Nanosponges – An Innovative and Novel Drug Delivery System for drug targeting

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Abstract- **An innovative and developing technology known as the nano sponges has an ability to target the drug to the desired site, where the drug is released in an exact and controlled manner. Nanosponges are spherical, porous, nanosized drug carriers with a three-dimensional structure created by crosslinking polymers. They can load wide variety of drugs, antibodies, proteins, vaccines and enzymes into their nanocavity and deliver them to the targeted site. These can be manufactured as oral, parenteral, topical, or inhalation dosage forms. Nanosponge's applications include cancer, carrying enzymes and biocatalysts, delivering oxygen, enhancing solubility, immobilizing enzymes, poison absorbents and COVID 19 treatment. This article has discussions on the use, preparation techniques, assessment criteria, recent patents and applications of nanosponges.**

Keywords: **Nanosponges, solubility enhancement, oral, parenteral, topical, inhalation, drug targeting**

1. INTRODUCTION:

Targeting the medicament to the exact site in the human body and releasing that in a controlled manner are the two main problems medical researchers having from a long time. These problems can be overcome by nanosponges as a drug carrier. Nanosponges are a novel class of small particles whose structure look like sponge, which are used to treat many diseases and early experiments suggested that using this technology drugs can be targeted to the specific site for various types of cancers more effectively. [1] These particles are composed of holes which are nanometer-wide that can enclose a variety of medicinal ingredients and can entrap both lipophilic and hydrophilic compounds because of their inner hydrophilic and hydrophobic branching. [2] The backbone of nanosponges, which resemble a three-dimensional network, is a length of polyester combined with a crosslinking agent-containing solution. These crosslinking substances function as little hooks to connect various polymer components. They have a spherical colloidal nature and more solubilization capacity of drugs which have minimum solubility and hence improve their bioavailability. [3]

2. ADVANTAGES:

- This technique reduces negative effects while entrapping the substance.
- At temperatures as high as 130^0C, these compositions remain stable.
- The majority of vehicles and substances can use these kinds of combinations.
- Stability, elegance, and formulation flexibility have all improved by nanosponges. [4]
- The nanosponges assist in covering the unpleasant taste of drugs that are orally administered or through the buccal route. The negative effects of various substances can be minimized since they are getting entrapped within the nanosponges during formulation. [5]
- Nanosponges have stability up to 300°C temperature and pH ranges of one to eleven. Improved compatibility is seen when using various solvents and parts. They aid in modifying the pace at which medicine formulations release their active ingredients. [6]
- As medication is administered less often, patient compliance rises. They are easily scaled up, so they may be sold fast. Nanosponges drug moieties may be hydrophilic or lipophilic.
- Nanosponges are made using crosslinkers and other ingredients to shield the drug from hepatic first pass metabolism.
- Utilizing environmentally friendly solvents, inert hot gases, gentle heating, and adjusting strength, nanosponges may be regenerate.
- They can keep functioning for as long as 12 hours thanks to its extended-release feature. [7]
- Systems using nanosponges do not cause discomfort, mutagenesis, allergic reactions, or cytotoxicity. [8]

3. DISADVANTAGES:

- Only nano sized molecules with <500 Daltons molecular mass may be captured by nanosponges; bigger molecules (>500 Daltons) cannot be contained by them.
- The extent of crystallization has an impact on the drug-loading capacity. For example, in cafadroxil nanosponge, the drug-loading capacities of crystalline and paracrystalline cyclodextrins were different. [9]
- The dumping of doses is a possibility.
- When incorporated into nanosponges, materials having elevated melting points do not have stability constant values of high range. [10]

4. TYPES OF NANOSPONGES:

Nanopaticles are distinguished into following groups based on their relationships with medications.

a) Encapsulating nanoparticles: Nanosponges and nanocapsules are used to illustrate these. For example, drug molecules are carried by several pores in alginate nanosponges. Poly (isobutyl-cyanoacrylate) (IBCA) nanocapsules are example of nanoparticles. Watery core of these objects are used to trap the drug molecules.

b) Complexing nanoparticles: The molecule is attracted to these nanoparticles by their electrostatic charges.

c) Conjugating nanoparticles: With the drug molecules, these nanoparticles established a strong covalent bond. [11]

