

REVIEW ARTICLE

Nanosponges in Solubility Enhancement: Formulation Approaches and Pharmaceutical Applications

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ABSTRACT

Poor aqueous solubility remains a critical challenge in drug development, particularly for BCS Class II and IV drugs, leading to inadequate dissolution and variable bioavailability. While conventional approaches such as micronization and solid dispersions offer partial solutions, they are often limited by stability and scalability concerns. Nanosponges, as cross-linked porous polymeric nanocarriers, provide an effective alternative by enhancing solubility through nano-cavity encapsulation, increased surface area, improved wettability, inhibition of recrystallization, and controlled drug release. These properties contribute to improved dissolution and bioavailability across various delivery routes. Although issues such as cross-linker toxicity and manufacturing scale-up must be addressed, nanosponges represent a promising and adaptable platform for improving the therapeutic performance of poorly soluble drugs.

KEYWORDS: Nanosponges, Solubility enhancement, Cyclodextrins, Controlled release, Drug delivery systems.

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INTRODUCTION

Biopharmaceutical Classification System (BCS) and solubility issues:

The Biopharmaceutics Classification System (BCS) provides a pragmatic framework to categorize drug substances according to their aqueous solubility and intestinal permeability, and it has become central to formulation strategy and regulatory decision-making. Under the BCS, a drug is considered "high solubility" when the highest marketed dose strength dissolves in 250 mL of aqueous media across the physiological pH range (pH 1.0–7.5) at 37°C; otherwise, it is classed as low-solubility. The system partitions drugs into four classes (I–IV) where Class II (low solubility, high permeability) and Class IV (low solubility, low permeability) contain compounds for which dissolution or solubility is often the rate-limiting determinant of oral absorption. The BCS has therefore guided both the selection of formulation strategies and the interpretation of in vitro dissolution tests as predictors of in vivo performance [1].

Impact of poor solubility on bioavailability:

Poor aqueous solubility compromises the fraction of drug that dissolves in the gastrointestinal lumen, thereby limiting the amount of active drug available for transepithelial absorption and systemic exposure. For BCS Class II drugs, where permeability across the gut wall is not limiting, inadequate dissolution translates directly into diminished and variable oral bioavailability, erratic pharmacokinetics, and challenges in achieving reproducible therapeutic effects. Moreover, low solubility often necessitates higher doses or special delivery systems, which can increase formulation complexity and cost. These constraints make solubility enhancement a primary objective during preformulation and lead optimization [2].

Conventional solubility-enhancement techniques:

A broad array of conventional physicochemical and formulation techniques has been developed to mitigate solubility limitations. Approaches include particle-size reduction (micronization, nanonization) to increase surface area and dissolution rate; salt formation for ionizable drugs; use of cosolvents, surfactants, and complexing agents; solid dispersions (amorphous carriers) to improve apparent

solubility and wettability; lipid-based formulations (self-emulsifying drug delivery systems, SMEDDS); and crystal engineering (polymorphs, cocrystals). Each technique has characteristic advantages and limitations for example, micronization increases dissolution rate but not equilibrium solubility, whereas amorphous solid dispersions can greatly enhance apparent solubility yet may suffer from physical instability (recrystallization). The choice of method is driven by the drug's physicochemical profile, dose, desired release kinetics, and downstream manufacturability [3].

Emergence of nanotechnology-based systems:

In recent years, nanoscale drug-delivery platforms have become prominent tools for overcoming solubility and bioavailability barriers. Nanotechnology approaches including nanocrystals, polymeric nanoparticles, lipid nanoparticles (including solid lipid nanoparticles and nanostructured lipid carriers), micelles, nanoemulsions, and nanogels can increase dissolution rate, enhance apparent solubility through molecular dispersion, and exploit size-dependent uptake pathways to improve absorption and targeting. These nanosystems can also protect labile actives from degradation, modify pharmacokinetics, and enable controlled or targeted release. The literature shows an accelerating trend toward tailoring nanoscale architectures to the biopharmaceutical profile of BCS Class II/IV candidates to enhance oral and parenteral performance [4].

Introduction to nanosponges as novel nanocarriers:

Nanosponges are a distinct class of porous, three-dimensional, crosslinked polymeric nanoparticles capable of entrapping a wide range of guest molecules within their internal cavities and on their surface. Cyclodextrin-based nanosponges produced by crosslinking native cyclodextrins with suitable bifunctional crosslinkers combine the inclusion complexation capability of cyclodextrins with a robust, insoluble network that affords higher loading, improved stability, and controlled release compared with simple cyclodextrin complexes. The porous nanosponge matrix can accommodate both hydrophilic and hydrophobic drugs either by inclusion into cyclodextrin cavities or by adsorption within the interstitial polymeric matrix; this dual mode of interaction enables enhanced apparent aqueous solubility, reduced crystallinity of the drug (amorphization), improved wettability, and protection from chemical degradation. Because of their tunable porosity, surface chemistry, and biodegradability, nanosponges have been widely investigated for oral, topical, parenteral, and targeted delivery applications where solubility enhancement and controlled release are desired. Critical reviews and experimental studies have documented significant solubility and dissolution improvements for multiple poorly soluble actives formulated as nanosponges, and ongoing work focuses on optimizing crosslinker chemistry, synthesis methods, safety profiles, and scale-up for translational development [5].

