz diffusion cells (for topical systems), or USP dissolution apparatus. Release profiles are analyzed using kinetic models such as Higuchi, Korsmeyer–Peppas, zero-order, and first-order equations to determine mechanisms such as diffusion, swelling, or erosion.[24] Nanosponge systems frequently show sustained or biphasic release patterns due to drug localization within both the CD cavities and porous polymeric matrix.[27]

5.9. Stability Studies

Stability studies under different temperature, humidity, and light conditions assess physical integrity, aggregation tendencies, and drug retention over time.[17] Stability is particularly important for nanosponge gels, topical formulations, and aqueous dispersions that may undergo sedimentation or aggregation.

5.10. Cytotoxicity and Biocompatibility Testing

Biocompatibility is commonly assessed using in vitro assays such as MTT, resazurin, or live–dead cell viability tests on relevant cell lines.[14] Many nanosponge formulations demonstrate low cytotoxicity due to the biocompatibility of cyclodextrin and polymer-based materials, making them suitable for systemic, topical, and mucosal drug delivery.

**6. Mechanisms of Drug Loading**

Many non-covalent interactions and structural characteristics that result from the hyper-crosslinked, porous nature of the nanosponge matrix control drug loading into nanosponges. Nanosponges can encapsulate a variety of molecules with different physicochemical properties since they have both internal cavities and external porous surfaces. The loading efficiency and overall drug–carrier compatibility depend on molecular size, polarity, functional groups, crosslink density, and the physicochemical environment used during the loading process.[4,5]

**6.1. Inclusion Complexation in Cyclodextrin Cavities**

Cyclodextrin-based nanosponges retain the intrinsic hydrophobic cavities of individual CD units. These toroidal cavities allow hydrophobic parts of drug molecules to be accommodated through classic host–guest inclusion interactions.[6,7] Hydrophobic drugs such as resveratrol, camptothecin, and curcumin readily form inclusion complexes within CD cavities, improving solubility and stability.[14] Because nanosponge architectures contain a multitude of cyclodextrin units, the inclusion potential is significantly higher than that of a single CD complex.

**6.2. Adsorption onto Internal and External Porous Surfaces**

The porous lattice of nanosponges provides extensive surface area for adsorption-based drug loading. This technique is especially important for medications that are moderately polar or molecules that are too big to fit into CD cavities.[4] Van der Waals interactions, hydrophobic interactions, or mild electrostatic forces can all cause drugs to adsorb onto pore walls. The high surface-to-volume ratio of nanosponges makes adsorption a major contributor to overall loading capacity, especially in polymeric nanosponge systems.[8]

**6.3. Hydrogen Bonding and Electrostatic Interactions**

Functional groups including -OH, -COOH, -$NH_2$, and ester groups are found in many nanosponge matrices. These can interact with drug molecules via hydrogen bonding or ionic interactions, enhancing loading efficiency.[11] For example: Carboxyl groups in PMDA-crosslinked nanosponges can form hydrogen bonds with hydroxyl-containing drugs. Positively charged amino groups from chitosan-based nanosponges electrostatically draw negatively charged medication molecules.[17] Both loading and release behavior are influenced by the strength of these interactions.

**6.4. Intercalation within Polymeric Chains**

In polymeric nanosponges composed of PCL, polyesters, or hyperbranched CD polymers, drug molecules may become physically trapped or intercalated within the polymer chains.[8,14] This mechanism is particularly important for biodegradable polymeric nanosponges, hydrophobic or bulky drug molecules, and long-chain polymer networks where chain mobility allows interpenetration. Intercalation often leads to sustained or slow release due to the deeper embedding of molecules within the network.

### 6.5. Solvent-Assisted Diffusion and Swelling Mechanisms

Drug molecules can diffuse into interior pores during drug loading because the nanosponge matrix expands when submerged in an appropriate solvent. Upon solvent removal, the matrix contracts and traps the drug molecules inside.[3] Solvent polarity plays a significant role: hydrophobic drugs load more efficiently in organic or mixed solvent systems, whereas hydrophilic drugs require aqueous or hydroalcoholic environments.

