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Review Article

Nanosponges: An Emerging and Promising Strategy in Drug Delivery

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ABSTRACT

Nanosponges (NSs) are a novel class of nanomaterials that have garnered substantial interest due to their unique properties and potential applications in drug delivery. The primary objective of this review is to provide the basics of nanosponge-based drug delivery systems, preparation techniques, and evaluation methods. It also covers associated aspects like challenges phased in industry and research in the manufacturing of NSs. NSs are tiny, mesh-like structures that can be loaded with drugs to improve solubility, stability, extended release, and bioavailability across various dosage forms. They can encapsulate a wide range of substances, including proteins, enzymes, hydrophilic and lipophilic chemicals, vaccines, and antibodies, and can be made from either inorganic or organic materials. NSs offer several advantages, such as compatibility, sterility, cost-effectiveness, extended release, better stability, reduced side effects, versatility, taste masking, and formulation enhancement. The review also elucidates different types of NS, their preparation methods, prospective applications, and evaluation processes. Overall, NSs have demonstrated considerable promise, with the potential to transform nanomedicine.

Keywords: Drug delivery, Drug loading, Drug release mechanism, Evaluation, Applications, Nanosponges.

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INTRODUCTION

Nanosponges (NSs) are insoluble, high-absorption materials with a virus-like structure, allowing drugs to be loaded into them and directed to tumor cells. They can be synthesized by varying crosslinker ratios and are suitable for encapsulating proteins, enzymes, compounds, vaccines, and antibodies. NS can harden compounds and mask taste, making it 5 times better for breast cancer drugs than conventional methods and treating various diseases (Mahalekshmi *et al*., 2023). NS, a type of nanoparticle, can be regenerated through light heating, inert gases, solvents, and pH adjustments, with applications in flower culture, flame retardancy, pharmaceuticals, and cosmetics. NS, a type of nanoparticle, can be regenerated through light heating, inert gases, solvents, and pH adjustments, with applications in flower culture, flame retardancy, pharmaceuticals, and cosmetics (Shivani and Kumar Poladi, 2015). Poly(isobutyl-cyanoacrylate) nanocrystals with hydrophilic cores absorb medicinal molecules via electrostatic contact, offering higher entrapment efficiency and resistance to molecular degradation (Kerilos *et al*., 2024). NS, a 3D structure that can absorb liquid, is easy to create, but better at entrapping small molecules. Its crystallization degree affects drug loading, making it a potential drug delivery system for tablets or capsules (Shringirishi *et al*., 2014). The morphology of nanosponges is shown in Figure 1.

ADVANTAGES

Compatibility and Sterility: NS are compatible with many excipients and carriers. They are self-sterilizing due to 0.25 µM pore size, no microbial penetration (Bhowmik *et al*., 2018).

Cost Effective and Free Flowing: These can be inexpensive and free flowing.

Extended Release: NS can release for up to 12 hr, more flexibility and elegance to the formulation.

Better Stability and Less Side Effects: These topical oil control products offer lower doses, improved stability, and reduced side effects, while also modifying drug release profiles for improved systemic exposure.

Versatility: NS are versatile, can create new product forms and enhance physical, chemical and thermal stability of formulations.

Taste Masking and Formulation Improvement: NS can mask the unwanted taste and turn immiscible liquids into solid dosage

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forms, increase solubility and stability for poorly water-soluble drugs.

Biodegradable and non-toxic: The NS is both biodegradable and non-toxic, though totally free from allergens, mutagens and irritants.

Better products: The Carries drug in system to improve the therapeutic index and the duration of action is a better product.

Delivery: One can deliver hydrophilic and lipophilic substances through it, delay release from it, while increasing its absorption and solubility (Sultana, 2024).

DISADVANTAGES

Loading Capacity Variability: NS work depending on loading capacity and dose release rate.

Size Limitation: NS are better for smaller molecules than larger ones (Agrawal *et al.*, 2020).

Crystallization Impact: Crystallization in NS affects load bearing capacity and overall performance.

Para-Crystalline Variability: Different para-crystalline forms of NS have different loading capacities (Shinde *et al.*, 2024).

TYPES OF NANOSPONGE

NS can be developed into various types based on polymer, concentration, and production method. Cyclomaltoheptaose-based NS is a common type. Metal Organic Frameworks (MOFs) offer flexibility in design and synthesis, using methods like deployment, precipitation gelation, electrochemical deposition, and solvothermal gelation (Annammadevi and Anusha, 2022). Figure 2 shows the classification of nanosponges.

Monometallic nanosponge

It only contains one metal precursor; this type of metal NS is the most fundamental. In nanoporous applications, the first monometallic oxide has been synthesized in year of 1995, Antonelli and Ying reported on the invention of TiO_2, utilizing alkyl (trimethyl) bromide as a 3 nm pore surfactant during production. However, several metals, including copper, silver, golden, platinum, and palladium, are shown on the template-free single-metal NS.

Bimetallic nanosponge

Bimetal NS presents stability, diverse pores, and exceptional catalytic activity. Due to its availability and lower cost, Pd is the preferred choice. Researchers have successfully developed a three-dimensional, highly porous Pd-Cu bimetallic NS alloy using Al (NO_3) for improved electrocatalytic activity. Effective Al extraction is critical for attaining the necessary porosity and catalytic activity during the synthesis process (Kaur and Kumar 2019).