HISTORY AND DEVELOPMENT

The concept of nanosponge-type materials evolved from earlier studies on cyclodextrin inclusion complexes and hypercrosslinked polymer networks. Cyclodextrins (CDs) cyclic oligosaccharides produced from starch were first used in pharmaceuticals largely in the form of 1:1 inclusion complex that improve the solubility and stability of lipophilic drugs. By applying cross-linking chemistry to cyclodextrin units, researchers in the late 20th and early 21st centuries produced insoluble, hypercrosslinked CD polymers with nanoporous morphology and markedly different loading and release behaviour compared with monomeric CDs [6]. Over the past two decades the field broadened: (i) early CD-based networks demonstrated the practical advantage of higher loading and slower release compared with simple CD complexes; (ii) advances in cross-linker chemistry (e.g., carbonate, carbonyldiimidazole, diisocyanates, epichlorohydrin and others) enabled control over mesh polarity, pore dimensions, and swelling; (iii) synthetic methods (solvent, melt, emulsion/hypercrosslinking, ultrasound-assisted) allowed better control of particle size and morphology; and (iv) investigation expanded from CD-only systems to wholly polymeric and hybrid nanosponges, including biodegradable and stimuli-responsive variants. Reviews that trace the historical development emphasize that nanosponges matured from a conceptual extension of cyclodextrin chemistry into a practical, tunable platform for pharmaceutical applications particularly for solubility enhancement of poorly soluble actives [7].

TYPES OF NANOSPONGES

Nanosponges are typically grouped by their principal building blocks and synthetic strategies. The major categories used in pharmaceutical research are:

1. Cyclodextrin-based nanosponges (CD-NS):

Cyclodextrin-based nanosponges are the most widely studied subclass. They are produced by cross-linking α -, β - or γ -cyclodextrin units with multifunctional cross-linkers to form insoluble three-dimensional networks. The resulting material combines inclusion complexation (the canonical CD cavity

that can host small hydrophobic moieties) with adsorption/entrapment within inter-CD nanochannels and cavities generated by the polymeric mesh. By varying the type of cyclodextrin, the cross-linker identity and the degree of cross-linking, formulators can tune important attributes such as hydrophobic/hydrophilic balance, pore size distribution, surface charge and degradability. CD-NS have been reported to increase apparent aqueous solubility and dissolution rate, protect labile molecules from degradation, lower irritation for topical actives, and enable sustained or targeted release. Their biocompatibility and extensive literature support have made them the leading nanosponge platform for pharmaceutical investigations [5].

2. Polymeric nanosponges:

Polymeric nanosponges are synthesized from non-CD polymeric monomers or prepolymers and bifunctional cross-linkers to yield porous nanoscale networks. These polymers can be synthetic (e.g., hypercrosslinked polystyrene derivatives, polyesters, polyurethanes) or natural/biodegradable (e.g., polysaccharide-based, crosslinked gelatine or chitosan derivatives). Polymeric nanosponges broaden the chemical space beyond the CD cavity and permit additional functionalization strategies (e.g., responsive linkers that cleave under pH, redox, enzyme or temperature triggers). Because polymer chemistry is highly modular, polymeric nanosponges allow for the incorporation of targeting ligands, stealthing moieties (e.g., PEGylation), or reactive groups for conjugation, enabling advanced delivery concepts such as stimuli-responsive release or active targeting in addition to solubility enhancement. Recent studies highlight polymeric nanosponges' suitability when CD cavities are not optimal for the payload or when sustained biodegradability and stimulus responsiveness are required [8].

3. Hybrid nanosponges:

Hybrid nanosponges combine cyclodextrin units with other polymers, inorganic components or lipidic phases to obtain multifunctional materials that merge the desirable characteristics of each constituent. Examples include CD-polymer hybrids that exploit CD inclusion together with polymeric matrix entrapment, inorganic-organic hybrids (e.g., silica or metal-organic frameworks templated with CD-derived networks) and lipid-polymer hybrid sponges designed for both solubility enhancement and improved cellular uptake. Hybridization can improve mechanical stability, tune release profiles, provide imaging or stimulus-responsive capabilities, and facilitate scale-up by leveraging established polymer manufacturing routes. Hybrid nanosponges are an active area of current research where the design objective is to solve specific formulation problems for instance, combining rapid dissolution enhancement with site-specific release or imaging functionality for theranostic applications [9].

MECHANISM OF SOLUBILITY ENHANCEMENT BY NANOSPONGES

Nanosponges enhance the solubility and dissolution of poorly water-soluble drugs through a multifactorial mechanism that arises from their unique nanoscale architecture and physicochemical interactions. Their porous three-dimensional matrix creates internal nano-cavities and extensive surface area, enabling multiple pathways to enhance drug availability in aqueous environments [10].

