International Journal of Pharmacy and Industrial Research (IJPIR)

IJPIR |Vol.14 | Issue 4 | Oct - Dec -2024

www.ijpir.com

DOI : https://doi.org/10.61096/ijpir.v14.iss4.2024.395-403

ISSN: 2231-3656
Print: 2231-3648

Review

Advancements in Nanosponge -Based Drug Delivery Systems: Synthesis, Functionalization, and Applications

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Published on: 11 Nov 2024

Published by:
DrSriram Publications

Abstract

Nanosponges are encapsulating nanoparticles that encapsulate drug molecules, offering targeted site-specific delivery, reducing side effects, and converting liquid substances to solids. They can be produced easily, are non-irritating, mutagenic, allergic, and toxic. This review provides a detailed overview of the various types of nanosponges, including cyclodextrin-based, polymeric, and metal-organic framework (MOF) nanosponges, highlighting their synthesis and functionalization techniques. Key preparation methods such as emulsion solvent evaporation, ultrasound-assisted synthesis, and thermal polymerization are discussed in detail, with a comparison of their efficiencies and suitability for different applications. The merits of nanosponges—including their biocompatibility, high encapsulation efficiency, and ability to enhance the solubility and stability of loaded compounds—are examined in relation to specific use cases in drug delivery, pollutant removal, and catalytic processes. Evaluation techniques are also reviewed, focusing on methods such as scanning electron microscopy (SEM), X-ray diffraction (XRD), and thermal gravimetric analysis (TGA) used to assess nanoparticle morphology, surface properties, and stability. By synthesizing current advancements and identifying future challenges, this review underscores the potential of nanosponges to transform various industries and offers guidance for future research and application development.

Keywords: Nanosponge

INTRODUCTION

The pharmaceutical and health care industry has been creating and using nano-scale materials for resolving many physical, biological and chemical problems related with the treatment of disease. The hydrophobic nature of most of the drugs presents a challenge for effective in vivo delivery. Shrinking materials to nano size has profoundly enhanced the efficacy of such drugs. A number of polymers have been studied and used for formulating Novel drug delivery systems (NDDS) [1].

An ideal drug therapy attains effective drug concentration at the target site for a specified period of time and minimizes general and local side effects. To obtain a desirable therapeutic response, the correct amount of drug should be transported and delivered to the site of action with subsequent control of drug input rate. The distribution of drug to other tissues therefore seems unnecessary, wasteful and a potential cause of toxicity. Targeted drug delivery is the delivery of drug to receptor, organ or any part of the body to which one wishes to deliver the drug exclusively. Targeting drug delivery has long been a problem for medical researchers i.e., how to get them to the right place in the body and how to control the release of the drug to prevent overdoses. The development of new and complex molecule called Nanosponges has the potential to solve this problem [2].

Nanosponges are made of microscopic particles with few nanometers' wide cavities, in which a large variety of substances can be encapsulated. These particles possess the ability to carry both lipophilic and hydrophilic substances and thereby improving the solubility of poorly water-soluble molecules. The studies conducted in this field proves that the tiny mesh-like structures called nano sponges may revolutionize the treatment of many diseases and early trials suggest this technology is up to five times more effective at delivering drugs for breast cancer than conventional methods [3].

The nano-sponge is about the size of a virus with a 'backbone' (a scaffold structure) of naturally degradable polyester. They 'cross link' segments of the polyester to form a spherical shape that has many pockets (or cavities) where, drugs can be encapsulated. The polyester is biodegradable, which means that when it breaks down in the body, the drug can be released on a known schedule.

