INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Paper

Next-Generation Nanomedicine: Recent Advances in The Fabrication, Characterization, And Therapeutic Applications of Nanosponges

Divyamol A. K*, Dr. Arun Raj R., Aswathy Mohan, Athmika S Haika, Gayathri P M, Krishna Haridas, Praveena V A, Shabnam Shibu Sekumeeran

Department Of Pharmaceutics, Department Of Pharmaceutical Sciences, Rimsr, Centre For Professional And Advanced Studies (Cpas), Puthuppally, Kottayam, Kerala, India.

ARTICLE INFO

Published: 04 Aug 2026
Keywords:
Next-Generation Nanomedicine, The Fabrication, Characterization, And Therapeutic Applications of Nanosponges
DOI:
10.5281/zenodo.21786496

ABSTRACT

Nanosponges represent a transformative class of three-dimensional, porous nanocarriers that have redefined precision in drug delivery systems [1]Characterized by their unique hyper-crosslinked architecture, these nanoparticles—often derived from cyclodextrins—offer unparalleled capabilities in enhancing the solubility, stability, and bioavailability of therapeutic agents. This report provides a comprehensive review of the current landscape of nanosponge technology, focusing on advanced fabrication methods such as ultrasound-assisted, microwave-based synthesis, and traditional solvent and melt techniques.Key findings highlight the versatility of nanosponges in oncology, where they have demonstrated up to a five-fold increase in drug delivery effectiveness and significant reductions in tumor volume compared to conventional carriers. Their application extends beyond cancer therapy to include blood detoxification, antiviral treatments (including SARS-CoV-2 management), and specialized topical formulations for dermatological conditions such as psoriasis and fungal infections. Characterization studies reveal that these systems typically operate in the 400–500 nm range with drug loading efficiencies exceeding 95% for specific formulations like naproxen sodium and doxorubicin. Despite their promise, challenges remain in standardizing large-scale production and integrating these systems into personalized medicine. This review underscores the potential of nanosponges to serve as a cornerstone for next-generation nanomedicine, offering a path toward more effective, targeted, and less toxic therapeutic interventions.

***Corresponding Author:** Divyamol A. K.
Address: *Department Of Pharmaceutics, Department Of Pharmaceutical Sciences, Rimsr, Centre For Professional And Advanced Studies (Cpas), Puthuppally, Kottayam, Kerala, India.*
Email ✉: divyamolak2001@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

INTRODUCTION

Nanosponges are emerging as a breakthrough in nanotechnology, particularly within the realm of drug delivery and environmental remediation [1],[2],[3]These materials are defined by their three-dimensional, highly porous structure, typically formed by the crosslinking of polymers such as cyclodextrins into a complex network of nanocavities[4],[5].Unlike traditional linear polymers or simple inclusion complexes, the hyper-crosslinked nature of nanosponges allows them to encapsulate both hydrophilic and lipophilic substances within their internal voids, thereby significantly improving the solubility and stability of poorly water-soluble drugs [6],[7].The "silent revolution" in drug delivery facilitated by nanosponges is driven by their ability to provide targeted and regulated release of therapeutic agents [8],[9].By acting as protective shields, they prevent the premature degradation of sensitive molecules, such as proteins and enzymes, while simultaneously reducing the systemic toxicity of potent drugs like antineoplastic agents[10],[11].Recent advancements have expanded their utility from simple carriers to multifunctional platforms capable of sensing, blood detoxification, and even the delivery of gaseous molecules like oxygen to hypoxic tissues [12],[5],[3].Their small size and spherical shape enable them to be formulated into various dosage forms, including oral, parenteral, topical, and even inhalational routes, making them a versatile tool in modern pharmaceutics [13][14].

2. FABRICATION METHODS AND CROSSLINKING CHEMISTRY

The synthesis of nanosponges is a critical factor in determining their final physicochemical properties, including pore size, surface area, and drug-loading capacity. Several distinct methodologies have been developed to tailor these parameters for specific clinical needs.