Polymetallic nanosponge

In recent decades, the focus has shifted towards creating polymetal Nanostructures due to improvements in catalytic activity. These NS have potential applications in fuel cells, water purification, and catalysis. NaBH4 plays a role in producing template-free trimetal NS of Pt53Ru39Ni8, with hydrogen bubbles serving as a dynamic template. Polymetal NS have higher catalytic activity than bimetalic NS (Biswas *et al.*, 2016).

Metal Oxide nanosponge

Organic plastics including surfactant, starches, and polysaccharides are included in the synthesis, along with inorganic plastics like zeolite and alumina. These plastics are then utilized to replace or remove the template or to employ strong acids and foundations. Two types of template-based techniques are needed to synthesize the metal oxide NS.

Nanocasting nanosponge

Hard template approach uses strong, porous materials like polystyrene latex, zeolite, silica, alumina, and copolymer block as support materials. The frame is filled with metal ions, and extracted using methods like calcination, acid treatment, and basic treatment. This technology is recommended for its ease of use and adaptability, allowing architecture expansion into various forms, sizes, and lengths.

Endotemplate nanosponge

The soft template solution is a flexible framework made of cellulose-based components, polysaccharides, and surfactants. Surfactants create mesopore or micropore-functioning micelles, allowing for modification of nanostructure shape, size, and content. This technique was used to create mesostructured metal oxides in 1994. It is less expensive, easier to synthesize, and fairly successful compared to hard templates.

MATERIALS USED IN THE PREPARATION OF NANOSPONGE

Chemicals used in synthesizing NS depend on the type and extent of crosslinking, which affects drug release and encapsulation patterns and is influenced by the concentration of crosslinkers used (Tiwari and Bhattacharya, 2022). CDs combine with active pharmaceuticals to form complexes, increasing water solubility, concealing undesirable qualities, reducing adverse effects, and enhancing photographic stability. CD-based nanocarriers have high drug-loading capacity (Burad *et al.*, 2023). Various materials used in the preparation of nanosponges are given in Figure 3 (Rao *et al.*, 2013) (Ghurghure *et al.*, 2018).

METHODS OF PREPARATION OF NANOSPONGE

Hypercrossed linked β-CD method

Hyper-crosslinked β-CD NS are synthesized from the reaction between the β-CD of any type with a variety of cross-linking reagents, such as epichlorohydrin, diphenyl carbonate, or citric acid, in any polar or nonpolar solvents, like water, Dimethylformamide, or Dimethyl sulfoxide. The formation between 3D β-CD molecules is through covalent bonds. The product is washed, purified, and dried as NS characterized by high surface area.

Ultrasound-assisted synthesis of nanosponge

This method makes small, round NS of the same size. It does this by mixing a polymer and a crosslinker in a flask, heating it to 90°C, and breaking it into smaller pieces. The product is rinsed, cleaned using Soxhlet extraction with ethanol, and dried in a vacuum. These NS are good for delivering drugs and soaking up other substances (Thakre *et al.*, 2016). Pictorially the method has been explained in Figure 4.

Solvent method of nanosponge preparation

The method (Figure 5) involves using dimethylacetamide and acetonitrile as solvents, combining them with a polymer, and optimizing the crosslinker/polymer ratio. The mixture is then heated for 48 hr, cooled, and a surplus of bi-distilled water is added to extract the product. The product is vacuum-filtered and recovered (Yadav *et al.*, 2014).

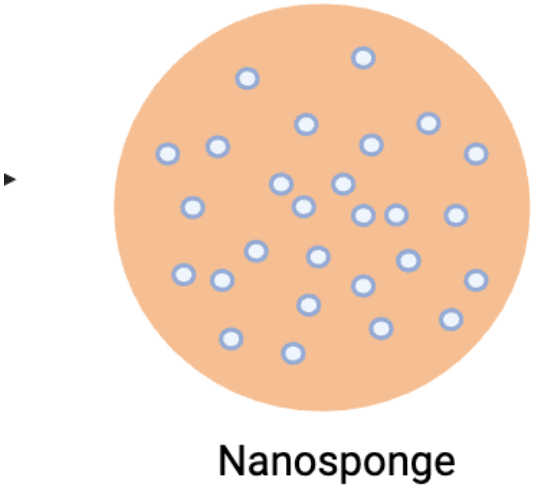

Figure 1: Morphology of nanosponges.

Melt method of nanosponge preparation

The melt procedure involves melting both β-CDs and the crosslinker. After finely combining the remaining components, put them to a 250 mL jar that has been heated to 100°C. Following that, the reaction is performed for 5 hr using attractive magnetic mixing. Allow to cool and break down, then wash with solvents to remove byproducts and excess (Poonam *et al.*, 2023).

Microwave synthesis of nanosponge preparation

In the microwave synthesis approach, this polymer, along with crosslinkers, can be mixed in an appropriate solvent. The mixture is then exposed to microwave irradiation, which rapidly heats up the components and accelerates the cross-linking process, developing a porous three-dimensional NS structure. The product then undergoes purification by washing and can be dried in a vacuum. This method will, therefore, provide faster, energy-efficient synthesis of uniform NS with a higher surface area for different applications.

Co-solvent evaporation method of nanosponge preparation

To create an inner phase, the NS was prepared using polymers and Eudragit RS 100, a solvent. The medication was dissolved at 35°C and mixed with PVA's exterior phase, acting as an emulsifier. The solution was stirred for 3 hr at ambient temperature and dried in a hot-air oven at 40°C for 12 hr (Figure 6).