1. Drug Encapsulation within Nano-Cavities:

Nanosponges possess a highly porous network of nano-sized cavities that can entrap drug molecules either by physical inclusion or non-inclusion interactions. The cavities provide a localized microenvironment where poorly soluble molecules can reside in a dispersed state rather than in bulk crystalline form. Encapsulation reduces the need for drugs to independently interact with bulk solvent molecules for dissolution, thereby enhancing *apparent solubility* [11].

In cyclodextrin-based nanosponges, for example, cyclodextrin units form inclusion complexes within their toroidal cavities, while the cross-linked network provides additional adsorption sites external to these cavities. This dual mode of drug interaction increases drug entrapment efficiency and solubility relative to simple cyclodextrin complexes [12].

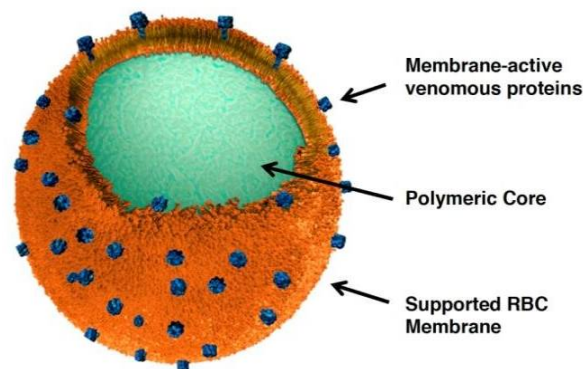


Figure 1: Schematic representation of the mechanism of solubility enhancement by nanosponges.

2. Increased Surface Area:

The nanoscale size and porous structure of nanosponges dramatically increase the total surface area available for drug-solvent contact. Smaller particles and porous networks expose greater surface area per unit mass, which accelerates the dissolution process according to classical dissolution principles (Noyes-Whitney relationship). Higher surface area facilitates faster drug release into the dissolution medium and thereby improves apparent solubility and rate of dissolution [13].

3. Molecular Dispersion:

Nanosponges can maintain drug molecules in a molecularly dispersed or amorphous state within their internal network. Unlike crystalline drugs which require significant energy to dissolve due to their ordered lattice structure amorphous or molecularly dispersed drugs have higher free energy and enhanced interaction with solvent. This state reduces the energy barrier for dissolution and increases the concentration of dissolved drug at equilibrium [14].

4. Improved Wettability:

Entrapment of hydrophobic drug molecules within the hydrophilic environment of nanosponges enhances wettability- the ability of water molecules to interact with drug surfaces. Enhanced wettability increases wetting of poorly water-soluble molecules, making them more amenable to dissolution. The hydrophilic surface provided by the polymer or cyclodextrin moieties further supports rapid hydration and dissolution of drug molecules [15].

Nanosponges can also “mask” hydrophobic groups of drug molecules from the surrounding aqueous phase, reducing interfacial tension and improving dispersion in biological fluids [16].

5. Prevention of Drug Crystallization:

By physically confining drug molecules within nano-cavities and maintaining them in an amorphous or dispersed state, nanosponges help prevent recrystallization during dissolution. Recrystallization often reduces solubility and slows dissolution as drug molecules re-form stable crystals. Occupancy of porous nano-cavities restricts molecular mobility and impedes the orderly alignment required for crystal lattice formation, maintaining the drug in a state more prone to dissolution [17].

6. Controlled and Sustained Release Behaviour:

Although controlled release per se is distinct from solubility enhancement, nanosponge encapsulation slows the release of the drug into bulk media in a regulated manner, helping to maintain supersaturation for longer durations. Sustained release occurs because drug molecules must diffuse out of internal cavities and pores before entering the dissolution medium; this diffusion-controlled release can maintain local drug concentrations above equilibrium solubility for extended times and enhance systemic uptake [18].

Such controlled release behaviour also minimizes burst release, reduces variability in plasma levels, and can improve oral bioavailability by prolonging the window for drug absorption [19].

MATERIALS USED IN NANOSPONGE FORMULATION

Nanosponges are engineered polymeric carriers whose composition determines their porous architecture, drug-loading capacity, solubility enhancement capability, biocompatibility, and release behaviour. The key components in nanosponge formulation include cyclodextrins, cross-linking agents, polymers, and surfactants/stabilizers. Each plays a critical role in defining the physicochemical and functional attributes of the final nanosponge system [20].

Cyclodextrins (β -CD, HP- β -CD):

Cyclodextrins are cyclic oligosaccharides composed of α -1,4-linked glucopyranose units that create a truncated cone with a hydrophobic internal cavity and a hydrophilic outer surface. This amphiphilic architecture enables cyclodextrins to form inclusion complexes with hydrophobic drugs, enhancing their solubility and dissolution [8].

