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A REVIEW ON NANOSPONGE AS A POTENTIAL NANOCARRIER FOR EMERGING DRUG DELIVERY

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ABSTRACT
For a long time, effective targeted drug delivery systems have been a dream, but the complex chemistry involved in developing new systems has delayed progress. The most recent advancement in nanotechnology demonstrates that the current enhanced concentration is the supramolecular gathering of simple elements for medicinal and diagnostic purposes. Nanosponges are extremely small sponges around the size of a virus that can be packed with a variety of medications. These tiny sponges can circulate throughout the body until they come across a specific target spot, where they will attach to the surface and begin to release the medicine in a controlled and predictable manner. Nanosponges are solid porous particles with the ability to load medicines and other actives into their nanocavity; they are available in oral, parenteral, topical, and inhalation dose forms. This review attempts to highlight the development methodologies, characterization techniques, and potential uses of nanosponge drug delivery devices.

KEYWORDS: Nanosponges, Nanotechnology, Effective targeted drug delivery.

INTRODUCTION

Nanotechnology is described as the development and manipulation of nanoscale materials to produce products with unique properties. Nanotechnology has resulted in numerous formulation variations such as nanoparticles, nanocapsules, and nanospheres, nanosuspensions. Targeting drug delivery systems to achieve the desired result has been a long-term goal. Nanosponge drug delivery systems were originally only available as a topical administration system, but in the twenty-first century, Nanosponges can now be administered via oral and intravenous (IV) routes.[1,2]

Nanosponges are a new type of material made up of microscopic particles with a few nanometer-wide cavities into which a wide range of substances can be encapsulated. These particles can carry both lipophilic and hydrophilic substances and improve the solubility of molecules that are poorly water soluble.[3] The nanosponge has a backbone (Scaffold structure) made of naturally degradable polyester and is about the size of a virus. The long polyester strands are mixed in a solution with small molecules known as cross-linkers, which have an affinity for specific parts of the polyester. They 'cross link' segments of polyester to create a spherical shape with many pockets (or cavities) for storing drugs. Because the polyester is predictable biodegradable, the drug can be released on a predictable schedule once it breaks down in the body.[4]

The nanosponges are a three-dimensional polyester scaffold (backbone) or network that can degrade naturally. Nanosponges are made by combining these polyesters with a crosslinker in a solution. Because polyester is generally biodegradable, it breaks down slowly in the body. When the scaffold of nanosponges breaks down, the drug molecules that are loaded are released in unfavourable manner.[5]

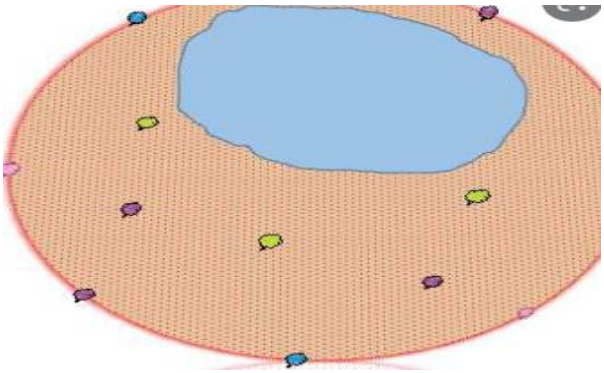

Fig 1: Nanosponge structure with drug loading cavity.[6]

Characteristics of nanosponges

- Nanosponges come in a variety of sizes (1 m or less) and have polarity that can be adjusted. By varying the cross linker to polymer proportion, nanosponges

of specific size and adjustable polarity can be created.[7]

- Depending on the process conditions, they could be either para-crystalline or crystalline. The crystal structure of nanosponges plays a critical role in their drug complexation. The degree of crystallisation determines the drug loading capacity of nanosponges. Drug loading capacities of para-crystalline nanosponges have been reported.
- They are nontoxic, porous particles that are immiscible in most organic solvents and can withstand temperatures of up to 300^0 Celsius.[8]
- Nanosponges as formulations are stable from pH 1 to 11 and up to 130 °C.
- In water, they form clear and opalescent suspensions that can be regenerated using simple thermal desorption, solvent extraction, microwaves, and ultrasounds.[9]
- Their three-dimensional structure allows for the capture, transportation, and selective release of a wide range of substances. Because of their ability to be linked with different functional groups, they can be targeted to different sites. Nanosponges can bind to the target site preferentially thanks to chemical linkers. With different drugs, they form inclusion and non-inclusion complexes.[10]
- Nanosponges can also be given magnetic properties by incorporating magnetic particles into the reaction mixture.[11]