Solvent displacement method of nanosponge preparation

In the solvent displacement method different ratios of Ethyl Cellulose (EC) and Polyvinyl Alcohol (PVA) are employed. PVA is introduced into the aqueous solution, followed by dissolving the medication and polymer in chloroform, stirring at 1000-1500 rpm, and drying at 40°C in a hot air oven (Figure 7).

Bubble electrospinning method

The bubble electrospinning method involves electrospinning a polymer solution under a voltage of high magnitude; additionally, gas bubbles were created in the solution. Porous NF network produces a NS structure (Pandya *et al.*, 2023).

Solvent evaporation method

NS is produced by dissolving EC in dichloromethane and mixing it with PVA aqueous solution. Magnetic mixing extends the reaction for 5 hr, followed by filtering and drying in an oven at 40°C for 24 hr (Chilajwar *et al.*, 2014). Table 1 shows the Characteristics of NS Prepared by Various Methods.

Table 1: Characteristics of NSs Prepared by Various Methods.

Manufacturing Method	Particle Size (nm)	Advantages	Disadvantages
Hyper crosslinked Method	350-500	Customizable properties (porosity, rigidity). High porosity for enhanced drug loading. Superior thermal and chemical stability.	Time-consuming process requiring precise control. High production cost due to specialized crosslinkers. Potential toxicity of crosslinking agents.
Ultrasound-assisted Synthesis	97-325	Energy-efficient compared to thermal methods. Faster synthesis process. Improved particle dispersion and uniformity.	Risk of overheating, which may alter structure. Expensive ultrasonic equipment required. Difficult to scale up for large-scale production.
Solvent Method	316-911	Scalable for industrial production. Simple and straightforward synthesis. Customizable solvent choice to modify properties.	Energy-intensive due to solvent removal and purification steps. Use of hazardous solvents like dimethylformamide. Solvent residues may affect product safety.
Co-solvent evaporation method	105-842	Uniform particle size. High drug loading efficiency. Simple, cost-effective process.	Batch-to-batch variability due to manual solvent evaporation. Limited to hydrophobic drugs. Residual solvents may remain, affecting safety.
Microwave Method	153-400	Uniform heating, leading to more uniform Nanosponge size. Faster reaction times (minutes vs. hours). Energy-efficient synthesis.	Risk of uneven heating in larger batches. Requires specialized microwave reactors. Limited scalability for large-scale production.

Challenges are currently being addressed in research and industrial settings

In both research and industrial environments, several innovative techniques are being explored to overcome the problems related to the manufacturing of NS. In the case of the solvent evaporation method, slow solvent removal and contamination with residual solvents are overcome by incorporating supercritical fluid technology to remove solvents quickly and efficiently and also by using microwave-assisted solvent evaporation to offer uniform heating and minimize processing time. Further, environmentally friendly, low-toxicity solvents or even solvent-free methods are being researched to reduce environmental impact and increase safety. In the solvent displacement method, uniform dispersion of NP and control of size are the problems overcome by optimizing the concentration of polymer and types of surfactants, and employing high-shear mixing and ultrasonication techniques for better consistency. The sonication method suffers from heat generation and uneven crosslinking; however, these are mitigated by optimizing sonication parameters, using cooling systems to prevent thermal degradation, and improving control over sonication time and power. Uneven heating and size distribution are the challenges being overcome in microwave-assisted synthesis by optimizing microwave power levels and using multi-mode microwave reactors, which ensure uniform energy distribution. The electrospinning technique suffers from the problem of poor thickness and uniformity control, although this is improved with recent advances in co-spinning techniques, better electrospinning equipment, and improved environmental controls such as humidity and temperature. Problems arise in the bubble electrospinning technique in terms of size control of the bubbles and porosity. The use of surfactants in the process to stabilize the bubble formation helps, along with the optimization of electrospinning parameters for better control over the final structure. All of these methods indicate that the current research in process development is focused on the optimization of process control, reproducibility, and scalability that can meet the ever-increasing demand for high-quality NS in drug delivery,

tissue engineering, and environmental applications (Bano *et al.*, 2019).

FACTORS GOVERNING THE PREPARATION OF NANOSPONGE

Different polymers used

The various polymers employed impact the performance and formulation of the NS structure. To accommodate a drug molecule and to interact the drug with the NS. The particle dimension of NS must be in the right specific range.

Temperature

Variations in temperature have an effect on a complex's stability constant. The apparent stability is decreased at high temperatures due of the diminished forces that hold the medication on to the NS.

Degree of substitution

More significant degrees of linking lead to porous NS, and the conditions employed in the preparation procedure impact the primary physicochemical attribute. Substitution, number of positions in polymeric molecules controls NS complexation (Gardouh *et al.*, 2022).

Type drugs

The drug molecules should possess some properties to make a complex with NS. They include molecular weight, which must be between 100 and 400 nm and less than five condensed rings. The medication must melt at no more than 250°C and have a water solubility of not more than 10 mg/mL.

Drug-nanosponge complexation

The drug-NS complexation can be disrupted by introducing the active pharmaceutical molecule into the NS. The expert approach determines the kind of polymer and the pharmaceutical molecule. The freezing process is the most effective method for medication complexation (Pritesh Patel, 2014).

Nanosponge interaction

The drug molecules whose molecular weights lie between the range of 100-400 Da must successfully saturate so that they can interact with the NS in the nanocavities. The best possible chemical and physical qualities are a must for interaction.

