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A Review on Nanosponges

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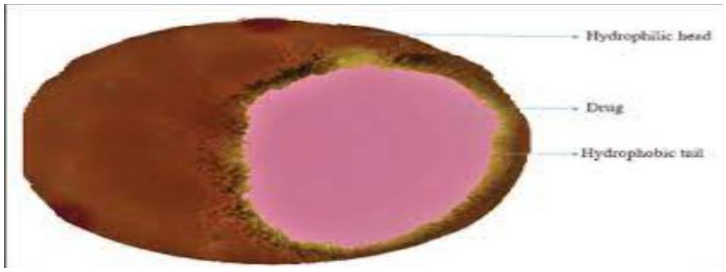
ABSTRACT
Nanosponge formulation is the ongoing research in drug delivery systems. Nanosponge is a solid, tiny sponge filled with various drug molecules in their cavities and are excellent drug delivery systems. They are biocompatible and versatile, with applications extending beyond pharmaceuticals to detoxification, chemical catalysis, and gas adsorption. They can improve the aqueous solubility and bioavailability of drugs as they can load water and lipid-soluble drug molecules and reduce their side effects, in various dosage forms for controlled drug delivery such as oral, parenteral, topical.They can also be employed as a biocatalyst carrier in drug delivery by developing drug delivery systems for enzymes, proteins, vaccines, and antibodies. The current review describes the methods of preparation of Nanosponges, types of Nanosponges, factors influencing their productionand evaluation tests.Their applications and ease of fabrication, scalability, and ability to protect encapsulated drugs from degradation, they hold great promise for next generation nanomedicine and multifunctional therapeutic delivery.

Key Words:Nanosponge, Drug delivery, Solubility, Bioavailability, Biocatalyst

I. INTRODUCTION

Nanomedicines and nanotechnology offer a solution for various unsolved issues of drug delivery therapeutics and represent a burgeoning branch of science (1). In the last two decades, nanosponges have attracted an increased interest of the research community owing to their highly versatile nature, combined with very simple and cheap fabrication protocols [2]. In recent years, pharmaceutical scientists have explored nanotechnology for temporal and targeted drug delivery systems. There have been various nanocarriers systems including metallic, polymeric-nanoparticles, nano-suspension, nano-tubes, nanofibers and nanosponges extensively used for the effective treatment of infectious diseases.The well-known categories of Nanosponges include polystyrene nanosponges, titanium-based nanosponges, silicon nanosponges and cyclodextrin-based nanosponges. (3)

Nanosponges are formed as three-dimensional networks of spherical porous particles having colloidal sizes with a mean diameter of less than 1 μm and narrow size distribution and form opalescent suspensions when dispersed in water. Nanosponges are considered to be one of the most promising nanosized delivery system because of its high stability, high carrier capacity and feasibility of incorporation of both hydrophilic and hydrophobic substances. Moreover, nanosponges can improve the solubility, chemical stability and, consequently, the bioavailability of lipophilic drugs. Nanosponges have been tested to deliver drugs, biocatalysts and gases, adsorption of toxic materials.(4)



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Chemicals used for the synthesis

Polymers and cross-linkers are the chief ingredients in the formulation of Nanosponges on the polymer structure and the drug formulation. Polymers are frequently used in the The polymer used can influence the content and development of NS. It can bind to specific ligands, . It can bind to specific ligands, The chemicals used in the preparation method are listed below:

Polymer	Copolymer	Crosslinker	Polar solvents
• Hypercrosslinked polystyrene • CD (alkoxy carbonyl CD) • Methylβ-CD • Hydroxy propyl β-CD • Poly-valerolactone • Eudragit RS100 • Acrylic polymer	• Poly (Valerolactone allyl valerolactone) • Poly (Valerolactone allyl valerolactone oxypanedione) • ECPVA	• Carbonyl diimidazole (CDI) • Carboxylic acid dianhydrides • Diarylcarbonates • Dichloromethane • Diisocyanates • Glutaraldehyde • Pyromellitic anhydride 2,2bis(acrylamide) acetic acid	• Ethanol • Dimethylacetamide • Dimethylformamide