Advantages[12,13]

- Increase the aqueous solubility of a drug that is poorly water soluble.
- Bacteria cannot penetrate the nanosponges because of their small pore size (0.25 m), so they act as a self-sterilizer.
- Long-acting - up to 12 hours of continuous action.
- Enhance formulation flexibility while increasing formulation stability.
- Nanosponges complexes are stable across a wide pH range (i.e. 1-10).
- Nanosponges are non-irritating, non-mutagenic, and non-toxic drug delivery systems.
- Nanosponges can release drug molecules in a controlled manner.
- Nanosponges aid in the removal of toxins and venom from the body.
- Nanosponges are a drug delivery system that reduces side effects.
- Reduce the frequency of dosing.
- Drug profiles can be changed from quick to medium to slow release, suppressing more or less therapeutic dose.
- Patient compliance is improved
- Nanosponges are biodegradable
- Nanosponges can significantly reduce medication irritation while maintaining efficacy.

Disadvantages[14]

- Nanosponges are capable of containing just tiny molecules.
- Nanosponges can be semi-crystalline or crystalline in nature.
- Nanosponges' loading capacity is mostly determined by the degree of crystallisation.
- Different loading capabilities can be found in para crystalline nanosponges.

Composition of nanosponges[15,16]

These are the main components of nanosponges:

A. Polymer – The polymer used to make Nano sponges can have an impact on their formation and performance. The polymer chosen is determined by the required release and the drug to be contained. The chosen polymer must be able to bind to specific ligands.
Examples are hyper cross linked Polystyrenes, Cyclodextrines and its derivatives such as Methyl β-Cyclodextrin, Copolymers like Ethyl Cellulose & PVA.

B. Crosslinking agent – The selection is based on the structure of the polymer and the drug to be formulated.
Diphenyl carbonate, Dichloromethane, Diaryl carbonates, and Diisocyanates are some examples.

C. Drug substance - Molecular weight between 100 and 400 Daltons. A drug molecule is made up of no more than five condensed rings. In water, solubility is less than 10 mg/ml. The melting point of the substance is less than 250 °C.

Table 1: List of Polymer and Cross linkers.

Sl. No.	Composition of nanosponges	Example	Reference
1.	Polymer	Ethyl cellulose	[17]
		Hyper crosslinked Polystyrene	[18]
		β-cyclodextrine	[19]
		Polyvinyl alcohol	[20]
2.	Crosslinkers	Diphenyl carbonate	[21]
		Diisocyanates	[22]
		Pyromellitic anhydride	[23]
		carbonyldiimidazole	[24]

Types of nanosponges[25]

1. Cyclodextrin based nanosponges -
a. Cyclodextrin based carbonate nanosponges.
b. Cyclodextrin based carbamate nanosponges.
c. Polyamidoamine nanosponges.
d. Cyclodextrin based ester nanosponges.
e. Modified nanosponges
2. Hyper crosslinked polystyrene nanosponges.
3. Silicon nanosponge particles.
4. Titanium based nanosponges.

Mechanism of drug release[26]

Cross-linking polymer nanosponges have a three-dimensional structure. Depending on how much cross-linking polymer is added to the formulation, the entrapment and solubilizing efficiency of nanosponges can be altered. Nanosponge's toroidal shape allows for the creation of a cavity within the structure that can accommodate a variety of drug molecules. As long as the active compound is compatible with the geometry and polarity of the cavity, the drug will release at the target site. The structure of the nanosponge plays a critical role in determining when these active compounds will be delivered, and it can be modified based on drug release requirements. Several ligands or carriers can be attached to the nanosponge's surface to direct molecules to specific locations within the body.