Types of CD and crosslinkers

The type polymeric determines about formation and performance towards NS; hydrophilic NS enhance reabsorption of drugs and act as carriers making it possible to solubilize drugs in water for sustained release (Sherje *et al.*, 2017).

CHARACTERIZATION OF NANOSPONGES

Solubility studies

The phase solubility technique is a widely used method for studying inclusion complexation and drug solubility, using phase diagrams and an Erlenmeyer flask, purified, and determined using HPLC.

Zeta potential

Zeta potential measures surface charge, and can be used in particle size measurement devices. NS samples are diluted with KCl and placed in an electrophoretic cell with 15 V/cm electric field.

Polydispersity Index (PDI) and particle size

Dynamic light scattering measures particle size using a 90 Plus particle sizer and MAS OPTION program, calculating mean diameter and PDI, which indicate the variation in particle size distribution between monodisperse and polydisperse samples.

$$\textbf{Polydispersity index} = \frac{\boldsymbol{\Delta d}}{\boldsymbol{davg}}$$

The particle size may be measured using the following techniques: Freeze fracture electron microscopy, TEM, SEM, and atomic force microscopy (Arvapalli *et al.*, 2017).

Sl. No.	PDI	Type of dispersion
1.	<1	Single disperse Standard
2.	0.1-0.25	Nearly Single disperse
3.	>0.1	Mid-range multi dispersity
4.	>0.5	Very multi disperse

d-Average particle size shown mV(nm); davg-Represents the breadth of the distribution.

Scanning Electron Microscopy (SEM)

SEM is used to analyse morphological structures of NS, characterizing detailed particle structures. Samples are vacuum-sealed and coated with palladium or gold using a scanning electron microscope sputter coater unit at 15 kV acceleration voltage (Subramanian *et al.*, 2012).

Fourier Transform Infrared spectroscopy (FTIR)

The NS formulation was optimized using potassium bromide and NS in a 1:90 ratio, compressed under 15 tons of pressure, and recorded using FTIR spectra in the 4000-400 cm^{-1} wavelength region, observing changes in optimized primary peaks over time.

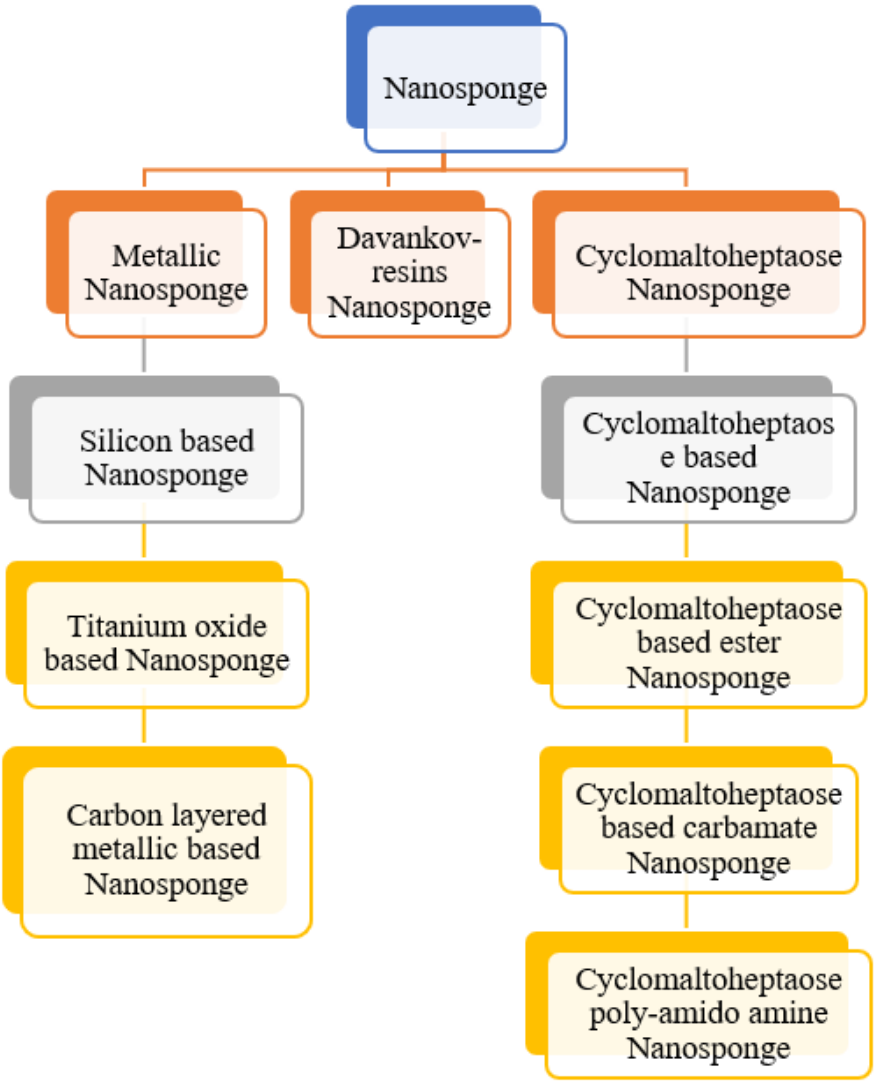

Figure 2: Classification of NSs.

Differential Scanning Calorimetry (DSC)

DSC, the formulation batch of optimized NS was thermographed. Samples of nanosponges were stored in an aluminium pan, sealed, and heated between 40 and 400°C at a steady rate of 10°C per min. by using a 100 mL/min flow rate to purge nitrogen.