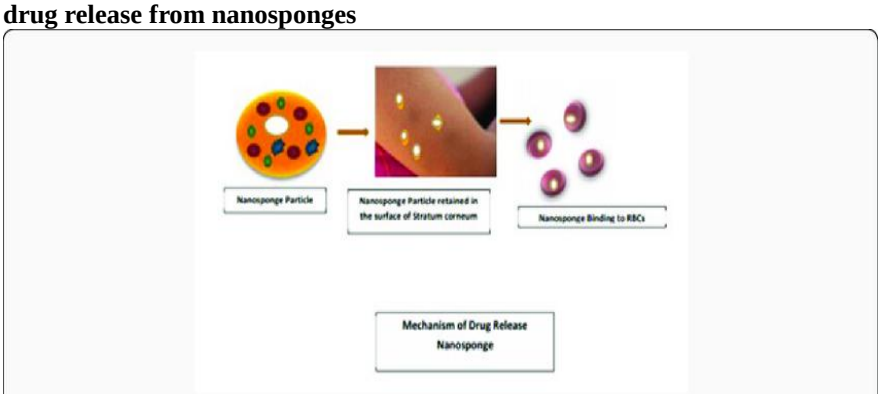
Drugs captured in Nanosponges

Drug	Therapeutic activity	NS vehicle	Attribute	Administration route	Reference
Itaconazole	Antifungal	β-CD, copolyvidonum	Enhanced drug solubility	Oral, topical	Swaminathan *et al.* (2007)
Dexamethasone	Anti-inflammatory	β-CD, DPC	Enhanced drug solubility	Oral, parenteral	Cavalli *et al.* (2006).
Flurbiprofen	Anti-inflammatory	β-CD, DPC	Sustained drug release	Oral	Cavalli *et al.* (2006).
Doxorubicin	Antineoplastic	β-CD, DPC	Sustained drug release	Parenteral	Cavalli *et al.* (2006).
Nelfinavir mesylate	Antiviral	β-CD, dimethylcarbonate	Enhanced drug solubilisation	Oral	Swaminathan *et al.* (2016)
Gamma-oryizanol	Antioxidant	β-CD, DPC	Enhanced drug stability, solubility, permeation	Topical	Swaminathan *et al.* (2016)
5-Fluorouracil	Antineoplastic	β-CD	Enhanced drug stability	Parenteral, topical	Torne *et al.* (2013)
Tamoxifen	Antiestrogen	β-CD, CDI	Enhanced bioavailability, solubility	Oral	Swaminathan *et al.* (2016)
Resveratrol	Antioxidant	β-CD, CDI	Enhanced drug stability, permeation, cytotoxicity, controlled drug release.	Oral, topical	Ansari *et al.* (2011)
Acetylsalicylic acid	Anti-inflammatory	β-CD, PMDA	Prolonged drug release	Oral	Trotta *et al.* (2012)
Curcumin	Antineoplastic	β-CD, dimethylcarbonate	Enhanced activity, solubilization	Parenteral	Swaminathan *et al.* (2016)

Advantages of nanosponges

- ❖ Increase aqueous solubility of the poorly water-soluble drug.
- ❖ Because of their tiny pore size (0.25 µm), bacteria cannot penetrate the nanosponges and they act like a self-sterilizer.
- ❖ Nanosponges drug delivery system are non-irritating, non-mutagenic and non-toxic.
- ❖ Nanosponges help to remove the toxic and venom substance from the body. Nanosponges drug delivery system minimizes side effect.
- ❖ Increase formulation stability and enhance the flexibility of the formulation. Reduce dosing frequency. Better patient compliance.
- ❖ Nanosponges complexes are stable over wide range of pH (i.e. 1to 11) and a temperature of 130 °C.

