REVIEW ARTICLE

A Narrative Review on Drug Loaded Nanosponges as a Carrier for Drug Delivery

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ABSTRACT

Long-term attempts to create efficient, targeted medication delivery systems have been delayed by the complexity of the chemical interactions required to build drug delivery systems. Colloidal nanosponges may be adapted to operate with hydrophilic or hydrophobic medicines. This implies that issues with medicine toxicity, reduced bioavailability, and widespread drug release might all be addressed. A nanosponge is a microscopic sponge that can navigate its way to the required location within a living organism. The drug is gently released as the patch clings to the skin of the afflicted region. The nanosponge's porous construction allows it to trap drug molecules and release them gradually. Perhaps the most exciting development in the pharmaceutical industry is the nanosponge drug delivery device (NSDDS). This review aims to give readers an in-depth look at how nanosponges are made, evaluated, and put to use in the medical field.

Keywords: Controlled release, Crosslinking, Nanosponges, Cyclodextrins.

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INTRODUCTION

Some have even said that nanotechnology is more revolutionary than the Industrial Revolution itself. In addition to nanoparticles, nanocapsules, nanospheres, nanosuspensions, nanocrystal, and nano-erythosomes have all been created thanks to nanotechnology. Nanoscale fabrication and modification techniques enable nanotechnology to produce unique materials and devices. At this time, nanomaterials are the subject of intensive study. In 1959, Caltech physicist Richard P. Feynman provided an informed opinion on the topic of nanomaterials. He argued that the key to the future of nanotechnology was to start small and work up from the nanoscale. Any substance with at least one dimension between 1 and 100 nm is considered a nanomaterial. Biocompatible materials, functionalized textiles, UV-protective coatings, and agents that speed up the killing of germs, carry medicines, transfer DNA, and immobilize enzymes are just some of the many products that make use of nanoparticles.[1]

For quite some time, the administration method of desired medications has been the focus of such efforts. Like other modern medicines, nanosponges may be injected or taken orally in the 21st century. Nanosponges were originally developed for topical (skin) medication administration (IV). A nanosponge, a contemporary material, consists of very small particles that are closely packed together. Many items can be stuffed into these little spaces. The microscopic particles may carry both hydrophilic and lipophilic drugs. Drugs and other chemicals that don't dissolve easily in water are stabilized in this manner. The nanosponges are likely to decompose in live organisms since they are constructed from a polyester network or a three-dimensional scaffold. These polyesters and a cross-linker are combined in a liquid form to create Nanosponges. Polyester is biodegradable. Therefore, it disintegrates when ingested. Toxic drug molecules are released when the framework of the nanosponges breaks down.[2]

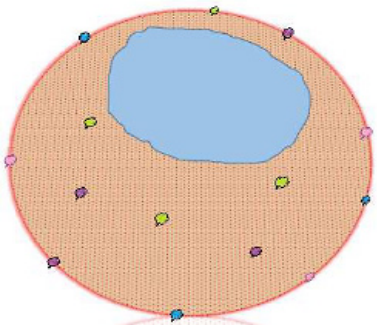

Figure 1: Nanosponges with a cavity for drug loading, structurally.

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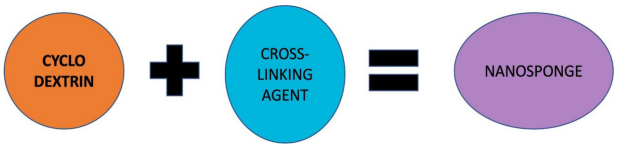

Figure 2: Formation of Nanosponges.