X-ray Diffractometry structure analysis (X-RD)

XRD is crucial for identifying solid-state inclusion complexes in drug molecules, with changes in diffraction patterns indicating new structures. Powder X-ray Diffraction (PXRD) patterns show solid phase formation, and complexes may produce additional peaks (M. R. P. Rao and Shirsath, 2017).

Thin layer chromatography

Thin-layer chromatography was used to determine the R_f values in these NS complex pharmaceutical molecules. The lower Rf value confirmed the presence of a complex between the NS and the drug molecule.

Raman spectroscopy

Raman spectroscopy, a molecular method using laser light, is used to identify chemical fingerprints, study molecular bond modifications, and identify vibrational modes. It offers advantages over FTIR spectroscopy, including minimal sample preparation and insensitivity to water absorption bands (Tejashri *et al.*, 2013).

Resilience tests

NS's toughness can be adjusted to create softer or tougher beadlets, and as crosslinking increases, the release rate decreases, allowing for improved resilience of sponges by considering the release sequence as a result of cross-linking (Singh *et al.*, 2016).

Table 2: Marketed drugs in Nanosponge formulations.

Sl. No.	Drug	Uses	Brand Name	Manufacturer
1	Tamoxifen	Breast cancer	Nolvadex, Soltamox.	AstraZeneca, Xanodyne Pharmaceuticals.
2	Iodine	Anti-septic	Iodex, Iodoflex, Iodosorb.	Smith and Nephew.
3	Alprostadil	Erectile dysfunction	Caverject, Edex, Prostin VR.	Pfizer, Endo Pharmaceuticals, Upjohn.
4	Dexamethasone	Used to treat inflammation	Neofordex, Glensoludex, Martapan.	Aspen, Hikma Pharmaceuticals.

Efficiency loading and entrapment

A measured number of packed NS groups needs to be dispersed in a suitable solvent, sonicated, and then adequately diluted before being analyzed using a UV spectrophotometer or HPLC. The loading efficiency of NS may be calculated using the formula below.

$$AD = \frac{FE}{CDC} \times 100$$

AD = Actual drug,

FE = Filling Efficiency,

CDC = Calculated drug content.

Reaction Yield (RY)

The initial and finish weights of the basic materials may be used to calculate the RY.

$$PM = \frac{RY}{TY} \times 100$$

PM = Practical mass,

RY = Reaction yield,

TY = Theoretical yield (polymer+drug).

Actual drug content

A 10 mg dose of drug-containing NS was mixed with 100 mL of phosphate buffer pH 7.4 solution and swirled for an hour. Filtered samples were analysed using a UV-visible spectrophotometer at 232 nm, beside a blank.

$$\text{Actual Drug content (\%)} = \frac{Nacm}{Nma} \times 100$$

Where Nacm=actual content in a measured amount of NS

Nma=Measured amount of NS

APPLICATIONS OF NANOSPONGE

Sustained drug delivery

Pharmaceuticals and Medical Devices Agency (PMDA) created insulin NS, sensitivity to pH, and efficacy in glipizide release after 12 hr, acyclovir for sustained release due to slow absorption in the gastrointestinal system.

NS as a carrier for gas delivery

In order to serve as gas carriers for gases like carbon dioxide and oxygen. The CD-based NS with improved penetration profiles. This allowed for a slower and more prolonged release of oxygen for topical administration.

Protein delivery

Lyophilization can cause permanent denaturement, requiring long-term stability for pharmaceutical production. Cross-linking β-CD with 2,2-bis-acrylamidoacetic acid or polyamido-amine chains creates stable, complexable poly(amidoamine) NS (Challa *et al.*, 2005).

Solubility and bioavailability enhancer

The solubility of hydrophobic medications may be improved by using NS in CD cavities. This can result in lower dosages, better treatments, fewer adverse effects, and more patient compliance. This has been used to treat cancer, including the creation of paclitaxel (Trotta *et al.*, 2012).

Nanosponge in cancer therapy

Tumours can be treated using anticancer drugs delivered by NS, which focuses on peptides attaching to radiation-activated cell surface receptors, potentially enhancing the solubility of camptothecin, thereby circumventing its limitations (Iravani and Varma, 2022).

Stability enhancer

NS enhances soluble, stable, and efficient dissolution of compounds like volatile oils, medications, Bovine Serum Albumin (BSA) proteins, and resveratrol, while genetic engineering improves enzyme stability, economy, and specificity.

Drug delivery

There are several ways to employ NP, including topical, parenteral, aerosol, tablet, and capsule forms. They are useful nanocarriers for the treatment of cancer because they increase the solubility of medications including TEL, paclitaxel, and econazole nitrate (Ahmed, 2012).

