REVIEW ARTICLE

Nanosponges as a Drug Delivery System: Methods, Characteristics and Applications

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ABSTRACT

Nanosponges, which are crosslinked polymer nanometers in sized used for drug transport, have a unique three-dimensional appearance. Their versatility lies in their ability to accommodate drugs of various sizes. The research approach, polymer type, and drug content determine the diversity of nanosponges. Nanosponges excel as delivery systems due to their capacity for controlled and targeted drug release. They offer the flexibility to regulate the duration of drug action and residence time. Their biodegradable composition ensures low toxicity and safe usage. Available voids, along with the size of the test molecule, play a crucial role in the efficiency of encapsulation. Nanosponges exhibit numerous applications such as cancer treatment, transportation of enzymes and biocatalysts, oxygen, modification of drug solubility, and immobilization of enzymes. This study emphasizes the preparation method, characterization, influencing factors, drug loading, recent advancements, and patents in the field of nanosponges.

Keywords: Controlled release, Crosslinked polymer, Nanosponge, Novel drug delivery, Targeted drug delivery.

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INTRODUCTION

Nanosponge, is innovative formulation of polymers with porous nature, small spherical particles with extensive porous surfaces and feature tiny holes ideal for biomimetic detoxification processes. Acting as three-dimensional networks or scaffolds, they are composed of long-length polyester backbones. The challenge of oral drug delivery has long perplexed medical researchers, focusing on precise delivery to specific body sites and regulating drug release to avoid overdose. Nanosponges represent a promising solution to these issues. They are advanced molecules that facilitate targeted drug delivery with controlled release, marking a significant advancement in pharmaceutical technology. Nanosponges represent a novel category formulated with the help of microparticles exhibiting nano-cavities capable of encapsulating a wide array of substances. They serve as effective carriers for oral drug delivery, accommodating a large category of drugs while exhibiting positive solubility characteristics. Constructed from a naturally degradable polyester backbone, nanosponges feature a mesh-like structure with crosslinked segments that form spherical shapes containing numerous pockets or cavities for drug storage, as shown in Figure 1. These solid particles can be available in the form of numerous dosage forms, including solid-oral tablets or capsules, where they are dispersed within excipient matrices comprising diluents and lubricants. For parenteral use, nanosponges can be easily mixed with sterile aqueous solutions such as water or saline.[1] Additionally, they can be incorporated into hydrogels for effective topical administration. Nanosponges thus offer versatility across oral, parenteral, topical, and inhalational routes of dosage form administration. These are novel delivery systems consisting of micro-sized particles with nano-sized cavities capable of encapsulating a wide range of substances.[2] These formulations can transport both water-soluble and lipid-soluble compounds, enhancing the solubility of drugs with solubility issues. Once circulating within the body, nanosponges can target specific sites where they adhere and release the drugs at a pre-determined rate. This approach increases drug effectiveness at lower dosages by ensuring release directly at the intended site rather than systemic circulation throughout the body.

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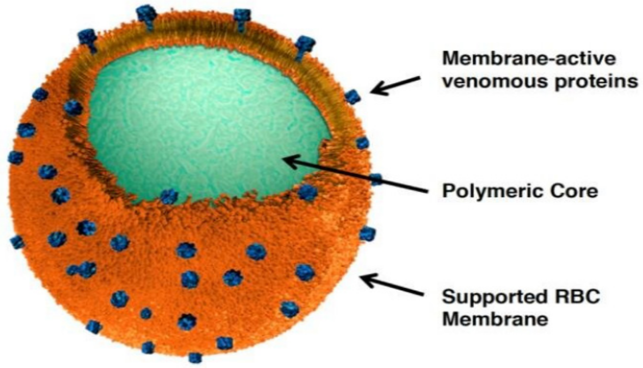

Figure 1: Morphological representation of nanosponge

Nanosponges typically have an average diameter below 1-µm, with some variants selected as small as 500 nm, while microsponges range from 10 to 25 microns in diameter. They also play a role in reducing side effects and protecting drugs from degradation. Nanosponges achieve encapsulation through the formation of complexes with various drug molecules.[1,2]

Merits[2]

- These are easily bio-degradable
- Also shows good stability over a temperature of 130°C
- Showed good compatibility towards number of excipients.
- Formulations are free-flowing with the most cost-effectiveness.
- Able to show enhanced stability, good elegance and formulation flexibility.