### 6.6. Factors Influencing Loading Efficiency

Several parameters significantly affect drug-loading outcomes:

**Crosslinker ratio and density**: Higher crosslinking reduces pore size but increases structural stability; lower crosslinking increases swelling and drug-accessible pores [5].

**Drug solubility and logP value:** Hydrophobic drugs load more efficiently due to compatibility with CD cavities and hydrophobic pore domains.[14]

**pH of loading medium:** Ionizable drugs show improved loading when pH favors their uncharged state.

**Temperature and solvent choice:** Controlled heating improves diffusion into the matrix, while appropriate solvents enhance solubilization and penetration.[8]

### 6.7. Examples of Enhanced Drug Loading

Numerous studies support the improved loading behavior of nanosponges:

**Resveratrol-loaded CD nanosponges** demonstrated significantly higher apparent solubility and stability.[41]

**Curcumin-loaded polymeric nanosponges** showed improved entrapment due to hydrophobic interactions and chain intercalation.[14]

**Camptothecin** exhibited increased encapsulation and protection against degradation within CD-based nanosponges.[42]

## 7. Mechanisms of Drug Release

Drug release from nanosponges happens via a variety of physicochemical processes that are influenced by the polymer composition, pore architecture, crosslinking density, and structural design of the nanosponge. Because nanosponges possess both internal cavities and extended porous networks, they can facilitate drug liberation through diffusion, swelling, erosion, or stimuli-responsive triggers, allowing fine-tuned control over therapeutic delivery.[3,4] Diffusion-controlled release is the most common mechanism, particularly in highly crosslinked cyclodextrin and polymeric nanosponge systems. Drug molecules in these structures follow a concentration gradient as they move from interior cavities and nanopores into the surrounding medium via aqueous channels.[5] The rate of diffusion is influenced by pore size, crosslink density, and drug–matrix affinity. Highly crosslinked networks slow molecular mobility, producing sustained release, whereas loosely crosslinked structures allow faster diffusion. Release profiles often fit the Higuchi or Korsmeyer–Peppas kinetic models, indicating a predominantly diffusion-driven mechanism.[24] Swelling-controlled release occurs mainly in hydrophilic or polymeric nanosponges whose matrices absorb water and expand, increasing porosity and facilitating drug mobility. When exposed to aqueous environments, these nanosponges swell due to polymer relaxation, generating channels that allow entrapped molecules to diffuse out.[8] This mechanism is particularly relevant for biodegradable polymeric systems such as polyesters, polycaprolactone, or chitosan-based nanosponges, where water penetration alters chain arrangement and promotes gradual drug liberation. Hydrolytic or enzymatic degradation of the polymeric matrix results in erosion-controlled release. In biodegradable nanosponge formulations, matrix erosion contributes significantly to long-term release, especially for hydrophobic drugs intercalated within polymer chains.[14] As erosion progresses, pores enlarge and entrapped molecules are freed, enabling controlled or extended release depending on polymer composition and environmental conditions. Stimuli-responsive release represents an advanced mechanism involving chemical or environmental triggers. Redox-sensitive nanosponges containing disulfide linkages release drugs in response to elevated intracellular glutathione (GSH) levels typical of cancer cells.[20] pH-responsive nanosponge matrices release drug preferentially in acidic environments such as tumors or inflamed tissues due to protonation-induced matrix loosening.[35] Enzyme-responsive systems incorporate cleavable bonds that degrade in the presence of specific enzymes, enabling site-specific and on-demand delivery. Environmental inputs, polymer chemistry, and structural elements interact

to produce nanosponge drug release mechanisms. Nanosponges are very effective nanocarriers for enhancing therapeutic performance and reducing dose frequency because of their capacity to deliver sustained, regulated, and targeted release.[17]