2.1 Solvent Method and Reaction Parameters

The solvent method is one of the most widely utilized techniques for preparing cyclodextrin-based nanosponges. In this process, the polymer (often β-cyclodextrin) is dissolved in a polar aprotic solvent such as dimethylformamide (DMF) or dimethyl sulfoxide (DMSO)[15],[10].A crosslinker is then added to facilitate the formation of the 3D network. Common crosslinkers used in this method include:

- **Carbonates**: Diphenyl carbonate (DPC), dimethyl carbonate, and daryl carbonates[12],[4],[16]
- **Anhydrides**: Pyromellitic dianhydride (PMDA) and carboxylic acid dianhydrides[12],[4]
- **Others**: Carbonyl diimidazole (CDI), diisocyanates, and 2,2-bis(acrylamido) acetic acid[15],[4]

The crosslinker-to-polymer molar ratio typically ranges from 1:4 to 1:16 [12],[4],[16].The reaction is carried out under reflux conditions or at temperatures ranging from 10°C to 100°C for durations spanning 1 to 48 hours [15],[4],[10].This method allows for precise control over the degree of crosslinking, which directly influences the sponge's ability to hold and release guest molecules.

2.2 Ultrasound-Assisted Synthesis: A Greener Alternative

As a more efficient and potentially "greener" alternative, ultrasound-assisted synthesis has gained prominence. This technique involves reacting the polymer and crosslinker (often without the need for bulk organic solvents) in an ultrasonic bath at elevated temperatures, typically 90°C, for approximately 5

hours[15],[17],[4],[16].For example, reacting β-cyclodextrin with diphenyl carbonate at 50% amplitude for 4 hours yields nanosponges with high crystalline integrity [18].Ultrasound waves facilitate the cavitation process, which accelerates the crosslinking reaction and leads to the formation of more uniform, spherical nanoparticles with enhanced stability[15],[12].

2.3 Melt Method and Solvent-Free Fabrication

The melt method is a solvent-free fabrication technique where the polymer and crosslinker are blended and heated to a molten state. A common protocol involves mixing cyclodextrins with diphenyl carbonate and heating the mixture to 100°C for at least 5 hours[18].The resulting solid mass is subsequently washed and processed to obtain the final nanosponge powder[17],[19].This method is advantageous due to the absence of toxic organic solvents, making it highly suitable for pharmaceutical applications where solvent residue is a concern.

2.4 Emulsion and Quasi-Emulsion Solvent Diffusion

For the delivery of hydrophobic drugs and the creation of specialized polymeric structures, emulsion-based techniques are frequently employed. In the emulsion solvent diffusion method, a mixture of a polymer (e.g., ethyl cellulose) and the drug is dissolved in an organic phase (like dichloromethane) and then emulsified in an aqueous phase containing a surfactant such as polyvinyl alcohol (PVA)[18],[20].

. High-speed stirring (e.g., 1000 rpm) or homogenization is used to create stable droplets, followed by solvent evaporation to solidify the nanosponges[16],[20].This method is particularly effective for encapsulating drugs like naproxen sodium, where trial formulations have successfully achieved loading efficiencies as high as 98.9%[20].

2.5 Advanced Techniques: Microwave and Microwave-Assisted Synthesis

Recent innovations include microwave-assisted synthesis, which utilizes microwave radiation to provide rapid and uniform heating, thereby reducing reaction times significantly compared to traditional heating methods [21],[9].These advanced techniques enable the creation of highly tailored "modular" chemistry, allowing for controlled loading and release kinetics that can be specifically tuned for complex therapeutic regimens[3].

3. CHARACTERIZATION TECHNIQUES

Thorough characterization is essential to ensure the safety and efficacy of nanosponge-based delivery systems. Advanced analytical tools are used to verify the structural and functional attributes of these nanocarriers.