Demerits[2]

- Formulations can include only small drug molecules.
- Loading capacities is prime factor. [2]

Characteristic Features of Nanosponges [2,3]

Nanosponges display dimensions typically below 1-µm, featuring cavities whose polarity can be adjusted. This adjustability in size and polarity of nanosponges is achieved through variations in the ratio of cross-linker to polymer during synthesis.

Nanosponges can exist in either a para-crystalline form and/or in crystal form, dependent upon specific conditions of the process used during their fabrication. The crystal structure of nanosponges significantly influences their ability to complex with drugs. The drug loading capacity of the formulation is primarily decided using the extent of crystallization. Para-crystalline formulations have demonstrated diverse capacities for loading different drugs.

Nanosponges are non-toxic, porous particles that are non-soluble in a large number of organic solvents and exhibit stability at rising temperatures till 300°C.

When immersed in water, the formulation gives suspension, which is translucent in nature, which can be re-formulated using the thermal desorption method, solvent extrication method, or using microwave and ultrasound assisted techniques.

The 3D spatial arrangement facilitates the entrapment and re-determined release desired drug. Through linkage with various drugs, nanosponges can be delivered to specific sites. Linkers using chemical bonds enable nanosponges to selectively bind to these target sites. They are capable of forming all types of complexes with diverse drugs. Additionally, nanosponges can possess magnet-like characteristics by incorporating magnetism into their synthesis process. [3]

Composition and Structure of Nanosponges

Nanosponges enclose three components (polymer, drug, cross-linkers) as a part of a system.

Polymer

The nature of the polymer incorporated significantly influences the overall action of nanosponges. For effective complexation, the cavity of nanosponges must be fit enough for drug molecules of specific sizes. The polymer crosslinking owes to its active groups, which are available for substitution. The polymer choice is based on a targeted release pattern and the type of drug encapsulated must be employed either to encapsulate the drug or to interact with the drug. To achieve pre-determined release pattern, the polymer must connect with ligands.

Crosslinking agent

The choice is based on the polymer and drug type to be encapsulated. Table 1 presents a list of polymers and crosslinking agents.

Drug substance

Drug molecules intended for formulation as nanosponges must exhibit below properties:

- A MW between 100 and 400.
- Aqueous solubility of not more than 10 mg/mL
- Must melt below 250°C. [4, 5]

Formulation of Nanosponges

Solvent Diffusion Method

Both organic and non-organic phases are involved. PVA makes up the non-organic phase, whereas the organic phase includes drug-polymer. Thus prepared systems gradually mixed with non-organic phase. This was agitated for at least a couple of hours after the drug and polymer had been dissolved in an appropriate organic solvent. Following filtration, the nanosponges are collected, cleaned, and dried for a full day at ambient temperature or for a day in a vacuum oven at 40°C. [5-7] Apart from this method, different manufacturing techniques are presented in Figure 2.

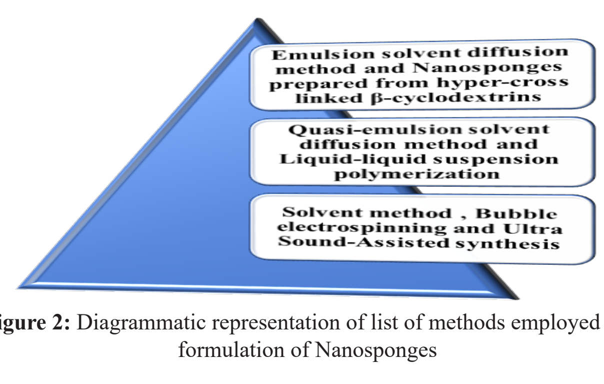

Figure 2: Diagrammatic representation of list of methods employed for formulation of Nanosponges