**8. Types of Nanosponges**

Based on their structural structure, crosslinking chemistry, functional components, and intended uses, nanosponges can be generally divided into a number of groups. Cyclodextrin-based nanosponges, polymeric nanosponges, mesoporous and hybrid nanosponges, stimuli-responsive nanosponges, and green-synthesized nanosponges are the main varieties. Different physicochemical traits that affect drug loading, release behavior, and therapeutic efficacy are present in each group.[5,6]

8.1. Cyclodextrin-Based Nanosponges

The first and most extensively researched class of nanosponges is based on cyclodextrin. They are synthesized by crosslinking β-cyclodextrin with diphenyl carbonate (DPC), carbonyl diimidazole (CDI), or pyromellitic dianhydride (PMDA), resulting in a three-dimensional porous network containing intrinsic CD cavities and interconnected nanopores.[6,7] These nanosponges demonstrate excellent loading capacity for hydrophobic drugs such as camptothecin, resveratrol, and griseofulvin, owing to dual encapsulation mechanisms—traditional inclusion complexation and adsorption within the porous matrix.[11] They are widely used in oral, topical, transdermal, and anticancer formulations due to their stability and solubility-enhancing capabilities.[4]

8.2. Polymeric Nanosponges

Polymers like polycaprolactone (PCL), chitosan, polyesters, polyamidoamine derivatives, and hyperbranched cyclodextrin polymers are used to create polymeric nanosponges. These systems provide tunable biodegradability, mechanical durability, and structural flexibility, making them suitable for sustained-release and long-acting drug delivery applications.[8,14]
Their functional groups (–OH, –COOH, –$NH_2$) facilitate hydrogen bonding and electrostatic interactions with drugs, improving entrapment efficiency. Polymeric nanosponges are widely employed in topical, transdermal, ophthalmic, and mucosal formulations because of their biocompatibility.[15]

8.3. Mesoporous and Hybrid Nanosponges

Inorganic or metallic elements are incorporated into the framework of mesoporous and hybrid nanosponges. Gold nanorods embedded in the organic matrix, magnetic nanostructures, and silica nanoparticles are a few examples.[5] Additional features including magnetic responsiveness, photothermal effects, enhanced imaging capabilities, and increased surface area are offered by these hybrids. Because of their versatility, they are useful for theranostic applications, which combine therapy and imaging into a single nanosystem.

8.4. Stimuli-Responsive Nanosponges

Drugs are released by stimuli-responsive nanosponges in reaction to particular internal or external stimuli. Redox-sensitive nanosponges containing disulfide linkages respond to high intracellular glutathione levels in tumor cells, while pH-responsive systems selectively release drugs in acidic tumor or inflamed microenvironments.[20,35] Enzyme-responsive nanosponges degrade in the presence of disease-associated enzymes, enabling on-demand, site-specific drug delivery. These systems show great promise for targeted delivery applications, antimicrobial therapy, and cancer.

8.5. Green-Synthesized Nanosponges

Green-synthesized nanosponges are designed using environmentally friendly approaches, including biodegradable crosslinkers such as citric acid and solvent-free or water-based synthesis routes.[4] These eco-friendly systems reduce toxic residues, improve safety profiles, and maintain high drug-loading capabilities. They are especially appealing for topical, pediatric, and oral formulations where biocompatibility is crucial.

**9. Pharmaceutical Implementations**

Nanosponges have garnered considerable interest across various pharmaceutical sectors due to their distinctive capability to augment solubility, stability, permeability, and regulated release of an extensive range of therapeutic compounds. Their tunable porosity, high loading capacity, and compatibility with different administration routes make them versatile platforms for oral, topical, transdermal, ophthalmic, anticancer, antimicrobial, and antioxidant drug delivery.[1,3]

9.1. Oral Drug Delivery

Oral administration is one of the most common routes where nanosponges have demonstrated considerable improvements in the biopharmaceutical performance of poorly water-soluble drugs. Cyclodextrin-based nanosponges significantly enhance aqueous solubility, dissolution rate, and intestinal permeability of hydrophobic drugs such as paclitaxel, nicardipine, griseofulvin, and resveratrol.[4,22] For example, β-cyclodextrin nanosponges increased the oral bioavailability of paclitaxel several-fold compared to conventional formulations, attributed to improved solubilization and controlled release in gastrointestinal fluids.[3] Nanosponge formulations also protect acid-labile drugs, enhance mucosal adhesion, and reduce food-effect variability, offering promising potential for oral delivery of poorly soluble therapeutic agents.