3.1 Particle Size, Polydispersity, and Colloidal Stability

The therapeutic performance of nanosponges is heavily dependent on their particle size, which typically remains within the nano-range (sub-1000 nm). Studies on 5-fluorouracil (5-FU) loaded nanosponges reported an optimum particle size of 405.46 ± 30 nm with a polydispersity index (PDI) of 0.328, indicating a relatively uniform distribution[22]. In formulations of naproxen sodium, most trial formulations successfully maintained sizes in the nano-range, though variations in PDI were observed depending on the homogenization parameters[20].

Smaller particle sizes are generally preferred for parenteral administration to ensure prolonged circulation and better cellular uptake.

3.2 Surface Charge and Zeta Potential Analysis

Zeta potential is a key indicator of the colloidal stability of nanosponge dispersions. Most cyclodextrin-based nanosponges exhibit a negative surface charge, which helps prevent aggregation through electrostatic repulsion. For instance, 5-FU formulations showed a zeta potential of -18.75 ± 1.8 mV [22].while naproxen-loaded versions ranged from -0.106 to -9.75 mV [20].These negative values suggest moderate stability in biological fluids, though the addition of certain drugs or functional groups can alter these charges and impact the system's biodistribution.

3.3 Morphology and Porosity Assessment (SEM/AFM)

Scanning Electron Microscopy (SEM) and Atomic Force Microscopy (AFM) are the gold standards for visualizing the porous architecture of nanosponges. These techniques reveal a highly porous and crystalline nature, which is essential for the effective entrapment of drug molecules within the nanocavities[22].The porous network is not merely a surface feature but extends throughout the 3D structure, providing a high surface-area-to-volume ratio for drug interaction[23],[7].AFM further provides high-resolution topographic images that help characterize the surface roughness and pore distribution at the sub-nanometer scale.

3.4 Drug Loading, Entrapment Efficiency, and Complexation

Nanosponges are noted for their exceptional drug-loading capacities, which often exceed those of traditional nanocarriers. Research has demonstrated that encapsulation efficiency is influenced by the available voids and the size of the guest molecule[11].Key performance metrics include:

- **Loading Efficiency**: Cyclodextrin-based formulations have reached drug-loading efficiencies of up to 98.9% for naproxen sodium and 95% for doxorubicin[23],[20].
- **Complexation Efficiency (CE)**: The molar ratio of crosslinker to polymer is a critical determinant of CE; for example, a 1:4 CD:DPC ratio was found to be optimal for 5-FU systems[22].
- **Apparent Stability Constant (Kst)**: Optimized formulas show high stability constants, ensuring that the drug remains encapsulated until it reaches the target site[22].

4. THERAPEUTIC APPLICATIONS

The multifunctional nature of nanosponges has led to their application across a diverse range of medical fields, addressing many of the limitations of conventional therapy.

4.1 Oncology: Precision Delivery and Improved Outcomes

Cancer therapy remains the most prominent application of nanosponge technology[18].Nanosponges enhance the delivery of potent chemotherapeutics—such as doxorubicin, paclitaxel, camptothecin, and erlotinib—by improving their solubility and providing targeted delivery to tumor sites[18],[4]. Key clinical outcomes include:

- **Enhanced Effectiveness**: Nanosponges have shown up to five times greater effectiveness in cancer drug delivery compared to free drug solutions[19].
- **Tumor Volume Reduction**: Paclitaxel encapsulated in nanosponges exhibited a 2.5 times higher bioavailability, leading to significant reductions in tumor volume in animal models[15],[10],[16].

- **Selectivity**: Systems co-delivering doxorubicin and EMD have demonstrated synergistic anticancer activity with improved selectivity toward cancer cells, minimizing damage to healthy tissues[24].
- **Overcoming Barriers**: They facilitate the delivery of oligonucleotides, overcoming biological barriers and endosomal inactivation to improve gene-based cancer management [25].

4.2 Blood Detoxification and Toxin Sequestration

One of the most innovative uses of nanosponges is in blood detoxification and the management of drug overdoses[26].

. These carriers act as "molecular decoys" or absorbents that can effectively bind and remove toxins, such as heavy metals and bacterial endotoxins, from the bloodstream[19],[26].