Mechanism of drug release from nanosponges



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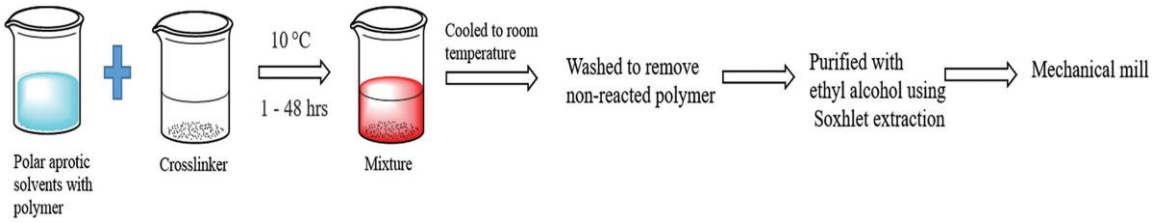
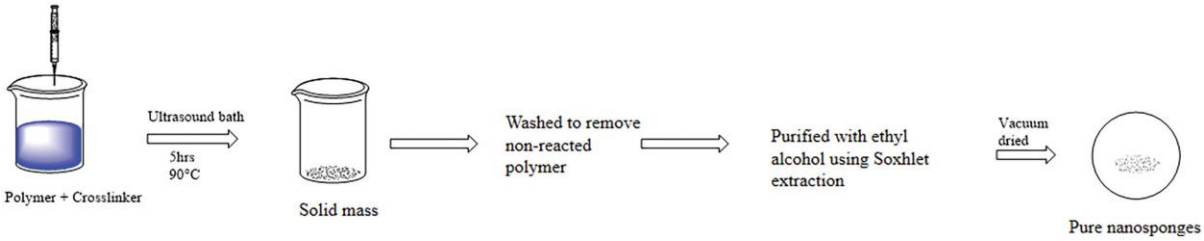
Methods of preparation

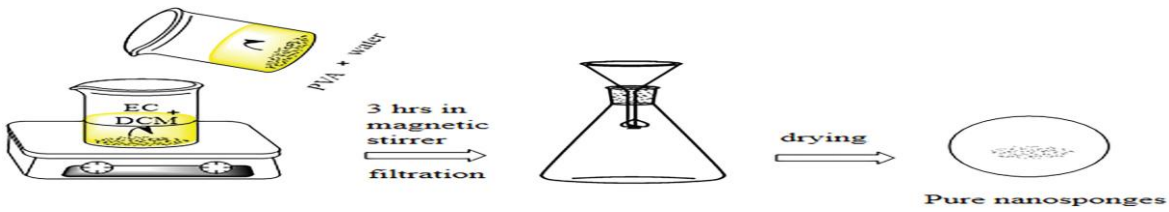
Solvent method: The suitable chemicals such as a polymers and a suitable solvent, particularly aprotic polar solvents were mixed to form a mixture. Then the mixture is add to a sufficient quantity of cross-linker. The reaction is conducted at temperatures ranging from 10°C. Filtration is used to recover the product under vacuum. Finally, the end product was dehydrated under a vacuum and was used to minimize the size to create a uniform powder.



Ultrasound-assisted synthesis: Nanosponges is formed by sonicating the polymers with the cross-linkers without using a solvent. A flask was filled with the polymer and the cross-linker at a certain molar ratio. After that, it was held for 5 hours under continuous effective sonication in an ultrasound bath device filled with water that had been heated to the temperature up to 90°C. The non-reacted polymer was then removed by adding too much water, then by using ethanol it was extracted for a long-time. Finally, the product was then desiccated at 25°C under a vacuum.