9.2. Topical and Transdermal Delivery

Nanosponges are highly beneficial for topical and transdermal applications due to their ability to provide localized, sustained release while minimizing irritation. Benzoyl peroxide nanosponge gels have shown significantly reduced skin irritation and enhanced penetration in acne therapy compared to conventional preparations.[11] Anti-inflammatory drugs such as diclofenac, etodolac, and COX-2 inhibitors demonstrate superior dermal penetration, prolonged therapeutic effect, and reduced systemic exposure when formulated into nanosponge-based gels.[23,28] Topical nanosponge hydrogels are also being explored for antifungal therapy, wound healing, and localized antimicrobial action, providing improved patient compliance and enhanced drug retention at the application site.[27]

9.3. Ophthalmic Delivery

Ocular drug delivery is often limited by rapid tear turnover and low residence time. Hydrophilic cyclodextrin nanosponges overcome these barriers by prolonging precorneal retention and providing sustained release of ophthalmic drugs.[15] Formulations of anti-inflammatory, antimicrobial, and antioxidant agents using nanosponges have shown improved corneal permeation, enhanced bioavailability, and reduced dosing frequency, making them promising candidates for ophthalmic gels, drops, and in situ-forming systems.[17]

9.4. Anticancer Drug Delivery

Nanosponges offer significant advantages in oncology, where drug solubility, stability, and targeted delivery are critical challenges. Drugs such as camptothecin, paclitaxel, doxorubicin, and tamoxifen exhibit enhanced cytotoxicity, improved intracellular uptake, and reduced off-target toxicity when delivered through nanosponge carriers.[1,35] Stimuli-responsive nanosponges, particularly redox- and pH-sensitive systems, release anticancer drugs selectively in the tumor microenvironment due to high glutathione levels or acidic pH, enhancing therapeutic efficacy while minimizing systemic toxicity,[20] Hybrid nanosponge systems incorporating imaging or photothermal agents further enable theranostic applications that combine cancer diagnosis and therapy in a single platform.[5]

9.5. Antioxidant and Antimicrobial Delivery

Nanosponges significantly enhance the stability, solubility, and therapeutic action of natural antioxidants such as resveratrol and curcumin. These bioactive molecules exhibit improved photostability, extended release, and superior antioxidant efficiency when embedded in nanosponge matrices.[14] Antibiotics, antifungals, and antiviral drugs also benefit from nanosponge delivery. Enhanced permeation and dissolution of norfloxacin, cephalexin, fluconazole, clotrimazole, and griseofulvin have been demonstrated in nanosponge-based forms, improving antimicrobial and antifungal efficacy.[22,23,30] Dual-action hydrogels and vaginal gels containing nanosponge-loaded antifungals provide prolonged retention and improved therapeutic outcomes.[29,31]

9.6. Buccal, Mucosal, and Transmucosal Delivery

The mucoadhesive properties of certain nanosponge coatings (e.g., chitosan) enhance retention time and permeation across oral and nasal mucosal.[15] Buccal nanosponge formulations offer pain-free, non-invasive alternatives with enhanced drug absorption, particularly for unstable or highly potent molecules requiring bypass of first-pass metabolism.[21]

9.7. Drug Delivery for Pediatric and Geriatric Use

Nanosponge dispersions and suspensions are ideal for pediatric and geriatric populations due to their improved palatability, enhanced solubility, and reduced dosing frequency. Griseofulvin nanosponge dispersions for pediatric formulations exemplify how nanosponges improve drug handling and therapeutic performance.[23]

9.8. Theranostic and Advanced Biomedical Applications

Hybrid nanosponge systems, incorporating metallic or magnetic materials, can function as dual-purpose carriers for imaging and therapy. These platforms facilitate photothermal treatment, precise imaging, and concurrent pharmaceutical administration in oncological and neurological contexts. Such multifunctional nanosponge architectures are emerging as avant-garde instruments for precision medicine.