Table 1: Components of Nanospsonge Formulation

Example of polymer	*Co-polymer*	*Cross-linker*	*Polar solvents*
Hyper- crosslinked polystyrene	Ethyl Cellulose	Carbonyl di-imidazole	Ethanol
Cyclodextrin	Polyvinyl Alcohol	Glutaraldehyde	Dimethylacetamide
Eudragit RS100	HPMC	Dichloromethane	Dimethylacetamide
Eudragit LS100			
Acrylic polymer			
Poly-Valerolactone			

Quasi-emulsion solvent diffusion method

The method involves the generation of a quasi-emulsion composing internal and external layers, like the traditional dosage form. The inner phase is composed of a solution of drug and polymer in a volatile solvent such as ethanol, acetone, or dichloromethane, while the outer phase is polyvinyl alcohol (PVA). Both phases are mixed in a state of continuous stirring. Triethylcitrate (TEC) is incorporated in an appropriate amount to facilitate plasticity. The stirring process results in dispersed quasi-emulsion globules. The remnant is then removed from these globules, leading to the formation of non-soluble micro-particles. After 60 minutes, the resultant nanosponges are separated and then are subsequently air-dried in an oven at 40°C for 12 hours. [8-10]

Solvent method

This method deals with combining the polymer with a polar solvent of aprotic nature such as DMF or DMSO. After that excess of cross-linker, maintaining a 4 to 16 molar ratio was added. Cool, filter using bi-distilled water, purify and dehydrate in a vacuum, and grind to get powder.[9, 10]

Ultra Sound-Assisted synthesis

NSs are made by polymer-cross linkers reaction without using a solvent, employing sonication. The resulting nanosponges are uniform and spherical in size. Begin by mixing both rectors in a specified ratio in a reaction vessel. After ultra-sonication at 90°C for 5 hours and allowing the recants to back to normal temperature and separate the product. Water wash to remove any residual unreacted reactors, followed by purification and stored at 25°C. [10]

Hyper-cross linked β-cyclodextrins

These function as nanoporous formulations employed in drug delivery systems. These structures form three-dimensional networks resembling roughly spherical shapes comparable to protein sizes, featuring internal channels and pores. Cyclodextrins are reacted with cross-linkers, including di-isocyanates, diaryl carbonates, or carbonyl di-imidazole, to control sponge size, porous nature, and surface charge density for attachment. They are formulated from solid particles and can adopt a crystalline structure. They exhibit the capability to encapsulate drugs with diverse natures, effective for poorly-water soluble drugs. [7]

Liquid-liquid suspension polymerization

In this method, monomeric units with drug molecules are dissolved in a monomeric solution and then dispersed into a non-organic phase using excipients, surfactants and suspending agents. A catalyst is introduced to initiate lymerization, increasing temperature, or using irradiation for a specified duration. Monomers or combinations thereof are selected, and polymerization begins to form monomer chains that crosslink to create a ladder-like structure. These monomer ladders fold to form spherical particles, aggregating into nanosphere clusters that eventually bind together to form nanosponges. Nanosponges, resembling reservoir systems, feature open surface pores formed during their formation. Inert liquids, not soluble in water but easily mixed with monomers, can be incorporated during polymer reactions to create a porous network. After a complete polymer reaction, these liquids are evacuated, leaving behind porous nanospheres or nanosponges. Solvents can expedite and enhance the incorporation of drug substances during this process. Nanosponges serve as carriers for delivering various functional substances topically, including anti-acne, anti-inflammatory, anti-purifying, antifungal, and rubefacient agents. [6-7]