. Advanced "cellular nanosponges" have been engineered to neutralize specific toxins like Vibrio vulnificus hemolysin and neurotoxins, offering a promising strategy for acute poisoning treatment and neuroprotection[27],[28].

. They also help mitigate the effects of environmental contaminants by adsorbing pollutants from the circulatory system[26].

4.3 Antiviral Therapy and Infectious Disease Management

Nanosponges have shown significant potential in the treatment of viral infections. They enhance the bioavailability of anti-HIV drugs like zidovudine and saquinavir, enabling sustained release and improved patient compliance [4],[10].During the COVID-19 pandemic, nanosponges were investigated for their ability to neutralize the SARS-CoV-2 virus and block its entry into host cells[16].Their ability to accommodate higher drug loads and offer controlled release at target sites minimizes the side effects often associated with long-term antiviral regimens[7].

4.4 Topical, Dermal, and Transdermal Delivery

In dermatology, nanosponges provide a controlled-release platform that avoids systemic circulation and reduces skin irritation. They are used for the topical delivery of local anesthetics, anti-fungal agents, anti-acne medications, and treatments for psoriasis and wrinkles[17], [29].Curcumin-loaded nanosponges, for instance, have shown a 2.2 times reduction in cytotoxicity (IC50) while enhancing the solubility of the phytochemical by 63.98% [12],[30].These systems also improve skin penetration, ensuring that therapeutic agents reach deeper dermal layers to treat infections effectively[2],[17].

4.5 Emerging Frontiers: Oxygen Therapy and Protein Delivery

Beyond small molecules, nanosponges are capable of transporting gaseous molecules and biological macromolecules. They have been successfully used to encapsulate and deliver oxygen to hypoxic tissues, which is particularly relevant in wound healing and cardiology [12],[10],[11].Furthermore, they provide a stable environment for the immobilization of enzymes (like lipases) and the delivery of sensitive proteins, vaccines, and antibodies, protecting them from enzymatic degradation and inactivation by biological components [6], [25],[10],[14].

5. COMPARATIVE ANALYSIS AND PERFORMANCE METRICS

The performance of nanosponges is frequently measured against conventional inclusion complexes or free drug solutions. In almost all

cases, nanosponge formulations offer superior results across multiple metrics:

- **Solubility Enhancement**: Nanosponges can improve the solubility of BCS Class II drugs by over 27-fold [19].Itraconazole solubility was improved 27-fold, while resveratrol solubility was enhanced by 33-44 fold through nanosponge encapsulation[10],[16].
- **Release Kinetics**: They provide extended drug release, often lasting up to 12 hours or more, compared to the rapid clearance of free drugs [4].In specific trials, naproxen-loaded nanosponges released approximately 89.62% of their payload within 50 minutes, demonstrating high efficiency in targeted environments [20]. 5-FU nanosponges showed a release rate of 56% in the first hour, which was significantly higher than the 5-FU-BCD inclusion complex [22].
- **Toxicity and Safety**: Formulations have shown low toxicity profiles, with some being safe at dosages as high as 2000 mg/kg body weight[15].They are generally classified as non-toxic, non-abrasive, non-mutagenic, and non-irritating to the skin[4], [11].

6. LIMITATIONS AND RESEARCH GAPS

While the potential of nanosponges is vast, several limitations must be addressed to facilitate widespread clinical adoption. A significant challenge is the lack of standardization in fabrication; unique process parameters like precise molar ratios and reaction conditions are often not detailed in early reports [1], [8], [6].

. Furthermore, while nanosponges exhibit high drug loading (up to 98.9%), the efficiency can vary depending on the crystallization degree of the polymer and the specific molecular size of the guest drug [31],[11].

Future research is expected to focus on the integration of nanosponges with personalized medicine and gene therapy[32].

. There is also a need for more detailed studies on the long-term biosafety and environmental impact of these nanomaterials, particularly as they move toward advanced technologies like antimicrobial coatings, chemosensors, and biosensors [3], [33], [34].