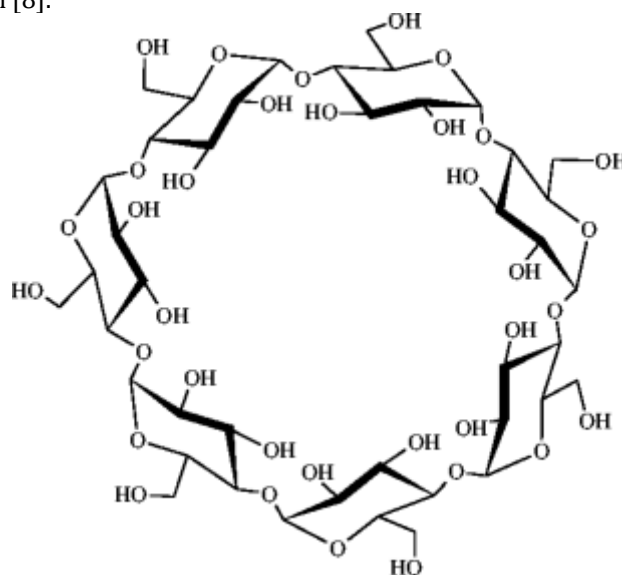


Figure No. 2: Structural representation of cyclodextrins used in nanosponge formulation (β -CD and HP- β -CD) and schematic of drug inclusion within the hydrophobic cavity.

In nanosponge formulation, β -cyclodextrin (β -CD) is the most frequently used derivative due to its optimum cavity size, biocompatibility, low toxicity, and affordability. β -CD units serve as the building blocks of the nanosponge matrix; when cross-linked, they create a porous network with multiple drug entrapping sites [21].

Modified cyclodextrins such as 2-hydroxypropyl- β -CD (HP- β -CD) and other substituted derivatives (e.g., carboxymethyl- β -CD, sulfobutylether- β -CD) are used when enhanced aqueous solubility, reduced crystallinity, and improved complexation with specific drug molecules are desired. The choice of CD derivative affects the polarity of nano-cavities and the strength of host-guest interactions, which in turn influences solubilization efficiency and drug release characteristics [22].

Cross-Linking Agents:

Cross-linking agents are bifunctional or multifunctional molecules that react with hydroxyl groups of CDs or polymer chains to form covalent bonds, stabilizing the nanosponge's three-dimensional network. The nature of the cross-linker influences pore size distribution, degree of swelling, mechanical stability, and ultimately drug encapsulation and release behavior [23].

Typical cross-linkers include:

- Carbonyl compounds such as *diphenyl carbonate (DPC)* and *dimethyl carbonate (DMC)* these react with cyclodextrin hydroxyls to form carbonate bridges that generate a rigid, porous network. DPC has been widely used in β -CD nanosponges for solubility enhancement and controlled release applications [24].
- Carbonyldiimidazole (CDI) reacts with hydroxyl groups to form carbamate linkages, and its use can influence loading capacity and network rigidity[25].

Polymers (Eudragit, Ethyl Cellulose)

While cyclodextrin-based networks are the most common, polymers other than CDs are also used to construct nanosponges or to blend with CD units:

- Ethyl cellulose a biodegradable and biocompatible polymer used in nanosponge formulations to impart sustained release properties, enhance mechanical strength, and modulate drug diffusion kinetics. Studies have used ethyl cellulose in combination with surfactants such as Kolliphor P-188 to formulate polymeric nanosponges with improved drug encapsulation and release profiles [26].
- Eudragit® polymers methacrylate-based polymers widely used in controlled release systems, can be incorporated into nanosponges to provide pH-responsive behavior or enteric protection in oral formulations. Although not cyclodextrin units per se, such polymers serve as matrices for hybrid nanosponge systems and provide delivery attributes beyond simple solubility enhancement [27].

Surfactants and Stabilizers:

Surfactants and stabilizers are often employed in nanosponge formulation to improve dispersion stability, prevent aggregation, and enable fine particle size control during synthesis and drug loading processes. These agents reduce interfacial tension and stabilize nanosponge suspensions, which is crucial for achieving consistent drug encapsulation and reproducible release kinetics [28].

Common surfactants include:

- Poloxamers (e.g., Kolliphor P-188 / Pluronic®)- block copolymers that stabilize nanosponge particles in aqueous media and enhance wettability of hydrophobic drugs [29].
- Polyvinyl alcohol (PVA)- frequently used in double-emulsion and solvent evaporation techniques as a stabilizer to control particle size and prevent coalescence.
- Polyvinylpyrrolidone (PVP)- can act as both stabilizer and solubilization enhancer due to its hydrophilic properties, aiding dispersion of the drug–nanosponge complex.

Formulation Approaches:

Nanosponges are prepared by a variety of synthetic routes that determine particle size, porosity, surface chemistry and ultimately drug-loading and release behaviour. The principal methods used in the literature are summarized below along with common procedural details, key advantages and limitations.