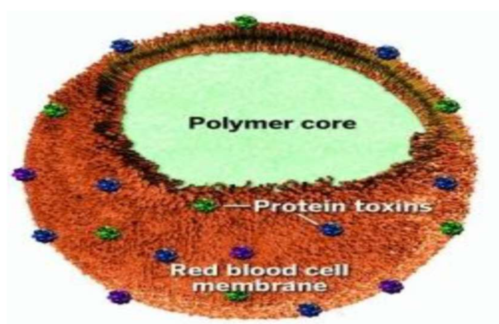
Nano sponge

The nanosponges are encapsulating type of nanoparticles which encapsulates the drug molecules within its core. Based on the method of associating with drugs, the nanoparticles are classified into encapsulating nanoparticles, conjugating nanoparticles and complexing nanoparticles.

The encapsulating nanoparticle is represented by nanosponges and nanocapsules. Nanosponges such as alginate nanosponge, which are sponge like nanoparticles contains many holes that carry the drug molecules. The second category is conjugating nanoparticle, which links to drugs through covalent bonds. The third type is complexing nanoparticle, which attracts the molecules by electrostatic charges [4].

Difference between Nanoparticles and Nanosponges

The thin line of distinction among nanoparticles and nanosponges is the difference in porosity and size. Nanoparticles have size in nanometer whereas nanosponges have pores in nanometers while their overall size can extend up to micrometers, and are usually smaller than 5μm. Many time nanosponges have been reported as nanoporous nanoparticles / microparticles. Nanosponges show diverse domains in their structure, since they have both hydrophobic and hydrophilic groups.



Advantages of Nano-sponge[5,6]

1. Targeted site-specific drug delivery.
2. Can be used to mask unpleasant flavors and to convert liquid substances to solids.
3. Less harmful side effects (since smaller quantities of the drug have contact with healthy tissue).
4. Nano sponge particles are soluble in water, so the hydrophobic drugs can be capsulated with in the nano sponge, after mixing with a chemical called an adjuvant reagent.
5. Particles can be made smaller or larger by varying the proportion of cross-linker to the polymer.
6. Production through fairly simple chemistry called "click chemistry"(methods for making the Nano sponge particles and for attaching the linkers).
7. Easy scale-up for commercial production.
8. The drug profiles can be tailored from fast, medium to slow release, preventing over or under-dosing of the therapy.

9. The material used in this system can provide a protective barrier that shields the drug from premature destruction with in the body.
10. Improved stability, increased elegance and enhanced formulation flexibility.
11. Nanosponges systems are non-irritating, non-mutagenic, non-allergenic and non-toxic.
12. These are self-sterilizing as the average pore size is 0.25µm, where bacteria cannot penetrate.
13. Hydrophobic drugs can be encapsulated within the Nano-sponge.
14. Extended release-continuous action up to 12 h.
15. Biodegradable.

Disadvantages

1. The main disadvantage of these nano-sponges is their ability to include only small molecules.
2. The nano-sponges could be either Para crystalline or in crystalline form. The loading capacity of nano-sponges depends mainly on degree of crystallization. Para crystalline nano-sponges can show different loading capacities.
3. The nano-sponges can be synthesized to be of specific size and to release drugs overtime by varying the proportion of cross linker to polymer.

Characteristic features of nanosponges [7]

- Nanosponges of specific size can be synthesized by changing the crosslinker to polymer ratio.
- They are nontoxic, porous particles, insoluble in most organic solvents and stable up to 300ºC. They are stable at the pH range of 1-11.
- They form clear and opalescent suspension in water.
- They can be reproduced by simple thermal desorption, extraction with solvents, by using microwaves and ultrasounds.
- Their three-dimensional structure allows capture, transportation and selective release of a variety of substances.
- Chemical linkers permit nano-sponges to bind preferably to the target site.
- By complexing with different drugs nano sponges can form inclusion and non-inclusion complexes.
- By adding magnetic particles into the reaction mixture, magnetic properties can also be imparted to nanosponges.

Mechanism of Drug Release [8]

The sponge particles have an open structure and the active is free to move in and out from the particles and into the vehicle until equilibrium is reached. In case of topical delivery, once the finished product is applied to the skin, the active that is already in the vehicle will be absorbed into the skin, depleting the vehicle, which will become unsaturated, therefore disturbing the equilibrium. This will start a flow of the active from the sponge particle into the vehicle and from it to the skin until the vehicle is either dried or absorbed. Even after that the sponge particles retained on the surface of stratum corneum will continue to gradually release the active to the skin, providing prolonged release overtime.