Bubble electro-spinning

Initially, the monomeric unit and drug dissolve in a compatible solvent and then are dispersed to a non-organic phase with surfactants. Polymerization is triggered by catalyst addition, temperature increase, or irradiation over a specific period. Selected monomers or combinations undergo polymerization, forming chains that crosslink to create a ladder-like structure. These folded monomer chains aggregate into spherical particles, clustering into nanospheres that eventually aggregate to form nanosponges. Nanosponges, designed as reservoir systems, develop open surface pores during formation. Inert liquids, not mixing with water but fully compatible with monomers, can be used to establish the pore network during polymerization. Post-polymerization, these liquids are extracted, leaving behind porous nanospheres or nanosponges. Solvents play a vital function in facilitating and enhancing the incorporation of active substances during this process. Nanosponges act as carriers for delivering various functional substances topically, including treatments for acne and inflammation, purifying agents, antifungal medications, and rubefacients.[8]

Drugs loading in Nanosponges[7-9]

NSs have been used to load various drugs, resulting in a larger drug contact time in the targeted site and lowering the required drug concentration for administration. The types of drugs that can be potentially used in formulation are listed in Table 2.

Evaluation of Nanosponges

Organoleptic properties[10,11]

Different physicochemical properties of a drug, including color, odor and appearance, were observed

Melting Point

The M.P. of the substance was observed using the capillary technique with a digital apparatus (Veego VMPI, India). A fine powder of the drug was carefully filled into a tube, followed by sealing at one end. Special attention must be gen to ensure equal heat distribution of the silicon bath. The temperature range over which the drug began to melt until complete liquefaction was observed as the melting range. This value was then compared with literature data for validation.[9-11]

Fourier transforms infrared (FTIR) spectroscopy

The spectra of the sample can be obtained through FTIR analysis using an instrument made of FTIR 4100, Jasco, Japan. A test sample was prepared by triturating the drug with potassium bromide (KBr) in a glass mortar. Subsequently, the prepared sample was placed in a spectrophotometer holder and analyzed from 4000 to 400 cm^{-1}. The spectra obtained were then compared with reference spectra reported in the literature.[12-15]

Solubility Analysis

The solubility of pure dug was observed with the shake flask method. The drug was added in excess to separate test tubes containing 10 mL of ethanol (95%), methanol, and water, respectively, to ensure saturation of the solid phase in each solvent. The solutions were vortexed for 15 minutes and kept stagnant for an hour to ensure complete saturation. Solid and liquid phases were separated using filtration.[16-18]

U.V. visible spectroscopy

The pre-weighed amount of sample after dilution is subjected to spectrophotometric analysis. The corresponding concentration of a given drug sample can be obtained after plotting the calibration curve of absorbance *versus* known concentrations.[19-21]

Table 2: Examples of suitable drug candidates for NS

Category of drug	*Example*
Antidiabetic drugs	Glibenclamide, glipizide,
Antifungal	Griseofulvin, itraconazole, ketoconazole
Antihistamines	Terfenadine
Antihypertensives	Felodipine, nicardipine, nifedipine, telmisartan
Antineoplastic agents	Exemestane, flutamide, paclitaxel, raloxifene
Antianxiety drugs	Lorazepam

Compatibility Study of Drugs with the Selected Excipients

FTIR Spectroscopy

To identify the probable interaction between drug and excipient in nanosponge formulations. The pellets of sample and potassium bromide were made using a press.[22-24]

Determination of percentage yield

The % yield of nanosponges can be calculated using the formula mentioned below[13,14, 25]

$$\text{Percent yield} = \frac{\text{Practical yield of nanosponges}}{\text{Theoretical yield of nanosponges}} \text{ x } 100$$

Determination of entrapment efficiency

A pre-measured quantity of the test sample was grounded, made soluble in 20 mL of methanol, with shaking for about 60 minutes. The supernatant was then taken out, diluted, and analyzed using spectrophotometry. The following equation was used for calculation: [23, 26-30]

$$\text{\% Entrapment efficiency} = \frac{\text{Acual amount of drug}}{\text{Theoretical amount of drug}} \text{ x } 100$$