5. DRUG RELEASE MECHANISM FROM NANOSPONGES:

Until equilibrium is attained, the active drug moiety continuously enters and exits the open-structured sponge particles in the vehicle. The active ingredient in the vehicle used for the topical administration will be penetrated into the skin layers, after the finished dosage form is applied, the vehicle will be depleted and become unsaturated and alter the equilibrium. The active medication will flow until the solvent is either dry or absorbed, starting from the nanosponge particles into the solvent and then from the solvent into the skin. The nanosponges will deliver the drug's active ingredient into the skin over time even after that, staying on the stratum corneum's surface. [12]

6. FACTORS INFLUENCING FORMATION OF NANOSPONGES:

a) Drug: To be encapsulated inside nanosponges, drug molecules must meet following requirements.

- Water solubility should not be > 10mg/ml.
- Within 100- 400 Daltons should be the molecular weight.
- Five or less condensed rings should be present in the drug molecule’s structure.
- Below 250^0 C should be the melting point. [13]

b) Polymer: The development and performance of these nanoparticles will be influenced by the polymer type. A nanosponge's cavity should be big enough to fit the medicament of a certain size for complexation**.** By changing the crosslinking degree, following nanosponges are formulated.

i. Hydrophilic Nanosponge: For the purpose of making hydrophilic nanosponge, epichlorohydrin is utilized as a cross-linker. Hydrophilic nanosponges are an efficient drug transporter because they can alter the drug release rate even in dosage forms for quick release and increase drug absorption via biological barriers.

ii. Hydrophobic Nanosponge: For the purpose of making hydrophobic nanosponges, diphenyl carbonate, pyromellitic anhydride, diisocynates, and carbonyl diimidazole are utilized as a crosslinker. For medications that are water soluble, including peptides and proteins, they serve as sustained release carriers. [14]

c) Temperature: The changes in temperature will impact the complexation of drug and nanosponge. With an increase in temperature, a drop in the drug-nanosponge complex's apparent stability constant can be seen. This results in decrease of drug/nanosponge interaction forces, such as vander waal forces and hydrophobic forces, when the temperature rises. [15]

d) Method of preparation: Drug/nanosponge complexation can be affected by the way the drug is loaded into the nanosponge. By freeze drying method, the highest efficient drug complexation was accomplished.

e) Degree of substitution: The nanosponge’s complexation can be more significantly impacted by the quantity, location and type of the parent molecule's substituents. [16]

7. CHARACTERISTIC FEATURES OF NANOSPONGES:

- With variable polarity, nanosponges offer cavities with different dimensions of 1µm or less. [17]
- Aqueous solubility is a main characteristic of these sponges, which enables the successful application of these systems for drugs with limited solubility.
- The nanosponges are able to carry both hydrophilic and lipophilic drugs.
- With this technology, adverse effects are decreased, stability is increased, elegance is increased, and formulation flexibility is raised.
- Nanosponges do not cause irritation, are not mutagenic, allergenic, or poisonous. [18]

- By altering the crosslinker to polymer ratio, it is able to create nanosponges of a particular size
- Due of their possibility to connect with several functional groups, nanosponges have the ability to target to different sites.
- Nanosponges can also acquire magnetic characteristics by including particles which has magnetic properties, in the reaction mixture.
- Compared to other nanocarriers, nanosponges are not toxic, porous in nature and thermostable at high temperatures like 300 °C. They are not soluble in organic solvents and water.
- These can be found in both crystalline and para-crystalline forms, depending mostly on the processing circumstances. Crystallinity degree aids in estimating its drug loading potential.
- They are water soluble and take the form of translucent, opalescent suspensions. They may be recovered by easy thermal desorption, solvent extraction, microwave treatment, and ultrasonic treatment. [19]
- Drug or active compounds may be included within nanospomges as inclusion or non-inclusion complexes. In inclusion complex nanosponges, cyclodextrin and the drug create a mono molecular inclusion complex. In other case, drug molecules are absorbed or trapped within the porous architectures of non-inclusive complex nanosponges. [20]
- Since crosslinkers are included in the nanosponges preparation, they enable targeted medication delivery to the chosen target.
- They are readily regenerable using techniques like washing, breaking with little inert gases, using liquids that are beneficial to the environment, slightly raising the temperature, or varying the ionic or pH value. [21]