Method of preparation

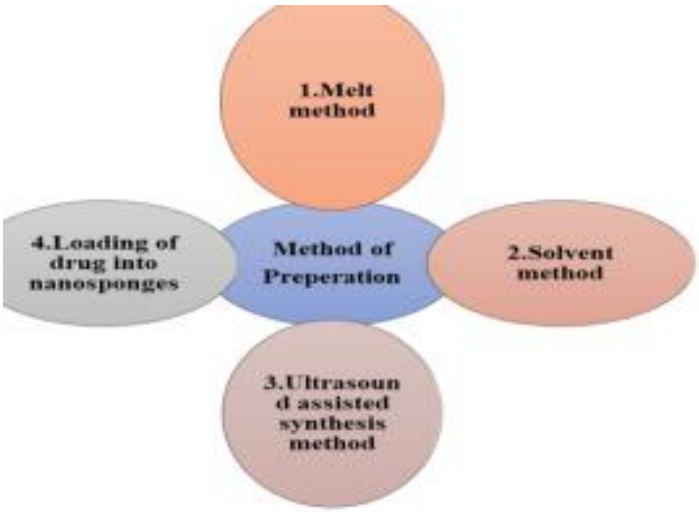

Fig. 2: Method of preparation.[27]

1. Melt method[28]

- Melt the cyclodextrin polymer with crosslinkers such as diphenylcarbonate, diisocyanate, glutarldehyde, and carboxylic acid anhydrides.
- All of the materials are coarsely blended before being placed in a 250 mL flask and heated to 100 degrees Celsius. The reaction is carried out in a magnetic stirrer for 5 hours.
- After permitting the mixture to cool, the product is broken.
- Unreacted excipients and byproducts are removed by washing the final product with appropriate solvents.

2. Solvent method[29]

- The polymer mentioned above can be combined with a polar aprotic solvent such as dimethylformamide or dimethylsulfoxide and mixed suitably.
- Then, in a 4:16 ratio, available cross-linkers are added to the mixture.
- For two days, a temperature of 10°C is maintained for polymer polymerization. The majority of carbonyl cross linkers are used (Dimethyl carbonate and Carbonyl diimidazole).
- After the reaction is finished, the product is allowed to cool at ambient temperature before being mixed with distilled water and filtered in an air oven. Purification is done using a soxhlet apparatus with ethanol for further extraction.
- To obtain a homogenous white powder, dry under vacuum once more and powder mechanically.

3. Ultrasound-assisted synthesis[30]

- In a flask, polymers are made to react with crosslinkers without the need of a solvent.
- The combination is sonicated for 5 hours in an ultrasonic bath that is filled with water and heated to 90°C.
- The product is subsequently broken into rough bits after cooling to room temperature.
- Finally, the non-reacting polymer is removed by washing the product with water, and nanosponges are refined using a soxhlet apparatus (ethanol).