Table 3: **Recent studies on Nanosponges.**

Sl. No.	Drug	Activity	Authors
1	Fluconazole	Enhanced transdermal delivery	(Abbas *et al.*, 2019)
2	Clobetasol propionate	Treatment of psoriasis	(Kumar *et al.*, 2021)
3	Lemon grass oil	Antifungal	(Aldawsari *et al.*, 2015)
4	Cinnamon oil	Antibacterial activity	(Kaur *et al.*, 2021)
5	Terbinafine Hydrochloride	Anti-fungal	(Ghose *et al.*, 2020)
6	Mupirocin	Diabetic foot ulcers	(Dhamak *et al.*, 2024)
7	Boswellia carterii oil	Anti-inflammatory activity	(Taleb *et al.*, 2024)
8	Kynurenic acid	Antioxidant activity	(Dhakar *et al.*, 2019)
9	Ferulic acid	Anticancer activity	(Rezaei *et al.*, 2019)
10	Limonene	Antibacterial	(Salehi *et al.*, 2021)
11	Paclitaxel	Anticancer activity	(Mognetti *et al.*, 2012)
12	Babchi Oil	Cytotoxicity	(Kumar *et al.*, 2018)
13	Vaccines	Activity	Authors
14	mRNA	Protection mRNA	(Abou Taleb *et al.*, 2022)
15	Influenza	Sustained Release	(Lembo *et al.*, 2018)
16	Tumor-associated antigens (TAA)	Cancer immunotherapy	(Swaminathan *et al.*, 2016)
17	Enzymes	Activity	Authors
18	Glutathione Peroxidase	Detoxification	(Daga *et al.*, 2020)
19	Lipases	Hydrolytic	(Boscolo *et al.*, 2010)

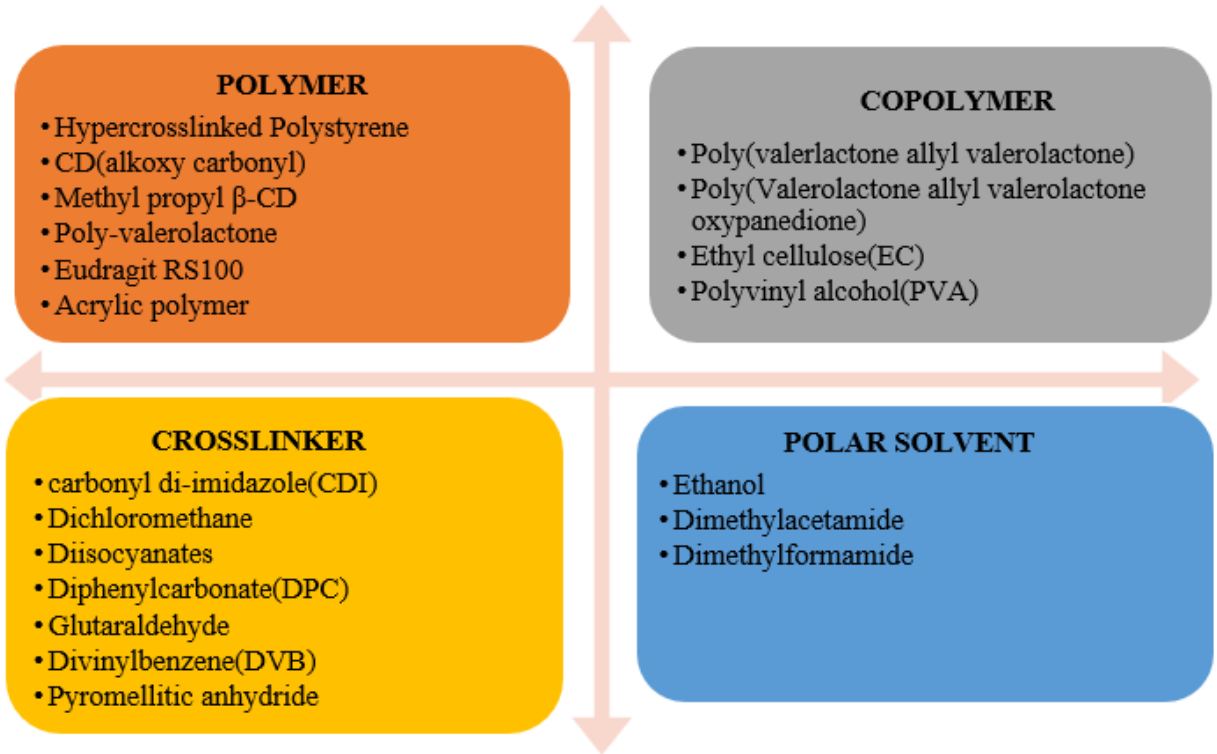

Figure 3: Materials used in preparation of NSs.

Table 4: ***In vitro, in vivo*** **studies, and clinical trial references where NSs have shown promising results.**

Study Type	Drugs Used	Application	Outcomes
In vitro	Doxorubicin (anticancer drug)	Cancer drug delivery and controlled release.	Increased drug stability, controlled release, and reduced toxicity (Argenziano *et al.*, 2020).
	Ibuprofen (NSAID)	Controlled-release drug delivery.	Prolonged drug release and enhanced solubility
	Antimicrobial peptides (AMPs)	Antimicrobial coatings for medical devices.	Enhanced antimicrobial activity and reduced bacterial resistance.
	Methotrexate (chemotherapeutic agent)	Rheumatic arthritis	Sustained drug release, increased therapeutic efficacy (Banjare *et al.*, 2020).
	Resveratrol (antioxidant)	Drug delivery for neurodegenerative diseases.	Enhanced solubility and stability of resveratrol.
In vivo	Paclitaxel (anticancer drug)	Cancer therapy	Improved drug bioavailability, reduced systemic toxicity, and targeted delivery (Clemente *et al.*, 2019).
	Quercetin (antioxidant)	Neuroprotective therapy.	Enhanced brain bioavailability and neuroprotective effects.
	Econazole (antifungal drug)	Antifungal drug delivery.	Higher antifungal activity, prolonged action, and reduced dosage frequency (Srivastava *et al.*, 2021).
	Rifampicin (anti-tuberculosis drug)	Anti-tuberculosis drug delivery.	Enhanced permeability, controlled release, and reduced toxicity.
	Indomethacin (NSAID)	Anti-inflammatory drug delivery.	Reduced gastrointestinal side effects and sustained release.
	Vaccines (antigen delivery)	Controlled vaccine delivery.	Sustained antigen release and enhanced immune response.
Clinical trials	Paclitaxel	Cancer therapy	Ongoing clinical evaluation for improved efficacy and reduced side effects.
	Doxorubicin	Cancer therapy	Clinical studies focusing on sustained release and reduced cardiotoxicity.
	Insulin	Diabetes treatment	Evaluation of oral insulin delivery for improved absorption and bioavailability.
	Curcumin	Cancer, anti-inflammatory treatments.	Early-stage trials for enhancing curcumin bioavailability and therapeutic potential.
	Fluconazole	Antifungal drug delivery.	Clinical studies to improve fluconazole release and therapeutic efficacy.