8. CHEMICALS REQUIRED:

a) Polymers: The development and effectiveness of nanosponges may be influenced by the polymer choice. To integrate the specific medicinal molecule, the nanosponge cavity size must be appropriate. When selecting a polymer, the kind of release and the item to be contained are taken into account. The chosen polymer must to be capable of binding to particular ligands. Examples are

- Polystyrene Cyclodextrin (alkoxycarbonyl cyclodextrins)
- Methyl beta cyclodextrin
- Hydroxyl propyl beta cyclodextrin
- Eudragit RS100
- Acrylic polymer

b) Crosslinking agents: The choice of a cross-linking agent can be done based upon the structure of polymer and the medicine that is being developed. Examples are

- Carbonyl dimedazole
- Carboxylic acid dianhydrates
- Diarylcarbonates
- Glutaraldehyde
- Pyromellitic anhydride
- 2,2bis(acrylamide) Acetic Acid [22]

c) Solvents: Solvents are used as vehicle. Examples are

- Ethanol
- Dimethylacetamide

d) Drug substance: Ideal properties of drug substance are

- The ideal range for molecular weight: 100- 400 daltons.
- < 5 condensed rings make up a drug's molecule.
- Drugs should have Water solubility is < 10 mg/mL.
- Melting point of the drugs should be less than 250°C. [23]

9. PREPARATION OF NANOSPONGES: These can be prepared by following methods

a) Melt method
b) Solvent method
c) Hyper cross-linked β-cyclodextrin
d) Emulsion solvent diffusion method
e) Ultrasound-assisted synthesis
f) Quasi-emulsion solvent diffusion method

Melt method: Cyclodextrin and suitable Crosslinker are melted together in this process. The materials are all well combined and then added to a 250 ml flask that has been heated to 100°C for five hours using a magnetic stirrer. After

the reaction mixture has cooled, the result has been broken down; it is repeatedly washed with appropriate solvents to get rid of unreacted excipients and byproducts. [24]

Solvent method: This procedure made use of appropriate solvents, like polar aprotic solvents (dimethyl formamide and dimethyl sulfoxide). The polymer and solvent were properly combined. An ideal crosslinker/polymer ratio is 1:4. To this, the above mixture was added. After the previous mixing, it was allowed to react for 48 hours at a 10 °C temperature and up to solvent's reflux temperature. After the reaction was finished, the solution was cooled until it reached room temperature. To extract the product from the above-cooled solution, excessive amounts of bi-distilled water were added. The product was then collceted by vacuum filtering. [25]

Hyper cross-linked β-cyclodextrin: β-cyclodextrin nanosponges can hold both drugs having lipophilic and hydrophilic characteristics. Cross-linker like diphenyl carbonate diisocyanates and cyclodextrin are used to create nanosponges. Hyper cross-linked cyclodextrin block that is transparent is coarsely ground, and the solvent should be washed away with excess water. Purification of the produced product is done by ethanol-based soxhlet extraction. Overnight drying at 60^0C was done for the finished product. [26]

Emulsion solvent diffusion method: Ethyl cellulose (EC) and polyvinyl alcohol (PVA), in different ratios, are the major polymers utilized in this process. EC and the drug are added to 20ml of dichloromethane and dissolve to form dispersed phase. Formation of contionous phase is done by dissolving PVA in distilled water (150ml) to form continuous phase. To the continuous phase, the dispersed phase is added drop wise. After that, it is allowed to stir for roughly two hours at 1000 rpm. The obtained nanosponges are gathered, filtered, oven dried for approximately one day, and then kept in desiccators. [27]

Ultrasound-assisted synthesis: Nanosponges which are spherical and uniform are obtained by utilizing polymers with carbonyl cross linkers without a solvent and keeping them for sonication.In a flask, combine the cross-linker and polymer in an adequate amount. For ultrasonication, the flask is filled with water and heated until to get 90°C. Continuous sonication is done for 5 hours. The product is then purified with a soxhlet extractor using ethanol, after the mixture has been cooled and rinsed with distilled water. At 25 ^{0}C, the finished product is dried, and white powder is collected and stored away from humidity.