Nanosponges are a new type of hyper-cross-linked polymer-based colloidal structure consisting of solid nanoparticles with colloidal and nanosized cavities (Figure 1). Examples (Table 1) of well-known nanosponges include those made of hyper-cross-linked polystyrene, silicon nanosponge particles, titanium nanosponges, and cyclodextrin. Changes in the pharmacokinetic characteristics of the active components are responsible for the increased bioavailability of drugs when delivered on nanosponges. This is achieved by improving the solubility of pharmaceuticals in water, so facilitating a controlled release over time. The hydrophobic inside of a nanosponges chamber contrasts with the hydrophilic outside, making it capable of transporting both hydrophilic and hydrophobic medicinal substances. Nanosponges are constructed from a scaffold or network that extends in three dimensions. In order to create nanosponges, polyesters (cyclodextrins) are blended with crosslinking agents (Figure 2) to form a unique nanostructured material.[3]

Changes in the cyclodextrin-to-cross-linker ratio during preparation may boost drug load capacity and provide for a tailorable release profile. The nanometric structure of nanosponges is far more permeable than that of their parent cyclodextrin molecules, allowing for inclusion and non-inclusion interactions between drug molecules. This implies that more illicit substances can be carried. Nanosponges are made of solids in nature. Due to their shown safety for intravenous and oral administration, they may one day serve as natural drug carriers. Because of their diminutive size, nanosponges may be administered through the respiratory and cardiovascular systems. Mixing the drug with an excipient matrix makes it orally bioavailable (diluents, lubricants and anti-caking agents). The complex dissolves quickly and cleanly in sterile water, saline, or other aqueous solutions for parenteral administration. They combine nicely with hydrogen for dermal delivery. The nanosponge's centre core is enveloped with drug-carrying nanoparticles. The nanosponge travels through the body, attaches to the target, and then slowly releases the medicine.[4]

Characteristic Features of Nanosponges

- Nanosponges come in different sizes (1-µm or less), and the polarity of the cavities can be changed.
- Changing the amount of cross-linker to polymer makes it possible to make nanosponges of a certain size.
- Depending on how they are made, they can be either paracrystalline or crystalline. The way nanosponges are made of crystals is very important during complexation with drugs.
- The amount of crystallization affects the amount of drug that can be loaded.
- Paracrystalline nanosponges can show how much of a drug they can hold.
- They are porous particles that are not toxic, don't dissolve in most organic solvents, and are stable up to 300°C.
- They are stable at pH levels between 1 and 11.
- In water, they make a clear and cloudy suspension.
- They can be made again with simple thermal desorption, solvent extraction, microwaves, and ultrasonic waves.
- Because they are three-dimensional, they can hold, move, and release different substances in a controlled way.
- Because they can connect to different functional groups, they can be put in many different places.
- Chemical linkers make it possible for nanosponges to stick to the target site.
- Nanosponges can make both inclusion and non-inclusion complexes by binding to different drugs.
- When magnetic particles are added to the reaction mixture, nanosponges can also take on magnetic properties.[5,6]

Advantages of Nanosponges

- Make the drug that doesn't dissolve well in water dissolve better.
- Nanosponges can let the drug molecules out in a way that can be predicted.
- Because the pores in nanosponges are so small (0.25 µm), bacteria can't get through them. This makes them act like self-sterilizer.
- Nanosponges are non-irritating, don't cause mutations, and are safe to use.
- Nanosponges help get rid of poisonous and poisonous substances in the body.
- Nanosponges are a system for delivering drugs that reduces side effects.
- Increase the stability of the formulation and make it more flexible.
- Reduce dosing frequency. Better patient compliance.
- Nanosponges complexes are stable at temperatures of 130°C and pH levels from 1 to 11.

Disadvantages of Nanosponges

- Nanosponges can encapsulate small molecules but aren't good for encapsulating larger molecules. Sometimes, dose dumping can happen.[7]

PREPARATION METHODS FOR NANOSPONGES

Solvent Method

Polymers are mixed with polar aprotic solvents like dimethyl sulfoxide (DMSO) and dimethylformamide to make Nano sponges (DMF). Then, the cross-linker is applied at a 1:4 ratio. In order to raise the temperature of the solvent, the aforementioned reaction must be conducted at 10°C for 1 to 48 hours. After the product has been cooled to room temperature, it is diluted with bi-distilled water. After being recovered from the vacuum filter, the product is cleaned with Soxhlet extraction and ethanol before being dried.[8]

Emulsion Solvent Diffusion Method

To create nanosponges, ethyl cellulose and polyvinyl alcohol are mixed together in different concentrations. This strategy involves combining and separating phases. The medication is combined with ethyl cellulose to create a dispersed phase. Adding 20 mL of dichloromethane and some polyvinyl alcohol (PVA) turns the dispersed phase into the continuous phase (aqueous). After that, it's agitated for around two hours at a speed of 1,000 rpm. The final result is nanosponges, which are obtained by filtering. The last stage is drying in a preheated 400°C oven.[9]

