A Review on Nanosponge: An Effective approach for Novel drug delivery system

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Abstract:
Crosslinking polymers results in nanosponges, which are drug carriers that are nanoscale and have a three-dimensional structure.Nanosponges may offer targeted drug delivery along with a regulated drug release pattern, nanosponges are better than alternative delivery methods. Both the duration of action and the duration of the drug's residency can be controlled. It is safe to use and has a minimal toxicity because it is composed of biodegradable components. The size of the medicine determines how well it is encapsulated. Molecule and the quantity of accessible vacant space. Applications for nanosponges include cancer, oxygen delivery, enzyme and biocatalyst transport, solubility improvement, enzyme immobilization, and toxin absorption and others.

Key Words
Bioavailability, Controlled release, Drug delivery, Nanosponges, Oral delivery, Solubility enhancement.

Introduction:
Nanosponges are tiny structures that resemble meshes and can contain a wide range of materials, including drug compounds. Their spherical colloidal structure allows them to improve the solubilization of both lipid-soluble and water-soluble medicines. They improve the bioavailability of medications with extended release.[1]With a void space of 5–300 µm and a diameter of 10–25 µm, NSs are superior than microsponge since the latter have a diameter of less than 1 µm. Micro sponges are stiff but break down once the temperature reaches 130°C. In contrast, these NSs are robust up to 300°C.[2] to improve drug loading and provide a personalized solution, the ratio of cross-linking to cyclodextrin can be altered during preparation.[1]

Fig: 1 (Nanosponges Diagram)

Silent Features of Nanosponges:

- Nanospones have configurable cavity polarity and a range of sizes (1 µm or less).
- They can be regenerated by straightforward thermal desorption, solvent extraction, microwave and ultrasonic methods, and by forming transparent and opalescent suspensions in water.[3]
- A wide range of compounds can be captured, transported, and selectively released to a particular area thanks to their three-dimensional structure.[4]

Types of Nanosponges:

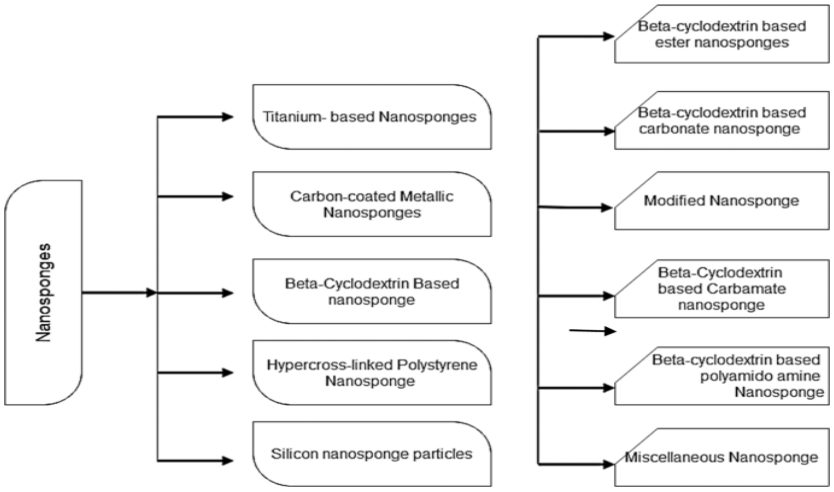

Fig: 2 (Types of Nanosponges) [5]

MATERIALS USED IN SYNTHESIS OF NANOSPONGES:

- **Polymer**:
  The nanosponge's cavity size should be appropriate for complexation in order to hold a single molecule of a specific size. The functional groups and active groups that need to be changed determine the polymer's capacity for cross-linking. The medicine to be encapsulated and the necessary release determine which polymer is best. **Ex-** Hyper cross linked polystyrenes, Cyclodextrin and its derivatives.
- **Co-polymers:** Ethyl cellulose, polyvinyl alcohol, Poly (Valerolactone allylvalerolactone.
- **Cross-linkers:** The medicine to be formulated and the polymer's structure determine which cross linkers should be used. **Ex:** Carbonyl diimidazoles, Carboxylic acid dianhydrides.
- **Drug substances:**
  A molecular weight of 100–400 Dalton's.
  There are less than five condense rings in a drug molecule
  It is less than 10mg/ml soluble in water.
  The substance's melting point is lower than 250°C.[6]

Methods of formulation of nanosponges:

Quasi-emulsion solvent diffusion:

In this method the inner phase was prepared by dissolving Eudragit RS100 in an appropriate solvent. Then, drug can be added to the solution and dissolved under ultra-sonication at 350 c. The inner phase was poured into the PVA solution in water (outer phase) and allowed for stirring for 1 hr., then the mixture is filtered to separate the nanosponges. The nanosponges are dried in an air-heated oven at 40°C for 12 hrs.[7]

Solvent method:

Combine the polymer with an appropriate solvent like Dimethylformamide and others. This combination should then be added to excess cross-linked, ideally in a cross-linked polymer molar ratio of 4 to 16. For 1-48 Hrs. conduct the reaction at temperatures between 100°C and the solvent's reflux temperature. Dimethyl carbonate and carbonyldi imidazole. Allow the solution to cool, then add a significant amount of bid stilled water to recover the product using vacuum filtration and then purify it using a protracted Soxhlet process.[8]

Hyper cross-linked method:

In a round-bottomed flask, 17.42 g of anhydrous-cyclodextrin and 100 ml of anhydrous Dimethyl Formamide were added. The liquid was gently swirled until it was completely dissolved. After adding 9.96 g of carbonyl imidazole to this mixture, the reaction was run for four hours at 100 °C. After condensation polymerization is complete, a hyper-cross-linked cyclodextrin is produced in the Round Bottom Flask. To remove any extra Dimethyl Formamide from the combination above, a large amount of deionized water should be added. Lastly, unreacted compounds are removed via Soxhlet extraction based on ethanol.[9]

Microwave irradiation method:

This method reduces a four-fold decrease in reaction time compared to traditional heating methods and also produced homogeneous particle size distribution with uniform crystallinity. Singireddy et al. performed an experiment to ascertain beneficial effects of microwave-assisted heating in comparison to conventional heating during the synthesis of CD-based NSsAccording to the research's findings, NSs made with microwave assistance have increased the model drug's drug-holding ability. According to the results of high resolution-transmission electron microscopy (HR-TEM), the NSs produced by microwave synthesis were extremely crystalline, exhibited a limited size distribution, and a higher degree of complexity.[10]

Comparison between different preparation methods of Nanosponges on the basis of different physicochemical properties.

Methods	**Parameters**				
	Particle size	**Shape of particle**	**Stability**	**Zeta Potential**	**Reference**
Quasi emulsion solvent diffusion	152.355 nm	spherical shape	Stable.	-0.106 to -9.75 mV.	**[11]**
Ultrasound-assisted synthesis	405.46±30 nm	Sponge like structure favorable for greater drug loading.	Physically stable	-18.75±1.8	**[12]**
Solvent method	316.4 ± 8.5 nm	spherical	stable at 40 °C for 3 months	− 18.5–– 11.8	**[10]**
Hyper cross-linked method	68.55 ± 2.35	Approximately spherical	Stable at 4 ˚C up to 6 months	−24.75 ± 1.8	**[13]**
Microwave irradiation method	198.3 ± 1.7 nm	Spherical shaped	Stable	8.69 ± 0.36 mV	**[14]**
Polymerization	190 ± 20 nm	Spherical	Stable	-	**[15]**

FACTORS AFFECTING THE FORMATION OF NANOSPONGES:

Types of polymers and Cross linkers:

Low column efficiency for enantioseparations in capillary liquid chromatography (CLC) is a major problem commonly encountered with β-cyclodextrin (β-CD) functionalized polymer-based monoliths. Monomer units of various chemical types are arranged in an orderly fashion to generate macromolecules known as sequence-controlled polymers. **Example**: Methyl β-cyclodextrin, Hydroxy propyl β-cyclodextrin..[16]

Many-component monovalent polymers can be used to combine beneficial properties like dynamicity and innovative functionality.

Example: Ethyl cellulose, polyvinyl alcohol.[17]

Types of drug:

- Drug molecule consists of less than 5 condensed rings.
- It dissolves less than 10 mg/ml in water. And so many others properties.[18]

The drug's mass should range from 100 to 400 Da, and melting point should be less than 250 °C.[19]

Cross-linking substitute degree:

The degree of crosslinking is closely related to the number of substitutions present. The likelihood that crosslinking may occur rises in proportion to the amount of substituents. A mesh-like network is formed as a result of a higher degree of cross-linking, which produces highly porous nanosponges.[20]

Natures Complexity*:* Temperature variations have an impact on the drug and the Nano sponge complexation. The drug's consistency remains constant as the temperature rises, and the nanosponges.[21]

Nano sponge's characterization:

Solubility Studies: The phase solubility method, as outlined by Higuchi and Connors, is the most used technique for studying inclusion complexation. It looks at how nanosponges affect the solubility of drugs. Diagrams of phase solubility show the level of complexation. To ascertain the medication concentration, high performance liquid chromatography was used to analyze the resulting solution.[22]

Microscopic Studies:

The NIH was utilized to measure the particle size using a Philips CM 10 transmission electron microscope. Program for images. Before being observed, formvar-coated copper grid was sprayed with diluted nanosponge aqueous solutions and allowed to air dry.[23]

Thermodynamic studies:

Using thermal analysis, the melting point (Tm), temperature for crystallization (Tc), degree of crystallinity (Xc), and pure medicine are all defined.[24]

Polydispersity index (PDI): The zeta potential provides a clear indication of the lipid nanocarrier's surface charge. The lipid carrier's positive value causes it to interact with the biological membrane's negative charge, increasing cellular absorption.[25]

Thin Layer Chromatography (TLC): TLC helps assess the formation of complexes between the drug and nanosponges by lowering the retention factor (RF) value of a medicinal component to a significant range.[26]

Percentage yield, Drug Loading Efficiency, Infra-red (IR) Spectroscopy, In Vitro drug release, Powder X-ray diffraction experiment, Thermal Analysis, Raman Spectroscopy, Stability Study are also characteristics of nanosponges.[27-33]

RECENT ADVANCEMENT IN NANOSPONGES:

1) **Project Name:** Design and development of nanosponge loaded topical gel of cur cumin and caffeine mixture of augmented treatment of Psoriasis

Finding Note: According to the findings, the combination of CUR and CFN has shortened the amount of time needed to demonstrate anti-psoriatic efficacy to 10 days as opposed to about 20 days with CUR alone.