Quasi-emulsion solvent diffusion method: In this procedure, different polymer concentrations are employed, to create nanosponges. By dissolving eudragit RS100 in a desired solvent, the dispersed phase was created. The drug is then added to the mixture and dissolved using ultrasonication at 350°C. The water-based PVA solution (dispersion phase) was added slowly to the dispersed phase, and then it was agitated for an hour. After agitation, nanosponges are separated by filtration technique. The obtained nanosponges are oven dried at 40 ° C for 12 hours. [28]

10. LOADING OF DRUG INTO NANOSPONGES:

To attain a mean particle size of 500 nm or below, these nanoparticles are pretreated. To stop the formation of the aggregates and particles, nanosponges were incorporated into the water and sonicated and then separeted to get colloidal fraction. Supernatant is isolated from the sample mixture and dried by freezing and drying. The next step involves creating an aqueous nanosponge suspension and dispensing more drugs to keep the solution constantly stirred for a certain amount of time, in order to facilitate complexation. The complexed drug and undissolved drug can be separated by centrifugation process. This procedure aids in the formulation of nanosponge solid crystals by freeze drying or solvent evaporation method. [29]

11. COMPARITIVE STUDIES:

Few examples of drug carrier systems which are nanometric in size are liposomes, niosomes, ufasomes, bilosomes, ethosomes, transferosomes, and nanosponge. Comparing these vesicular systems to nanosponges reveals that some of them have stability issues. While the formulation instability in liposomes is caused by the oxidation of phospholipids and cholesterol, niosomes exhibit drug hydrolysis after encapsulation, transferosomes are prone to oxidative destruction, which makes them chemically unstable. These are the few issues that vesicular systems frequently encounter. Nanosponges are a brand-new class of colloidal structures made of hyper-crosslinked polymers that are composed with colloidal sizes and voids of nanosize. They consist of crosslinkers, surfactants, and polymers. The bioavailability of dosage forms, drug release, and side effects are all modified using nanosponges, which are chemically and physically stable. [30]

12. EVALUATION:

a) Appearance

The physical appearance of the created nanosponges were observed visually. Observed was the whitish, spongy powder. The spherical appearance of nanosponges is influenced by the polymer solution's viscosity. [31]

b) Solubility

Higuchi and Connors' phase solubility methodology is commonly used approach for examining inclusion complexation since it looks at how nanosponges affect drugs solubility. The complexation level is observed in phase solubility diagrams.

This procedure involved adding the medication to an Erlenmeyer flask which was filled prior with an aqueous solution containing nanosponges in varying percentages. At room temperature, the agitation of Erlenmeyer flask was done with mechanical shaker. A 3000 Dalton molecular filter (MICRON YN 30, Millipore Corporation, Bedford MA 1730 U.S.A.), used in centrifugation, in order to filter the suspension once a steady state had been attained. The drug concentration of a resulting solution can be examined by High performance liquid chromatography (HPLC). [32]

c) Swelling index

To assess swelling and water absorption, the produced nanosponges are soaked in aqueous solvent. The following formula is used to determine swelling and water absorption.

*Water uptake =marking of cylinder at specific time /initial marking before soaking *100*

*Swelling index =mass of hydrogel after 72 hours/initial mass of polymer *100* [33]

d) Microscopy

SEM and TEM can both be employed for evaluating the microscopic features of a medicine, nanosponge, or product. According to the difference in crystallization states, inclusion complexes are formed. [34]

e) X-RAY Diffraction

A solid-state mono molecular complex is found using powder X-ray diffractometry. Nano sponge creation modifies the drug's crystalline structure and diffraction patterns. The complex's creation results in peak sharpening, peak shifting, and formation of peak. The change in the diffraction pattern was noticed when complex is formed. If the drug is solid, contrast the diffractograms of the expected complex with a combination of drug and polymer molecules. The chemical degradation and complex creation in Nano sponges are identified by the diffraction peaks of a mixture. [35]

f) FTIR

In the FTIR investigation, the improved nanosponges formulation was used. Before crushing the pellet under 15 tonnes of pressure, potassium bromide (KBr) was combined with the nanosponges in a 1:90 ratio. The FTIR spectra of the batch of nanosponges formulation was captured between 4000 and 400 cm^{-1}. In the spectra of optimized nanosponges, it was seen how the primary peaks altered. [36]

g) Zeta potential

To determine the speed at which particles travel in an electric field and their charge, the zeta potential was measured. Using demineralized water as a dilution agent, prior to analysis, nanosponges were 10 times diluted. [37]

h) Polydispersibility index

The polydispersity index measures how widely the size distribution of particles is spread out or how much it varies. To determine PDI, dynamic light scattering techniques (DLS) may be employed. The polydispersibility index value of a monodisperse sample is lower than that of a polydisperse sample, which indicates the particles distribution of different size ranges. The following equation is used to calculate PDI