1. Solvent method (solution/condensation approaches):

The solvent method (also called solution or interfacial condensation in some reports) typically involves dissolving the cyclodextrin (or polymeric precursor) in a suitable solvent system and adding a bifunctional cross-linking reagent under controlled temperature and time to effect network formation. Polar aprotic solvents such as dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) are commonly employed because they solubilize both the cyclodextrin and many organic cross-linkers (e.g., diphenyl carbonate, carbonyldiimidazole) and allow homogeneous reaction conditions. The reaction is normally performed at reflux or elevated temperature for periods ranging from 1–48 h, after which the crude product is precipitated (typically into water), washed repeatedly to remove unreacted reagents and solvent, and then dried. The resulting nanosponges can be milled and fractionated to the desired particle size before drug loading. The solvent method offers good control over crosslinking stoichiometry and network homogeneity but requires exhaustive solvent removal and careful handling of toxic organic media in scale-up [30].

Typical workflow (solvent method): In the solvent method, cyclodextrin is dissolved in an alkaline or organic solvent, followed by addition of a cross-linker under reflux to form the cross-linked network. After completion, the reaction is cooled and quenched, and the product is precipitated in water. The nanosponges are then purified by washing or Soxhlet extraction, dried, and subjected to size reduction and sterilization if required [31].

2. Melt method:

The melt method is a solvent-free or solvent-minimal approach in which the cross-linker (for example diphenyl carbonate, DPC) is heated to its melting point and the cyclodextrin is then added to the molten cross-linker. The reactants are mixed and maintained at elevated temperature (for instance 70–120 °C depending on reagents) until the crosslinking reaction proceeds to a suitably cured network. The crude mass is then cooled, ground and washed (often using Soxhlet extraction with organic solvents such as acetone) to remove free reagents and by-products. The melt route avoids large volumes of organic solvents, can give high yields and in many studies has produced nanosponges with favourable entrapment efficiency and photostability for sensitive actives. However, high temperatures may restrict its use for thermally labile drugs if drug is present during synthesis (drug loading is therefore usually performed post-synthesis) [32].

Advantages / limitations: solvent-saving and simpler downstream purification vs. risk of thermal degradation and potentially broader particle size distributions that require milling [12].

3. Ultrasound-assisted synthesis (sonochemical methods):

Ultrasound (sonication) and other wave-assisted techniques (microwave combined with ultrasound) have emerged as rapid, energy-efficient tools for nanosponge synthesis. Ultrasonic irradiation promotes localized cavitation, micro-mixing and enhanced mass transfer, which can accelerate cross-linking kinetics and promote formation of smaller, more uniform particles relative to conventional heating. Sonochemical methods often operate at lower bulk temperatures and shorter reaction times, improving throughput and sometimes affording materials with higher surface area or more homogeneous porosity. Reports have demonstrated that ultrasound-assisted synthesis can yield nanosponges with comparable or improved entrapment efficiency and reduced reaction times compared with thermal methods. As with other advanced energy-assisted methods, process parameters (power, pulse, time, temperature) must be optimized to balance network formation and particle integrity [33].

4. Emulsion solvent-diffusion method:

The emulsion solvent-diffusion (or emulsion/solvent evaporation) method is widely used for polymeric nanosponges and hybrid systems, particularly when one aims to produce discrete, free-flowing nanoparticulate sponges suitable for topical or oral dispersions. In a typical procedure, the polymer (or CD-polymer mixture) and cross-linker are dissolved in an organic volatile solvent (e.g., dichloromethane, ethyl acetate). This organic phase is emulsified into an aqueous phase containing a stabilizer (PVA, poloxamer, etc.) under high shear to create an oil-in-water emulsion. Subsequent diffusion of solvent into the aqueous phase and evaporation results in precipitation/solidification of nanosponge particles which can then be collected by centrifugation, washed and dried. This technique enables control of particle size by varying emulsification energy, surfactant concentration and organic: aqueous phase ratio, and is especially useful for preparing nanosponges intended for dermal application or when using hydrophobic polymer matrices (e.g., ethyl cellulose). Notably, several early and influential nanosponge studies used emulsion solvent-diffusion to produce particles with porous “orange-peel” morphology and satisfactory drug-release behavior [34].

5. Hyper-crosslinking method:

Hyper-crosslinking describes strategies to produce highly crosslinked, rigid polymer networks with ultramicroporosity and high surface area. In the nanosponge context, hyper-crosslinked cyclodextrin or polymer precursors are subjected to post-crosslinking steps (for example Friedel–Crafts type reactions, or additional crosslinker dosing and activation) that create secondary networks and micropores within a preformed polymer matrix. Hyper-crosslinked nanosponges often display exceptional adsorption capacity, high surface area (useful for loading small hydrophobic molecules) and robust mechanical stability. These materials can be engineered by controlling the sequence of crosslinking steps (direct vs. post-crosslinking) and the nature of catalysts/activators used. While hyper-crosslinking boosts capacity and surface area, it can also reduce pore accessibility for larger molecules if excessive, so optimization of crosslinking density is critical [35].