Factors affecting drug release from nanosponges [8]

- Physical and chemical properties of entrapped actives.
- Physical properties of sponge system like pore diameter, pore volume, resiliency etc.
- Properties of vehicle in which the sponges are finally dispersed.
- Particle size, pore characteristics, composition can be considered as imperative parameters.
- External triggers like temperature, pressure, and solubility of actives.
- **Pressure:** Pressure or rubbing can release active ingredient from Nanosponges onto skin.
- **Temperature:** Some entrapped actives can be too viscous at room temperature to flow spontaneously from sponges onto the skin but increased skin or environment can result in increased flow rate and ultimately drug release.
- **Solubility:** Sponges loaded with water soluble drug like antiperspirants and antiseptic release the ingredients in the presence of water.

Preparation of nano-sponges [9]

Nanosponges are prepared depending on type of delivery system, polymers and nature of drug and solvents. Various approaches used for formation of Nanosponges are:

Nanosponges prepared from hyper-cross linked β-cyclodextrins

β-cyclodextrin nano-sponges were prepared by placing 100ml of dimethyl formamide (DMF) in a round bottomed flask and 17.42g of anhydrous β-CD was added and shaken to achieve complete dissolution. Then 9.96g of carbonyl diimidazole (61.42m mol) was added and the solution was allowed to react for 4hrs at 1000°C. Once condensation polymerization was complete, the block of hyper cross linked cyclodextrin was roughly ground and an excess of deionized water was added to remove DMF. Finally residual by-products or unreacted reagents were completely removed by Soxhlet extraction with ethanol [10]. The white powder thus obtained was dried overnight in an oven at 600°C. The fine powder obtained was dispersed in water. The colloidal part that remained suspended in water was recovered and lyophilized. The obtained nano-sponges are sub-micron in dimension and with a spherical shape [11].

Polymerization

The polymerization process leads to the formation of a reservoir type of system, which opens at the surface through pores. A solution of non-polar drug is made in the monomer, to which aqueous phase, usually containing surfactant and dispersant to promote suspension is added. Polymerization is affected, once suspension with the discrete droplets of the desired size is established; by activating the monomers either by catalysis or increased temperature.

Quasi-emulsion solvent diffusion

The inner phase is prepared using Eudragit RS 100 and added to a suitable solvent. Drug to be incorporated is made into a solution and dissolved under ultrasonication at 35ºC. This inner phase added into external phase containing polyvinyl alcohol which acts as emulsifying agent. The mixture is then stirred at 1000-2000 rpm for 3hr at room temperature and dried in an hot air oven at 40ºC for 12hr [11].

Emulsion solvent diffusion method

Nanosponges can be prepared by using different proportion of ethyl cellulose and polyvinyl alcohol. The dispersed phase containing ethyl cellulose and drug was dissolved in 20ml dichloromethane and slowly added to a definite amount of polyvinyl alcohol in 150ml of aqueous continuous phase. The reaction mixture was stirred at 1000 rpm for 2hrs in a magnetic stirrer. The nano-sponges formed were collected by filtration and dried in oven at 40°C for 24hrs. The dried nano-sponges were stored in vacuum desiccators to ensure the removal of residual solvents [12].