**10. Chosen Empirical Analyses from Scholarly Articles**

**Resveratrol β-CD nanosponges:** Ansari et al. (2011) devised β-cyclodextrin nanosponges (~400–500 nm, >80% EE), substantially augmenting solubility, stability, and dermal permeation of resveratrol.

**Camptothecin nanosponges:** Swaminathan et al. (2010) synthesized camptothecin-encapsulated CD nanosponges utilizing ultrasonic methodology, realizing enhanced stability, prolonged release, and increased in vitro cytotoxicity.

**Paclitaxel oral nanosponges:** Torne et al. (2010) documented improved oral bioavailability of paclitaxel employing β-CD nanosponges, ascribed to enhanced solubilization and regulated release.

**GSH/pH-responsive strigolactone nanosponges:** Argenziano et al. (2018) created dual-responsive nanosponges (200–250 nm) that exhibit enhanced cytotoxicity against prostate cancer cells and selective drug release in tumor-like conditions.

**GSH-responsive resveratrol nanosponges:** Palminteri et al. (2021) created redox-sensitive CD nanosponges (~200 nm) that enhanced intracellular delivery and apoptosis in cancer cells.

**Griseofulvin pediatric nanosponges:** Omar et al. (2020) developed β-CD nanosponges for oral usage in children, resulting in significantly increased griseofulvin solubility, dissolution, and bioavailability.

**11. Comparative Evaluation Table**

**Table 1 represents comparative evaluation of different nanosponges.**

| Drug | Matrix/Crosslinker | Size (nm) | EE% | Key Findings | Reference |
|---|---|---|---|---|---|
| Resveratrol | β-CD / CDI | 400–500 | >80 | ↑ Solubility, ↑ stability, ↑ permeation | (Ansari et al., 2011) |
| Camptothecin | β-CD / DPC | ~300 | High | Controlled release, ↑ cytotoxicity | (Swaminathan et al., 2010) |
| Paclitaxel | β-CD nanosponge | ~300 | High | ↑ Oral bioavailability | (Torne et al., 2010) |
| Strigolactone | GSH/pH-responsive CD NS | 200–250 | High | Tumor-selective release, ↑ efficacy | (Argenziano et al., 2018) |
| Resveratrol | GSH-responsive CD NS | ~200 | High | ↑ Intracellular delivery, apoptosis | (Palminteri et al., 2021) |
| Griseofulvin | β-CD nanosponge | 200–300 | High | ↑ Solubility, better pediatric dosing | (Omar et al., 2020) |

**12. Benefits of Nanosponges**

Nanosponges are a great fit for contemporary pharmaceutical applications because they provide a number of important benefits. A variety of medications can be encapsulated using their special hyper-crosslinked, porous structure, which enhances solubility, stability, release control, and therapeutic action.

Nanosponges markedly enhance the solubility and dissolution of poorly water-soluble drugs due to their dual loading mechanisms—cyclodextrin cavity inclusion and adsorption within the porous network.[5,11] This results in substantially improved bioavailability for drugs such as paclitaxel, griseofulvin, resveratrol, and other BCS Class II molecules.[3,22]

Another major advantage is improved stability. Nanosponges protect encapsulated drugs from hydrolysis, oxidation, photodegradation, and thermal degradation because the drug is shielded within the internal cavities or bound to the nanosponge matrix.[1,14] This enhances the shelf-life and formulation robustness of sensitive therapeutic compounds.

Nanosponges provide excellent control over drug release, enabling sustained, prolonged, or stimuli-responsive delivery depending on the crosslinker type and matrix composition.[20,24] Controlled release reduces dosing frequency, minimizes fluctuations in plasma drug levels, and improves patient compliance, particularly in chronic therapies.