CONCLUSION

Nanosponges represent a significant advancement in nanomedicine, offering a versatile and efficient platform for the targeted delivery of a wide range of therapeutic agents. Their unique 3D porous structure, fabricated through advanced methods like ultrasound-assisted and microwave-based synthesis, allows for remarkable improvements in drug solubility, stability, and bioavailability. From oncology and detoxification to antiviral therapy and oxygen delivery, the applications of nanosponges continue to expand, addressing many of the pitfalls of conventional drug delivery systems. As research moves toward more personalized and multifunctional applications, nanosponges are poised to play a central role in the future of precision medicine and the management of complex diseases.

REFERENCES

1. Shweta Kothari, Dr. Nayana Baste, Jay Pardeshi Redefining Precision in Drug Delivery Systems. Repository;ijps 2025;3(5): 2127-2134.
2. Jayashri Dandale, Sadhana Shahi, Tejas Khatavkar, Shweta Patil, Nanosponges: A New Generation of Nanoporous Materials for Biomedical Application, Int. J. of Pharm. Sci., 2024, Vol 2(12), 3280-3301.
3. Ankem b, Kucharlapati slt, Magapu sd, b b. nanosponges - a revolutionary targeted drug delivery nanocarrier: a review. Asian J Pharm Clin Res. 2023;:3-9.

4. Singh S, Sharma K, Sharma H. Cyclodextrin Nanosponges: A Revolutionary Drug Delivery Strategy. PNT. 2024;12(4):300-313.
5. Dasari S, K RK, Chandu BR. A Review on Nanosponges. Int J Indig Herb Drug. 2025;:8-12.
6. Shruti I Meshram, Pooja R Hatwar -, Ravindra L Bakal, Samiksha B Rotake. An outlook towards nano-sponges: A unique drug delivery system and its application in drug delivery. Repository; 2025. 29(03), 089–098.
7. Maheshbabu Jalli , Vinay Kumar D, Satya Hima Supriya P, Uma Rajeswari M and Jithendra Lakshman Sai S The silent revolution in drug delivery: Exploring the extraordinary potential of nanosponges in modern medicine. Repository; 2025. 31(03), 317-329.
8. Salunkhe A, More S, Dhole S. A Narrative Review on Drug Loaded Nanosponges as a Carrier for Drug Delivery. IJPQA. 2023;14(01):244-249
9. Desai MM, Jadhav SA, Koparde AA. Nanosponges as a Drug Delivery System: Methods, Characteristics and Applications. IJDDT. 2024;14(03):1758-1764.
10. Muni Raja Lakshmi K, Suma Shree C, Lakshmi Priya N. Nano Sponges: A Novel Approach for Targeted Drug Delivery Systems. J. Drug Delivery Ther.. 2021;11(2):247-252.
11. Jawaharlal S, Subramanian S, Palanivel V, Devarajan G, Veerasamy V. Cyclodextrin-based nanosponges as promising carriers for active pharmaceutical ingredient. J Biochem & Molecular Tox. 2023;38(1).413-420.
12. Mahalekshmi V, Balakrishnan N, Parthasarathy V. Recent advancement of nanosponges in pharmaceutical formulation for drug delivery systems. J Appl Pharm Sci. 2023. 13(08):084–100.
13. Tiwari K, Bhattacharya S. The ascension of nanosponges as a drug delivery carrier: preparation, characterization, and applications. J Mater Sci: Mater Med. 2022;33(3).
14. J. A, Girigoswami A, Girigoswami K. Versatile Applications of Nanosponges in Biomedical Field: A Glimpse on SARS-CoV-2 Management. BioNanoSci.. 2022;12(3):1018-1031.
15. Burad S, Markad K, Kulkarni N, Dhole S. assessment and outcome on preparations, characterization of topical targeted nanosponge based drug delivery: critical review. Asian J Pharm Clin Res. 2023;:19-26.
16. Sandeep RKane, Shrinivas K Mohite. Revolutionizing Nanomedicine: The Multifaceted Role of Nanosponges in Modern Drug Delivery. Repository; 2025.vol13(7):233-255.
17. Fizza Ilyas, Muhammad Jamsahid, Irfan Bashir, Rabia Aslam, Tooba Mehboob, Naila Tabassam, Muhammad Nadeem Alvi. Solvent Diffusion Method: An Effective Approach to Formulate Nanosponges Loaded with Naproxen Sodium. RADS J. Pharm. Pharm. Sci. 2020.vol ; 8(2):74-80.
18. Sardar Shelake, Nilesh Chougule -. Nanosponges: carrier for advanced drug deliver. Repository; IJDDR.2024.vol 2 (3):500-508.
19. Jasim IK, N. Abd Alhammid S, A. Abdulrasool A. Synthesis and evaluation of B-cyclodextrin Based Nanosponges of 5-Fluorouracil by Using Ultrasound Assisted Method. IJPS. 2020;29(2):88-98.
20. Deepika, Yogita Tyagi, Srishti Morris, Arti Kori. Recent advances in nano sponge technology: from synthesis to applications. International Journal of Applied Pharmaceutics. 2026. *18*(1), 95–106.