Determination of drug content

This can be done by dissolving 10 mg of the test sample in Hydrochloric Acid. The resultant solution was then strained to discard non-soluble mass and observed using a UV-vis-spectrophotometer at a suitable wavelength. [2, 31]

Particle size analysis

This was determined using a particle size analyzer (NANOPOX-NX0088).[28, 32-34]

Poly-dispersity index

The poly-dispersity index measures the variation in particle size within a test sample. A set of objects is considered uniform if they share the same physical characteristics. The results were obtained with the help of the NANOPHOX instrument. [34-36]

Differential Scanning Colorimetry

A DSC Mettler STAR SW 9.20 differential scanning calorimeter with an intra-cooler. A 1 mg sample was placed in a pan, with an empty pan as the reference. N_2 gas was then purged at 25 mL/min to maintain an inert atmosphere and scanned at 10°C per minute. [37]

Powder X- ray diffraction study

Pure cinnarizine was measured by X-ray diffraction (XRD) at a resolution of 0.001 Å using a Philips (PW 3710) Expert Pro MPD Diffractometer (PAN Analytical Inc, Germany). A 0.5 mm-thick film of vacuum grease was applied to a glass slide, onto which a 10 mg sample of the pure medication was sprinkled and fixed before measurement. Radiation from a copper tube with a scan angle varying from 5° to 60° of 2θ was applied to samples. 40 mA and 40 kV, respectively, were the current and voltage that were employed. [34, 35-37]

Surface morphology (SEM)

The surface morphology can be studied using JEOL Scanning Electron Microscope (Model: JSM 6360 A, Japan). [35]

Zeta potential

This was observed using Zetasizer 2000 (Malvern Instruments). Test samples were made dilute and inserted into the apparatus. Readings were conducted via automatic operation. [35]

In vitro diffusion study

To conduct studies, soaked dialysis bags were, rinsed and then used for study. A dialysis sac containing HCl was used at room temperature. The dialysis bags were suspended in a conical flask on a magnetic stirrer set to 100 rpm. Samples were collected at specified intervals of up to 4 hours and analyzed using a spectrophotometer. The sink conditions were maintained by replacing it with fresh solvent. The dissolution data were analyzed to calculate the drug release.[36-38]

Applications of Nanosponges

Nanosponges for Oral Delivery

For oral applications, this drug delivery system modifies the solubilization pace of poorly water-soluble ingredients *via* engulfing them within these pores. The nanoscale size of the nanosponges significantly increases the area of the exposed surface, which boosts the solubilization rate. Additionally, the time the nanosponges system spends traversing the small intestine and large intestines is extended, thereby absorbing the maximum drug. [9, 38]

Oxygen delivery systems

A method for delivering oxygen has been devised using cyclodextrin nanosponges. The combination of hydrogel and β-cyclodextrin nanosponges can facilitate oxygen penetration across a silicone membrane. Oxygen can be stored in these nanosponges and released gradually over time. Oxygen-filled nanosponges may be able to provide hypoxic areas linked to a number of illnesses with oxygen.[2]

Cancer

Doctors often find that injected drugs for cancer patients sometimes fail to work effectively. This is typically due to two reasons: either they do not reach the target tumor or can be broken down by the immune response. This challenge has been partially addressed by using nanosponges. Experts suggest that encapsulating drugs in nanosponges ensures that the medications reach their target in significant quantities. One notable drug formulated using nanosponges is paclitaxel, the anti-cancer drug Taxol. Some studies have showcased that a single injection of these nanosponges on tumors in animal models: slowly-emerging breast cancer and rapidly developing mouse glioma. In both cases, they observed that delivering drugs *via* nanosponges increased cancer cell death and slowed tumor growth compared to other treatment models. [7,10]