The high loading capacity of nanosponges is another key benefit. They can encapsulate significant amounts of both hydrophobic and hydrophilic drugs due to their huge surface area and vast internal porosity.[5] This enables the design of compact, efficient dosage forms and reduces excipient burden. Additionally, there are a lot of different ways to administer nanosponges. They have been successfully applied in oral, topical, transdermal, ophthalmic, parenteral, nasal, buccal, and mucosal delivery systems.[17] Their tunable size, surface characteristics, and biocompatibility support broad applicability across pharmaceutical dosage forms, including gels, creams, suspensions, tablets, hydrogels, and injectables.

Biocompatibility is another critical advantage. Cyclodextrin and polymer-based nanosponges are generally well-tolerated, exhibiting low cytotoxicity and good biodegradation profiles, making them suitable for systemic and localized drug delivery.[8,16]

Furthermore, nanosponge platforms support surface functionalization with targeting ligands such as peptides, antibodies, sugars, or polymers, enabling targeted drug delivery to tumors or specific tissues.[35] This improves therapeutic index, reduces off-target effects, and enhances precision medicine applications.

Stimuli-responsive nanosponge systems offer highly selective drug delivery by responding to pH, redox conditions, or enzymes, making them promising candidates for cancer therapy, inflammation-targeted treatments, and controlled intracellular delivery.[8]

Overall, nanosponges combine high loading efficiency, enhanced solubility, improved stability, controlled release, targeting potential, and excellent biocompatibility, positioning them as advanced nanocarriers with strong promise for next-generation drug delivery.[1,17]

**13. Limitations of Nanosponges**

In order to successfully translate nanosponges into clinically authorized drug delivery systems, a number of their constraints must be addressed, despite their promising features. Reproducibility of formulation is one of the main challenges. The crosslinker type, crosslinking ratio, reaction conditions, and purification efficiency all have a significant impact on the properties of nanosponge. It is challenging to attain large-scale and batch-to-batch consistency because little changes in synthesis can drastically change particle size, porosity, drug-loading capacity, and release behavior.[10,19]

The possible toxicity of some crosslinkers and organic solvents employed in synthesis is another drawback. Residual crosslinking agents such as diphenyl carbonate (DPC), CDI, or dianhydrides may pose risks if not removed thoroughly, especially for formulations intended for systemic delivery.[7] Although green synthesis methods reduce this risk, they are not yet universally applicable across all drug types and nanosponge structures.[4]

Drug loading efficiency can also be limited in the case of certain hydrophilic drugs and large biomolecules. While nanosponges are highly effective for hydrophobic drugs, hydrophilic compounds may show poor encapsulation unless the nanosponge surface is chemically modified or functionalized to improve compatibility.[14] This limitation restricts the use of nanosponges for macromolecular drugs such as proteins, peptides, and nucleic acids without advanced modifications.

Stability issues may arise in aqueous dispersions, where nanosponges can aggregate over time. Aggregation affects particle size distribution, zeta potential, drug release, and biodistribution, necessitating the use of stabilizers or surface coatings that increase formulation complexity.[21] For topical or ophthalmic gels, sedimentation or inconsistent dispersion is common without proper rheological control.

Regulatory challenges also pose significant limitations. Nanosponges must adhere to strict safety, toxicity, biodegradation, and long-term stability regulations since they are categorized as nanomaterials. Regulatory approval is now hampered by a lack of uniform characterization parameters, inadequate toxicological profiling, and little clinical data.[16]

Potential long-term biocompatibility and biodistribution are another issue. While cyclodextrin-based and polymeric nanosponges are generally considered safe, their behavior, degradation byproducts, and accumulation in organs such as the liver or spleen require extensive investigation before widespread clinical use.[17]

Finally, the manufacturing scale-up of nanosponges is technically challenging. It might be difficult to scale methods like solvent evaporation, emulsion diffusion, and free-radical polymerization without sacrificing drug encapsulation effectiveness and nanosponge homogeneity.Achieving controlled porosity and structural consistency at industrial levels remains a major barrier.[8]