21. Thongsom S, Di Gianvincenzo P, Ciattaglia G, Subrati A, DiSilvio D, Birocco AM, D'Abramo M, Boonla C, Chanvorachote P, Moya SE. Cyclodextrin-based nanosponge co-delivery of doxorubicin and EMD: synergistic anticancer activity with improved selectivity toward cancer cells. RSC Pharm.. 2025;2(6):1514-1532.
22. Khairnar P, Kolipaka T, Pandey G, Phatale V, Shah S, Srinivasarao DA, Saraf S, Srivastava S. Nanosponge-mediated oligonucleotide delivery: A cutting-edge technology towards cancer management. Journal of Drug Delivery Science and Technology. 2024;91:105-226.
23. Sakhuja, Khushi, Jain, Chauhan, Singh. Nanosponges in Detoxification: Strategy for Toxin Removal and Drug Overdose Management.. Recent advances in drug delivery and formulation. 2025.
24. Wang D, Ai X, Duan Y, Xian N, Fang RH, Gao W, Zhang L. Neuronal Cellular Nanosponges for Effective Detoxification of Neurotoxins. ACS Nano. 2022;16(11):19145-19154.
25. Zou S, Wang Q, Zhang P, Wang B, Liu G, Zhang F, Li J, Wang F, Wang B, Zhang L. Biomimetic Nanosponges Enable the Detoxification of Vibrio vulnificus Hemolysin. IJMS. 2022;23(12):6821.
26. P Farsana, R Sivakumar. Hydrogel based nanosponges drug delivery for topical applications- Research J. Pharm. and Tech. 2021; 14(1):527-530.
27. Mundada AS, Borate SR. Formulation and Optimization of Curcumin Nanosponges to Enhance Biopharmaceutical Attributes for Possible Cosmeceutical Applications. BioNanoSci.. 2025;15(1).
28. Iravani S, Varma R. Nanosponges for drug delivery and cancer therapy: Recent advances. *Nanomaterials*. 2022;12(14):2440.
29. Bhimewad VR, Kshirsagar A, Ambore SM, Kawade SP. Nanosponges in drug delivery: Recent advances, applications, challenges, and future perspectives. *Int J Sci Res Technol*. 2026;4(6):1247–1266.
30. Verma, S., Preeti, K., Rana, A.S. and Sharma, S.K. (2025), Nanosponges for Chemosensors and Biosensors: Next Generation Functional Materials. Chem. Asian J., 20(24):30-47.
31. Malviya A, Yadav S, Srivastava AK. Nanosponges: A Targeted Drug Delivery System. Sch Acad J Pharm. 2024;13(05):189-197.

HOW TO CITE: Divyamol A. K, Dr. Arun Raj R., Aswathy Mohan, Athmika S Haika, Gayathri P M, Krishna Haridas, Praveena V A, Shabnam Shibu Sekumeeran, Next-Generation Nanomedicine: Recent Advances in The Fabrication, Characterization, And Therapeutic Applications of Nanosponges, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 8, 497-504, https://doi.org/10.5281/zenodo.21786496