Harvesting of rare Cancer Marker from Blood

A new type of nanoparticle is used to capture special protein groups from the heme, protecting them from enzymatic lysis within the bloodstream.[10]

As a carrier for biocatalysts and in the delivery and release of enzymes, proteins, vaccines and antibodies

A large number of industrial chemical reactions have drawbacks like high energy consumption due to the need for high temperatures and pressures, resulting in low product output and the requirement for large amounts of cooling water. Enzymes as biocatalysts can mitigate these issues with their high reaction speeds, specificity, and mild operating conditions. Enzymes and proteins can be delivered through hydrogels, liposomes, nanoparticles, and microparticles, which enhance protein stability *in-vivo*, modify pharmacokinetics, and protect against degradation. CD-based NSs are particularly effective in adsorbing proteins, enzymes, antibodies, and other macromolecules, retaining their activity and efficiency, extending operational life, increasing pH and temperature tolerance, and enabling continuous flow operations. Additionally, they can encapsulate or adsorb proteins and other macromolecules for transport. [10,11]

Solubility enhancement

Nanosponges have also been employed to modify the solubility and dissolution, as well as to achieve desired release profiles. Here, the size and structure are crucial factors that affect the inclusion of complex formation within nanosponges, making this approach not universally suitable for all substances. [9, 10]

In the removal of organic matter to produce ultrapure water for power regeneration

For many businesses that depend on high-purity water, such as electronics, pharmaceuticals, and power plants, the contact of organic contaminants in untreated water is a serious concern. Although they were less successful in removing total organic carbon (TOC), these CD-polymers have demonstrated the potential to extract up to 84% of dissolved organic carbon (DOC) from raw water. [10]

Antiviral application

Medication can be administered by nasal, pulmonary, and ocular means using nanosponges. They facilitate the targeted release of siRNA or antiviral medications to the lungs and nasal epithelia, specifically targeting viruses that cause respiratory disease. They work well against HBV, HSV, and HIV as well. Currently, available nano delivery methods include acyclovir (formulated with Eudragit), zidovudine, saquinavir, and interferon-α. [7, 10]

More effective than direct injection

According to recent studies, direct injection of tumor growth can be thwarted up to five times more successfully than with nanosponges. An anti-cancer medication is contained in virus-sized sponges in this drug delivery method. These sponges have chemical linkers linked to them that attach to tumour cell receptors. After that, the body is injected with the sponges. The sponges either stick to the surface of the tumor cell or are internalized by it when they come into touch with it. They release their powerful contents in a calculated and deliberate way. [10]

Table 3: Marketed preparation of nanosponges

Potential drug candidate	*Marketed name*	*Market*
Dexamethasone	Glymesason	Japan
Iodine	Mena-gargle	Japan
Alprostadil	Prostavastin	Europe, Japan, USA
Piroxicam	Brexin	Europe
Temoxifen	Nolvadex	Europe, Japan, USA
Paclitaxel	Taxol	Europe

Chemical Sensors

NS, classified under "metal oxides," function as chemical sensors for detecting hydrogen with high sensitivity, particularly using titania nanosponges. Initially, the structure of nanosponges lacks contact points, reducing electron transport hindrance. This leads to the formation of interconnected 3D nanosponges of titania that exhibit sensitivity to H2 gas. [10]

Marketed Preparation of Nanosponges[7]

Other examples of patented drugs used in nanosponges preparation are paclitaxel, camptothecin, tamoxifen, econazole nitrate, and peroxidize, while marketed formulations are mentioned in Table 3.

CONCLUSION

In conclusion, nanosponges represent a versatile and efficient drug delivery system due to their unique three-dimensional structure, controlled and targeted release capabilities, and biodegradable nature. Their ability to encapsulate various drugs, modify solubility, and immobilize enzymes makes them valuable in applications like cancer treatment and enzyme transportation. This review highlights their preparation, characterization, influencing factors, drug-loading techniques, recent advancements, and relevant patents, underscoring their significant potential in biomedical applications.

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