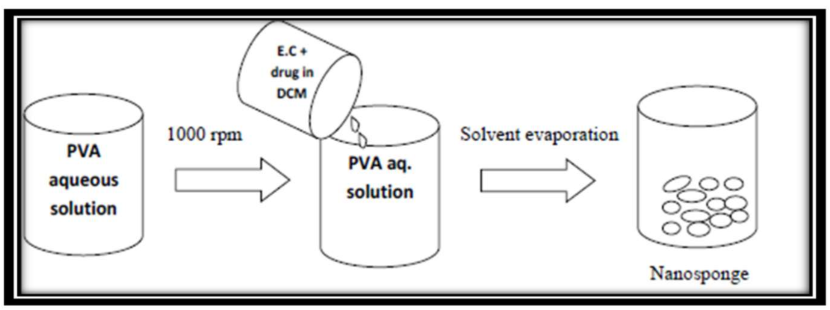


Fig 1: Preparation of nano-sponges by emulsion solvent diffusion method

Ultrasound- Assisted Synthesis:

In this method, polymers react with cross- linkers in absence of solvent and under sonication. Here, the polymer and cross- linker are mixed in a flask. Place the flasks in an ultrasound bath filled with water and heated to 90°C and then sonicate for 5 hrs. It was then allowed to cool and washed with water to remove the unreacted polymer. Dry the product under vacuum and store at 250°C [10].

Loading of drug into nanosponge

Suspend the prepared nano-sponges in water and sonicate to avoid the presence of aggregates and then centrifuge the suspension to collect the colloidal fraction. Separate the supernatant and then dry the sample by freeze drying. The aqueous suspension of nano-sponges was prepared and dispersed the amount of the drug to be loaded in it. Maintain the suspension under constant stirring for specific time required for complexation. After complexation, separate the un-complexed (undissolved) drug from complexed drug by centrifugation. Then obtain the solid crystals of nano-sponges by solvent evaporation or by freeze drying [11].

Polymers Used in Nano-sponge Preparation

There are various polymers and crosslinkers are used in the preparation of nano-sponges, listed in Table -1 Table -1

POLYMER	CO-POLYMER	CROSS LINKERS
• Hyper cross linked cyclodextrins • Alkyloxy carbonyl cyclodextrins • Methyl β – cyclodextrins • Hydroxy propyl β – cyclodextrin. • Ethyl cellulose	• Poly (Valero lactone allyl Valero lactone) • Poly (Valero lactone - oxepanedione) • Polyvinyl alcohol	• Carbonyl diimidazoles • Dianhydrides • Diaryl carbonate • Carbonate • Epichloridine • Glutaraldehyde • Pyromelliticanhydride,2,2 – bis (acrylamino) acetic acid • Dichloromethane

Characterization of nanosponges

Particle size determination:

The sizes of particles are maintained during polymerization for the formation of free-flowing powders having fine aesthetic appearance. Particle size analysis of loaded and unloaded nano-sponges can be carried out by laser light diffractometry or Malvern zeta sizer [13].

Determination of loading efficiency

The loading efficiency of prepared nano-sponge is determined by subtracting the un-entrapped drug from the total amount of drug. The un-entrapped drug must be estimated by any suitable method of analysis. The method used for separation of un-entrapped drug by gel filtration, dialysis and ultra centrifugation. The loading efficiency is calculated as:

$$\boldsymbol{Loading\ efficiency} = \frac{\boldsymbol{Actual\ drug\ content\ innanosponge} * \mathbf{100}}{\boldsymbol{Theoritical\ drug\ content}}$$

Compatibility Studies

The drug should be compatible with the polymers which are used for the preparation of nano-sponges. The compatibility of drug with adjuvants can be determined by Thin Layer Chromatography (TLC) and Fourier Transform Infrared Spectroscopy (FT-IR). Crystalline characteristics can be studied by powder X-ray diffraction (XRD) and Differential Scanning Colorimetry (DSC) [14].

Zeta Potential

Zeta potential is a measure of surface charge. The surface charge of Nano-sponge can be determined by using Zeta sizer [15].

Solubility studies

The most widely used approach to study inclusion complexation is the phase solubility method described by Higuchi and Connors, which examines the effect of a nano-sponge, on the solubility of drug. Phase solubility diagrams indicate the degree of complexation [16].

Drug release kinetics

To investigate the mechanism of drug release from the nano-sponge the release data was analyzed using Zero order, First order, Higuchi, Korsmeyer-Peppas models. The data can be analyzed using DD solver software. The software estimates the parameters of a non-linear function that provides the closest fit between experimental observations and non- linear function [17].