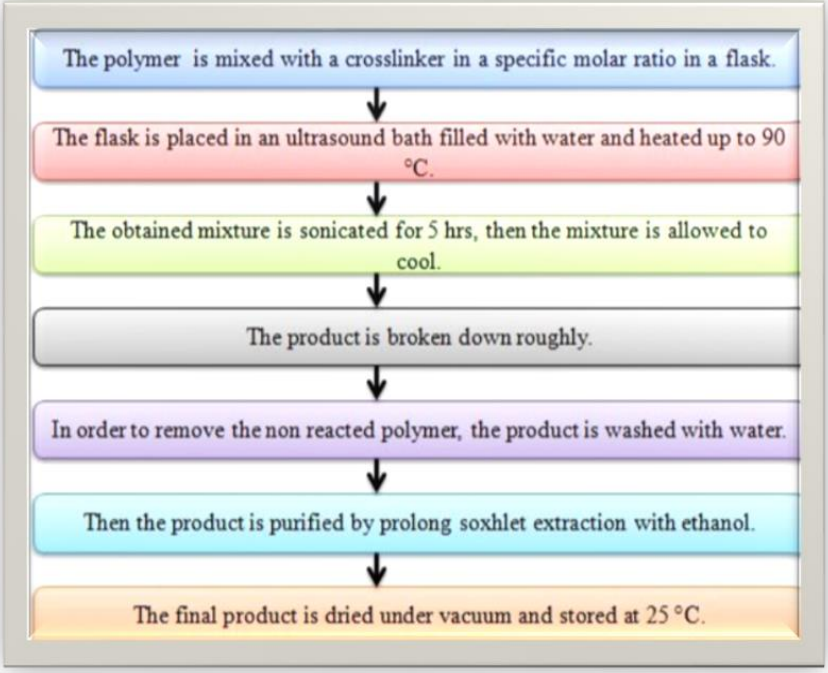

Fig. 2: Ultrasound assisted synthesis.[31]

4. Loading of drug into nanosponges[32]

- Dissolve the nanosponges in water and sonicate to remove any aggregates, then centrifuge the suspension to obtain the colloidal fragments.
- Separate the supernatant and freeze-dry the sample. Later, a suspension with aqueous nanosponges is created.
- It receives extra doses of the medication. Then it's kept under steady stirring for a set period of time to allow for complexation.
- Centrifugation separates the uncomplexed drug from the complexed drug once it has been complexed.
- Solvent evaporation is ultimately used to obtain the solid crystals of nanosponges.

Factors affecting in formulation of nanosponges

a) Type of polymer[33]

- The choice of appropriate polymer affects both the production and performance of nanosponge. The nanosponge's cavity or pore size should be large enough to accommodate a medication molecule of appropriate size.

b) Drug[34]

- Drug molecules should have the following qualities to be complex with nanosponges:
- The medication molecule's molecular weight should fall between between 100 and 400 Daltons.
- There should be no more than 5 condensed rings in the structure of a pharmacological molecule.
- The drug's water solubility should be less than 10 mg/ml.
- The medication should have a melting point of 250 degrees Celsius.

c) Temperature[35]

- Drug/Nanosponge complexation is influenced by temperature fluctuations. In general, when temperature rises, the apparent stability constant of the Drug/Nanosponge complex drops. This could be owing to a reduction in drug/nanosponge contact forces, such as van-der Waal forces.

d) Method of preparation[36]

- When a drug is loaded into a nanosponge, the complexation between the nanosponge and the drug can change. In any case, the success of a method is determined by the nature of the drug and polymer, and freeze drying has been shown to be the most effective way for drug complexation in a number of cases.

e) Degree of substitution[37]

- The quantity, position, and type of the parent molecule's substituent can all have an impact on the nanosponges' ability to complex.

Characterization of nanosponges

1. Particle size analysis[38]

The particle size was estimated using a Malvern system and vertically polarised light from a 40 mW argon-ion laser (Cyonics). Experiments were carried out at a temperature of 25.0 0.1oC and a measurement angle of 90o to the incident beam. Laser diffraction is based on the idea that particles travelling through a laser beam scatter light at an angle proportional to their size. The observed scattering angle grows logarithmically as the particle size decreases. The observed scattering intensity

varies with particle size and, to a decent approximation, decreases with cross-sectional area. As a result, large particles scatter light at narrow angles with high intensity, whereas microscopic particles scatter light at wider angles with low intensity.

2. Microscopic studies[39]

Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) can be used to analyse the microscopic characteristics of a drug, Nano sponge, or the product. The development of inclusion complexes is indicated by the difference in crystallisation state.

3. Solubility studies[40]

Inclusion complexes are a technique for determining a drug's solubility and bioavailability. This is the most extensively used technique for analysing nanosponge inclusion complexes. The plot of phase solubility can be used to determine the degree of completeness. Solubility studies are carried out to determine the drug's pH, solubilization outline, and factors affecting drug solubility.

4. X-ray diffractometry and single crystal X-ray structure analysis[40]

Inclusion complexation in the solid state can be determined using this method. When the drug substance is a liquid, and liquids have no inherent diffraction pattern, the diffraction pattern of a newly produced compound will obviously differ from that of an uncomplexed nanosponge. The complicated formation can be seen in this variety of diffraction pattern. When the drug material is a solid, a distinction must be established between the diffractogram of the approved complex and that of the mechanical mix of the polymer molecules and drug in the middle of the diffractogram.