$PDI=\Delta D/D_{avg}$

D= Distribution

D_{avg}= Mean particle size [38]

i) Encapsulation efficiency

Carefully weigh 10 mg of nanosponges and 5 ml of methanol and add in a volumetric flask before being shake vigorously for 1 minute with a help of vortex mixer to determine the entrapment effectiveness. The volume was made up to 10 ml, and then it was filtered and diluted, and the quantity of drug is determined using spectrophotometry to determine wavelength.

Loading Efficiency = Nanosponges Actual Drug Content/Theoretical Drug Content*100 [39]

j) Drug content

To investigate the pharmacological content, nanosponges were dissolved in 25ml of methanol to release the medication from them. The resultant solution underwent filtering. Using an ultraviolet-visible spectrophotometer, the quantity of methanol in the control samples and the quantity of drug contained in the methanolic extracts were differentiated.

(Actual Drug Content/Theoretical Drug Content) *100 = % Drug Content) [40]

k) In-vitro Drug release

To ascertain the quantity of drug that was released from the nanosponge, a dissolving apparatus USP xxiii with a modified basket constructed of 5m stainless steel and revolving at 150 rpm can be utilized. The solubilization of the API (active pharmaceutical ingredient) is considered while selecting the dissolving medium to guarantee sink condition. Using a proper analytical procedure, a sample from the dissolving media may be examined. Franz diffusion cells may also be used based on the formulation, in most of the cases. [41]

l) Resiliency

Sponge resilience (or viscoelastic properties) can be changed to produce softer or stiffer beadles based on the needs of the final composition. As the crosslinking increases, the rate of release will decrease. Sponge resilience will be evaluated and altered in accordance with the release function of cross-linking with time. [42]

13. DRUGS LOADED:

Table 2: Drugs entrapped in nanosponges [43-45]

DRUG	VEHICLE	CATEGORY
Paclitaxel camphoterisin	Beta-cyclodextrin	Anti-cancer
Tamoxifen	Beta-cyclodextrin	Breast cancer
Temozolamide	Poly (valerolactoneallylvalerolactone) and poly (valerolactoneallylvalerolactone – oxepanedione)	Brain tumor
Econazole nitrate	Ethyl cellulose	Anti-fungal
Antisense	Sodium alginate	Anti-cancer
Doxorubicin	β-CD, diphenylcarbonate	Anti neoplastic agent
Flurbiprofen	β-CD, diphenylcarbonate	Anti inflammatory
Nilfinavir	β-CD, diphenylcarbonate	Anti-viral
Gamma-oryizanol	β-CD, diphenylcarbonate	Anti-oxidant
Resveratrol	β-CD, carbonyldiimidazole	Anti-oxidant
Curcumin	β-CD, diphenylcarbonate	Anti-cancer
Acetyl salicylic acid	β-CD, pyromellitic dianhydride	NSAID

14. APPLICATIONS:

Nanosponges offer a variety of uses in pharma industry because of their bio acceptability and adaptability. The preparation of dosage forms such as pellets, granules, tablets, capsules, suspensions and solid dispersions can all include nanosponges as excipients. [46]

a) Enhancement of solubility

Itraconazole, a medication in BCS class II, has a low bioavailability and a slow rate of dissolution. As a consequence, using nanosponges increased the drug's solubility by more than 27 times. When copolyvidonum was introduced as a supporting component, it was discovered that the solubility was surpassed by 55 times. Nanosponges increase the solubility and bioavailability of the drug by either hiding the itraconazole's hydrophobic groups, enhancing the drug's wetting ability, or lowering the crystallinity of the medication. [47]

b) Cancer therapy

Although nanomaterials have been extensively studied as possible drug delivery carrier and cancer therapy agents, more thorough research is still needed to identify effective delivery methods with strong biocompatibility and biodegradability features for specialized and targeted therapy.