Ultra-sound Assisted Synthesis

A flask is all that's needed for a reaction between cross-linkers and polymers, and no solvent is required. The flask containing the mixture is placed in an ultrasonic bath containing water heated to 90°C, and sonication occurs there for 5 hours. After the material has cooled to normal temperature, it is divided into smaller pieces. The non-reactive polymer is removed during rinsing, and the ethanol used to create the nanosponges is refined using a Soxhlet apparatus.[10]

Loading of Drugs into Nanosponges

To create particles smaller than 500 nm in size, nanosponges must undergo pre-treatment. Here, nanosponges are dissolved or kept in water. So that the nanosponges in suspension don't clump together, they are sonicated vigorously. A limited number of colloidal particles may be created by rotating the fluid. The sample is freeze-dried after the supernatant has been removed. Aqueous solutions are used to create nanosponges. Too much of the medication is added to the suspension, and it is then agitated frequently over a certain period of time in order to ensure that it is evenly distributed. The complex drug is then separated from the simple drug using centrifugation, which follows complexation. Crystals of nanosponges may be formed in two ways: by freezing the material or by evaporating the solvent. The solid crystalline structure plays a crucial role in how well the medicine is attached to these nanosponges. Comparatively, crystalline nanosponges have a higher drug-loading capacity compared to their paracrystalline counterparts. Nanosponges with weakly crystalline structures are blended by hand during the drug loading procedure.[11]

Nanosponges Characterization

Solubility Studies

The dissolution and bioavailability of medicine may be modulated with the use of inclusion strategies. The solubility method is often used to investigate NS inclusion complexes. Phase solubility plots are typically calculated using the degree of completion. Solubility assays may be performed to determine how drugs dissolve, what variables impact their solubility, and the pH of molecules.[12]

Microscopic Analysis

The drug within the nanosponge is examined using transmission electron microscopes and scanning electron microscopes. The appearance of the combination and the many stages of crystallization under the microscope indicate that it was created *via* a multistep process.

Zeta Potential Determination

The zeta potential is significant because it describes the potential difference between the immobile boundary layer and the fluid-spreading medium. The stability of the colloidal dispersion in the sample may be evaluated by measuring the zeta potential. By connecting an additional electrode to the zeta seizer, zeta potentiation may be measured.

Thermodynamical Method

If the shape of the drug particles changes, thermal nanosponges will destroy the molecules *via* heat. Polymeric oxidation, melting, breakdown, and evaporation are often used in the exchange of drug chemicals.[13]

Polydispersity and Particle Size

The particle size may be calculated in 90 Plus by using dynamic light scattering. The distribution of nanoparticle sizes may be determined by dynamic light scattering (DLS). Finally, the final particle diameter and poly-dispersity index (PDI) are often assessed.

TLC Studies

A key advantage of thin-layer chromatography is the ability to separate combinations that evaporate fast or not at all. Using this technology, it is possible to gauge the effectiveness of the combination of Nanosponges and medication by measuring the RF value change of certain drug particles.

Infrared Spectroscopy

We can identify the solid-state connection between the Nanosponges and the active chemical using IR spectroscopy. Since the drug molecules are already in a solid state, IR spectroscopy may be employed to characterise them. Some particle bands in NSs might be altered with the use of composites. The nanosponges' spectra frequently merely covers some of the 25% of guest particles that are a component of the composite and drug spectra. Differentiating the participation complex from other approaches is not dependent on the chosen technique.[14]

Loading Efficiency

Ultraviolet spectroscopy coupled with the HPLC method for nanosponges is often used to evaluate the loading capacity of a nanosponge after a drug has been encapsulated inside it.[15]

Nanosponge's Applications

Because of their biocompatibility and adaptability, nanosponges offer a wide range of potential uses in the pharmaceutical industry. The examples are as follows.