In-vitro release studies

In vitro release kinetics experiments are carried out using a multi compartment rotating cell. An aqueous dispersion of nano-sponges (1ml) containing the drug is placed in the donor compartment, while the receptor compartment separated by a hydrophilic dialysis membrane is filled with phosphate buffer of requires pH. The experiment is carried out for 24hr. At fixed time intervals, the receptor buffer is completely withdrawn and replaced with fresh buffer. The amount of drug in the medium is determined by the suitable analytical method and drug release is calculated to determine the release pattern [18].

Microscopy studies

Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) can be used to study the microscopic aspects of the Nano-sponges. The difference in crystallization state of the raw materials and the product seen under electron microscope indicates the formation of the inclusion complexes [19]

Swelling and water uptake [20]

For swellable polymers like polyamido-amine nano-sponges, water uptake can be determined by soaking the prepared Nano-sponges in aqueous solvent. Swelling and water uptake can be calculated using equations.

Resiliency (Viscoelastic properties) [20]

Resiliency of sponges can be modified to produce beadlets that is softer or firmer according to the needs of the final formulation. Increased crosslinking tends to slow down the rate of release. Hence resiliency of sponges will be studied and optimized as per the requirement by considering the release as a function of cross-linking with time.

Comparison of Some Effective Vesicular Systems [20]

Liposome, niosome, ethosome, transferosome and nanosponge are colloidal drug delivery systems. They all are nanometric in size. Liposome, noisome and transferosomes have some stability problems which is discuss below in table but Nanosponge enhanced the stability of drug.

Table 3: Comparison of Nanosponge with Vesicular system

Liposome	Niosome	Ethosome	Transferosome	Nanosponge
Liposome consist of one or more concentric lipid bilayers, which enclose an internal aqueous volume	Niosomes are non- Ionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants. With or without incorporation of cholesterol or other lipids.	Ethosomes are lipid vesicles containing phospholipids, alcohol(ethanol and isopropylalcohol)in relatively high concentration and water.	Transferosomes are vesicular system consisting of phosphatidyl choline and surfactants	Nanosponge are novel class of hyper-crosslinked polymer based colloidal structures consisting of solid nanoparticles with colloidal sizes and nanosized cavities.
The composition of liposomes is phospholipids and cholesterol.	They composed of non-ionic surfactants and cholesterol.	They composed mainly of phospholipids, high concentration of ethanol and water.	They consists of phospholipids and surfactants.	They composed of polymers and cross linkers.
Stability problems: due the formation of ice crystals in liposomes, the subsequent instability of bilayers leads to the leakage of entrapped material The oxidation of cholesterol and phospholipids also leads to the formulation instability.	**Stability problems:** fusion, aggregation, sedimentation and leakage on storage The Hydrolysis of encapsulated drug.	Ethosomes has initiated a new area in vesicular research for transdermal drug delivery which can provide better skin permeation and stability than liposomes. Application of ethosomes provides the advantages such as improved entrapment and physical stability.	**Stability problem:** chemically unstable because of their predisposition to oxidative degradation	Nanosponge are chemically and physically stable They increase the stability and bioavailability, modify drug release and reduce side-effects.

Marketed formulations

Marketed formulations of nano-sponges

Drug	Administration Route	Trade name	Dosage form
Dexamethasone	Dermal	Glymesason	Tablet
Iodine	Topical	Mena- gargle	Solution
Alprostadil	I.V	Prostavastin	Injection
Piroxicam	Oral	Brexin	Capsule

Applications of nanosponge

Topical delivery [21]

Local anesthetics, antifungal and antibiotics are among the category of the drugs that can be easily formulated as topical Nano-sponges. A wide variety of substances can be incorporated into a formulated product such as gel, lotion, cream, ointment, liquid, or powder.