Targeted and sustained drug delivery and cancer therapy have both been researched using nanosponges with the right levels of penetration, absorption, biocompatibility, bioavailability, and stability.

Recently, titanium-based, metallic, -cyclodextrin, hypercrosslinked polystyrene, silicon-based, DNAzyme, and ethylcellulose nanosponges are developed. Nanosponges are excellent candidates for the encasing of many compounds due to their mesh-like/colloidal structures, including medicines, phytochemicals, volatile oils, antineoplastic agents, genetic materials, proteins/peptides, and more. [48]

c) Delivery of drug

Nanosponges are used as a safe drug delivery carrier for the treatment of a number of disorders, such as malignancies and tumors, cyclodextrin nanosponges have been created. These nanosponges offer distinctive qualities like biocompatibility, porous architectures, controlled-release behavior, and increased oral bioavailability. [49]

d) DNAnzyme nanosponges in cancer treatment

The rolling circle oligomerized DNAzyme-substrate frameworks and the captured pH-receptive ZnO nanomaterials were used to construct a DNAzyme-driven drug transport system. The created DNAzyme nanosponges might be targeted for delivery into malignant cells. [50]

e) Gas encapsulation

To create enclosing compounds with 1-methylcyclopropene, oxygen, and carbon dioxide, carbonates based nanosponges are used. The combination of carbon dioxide and oxygen has several advantages in biological applications where oxygen-filled nanosponges can effectively move to tissues that turns hypoxic. [51]

f) Diagnostic agents

Diagnostic materials are produced using beta-cyclodextrin on a large scale. Due to its great biocompatibility, extended blood circulation, homogeneous distribution of particle size for permeability, and easy to target to the desired site, cyclodextrin nanosponges can be utilized widely for diagnostic purpose. [52]

g) Topical application

The delivery system using nanosponge is a unique method for the release of topical medications in a controlled manner. This formula can be developed into powders, gels, creams, lotions, or ointments. In aim to increase the absorption of the foreign molecule by the skin, nanosponges must be able to improve solubility at the skin's surface. [53]

h) Protein delivery

The key challenge in developing protein formulations is maintaining the natural protein structure throughout the formulation process and during long-term preservation. Nanosponges 10 and 11 were created by cross-linking -cyclodextrins with 2, 2-bis-acrylamido amine derived from 2, 2-bisacrylamido acetic acid and 2, 2-methyl piperazine, respectively. Swaminathan et al. reported "The creation of these new swellable cyclodextrin-based poly (amidoamine) nanosponge. It was discovered that the produced poly (amidoamine) nanosponges based on -cyclodextrin were stable at 300°C and that they had a high capacity for protein complexation". [54]

i) Anti-fungal

The product is available as a cream, ointment, or lotion, and the Nanosponge is also utilized as an antifungal agent to topically relieve the symptoms of candidiasis, dermatophsis, and skin infections. [55]

j) Anti-viral

Use of antivirals Nasal and pulmonary delivery methods for nanosponges. It offers selectivity to deliver antiviral drugs on RNA to the lungs or nasal pathway using nanocarriers for targeting viruses that may cause RTI infection, such as influenza virus and rhinovirus. Saquinavir and zidovudine are two medications utilized as nanocarriers. [56]

k) COVID 19

It was discovered in one of the study articles that the two forms of cellular nanosponges are formed from plasma membrane from either human macrophages or type II lung epithelial cells. These nanosponges display a few protein receptors, both known and unknown, that the SARS-CoV-2 needs to enter cells. After that, SARS-CoV-2 is incubated with nanosponges, but it is neutralized and is unable to infect cells. Viral mutations are antagonistic to the nanosponge platform. The host cell has been identified as the virus target, and the nanosponge will neutralize it. [57-58]

15. CONCLUSION:

Nanosponges are multifunctional nanostructural carriers which are suitable for active compounds delivery in nanomedicine. They benefit from the ability to encapsulate both lipophilic and hydrophilic medicines and transport them to the target area in a regulated way. Both size of particle and release rate can be adjusted by altering the polymer to cross-linker ratio. As research in this area advances, nanopsonges will be helpful in a lot of sectors due to their vast range of applications.

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