6. Drug loading techniques:

Drug loading into preformed nanosponges is typically performed using one of several well-established approaches. Choice of method depends on drug properties (solubility, thermal sensitivity), desired loading efficiency and downstream processing considerations.

7. Incubation (equilibration) method:

Preformed, dried nanosponge powder is incubated with a concentrated drug solution (aqueous or organic, depending on drug solubility) under agitation for a defined period to allow diffusion of drug into internal cavities and adsorption sites. After equilibration, the loaded nanosponges are separated (centrifugation or filtration), washed to remove surface-adsorbed unbound drug, and dried. This method is simple, flexible (compatible with many solvents) and often yields high entrapment efficiencies for small molecules that readily diffuse into the nanosponge matrix³⁶.

8. Freeze-drying (lyophilization):

Lyophilization is commonly employed when loading thermolabile drugs or when one wants to preserve porous structure while removing solvent gently. The drug–nanosponge suspension (or drug solution containing dispersed nanosponges) is frozen and subjected to sublimation under reduced pressure to remove solvent and produce a dry, porous powder. Freeze-drying often preserves particle integrity and porosity better than thermal drying and can result in formulations with favourable redispersibility and shelf stability. However, freeze-drying incurs higher processing costs and potential cryoprotectant requirements³⁷.

9. Solvent-evaporation / co-precipitation:

In some protocols drug and nanosponge precursors (or preformed nanosponges) are co-dissolved in a volatile solvent and the solvent then evaporated under reduced pressure; the drug becomes trapped or entrapped within the forming network or adsorbs as solvent is removed. Solvent-evaporation can also refer to solvent exchange methods where the nanosponge is prepared in organic medium and the drug is present during formation (in-situ entrapment). This approach may yield high loading but risks drug degradation (if high temperature) and requires rigorous solvent removal for oral/parenteral use [38].

CHARACTERIZATION OF NANOSPONGES

Characterization is a critical component in the development of nanosponge-based drug delivery systems. It confirms structural integrity, physicochemical properties, drug loading, and release behavior all of which influence performance, stability, and safety. The following analytical techniques and evaluation metrics are routinely used in nanosponge research, with examples from recent studies.

1. Particle Size and Polydispersity Index (DLS):

Particle size determines biodistribution, cellular uptake, and dissolution rate of nanosponges. Dynamic light scattering (DLS) is the most common technique for measuring hydrodynamic diameter and polydispersity index (PDI), which reflects size distribution. Smaller and more uniform particles ($PDI < 0.3$) indicate homogeneous nanosponge populations with predictable behaviour *in vivo*. A higher PDI suggests broad size distribution and potential aggregation issues. For example, β -cyclodextrin nanosponges optimized for topical delivery exhibited a mean particle size of ~ 543 nm with a PDI of approximately 0.33 when measured by DLS, indicating moderate dispersity and colloidal stability [39].

2. Surface Morphology (SEM, TEM):

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) are essential for visualizing the surface texture, shape and internal structure of nanosponges. SEM reveals surface morphology and porosity, confirming the three-dimensional, sponge-like architecture. TEM provides high-resolution images of internal structures and particle shape at the nanoscale. In one study, SEM and TEM analyses showed that prepared nanosponges were spherical with a porous texture and that their average particle diameters were in the nanometer range [40].

3. Fourier Transform Infrared (FTIR) Spectroscopy:

FTIR spectroscopy identifies functional groups and molecular interactions between the drug and nanosponge matrix. Shifts in characteristic peaks (e.g., hydroxyl, carbonyl bands) indicate successful drug encapsulation and interaction with cross-linked polymers. FTIR can also confirm the absence of chemical incompatibilities between excipients. In the characterization of butenafine-loaded nanosponges, FTIR spectra were used to assess possible chemical interactions among pure drug, blank nanosponge and drug-loaded nanosponge formulations [41].

4. Differential Scanning Calorimetry (DSC) and X-Ray Diffraction (XRD):

DSC analyzes thermal transitions such as melting point shifts and glass transition temperatures, which indicate drug crystallinity and interaction with the nanosponge matrix. A disappearance or broadening of the drug's characteristic melting peak suggests conversion to an amorphous or dispersed state within the network. XRD complements DSC by identifying changes in crystal structure; loss of crystalline peaks indicates successful amorphization and improved solubility. In studies involving cyclodextrin-based nanosponges, DSC and XRD confirmed the reduction of drug crystallinity after encapsulation, suggesting improved dissolution potential [42].

5. Drug Entrapment Efficiency:

Entrapment efficiency (EE%) quantifies the percentage of drug incorporated into the nanosponge relative to the total drug used during preparation. High EE indicates effective incorporation and reduced waste. It is commonly measured by first separating loaded nanosponges (e.g., centrifugation), analyzing unbound drug in the supernatant and then calculating the percentage entrapped versus initial drug quantity. In topical nanosponge studies, entrapment efficiencies ranging from $\sim 51\%$ to $\sim 78\%$ were reported, and were found to correlate with formulation variables such as polymer concentration and particle size [43].