Solubility Enhancement

The nanosponges structure, which includes crosslinking agent and cyclodextrin chambers, facilitates facile interaction with active compounds. As a result of these characteristics, the perforations may be used to facilitate the dissolution of a wide variety of substances. Without altering the drug's

crystalline structure, the solubility or rate of dissolution of pharmaceuticals that don't dissolve well in water may be improved by creating inclusion complexes or solid dispersions with cyclodextrins. When the hydrophobic components of the complex are encapsulated inside the cyclodextrins internal cavity and the hydrophilic hydroxyl groups on the exterior are left exposed, a water-soluble complex is formed. A group led by Swaminathan investigated itraconazole nanosponges. More than a 27-fold improvement in drug solubility was seen after using nanosponges, and an additional 55-fold improvement was observed after adding copolyvidonum to the nanosponge combination. Nanosponges may have improved itraconazole surface adhesion and/or reduced its crystalline structure by masking the drug's hydrophobic components.[16]

Use of Nanosponges in Drug Delivery

Topical, parenteral, aerosol, tablet, and capsule dosage forms may all benefit from using nanosponges in their production. This is due to the fact that they are nanometric in size and have a round shape. The nanosponges contain the drug telmisartan. The inclusion complex has been proven to be the most soluble and to have the most effective drug release *in-vitro.* Cancer drug paclitaxel does not dissolve in liquid. Nanosponges based on B cyclodextrin are utilized to administer paclitaxel rather than cremophor EL since the latter hinders the drug's penetration into the tissue. The quantity of paclitaxel inside the cells is much increased after 72 hours of incubation compared to when using simple paclitaxel. Consequently, paclitaxel's biological activity in test tubes is significantly enhanced. Topical econazole nitrate is used for dermatophytosis, superficial candidiasis, and other skin diseases. Not much of the econazole nitrate you apply to your skin will really absorb. High concentrations of the medicine's active components are required for therapy to take effect. Nanosponges of econazole nitrate are prepared using the solvent diffusion emulsion process, and the resulting particles are subsequently enveloped in hydrogel to serve as a local depot for sustained drug release.[17]

Protein Delivery by Means of Nanosponges

Formulating proteins is challenging since it is difficult to maintain the protein's natural structure during the formulation process and long-term preservation. Nanosponges 10 and 11 are novel expandable cyclodextrin-based poly (amidoamine) nanosponges that were named by Swaminathan *et al.* In order to create them, -cyclodextrins were crosslinked with either 2, 2-bis-acrylamido acetic acid or a short polyamido-amine chain composed of 2, 2-bisacrylamido acetic acid and 2-methyl piperazine. Nanosponges based on cyclodextrin exhibited high thermal stability (300°C) and protein complexation capability.

Nanosponges in Enzyme Immobilization

Lipases benefit greatly from immobilization since it increases their stability and modifies their enantioselectivities and reaction speeds. This highlights the growing need for alternative, enzyme-friendly solid supports. Boscolo *et al.* demonstrated that a novel form of cyclodextrin-based nanosponges enhanced the catalytic activity of Pseudomonas fluorescent lipase.[18]

Gases Delivery by Nanosponges as a Carrier

Medicinal gases, both diagnostic and therapeutic, play a crucial role in patient care. Different disorders, including as cancer and inflammation, have been related to hypoxia. Providing the correct dose of oxygen in a therapeutic setting might be challenging. In order to make oxygen topical, Cavalli *et al.* created nanosponge combinations that could store and gradually release oxygen.

Table 1 : Formulations examples along with their route of administration and category

Drug	*Route of administration*	*Category*	*Methodology[1-23]*
Nateglinide	Oral	Anti-diabetic	Ultra sound assisted synthesis
Trimethoprim	Oral	Antibacterial	Freeze drying
Miconazole nitrate	Topical	Antifungal	Solvent evaporation
Lemmongrass	Topical	Antipyretic	Emulsion solvent evaporation
Glipizide	Oral	Anti-diabetic	Solvent evaporation
Flurbiprofen	Oral	Anti-inflammatory	Solvent evaporation
Voriconazole	Oral and Topical	Antifungal	Solvent evaporation
Omeprazole	Oral	Anti-ulcerative	Emulsion solvent diffusion
Econazole nitrate	Topical	Broad-spectrum anti-mycotic agent	Emulsion solvent diffusion
Telmisartan	Oral	Anti-hypertensive	Solvent evaporation
Lamotrigine	Oral	Antiepileptic	Emulsion solvent diffusion
Nystanin	Topical	Antifungal	Solvent emulsion evaporation
Gammma-oryizanol	Topical	Antihypertensive	Solvent evaporation
Ketoconazole	Topical	Antifungal	Solvent evaporation
Lansoprazole	Oral	Proton pump inhibitor	Emulsion solvent diffusion
Clotrimazole	Topical	Antifungal	Emulsion solvent diffusion