Enhanced Solubility [21]

The Nano-sponge system has pores, that increase the rate of solubilization of poorly soluble drug by entrapping such drugs in pores. Due to nano-size surface area significantly increased and increase rate of solubilization.

Nano-sponge as chemical sensor [21]

Nano-sponges which are the type of “metal - oxides” act as a chemical-sensors which is used in highly sensitive detection of hydrogen using Nano-sponge titania. Nano-sponge structure initially have no point of contact so there is less hinderance to electron transport and it results in higher 3D interconnect Nano-sponges titania which is sensitive to H2 gas.

Nanosponges in Drug Delivery[21]

Nanosponges have spherical shape and nanometric in size making them ideal in preparing various dosage forms like topical, parenteral, aerosol, tablets and capsules. It is found that highest solubility and in vitro drug release is observed in inclusion complex.

Nanosponges for Protein Delivery

The major obstacle in protein formulation development is the maintenance of the native protein structure both during the formulation process and upon the long - term storage. The nanosponges were found to be stable at 300°C and high protein complexation capacity was also observed.

Nanosponges in Enzyme Immobilization[22]

The enzyme immobilization is particularly relevant for lipases, as it improves their stability and modifies properties like enantioselectivity as well as the reaction rates. As a consequence, the demand for new solid supports, suitable for family of enzymes is constantly growing.

Nanosponges as a Carrier for Delivery of Gases[20]

Hypoxia (deficiency of adequate oxygen supply) is related to various pathologies, from inflammation to cancer. Sometimes it can be difficult to deliver oxygen in appropriate form and doses in clinical practice. Nanosponge formulations were developed as oxygen delivery systems for topical application which were having the ability to store and to release oxygen slowly over time.

Nano-sponges as Protective Agent -against Photo Degradation[23]

Nano-sponges were prepared by encapsulating gamma-oryzanol showing a good protection from photodegradation. Gamma-oryzanol (a ferulic acid ester mixture), an anti-oxidant and usually employed to stabilize food and pharmaceutical raw materials, moreover, used as a sunscreen in the cosmetics industry. Its applications are limited due to its high instability and photodegradation. With the gamma oryzanol loaded nanosponges a gel and an O/W emulsion are formulated.

Modulating Drug Release[24]

A drug loaded into the nanosponge is retained and released slowly over time. Hydrophilic nanosponges are employed to enhance the drug absorption across biological barriers, to modify the drug release rate and as a potent drug carrier in immediate release formulations. Hydrophobic nanosponges are utilized as sustained release carriers for water soluble drugs, including peptide and protein drugs and they protect the drug during its passage through the stomach. This drug is released very slowly at pH 1.1, whereas release is faster if pH is raised to 7.4.

Used as Taste masking agent.[24]

Future aspects

Nanosponges have a bright future ahead of them in medicine delivery and other uses. The versatility of nanosponges in encasing a broad range of substances, along with the progress made in nanotechnology, indicate that this technology has the potential to transform a number of industries, including catalysis, pollution management, and targeted medicine delivery. More research is probably needed to improve their loading capacity, stability, and selectivity, which will result in more effective medication formulations, particularly for the treatment of complicated illnesses like cancer and neurological disorders. Furthermore, investigating the possibilities of magnetic and metal-organic framework (MOF) nanosponges may lead to novel applications in medicine and diagnosis. Nanosponges are essential to the advancement of advanced personalised medicine because of the possibility of using them in protein and gene delivery systems as they improve.

CONCLUSION

In conclusion, nanoparticle technology has advanced with the development of nanosponges, which provide a flexible and effective platform for drug delivery among other uses. They are a vital technique in contemporary pharmaceutical development because of their capacity to increase the solubility, stability, and bioavailability of poorly soluble medicines while lowering side effects through targeted delivery. Nanosponges have the ability to be produced on a massive scale and are easily synthesized, which makes them a promising tool for both industrial and therapeutic applications. Wide-ranging uses and advancements in nanosponges will surely lead to better treatment tactics as well as solutions for industrial and environmental concerns as research proceeds.

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