5. Particle Size and Polydispersity[41]

Using a 90 Plus particle sizer with MAS OPTION particle sizing software, particle size can be determined using energetic light scattering. The polydispersity index and mean diameter can be calculated from this.

6. Zeta potential[41]

Surface charge is calculated using the zeta potential. Using an additional electrode in particle size instruments, it can be estimated.

7. Infra – Red spectroscopy[41]

This kind of spectroscopy is mostly utilised to determine the solid-state interaction between nanosponge and drug molecules. Nanosponge bands vary frequently during complex formation, and if the proportion of guest molecules contained in the complex is less than 25%, bands that may be assigned to the included part of the guest molecules are easily disguised by the bands of spectrum of nanosponges. Infrared spectroscopy can only be used on medications that have distinct bands, such as carbonyl or sulfonyl groups. The participation of hydrogen in various functional groups can be determined via infrared spectral investigations.

8. Thin layer chromatography (TLC)[42]

TLC is an evaporative or non-volatile mixture separation technique. If the Rf value of a drug molecule is within an acceptable range, this technique can be used to detect the development of a complex between the drug and the nanosponges.

9. Loading efficiency[43]

The numerical estimation of drug loaded into nanosponges by HPLC and UV spectrophotometer methods can be used to determine the loading efficiency of nanosponges.

Some of the Nanosponges based marketed formulation are listed in table 2.

Drug	Nanosponge vehicles	Indication	Reference
Resveratrol	β-cyclodextrine	Inflammation, cardiovascular diseases, dermatitis, gonorrhea	[44]
Econazole nitrate	Ethyl cellulose	Antifungal	[45]
Paclitaxel	β-cyclodextrine	Cancer	[46]
Antisense	Sodium alginate	Cancer therapy	[47]
Itraconazole	β-cyclodextrine	Antifungal	[48]
Campothecin	β-cyclodextrine	Cancer	[49]
Tamoxifen	β-cyclodextrine	Breast cancer	[50]

Applications[51]

Because of their biocompatibility and adaptability, nanosponges have a wide range of applications in the pharmaceutical industry. Nanosponges can be utilised as an excipient in the pharmaceutical industry to make tablets, capsules, granules, pallets, suspensions, solid dispersions, and topical dosage forms. Nanosponges can hold both lipophilic and hydrophilic drug molecules, i.e., those that fall within the biopharmaceutical classification system (BCS-class II) as well as those that are weakly water-soluble.

A. Nanosponges as a sustained delivery system[52]

For the treatment of herpes simplex virus infection, is one of the most extensively utilised antiviral agents. Its absorption in the GI tract is sluggish, partial, and inconsistent. The in vitro release profile of acyclovir from several types of Nano sponges revealed that the drug was released continuously.

B. Nanosponges for drug delivery[53]

Because of their microscopic porosity structure, nanosponges can contain water-insoluble drugs. Solubility and permeability of drug nanosponges complexes are important factors in increasing dissolution rate. It has been claimed that nanosponges based on -cyclodextrine are three to five times more effective at delivering drugs to the target site. Nanosponges are solid in nature and can be made into oral, parental, topical, or inhalation dose forms. The nanosponges complexes are dissolved in a suitable excipient such as lubricants, diluents, and anti-cracking agent for the manufacture of tablets, capsules, or oral administration.

C. Nanosponges for protein delivery[54]

The preservation of the original protein structure both during the formulation process and during long-term storage is a major challenge in protein formulation development. Swaminathan et al investigated innovative cyclodextrin-based poly nanosponges that swell. They discovered a very good swelling capacity that remained steady for 72 hours using water uptake trials. The model protein employed was bovine serum albumin, which was integrated into the nanosponge. It was discovered that the swelling property of the protein had improved, as well as the protein's stability. The lactone ring opens up and develops an inactive carboxylate form at physiological pH. The fusion of camptothecin in nanosponges results in a delayed release profile in an active state that prevents the lactone form from hydrolyzing, resulting in increased stability.