Protective Agent against the Photo Degradation

According to Sapino *et al*., the antioxidant gamma-oryzanol is employed as a sunscreen in the cosmetics and food and pharmaceutical industries. Due to its extreme instability and photodegradation, it has few practical applications. Nanosponges made from encapsulated gamma-oryzanol are a potent defence against the damaging effects of ultraviolet radiation. A gel and an O/W emulsion may be created by using nanosponges loaded with gammaoryzanol.[19]

Modulating Drug Release

The frequent dosing required by most conventional drug administration methods now on the market is a major drawback of these techniques. However, when placed within a nanosponge, the medicine remains there and slowly seeps out over time. As reported by Vyas *et al.,* Hydrophilic cyclodextrin nanosponges are utilised as a potent drug carrier in fast release formulations to modify the drug's release profile and facilitate its transport over biological barriers. Medications like doxorubicin, peptide, and protein medications need prolonged release carriers, and hydrophobic cyclodextrin nanosponges fit the bill. They serve to shield the medicine from stomach acid. This medication is delivered extremely gradually due to its pH value of 1.1. In contrast, the release rate increases with a pH of 7.4.[18,19]

Effective Delivery Carriers

Some cancer medications, including paclitaxel, camptothecin, and tamoxifen, may be more easily absorbed and used by the body if cyclodextrin nanosponges are employed as carriers. According to Torne *et al.,* drugs placed in nanosponges and tested on many cell lines inhibited the development of new cells. Drug combinations were more effective than the individual medicines in this study. Bioavailability of paclitaxel was found to be 2.5 times higher when the medication was encapsulated inside a nanosponge as opposed to being administered without one.[20]

Other Applications of Nanosponges

Nanosponges based on cyclodextrin are effective in removing organic molecules from water, and they do so even at minute concentrations. The selected polymer and cross-linker combination may also be employed to aid in the removal of bitter components in grapefruit juice. Through the use of micro porous, hyper-cross-linked nanosponges, size exclusion chromatography may be employed to achieve high-resolution separations of inorganic electrolytes. In order for peptides to be useful in proteomic applications, they must be fragmented. For medical diagnosis, biomarkers might be absorbed by nanosponges. It has been suggested that a nanosponge can extract a rare cancer signal from human blood.[21]

Patents

In 2021, Patent is granted to Dr. Sankha Bhattacharya for the Invention on a method for preparation of gemcitabine loaded cyclodextrin nanosponges and a combination thereof.

Another Patented inventions in relation to nanosponges are 'Method for preparing dextrin nanosponges' by Francesco Trotta and 'Silicon nanosponge particles' by Declan Farrell.[22-25]

SUMMARY AND CONCLUSION

Nanosponges are a novel kind of biocompatible, flexible drug carriers due to their capacity to form inclusion and non-inclusion complexes with hydrophilic and hydrophobic medications. The medications are administered intravenously, topically, or orally. Nanosponges improve the medicine's bioavailability by targeting and delivering the drug precisely where it's needed. Both the particle size and the rate of release may be tailored to the task at hand by adjusting the polymer to crosslinking agent ratio. Nanosponges may protect lipophilic drugs from physical and chemical degradation while also increasing their water solubility. These materials have been shown to be effective for novel medication delivery methods and the immediate use of technological solutions for drug capture. This method has applications beyond only drug delivery, including cosmetics, biomedicine, bioremediation, agro chemistry, catalysis, etc. The pharmaceutical industry might benefit greatly from clinical studies demonstrating the safety of medications administered using nanosponges in humans.

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