Enzyme entrapment

Enzyme entrapment is a significant challenge for lipases, impacting stability, enantio selectivity, and reaction speeds. A new, solid basis is needed for enzyme development, and Pseudomonas fluorescence lipase exhibits exceptional catalytic activity (Boscolo *et al.*, 2010).

Severe Acute Respiratory Syndrome (SARS)-CoV-2 inhibition

NS, or nanoparticles, can treat and prevent serious illnesses like SARS and Zika by imitating host cells to capture and kill SARS-CoV-2, using Angiotensin-Converting Enzyme 2 (ACE2)-containing plasma membranes (Zhang *et al.*, 2020).

Diagnostic test

β-CD is extensively employed in the formulation of multiple diagnostic products. CD-NS are favored for their excellent biocompatibility, prolonged circulation time in the blood, consistent particle size distribution that enhances permeability, and their efficient ability to reach specific targets (Gidwani and Vyas, 2015).

Cosmetics

NSs are used in the cosmetics industry to protect photosensitive components by prolonging the release of volatile oils and absorbing unpleasant bodily odours. They also subtly eliminate volatile substances, leaving oral cosmetics fresh for longer, and providing a long-lasting appearance in rouge and lipsticks (Bilensoy, 2011).

DRUG RELEASE MECHANISM AND PHARMACOKINETIC STUDIES

Nanosponges release drugs in a controlled release mechanism, where the medication migrates towards the skin's stratum corneum until fully absorbed, resulting in a pseudo-zero order pattern of drug release (Sujitha and Muzib, 2019).

RELEASE PROFILE

A rotating multicompartment cell with a dialysis membrane is used to test NS *in vitro* release. The donor phase contains drug-loaded NS complexes, while the receptor phase is removed and diluted. The USP Apparatus II can be used in various applications. The release data helps understand drug release mechanisms. First- and zero-order models are fitted, and data analysis software like GraphPad Prism is used to find optimal nonlinear functions and parameters (Pyrak *et al.*, 2024). Table 2 describes various drugs that are available in the market as nanosponge formulations.

Emerging Trends and Future Research Areas in NS Technology

NSs are being developed as a promising drug delivery platform for cancer therapy, infectious disease control, and environmental remediation. They can be used in stimuli-responsive drug delivery systems that respond to environmental triggers such as pH, temperature, or light to release drugs. They allow for site-specific delivery of drugs, which avoids side effects and improves the treatment outcome. Studies have also been done using NSs with dual-mode therapy, where a combination of chemotherapy with photothermal or photodynamic therapy degrades the tumor effectively. They are also of interest for oral delivery of biologics, where there is a problem of degradation within the gastrointestinal tract (Mohite *et al.*, 2024) Table 3 shows the list of recent studies on nanosponges.

Another rapidly expanding area includes the control of infectious diseases with the study of biomimetic NSs, mimicking human cell membranes, that neutralize pathogens. Clinics already

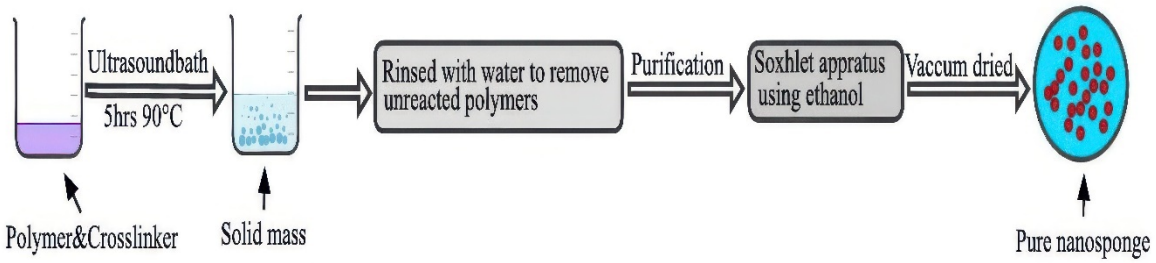

Figure 4: Ultrasound assisted synthesis of NSs.