D. Role of nanosponges for treatment of fungal infections[55]

Skin fungal infections are one of the most hazardous diseases in the world. Topical therapy is a popular alternative for treating coetaneous infections because it has several advantages, including the ability to focus medications directly to the infection site and the minimization of systemic side effects. The antifungal or pharmaceutical fungicide econazole nitrate (imidazole) is used topically to treat athlete's foot, ringworm, tineapityriasis versicolor, jock itch, and vaginal thrush. Cream, ointment, lotion, and solution are some of the econazole nitrate items available on the market. When applied to the skin, econazole nitrate does not absorb well, and successful therapy requires a high concentration of active drugs to be combined.

E. Nanosponges as a carrier for biocatalyst[55]

Nanosponges are used to transport enzymes, vaccines, proteins, and antibodies for use in diagnosis. In cyclodextrin nanosponge, proteins and other macromolecules are adsorbed and encapsulated.

Table 3: Formulation development research inspired by nanosponges.

Author Name	Drug used	Nanosponge ingredients	Result outcomes	Reference
Parbeen Singh *et al.*, Carbohydr Polym. 2018	Doxorubicin	Cyclodextrin nanosponges	After cholesterol hydrogen succinate was converted, cellular absorption of nanosponges was discovered and enhanced (CHS).	[56]
Yijie Chen *et al.*, ACS Nano. 2019	Organophosphates	Cloaked oil nanosponges	Oil nanosponges have been investigated as a multimodal detoxifying chemical prototype.	[57]
Zikhona Hayiyana *et al.*, Curr Pharm Des. 2016	Ocular drugs	Hydrophilic cyclodextrin based nanosponges	The outcome was investigated to enhance medication solubility and corneal penetration.	[58]
Maria Tannous *et al.*, Methods Mol Bio. 2021	Antibacteria, anticancer, antiviral drugs	Cyclodextrin nanosponges	Cyclodextrin nanosponges (CDNSs) are gaining a lot of attention from scientists for their capacity to address important bioavailability difficulties such inadequate solvency, slow disintegration, and restricted strength of several experts, as well as increase their survivability and reduce negative effects.	[59]
Ute Distler et al. ACS Nano. 2017.	Antibacterial drugs	Biomimetic nanosponges	It has been demonstrated that membrane-coated nanosponges combined with a variety of proteinomic compounds can be	[60]

			utilised as efficient "fishing aids" for the detection of dangerous substances specific to a particular cell type.	
Antonella Di Vincenzo et al. Beilstein J Org Chem. 2019.	Polyamionazides mixtures	Calixarene based nanosponges	Ingestion tests on a number of natural toxin model particles supported the nanosponges' perfect responsiveness to pH variations.	[61]
Monica Argenziano et al. Oncotarget. 2018	Anticancer drugs	Glutathione/pH-responsive nanosponges	It demonstrates that GSH/pH-NS are an effective tool for the managed transfer of SLs to heighten critical starvation and may raise the therapeutic potency of these substances.	[62]
Yacine Nait Bachir et al. Drug Dev Ind Pharm. 2019 Feb.	Salvia Officinalis essential oil	β-cyclodextrin nanosponges	Salvia officinalis is a basic nanoemulsion oil based on β-cyclodextrin-naphthalene dicarboxylic nanosponges that bring the highest potency and promising use in the drug industry	[63]
Martina Daga et al. Free Radic Biol Med. 2016.	Doxorubicin	glutathione-responsive cyclodextrin nanosponges(GSH-NS)	In xenograft tests, it was shown that GSH-NS prevented the growth of human tumours. It might be a practical drug delivery method in the future.	[63]

CONCLUSION

Nanosponges are a new type of drug delivery system that can treat hydrophilic and hydrophobic medicines by generating inclusion and non-inclusion complexes. They can provide medications orally, topically, or intravenously. Nanosponges can be used in lotions, creams, ointments, and other topical preparations in liquid or powder form. Targeting a medicine to a specific place decreases adverse effects, improves stability, increases formulation flexibility, and improves patient compliance. Nanosponges facilitate the release of insoluble medicines while protecting the active moieties from physicochemical degradation. Nanosponges can be used in a variety of dosage forms, including parenteral, aerosol, topical, tablets, and capsules, due to their small size and spherical shape.

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