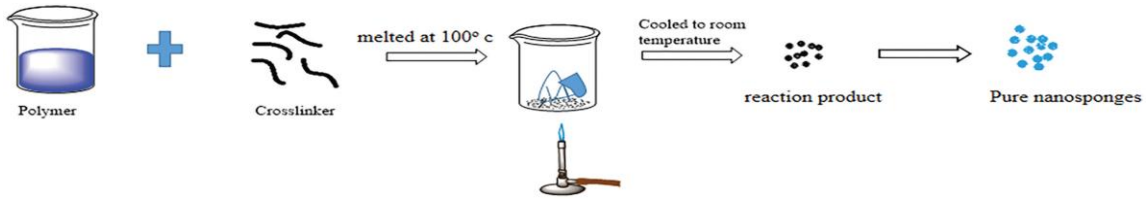


Solvent evaporation method: Nanosponges can be formed using suitable polymer. Here, dichloromethane, an organic solvent, was used to dissolve the dispersed phase EC and then it was thoroughly mixed with the PVA aqueous solution, the continuous aqueous phase. The reaction is then continued via magnetic mixing for 5 hours. Then finally after filtration, the product was dried for 24 hours at 40°C in an oven.



EC – Ethyl cellulose; DCM – Dichloromethane; PVA- Polyvinyl alcohol

Melt method: The crosslinker and β-CDs are fused when using the melting technique. The reaction is then carried out for 5 hours by magnetic mixing 100°C. The reaction mixture is allowed to cool, after which the result is broken down and repeatedly washed well with suitable solvents, i.e., ethanol. To eliminate unreacted byproduct



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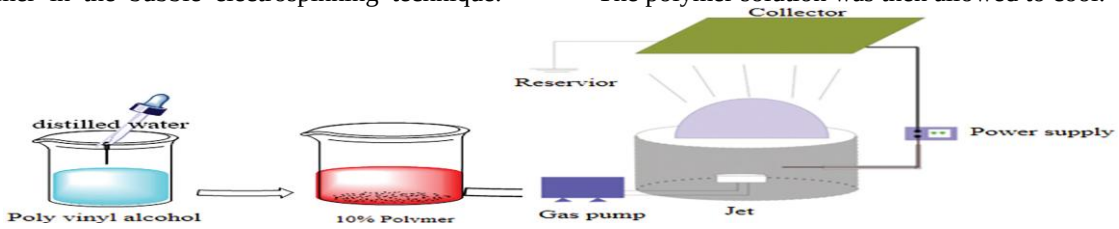
Bubble electrospinning: The amount of nanofibers production is one of the key restrictions that restrict their applicability. PVA can also be utilized as a polymer in the bubble electrospinning technique. The solution of polymer (10%) was organized by adding distilled water, it was then stirred at 80°C–90°C for 2 hours to produce a one-phase mixture. The polymer solution was then allowed to cool.



Types of nanosponges

- Titanium-based Nanosponge
- Silicon-based Nanosponge
- Hypercross-linked polystyrene Nanosponge
- Carbon-coated metallic nanosponge
- Beta-Cyclodextrin Based Nanosponge
- CD-based Nanosponges are further classified as carbamate Nanosponge, carbonated
- Nanosponge, ester Nanosponge, and polyamidoamine Nanosponge.

Factors influencing formulation of nanosponges:
Nature of polymer: The polymer used in the preparation of nanosponges can influence its formation and can also affect the pre-formulation. The size of the cavity of a nanosponge should be big enough to entrap a drug molecule of a particular size into it for complexation.

Drug: To be complex with nanosponges, the drug molecules should have some specific characteristics as mentioned below:
• The molecular weight of the drug molecule should be in range ranging from 100-400 Daltons.
• Structure of drug molecule should not consist of more than 5 condensed rings.
Temperature: Changes in the temperature can affect the complexation of drug or nanosponges. Increasing the temperature generally decreases the extent of the stability constant of the drug or the nanosponge complex which may be due to the reduction of interaction forces such as hydrophobic forces and Van der Waal forces of drug/nanosponges with an increase in the temperature.