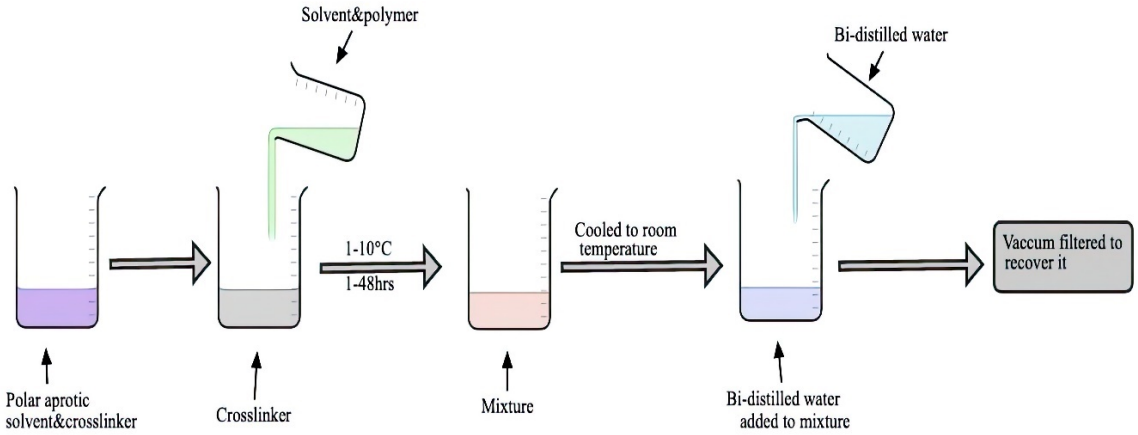

Figure 5: Solvent method of preparation of NSs.

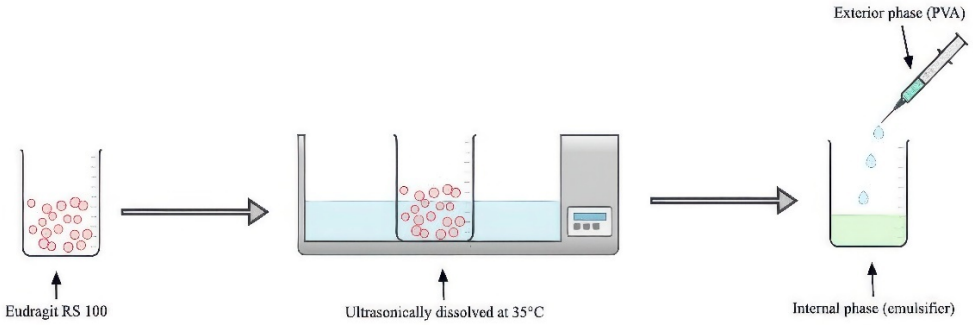

Figure 6: Co-solvent evaporation method of preparation of NSs.

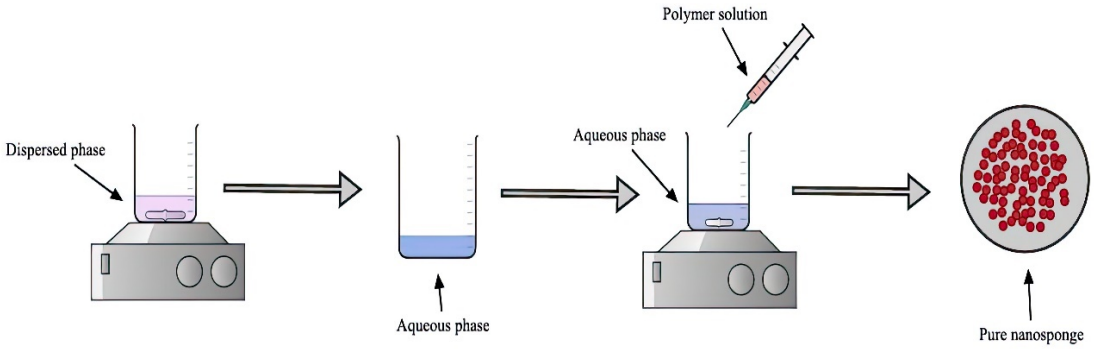

Figure 7: Solvent displacement method of NS preparation.

use antimicrobial-loaded NSs in wound dressings and medical devices to prevent infection. NS formulations for anti-viral drugs of COVID-19 and medications used in wound healing are showing productive results in clinical trials. Table 4 gives a list of nanosponge-based formulations in *in vitro, in vivo*, and clinical trial studies.

Environmental applications of NSs are also being explored regarding water purification and pollution control. NSs can adsorb heavy metals, dyes, organic solvents, and others from water, thus being an effective, sustainable, and cost-effective method of environmental remediation. Future focus will be placed on overcoming scalability, toxicity, and biocompatibility while improving large-scale production methods and incorporating nanorobotic systems for targeted drug delivery (Tannous *et al.*, 2020).

CONCLUSION

NS is a versatile class of nanomaterials with a large potential for use in different fields. Their distinctive features, such as high superficial expanse, adjustable aperture size, and functionality, make them promising candidates for numerous applications. NS can deliver both hydrophilic and lipophilic drugs via several routes, including oral, transdermal, rectal, and parenteral routes. In particular, β-NS Improves the solubility of drugs classified as BCS Class II. which is useful for certain drug delivery techniques. The formulation design, applications, characterization techniques, synthesis methods, and modifications of NS are discussed in this extensive review. Human health has already improved owing to recent approvals of drug delivery systems based on NS technology. At the same time, ongoing research continues to explore new pharmaceuticals that will help improve therapeutic outcomes. The safety and effectiveness of such medications delivered through NS as an innovation are expected to encourage pharmaceutical companies to adopt them.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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