6. In Vitro Release Studies:

In vitro drug release studies assess how the drug diffuses out of nanosponges under simulated physiological conditions, providing insights into release kinetics and potential *in vivo* behaviour. Various models (Higuchi, zero-order, first-order) are used to interpret release mechanisms (diffusion, erosion). While standardized methods vary, dialysis membrane and sample-and-separate techniques are common for nanoscale systems, permitting evaluation of sustained and controlled release profiles that distinguish nanosponges from conventional formulations [44].

7. Zeta Potential:

Zeta potential measures the surface charge of nanosponge particles, which influences colloidal stability and aggregation potential. Typically, absolute values above ± 30 mV suggest strong electrostatic repulsion and good stability. In cyclodextrin nanosponge research, zeta potential values around -33.8 mV contributed to favourable dispersion stability. Surface charge also impacts interactions with cellular membranes and can be tailored via formulation components [45].

PHARMACEUTICAL APPLICATIONS OF NANOSPONGES

Nanosponges are emerging as versatile drug delivery platforms capable of addressing solubility, stability, and controlled release limitations across multiple therapeutic routes. Their porous structure, high loading capacity, and tunable release kinetics make them suitable for oral, topical, parenteral, targeted, anticancer, and even protein/peptide delivery applications [46].

1. Oral Drug Delivery:

Improvement of Dissolution Rate

One of the most significant challenges in oral pharmacotherapy is the poor aqueous solubility of many new chemical entities, which limits dissolution and absorption in the gastrointestinal tract. Nanosponges can encapsulate poorly soluble drugs within their nano-channels and internal cavities, effectively increasing the surface area accessible for dissolution and presenting the drug in a dispersed or amorphous state that dissolves more readily than the crystalline form. For example, β -cyclodextrin nanosponges have been used to enhance the dissolution of rilpivirine, a BCS Class II antiretroviral, leading to increased drug release in dissolution media [47].

Enhanced Bioavailability

Enhanced dissolution often translates to improved oral bioavailability. By maintaining a supersaturated drug concentration over time and protecting labile drugs from degradation in the gut lumen, nanosponge formulations can increase the fraction of drug absorbed. The porous network provides sustained release that prolongs residence time in the gut and facilitates uptake. This approach has been reported for several poorly soluble drugs, including antihypertensives, antipsychotics, and antiretrovirals formulated with cyclodextrin-based nanosponges [48].

2. Topical Drug Delivery:

Controlled Release

Nanosponges have been effectively formulated into topical dosage forms for skin delivery where controlled and sustained release is desirable. Their ability to localize the drug on the skin surface and gradually release the active molecule into deeper layers enhances therapeutic efficacy while minimizing dosing frequency. Nanosponge suspensions or incorporated gels/creams can maintain drug availability on the stratum corneum longer than simple solutions or ointments [49].

Reduced Irritation

Topical formulations based on nanosponge systems can also reduce local irritation by minimizing high local concentrations of free drug and protecting sensitive tissues. The porous carriers buffer the release of potent actives and have been used to improve the tolerability profiles of irritating drugs in dermatological and cosmetic applications [50].

3. Parenteral Delivery:

Nanosponges can be engineered as injectable colloidal systems that improve solubility and stability of drugs for parenteral administration, enabling delivery of hydrophobic or labile molecules in aqueous formulations. Their tunable porosity and surface chemistry facilitate reduction of drug aggregation, controlled systemic release, and minimization of off-target toxicity. Both cyclodextrin-based and polymeric nanosponges have been evaluated for parenteral use, maintaining colloidal stability and sustained drug release in bloodstream models [51].

4. Targeted Drug Delivery:

Due to their nanoscale size and the possibility of surface modification, nanosponges are amenable to targeted drug delivery. Surface functionalization with targeting ligands, antibodies or peptides enables accumulation at specific tissues or cell types, thereby increasing therapeutic selectivity and reducing systemic toxicity. Studies demonstrate that nanosponge carriers can be engineered to preferentially deliver drugs to sites such as inflammatory tissues or tumors by exploiting receptor-mediated uptake or enhanced permeability and retention (EPR) effects [52].

5. Anticancer Drug Delivery:

Nanosponges are particularly promising for anticancer therapy because of their capacity to solubilize hydrophobic chemotherapeutics, control release kinetics and potentially improve tumor targeting. Encapsulation within the porous matrix allows drugs such as paclitaxel, tamoxifen, doxorubicin, and experimental anticancer agents to be delivered at therapeutic concentrations while sparing normal tissues. Cyclodextrin-based nanosponges have been used to enhance solubility and cytotoxic effects of anticancer compounds in vitro and in vivo, showing improved cell kill and reduced side effects compared with free drugs [8].

Additionally, nanosponge systems have been shown to produce longer circulation times and favor accumulation in tumor tissues via the EPR effect, further enhancing antitumor efficacy [53].