Overall, while nanosponges offer remarkable advantages in drug delivery, limitations including reproducibility issues, potential toxicity, hydrophilic drug incompatibility, aggregation, regulatory hurdles, and scale-up challenges underscore the need for continued research and optimization.[1]

**14. Future Directions**

It is anticipated that future developments in nanosponge technology would concentrate on creating more complex, multipurpose, and clinically transferable nanosystems. The creation of intelligent, stimuli-responsive nanosponges that incorporate several triggers—such as pH, redox state, enzymes, temperature, or external fields—to accomplish highly targeted, on-demand medication release.Dual- and multi-responsive nanosponge platforms are particularly promising for oncology and inflammation-related disorders, where disease-specific microenvironmental cues can be exploited for targeted therapy.[20,35]

Another significant future direction involves the incorporation of targeting ligands, such as antibodies, peptides, sugars, aptamers, and folate derivatives, to achieve precise tissue- or cell-specific delivery. Targeted nanosponge systems can increase therapeutic index, reduce off-target toxicity, and improve intracellular uptake, especially for anticancer and antimicrobial therapies.[17,35]

Green and sustainable nanosponge synthesis approaches are also expected to gain traction. The use of biodegradable crosslinkers, renewable materials, microwave-assisted synthesis, and solvent-free techniques may minimize toxicity, reduce environmental impact, and enhance scalability.[4] Such eco-friendly strategies align with the regulatory push toward safer excipients and manufacturing processes for pharmaceuticals.

Emerging research is increasingly focusing on hybrid nanosponges combining organic polymers with inorganic components, including gold nanoparticles, magnetic oxides, silica, or quantum dots. Theranostic applications that integrate drug administration, imaging, and photothermal or photodynamic therapy on a single platform are made possible by these multipurpose hybrids.[4] A viable path for further clinical development is their incorporation into precision oncology and customized medicine.

Investigating nanosponge systems for macromolecular and biologic treatments, such as peptides, proteins, nucleic acids, and vaccines, is another important area of future research. Surface-engineered or polymer-modified nanosponges may overcome current challenges in stability and cellular delivery for these delicate molecules.[8]

Translational research will increasingly emphasize comprehensive safety assessments, including long-term toxicity, biodegradation pathways, immunogenicity, and biodistribution. Robust clinical and toxicological data are essential to support regulatory approval and facilitate commercialization.[16] Development of standardized guidelines for nanosponge characterization, biocompatibility assessment, and manufacturing controls will further accelerate clinical translation.

Finally, industrial-scale manufacturing remains a major challenge. Future efforts must focus on optimizing high-throughput, reproducible, and cost-effective production methods that maintain structural uniformity and therapeutic performance. Strategies such as continuous-flow synthesis, supercritical fluid technology, and scalable solvent-free polymerization may enable commercially viable nanosponge production.[1,8]

Overall, the future of nanosponge research lies in the advancement of smart, safe, targeted, and multifunctional systems that bridge fundamental nanotechnology with scalable pharmaceutical innovation. How well nanosponges go from lab research to clinically authorized treatments will depend on ongoing advancements in materials science, biomedical engineering, and regulatory science.

## 15. Conclusion

A flexible and efficient nanocarrier platform, nanosponges can overcome the drawbacks of poorly soluble, unstable, and low-bioavailability medications. Their large loading capacity, controlled-release characteristics, and distinctive porous architecture allow for substantial enhancements in therapeutic efficacy, stability, permeability, and solubility across various delivery routes. Their use in oral, topical, ophthalmic, anticancer, antibacterial, and antioxidant drug delivery has been further expanded by developments in structural design, such as polymeric systems, hybrid designs, and stimuli-responsive networks. Nanosponges have several benefits, but there are still issues with large-scale production, repeatability, regulatory approval, and compatibility with some hydrophilic and macromolecular medications. It is anticipated that future studies would concentrate on creating greener synthesis techniques, platforms appropriate for biologics and precision medicine, and multifunctional and targeted nanosponge systems. Nanosponges have a great potential to develop into widely used and therapeutically feasible drug delivery technology with more research and development.

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