Evaluation of Nanosponges:
Solubility studies: The phase solubility method, proposed by Higuchi and Connors, was the method most frequently used to investigate inclusion complexation An Erlenmeyer flask is used to determine the solubility studies.
Efficiency of loading and entrapment: The quantity of loaded Nanosponges must be dissolved in a suitable solvent, broken up using a sonicator, and then adequately diluted. The following formula can be used to calculated.

$$ADC = \frac{LE}{TDC} \times 100$$

ADC = Actual drug content,
LE = Loading Efficiency,
TDC = Theoretical drug content

Production yield (PY) : It can be calculated by calculated by the initial weight of the raw materials and the final weight of the Nanosponges.

$$PMN = \frac{PY}{TM} \times 100$$

PMN = Practical mass of NS,
PY = Production yield,
TM = Theoretical mass (polymer + drug).
Microscopy Studies: Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) are employed to examine the microscopic properties of the drug and drug/NS complex. Fresh ingredients and products from various crystallization phases combine to generate inclusion complexes, which may be seen under an electron microscopy.

Polydispersity and particle size: Dynamic light scattering to calculate the particle size. The polydispersity index (PDI) and mean diameter may be computed. The PDI measures variance or dispersion within the particle size distribution. A sample is considered monodisperse if the PDI value is lower, whereas a sample is considered polydisperse if the PDI value is higher and displays a wider range of particle sizes. To calculate PDI, use the following equation:

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$$PDI = \frac{\Delta d}{davg}$$

Zeta potential: The zeta potential of a particle represents the overall charge of the particle and stability of the formulation. Zeta potential measurement was carried out using Zeta sizer Nano- ZS90, Malvern Instrument Ltd., UK by differential light scattering (DLS) technique. All measurements were carried out in triplicates at 25 °C.

Thermo-analytical methods: The three most frequently used parameters with thermograms are peak broadening, peak shifting, and the emergence and disappearance of certain peaks. Thermal degradation of the Nanosponges can be monitored with these thermo-analytical methods.

Application Of Nanosponges:

- Enhanced solubility
- In antiviral therapy
- In protein drug delivery
- Chemotherapy
- Topical delivery
- Enzyme immobilization
- Sustained delivery system
- SARS-CoV-2 inhibition
- Diagnostic tool

Other Applications:

- Biomedical Application
- For Hydrogen storage
- In Agriculture
- In Food Industry
- For water Purification
- For Oil Cleaning
- As Novel flame Retardants
- Against pore forming Toxins and superbug infections.

II. CONCLUSION:

It has been investigated that nanosponge-based systems, which feature tremendous porosity, straightforward functionalization procedures, distinctive topologies, eco-friendliness, and cost-effectiveness, are attractive substitutes for targeted drug delivery. Cyclodextrin nanosponges stand out among the others due to their distinctive qualities, excellent biocompatibility, low toxicity, and simplicity of surface modification, making them the most often tested nanosponges in nanomedicine. The appropriate size can be obtained by adjusting the polymer or other material concentration and crosslinker ratio. This also aids in improving the solubility of various drugs that are poorly soluble and poorlysoluble and safeguards them against degradation. The nanosponges offer applications in a variety of areas, including targeting, improving stability and solubility, preventing photodegradation of the medication, improving formulation flexibility, gas administration, blood purification, etc., which is not achievable with other nanocarriers.

It is important to note that while nanosponges show promising results in various areas like drug delivery, cancer, and COVID-19, further research and development are necessary to define their properties, optimize their performance, and ensure their safety. Ethical considerations, regulatory approvals, and scalability will also play a role in determining the practical applications and widespread adoption of nanosponges in future. Despite the applications discussed above, nanosponges have various other applications like environmental clean-up (absorption of pollutants and other contaminants) and industrial applications (absorb and recover valuable materials from waste during the manufacturing process).

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