6. Protein and Peptide Delivery:

Delivering biological macromolecules such as proteins and peptides orally or systemically is challenging due to poor stability, rapid degradation and low permeability. Nanosponges can protect biomolecules from harsh environments (e.g., gastric pH, proteases) and provide controlled release while preserving bioactivity. Their porous structure and ability to encapsulate large molecules make them potential carriers for protein and peptide delivery. Cyclodextrin-based nanosponges have been investigated for

enzyme and peptide encapsulation, offering protection against denaturation and prolonged action profiles [54].

ADVANTAGES OF NANOSPONGES

High drug-loading capacity:

Nanosponges typically exhibit higher drug-loading than comparable nanocarriers (e.g., simple cyclodextrin complexes or liposomes) because their porous three-dimensional network provides multiple binding modes: inclusion in CD cavities, adsorption in nanochannels, and entrapment within interstitial polymeric meshes. This structural multiplicity enables efficient loading of hydrophobic and amphiphilic drugs and, in many reports, drug-loading fractions considerably higher than conventional nanoparticles — an attribute especially valuable for high-dose or low-potency actives. Systematic reviews of CD-NS document consistently favourable loading efficiencies across therapeutic classes [46].

Improved physicochemical and chemical stability:

Entrapment within nanosponge architectures protects labile drugs from hydrolytic or oxidative degradation and from photolysis by physically sequestering the molecule from the bulk environment. The nanosponge matrix can also limit exposure to interfacial stresses and inhibit premature aggregation or precipitation — contributing to enhanced shelf life and in-use stability as reported in stability studies at accelerated conditions [59].

Controlled and sustained release:

The porous network and diffusion-limited escape pathways in nanosponges permit tailoring of release kinetics from rapid dissolution enhancement to sustained release over hours or days. Modulating cross-link density, pore size, surface functionalization and polymer composition provides a toolkit for customizing therapeutic profiles (e.g., reducing dosing frequency, maintaining supersaturation for absorption). This capacity for controlled release is documented across oral, topical and parenteral applications [60].

Potential for reduced toxicity and improved tolerability:

By controlling drug release and preferentially delivering payload to target sites (through passive EPR effects or active ligand modification), nanosponges can reduce peak systemic exposure and off-target toxicity. In addition, CD-based matrices can mask irritant properties of topically applied actives, lowering local adverse effects. However, toxicity reduction is formulation-dependent and must be demonstrated empirically for each carrier–drug pair [61].

LIMITATIONS AND CHALLENGES

Toxicity of cross-linkers:

Although cyclodextrins are generally well tolerated, the cross-linkers used in nanosponge preparation such as diphenyl carbonate, carbonyldiimidazole, pyromellitic dianhydride, and di-isocyanates may pose toxicological risks if not completely reacted and removed. Residual cross-linkers or low-molecular-weight by-products can cause irritation, sensitization, or systemic toxicity and represent a major safety concern. Therefore, rigorous purification, validated analytical methods for residual quantification, and comprehensive toxicological evaluation are essential to ensure formulation safety [62].

Reproducibility and batch-to-batch variability:

Reproducible control of degree of cross-linking, pore architecture, particle size and polydispersity is technically challenging yet essential because these parameters determine drug loading, release kinetics and biological behaviour. Small changes in reagent ratios, mixing energy, temperature profile, or solvent quality in bench-scale syntheses can lead to measurable differences in surface area, pore size distribution and accessible cavity volume and therefore to variability in entrapment efficiency and release profiles. Many laboratory reports note variability between batches when straightforward batch methods are used, particularly for solvent-based and emulsion procedures where micro-mixing and phase-separation dynamics are sensitive to scale. Such reproducibility issues complicate comparability studies and can obscure structure–function relationships that are necessary for rational optimization [63]. To improve reproducibility, researchers advocate for stringent process control (defined stirring/sonication energy, temperature, and addition rates), use of robust continuous or semi-continuous reactors (microfluidics, controlled emulsion devices), and implementing quality-by-design (QbD) principles early in development to identify critical process parameters and acceptable ranges. Robust in-process analytics (real-time particle sizing, spectroscopic monitoring of reaction conversion) can also reduce batch variability [64].

CONCLUSION

Nanosponges are a versatile nanocarrier system designed to overcome poor aqueous solubility and limited bioavailability, particularly for BCS Class II and IV drugs. Owing to their nanoscale structure, high surface area, and tunable porosity, they enhance drug dissolution, molecular dispersion, wettability, and enable controlled release. Cyclodextrin-based and polymeric nanosponges have shown potential in improving bioavailability, reducing irritation in topical delivery, and supporting targeted and anticancer therapy. Despite their advantages, challenges such as cross-linker toxicity, scale-up limitations, and regulatory complexity remain. Addressing these through safer chemistries and quality-by-design approaches is essential for successful clinical translation. Overall, nanosponges represent a promising platform for improving the efficacy and safety of poorly soluble drugs.

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