Conclusion: According to the trial results, the combination of CUR and CFN considerably increased the anti-psoriatic efficacy compared to the individual components and shortened the time needed for the effect to start. **[Published year2020]**[34]

2) **Project Name:** Systematic development and characterization of cur cumin-loaded Nano gel for topical application

Finding Note: In contrast to the dispersed gel, the CUR-loaded Nano gel had a greater delayed release, suggesting a longer duration of activity.

Conclusion: Because of its capacity to improve medication permeability in the skin and lengthen contact time with the skin, which results in better hydration and simplicity of administration, the current formulation may prove to be a viable substitute for traditional formulations like creams and gels. **[Published year2020** [35]

3) **Project Name:** Preparation and characterization of cyclodextrin Nano sponges for organic toxic molecule removal.

Finding Note: NS has several potential applications, including as medication delivery, transporting gasses and biocatalysts, immobilizing enzymes, and adsorbing harmful substances.

Conclusion: Toxic compounds were extracted from the GI fluids by synthesizing NS derivatives with β-CD and various cross linkers. It was demonstrated that they were successful in adsorbing the simulated hazardous chemical indole. With a high indole adsorption capacity of over 90%, toluene diisocyanate cross-linked CD-NS in particular showed promise in ridding the body of harmful substances. **[Published year2020** [36]**]**

4) **Project Name:** Formulation and ***in vitro*** evaluation of topical nan sponge-based gel containing butenafine for the treatment of fungal skin infection**.**

Finding Note: Since the nanocarrier may be able to penetrate the skin layer more deeply than conventional topical semisolid preparations, the nano-based gel formulation is perfect for the efficient treatment of fungal infections.

Conclusion: The discovered BTF loaded NS impregnated carbopol polymeric gel may be an effective antifungal drug delivery system (DDS) for treating fungal infections by maintaining drug release, which lowers the frequency of dosage and the recurrence of SFI. **[Published year2021**[37]**]**

Applications of Nanosponges:

- **Enzyme Immobilization:** In order to stabilize the enzyme, nanosponges have been utilized extensively. Compared to CD, CD-NS exhibits much higher inclusion constants and can be used to assist enzyme immobilization.[38]
- **Nanosponges as a Carrier for a biocatalysts:** Nanosponges act as carriers in the transmission of proteins, enzymes, vaccinations, and antibodies All of the restrictions such as Non-specific reactions, downstream process, temperature can be eliminated or significantly reduced by using enzymes as biocatalysts.[39]
- **In Covid:** Recent developments in Nano science and nanotechnology have brought about dramatic change in several study fields, most notably medicine. With encouraging inhibitory effects for biological neutralization and antiviral medication delivery applications, nanosponges have been used against SARS-CoV-2.[40-41]

- **Protective effect against light or Other Chemicals:**
  BO's (Babchi oil's) encapsulation in nanosponges produced an effective carrier system that improved the oil's solubility, photo-stability, and safety in addition to its handling qualities.[42]
- **IN Cancer:** The latest developments in drug delivery and the potential of Nano sponges (primarily cyclodextrin-based, DNAzyme, and ethyl cellulose Nano sponges) for cancer therapy are discussed here, with an emphasis on the significant obstacles and prospective directions for the future.[43]
- **In blood poison:** As all pathological agents must interact with host cells for bioactivity, nanospongesthe therapeutics design. Since all pathogenic agents need to interact with host cells in order to be bioactive, nanosponges circumvent the variety of these agents and provide neutralizing solutions that are both function-driven and broad-spectrum.[44]
- **In autoimmune disease, In Fungal Infections, In Stability,Solubility,and bioavailability, In Clinical Findings etc. and others.**[45-52]

Conclusion:

Research has shown that systems based on nanosponge technology, which have great porosity, simple functionalization processes, unique topologies, cost-effectiveness, and environmental friendliness, make an appealing alternative to targeted drug delivery. Cyclodextrin nanosponge is the most tested nanosponge in nanomedicine because of its unique properties, high biocompatibility, low toxicity, and ease of surface modification. The concentration of the polymer or other substance and the ratio of cross linker can be changed to get the desired size. This also protects them from deterioration and helps make a variety of poorly soluble medications more soluble. Nano sponges can be used for a number of purposes, such as enhancing solubility, reducing photo-degradation of the drug, and targeting. Drugs administered using nanosponge delivery have been shown to be secure and efficient.

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