Review Article

Nanosponges: A Versatile Novel Drug Delivery System

Nandish Kumar P D*, K Vineetha, Krishnananda Kamath K, A R Shabaraya
Department of Industrial Pharmacy, Srinivas College of Pharmacy, Valachil, Farangipete post, Mangalore, Karnataka, India-574143.
***Corresponding author's E-mail:** nandishkumarpd@gmail.com

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ABSTRACT

Nano sponges are tiny sponges that may circulate throughout the body and connect to the surface, releasing the substance in a controlled and predictable manner. The development of a nanosponge-based drug delivery system has been a significant step forward in tackling some biopharmaceutical issues. Nanosponge is a polymer-based sphere that can be used for both oral and topical medication delivery. For targeted drug delivery, a wide range of pharmaceuticals can be placed into nanosponge. Both lipophilic and hydrophilic medicines can be put into nanosponge. Another notable property is their aqueous solubility, which allows them to be utilized more consistently for drugs with low solubility, enhancing bioavailability, reducing drug toxicity, and preventing drug degradation. The goal of this paper is to explain the general introduction, characteristics, method of preparation, characterization and applications of nanosponges.

Keywords: Nanotechnology, Nanosponges, Encapsulation, Bioavailability, Novel drug delivery.

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INTRODUCTION

Nanotechnology has the potential to be the most significant engineering breakthrough since the industrial revolution. Nanotechnology has so far produced nanoparticles, nanocapsules, nanospheres, nano suspensions, nanocrystals, and nano-erythosomes, among other formulations. Nanotechnology is described as the synthesis and manipulation of materials at the nanoscale level in order to produce products with unique features. Nanomaterials have received a lot of interest in recent years. Richard P. Feynman, a physicist at Cal Tech, predicted nanomaterials in 1959. "There is lots of room at the bottom," he remarked, suggesting that scaling down to the nanoscale and beginning from the bottom was the key to future nanotechnology progress. Nanomaterials are materials with a minimum of one dimension within the vary of 1-100 nanometers.[1]

There are many different types of nanoparticles, including polymeric nanoparticles, solid-lipid nanoparticles, nanoemulsions, nanosponges, carbon nanotubes, micellar systems, and dendrimers, among others.[2] The compound can simply be transported for parenteral distribution in sterile water, saline, or other aqueous solutions. They can successfully be incorporated into topical hydrogel for topical administration.[3]

Nanosponges are a novel class of materials made up of small particles having a few nanometer-wide holes that may encapsulate a wide range of compounds. These particles are capable of transporting both lipophilic and hydrophilic molecules, as well as enhancing the solubility of molecules that are weakly water soluble.[4]

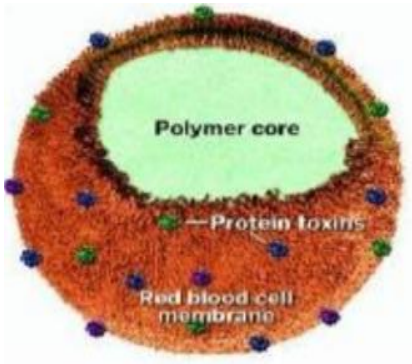

Figure 1: Structure of Nanosponges showing Loading of drugs

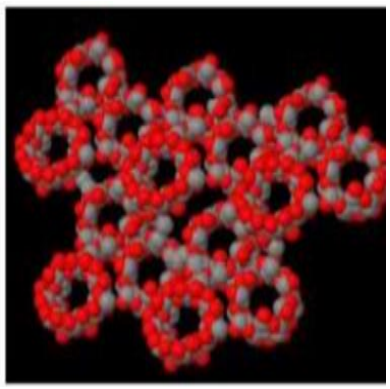

Figure 2: Molecular structure of cyclodextrin cavity for carbonates Nanosponges.

These microscopic sponges can move through the body until they reach the intended target region, where they adhere to the surface and start to release the medicine in a steady and controlled manner. For a given dosage, the drug will be more effective since it can be released at the precise target place rather than circulating throughout the body. These nanosponges also have an important property called aqueous solubility, which makes it possible to use these systems successfully for medications with limited solubility.[5]

Advantages of Nanosponges[6,7]

- Nanosponges allows components to be entrapped and thus reduces adverse effects.
- Remains stable at pH levels ranging from 1 to 11.
- They can withstand temperatures of up to 1300°C.
- They act like self-sterilizer, because of their tiny pore size (0.25m) which does not allow bacteria to penetrate.
- They are of low-cost and free-flowing.
- They improve the solubility of drugs that aren't easily soluble.
- They increase the bioavailability of drug.
- They have improved formulation flexibility, improved stability, and increased elegance.

Characteristics of Nanosponges[8-9]

There are several characteristics of nanosponges which make it different from other nanoparticles. Such characteristics are being discussed below:

- Nanosponges are insoluble in organic solvents & water, porous, nontoxic, and thermostable up to 300^{0}C, unlike other nanoparticles.
- Their size distribution is limited, with a mean diameter of less than 1 m.
- Carbonate nanosponges have a zeta potential of about 25 mV, which results with stable water suspensions that do not aggregate over time due to a higher zeta potential.
- Nanosponges protect the medication from physiological breakdown and are non-irritating, non-mutagenic, non-allergic, and non-toxic.
- By generating inclusion and non-inclusion complexes, nanosponges can encapsulate a variety of pharmacological compounds.
- Nanosponges are porous particles that are primarily utilized to encapsulate medications that are poorly soluble.

Demerits and Challenges[10-11]

- Nanosponges are only capable of encapsulating small molecules, making them unfit for bigger molecules.
- Dosing dumping may occur.

Types of Nanosponges[12]

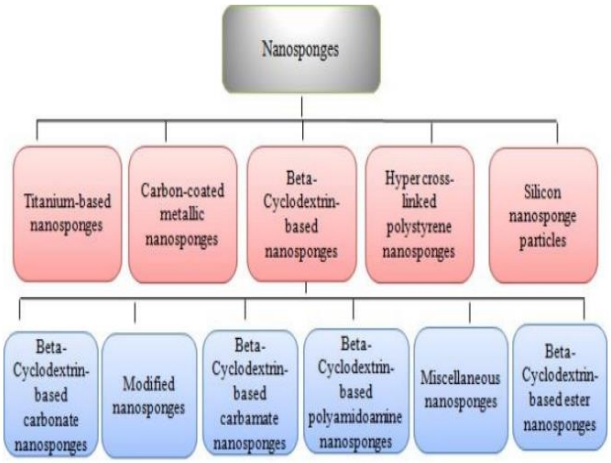

Figure 3: Types of Nanosponges

COMPOSITION OF NANOSPONGES

1. Polymer and copolymers

The choice of polymer can have an impact on the development and performance of nanosponges. The cavity size must be appropriate for incorporating the specific medication molecule. The polymer chosen is determined by the needed release and the medicine to be encapsulated. The chosen polymer should have the ability to bind to specified ligands.

Eg. Cyclodextrins and their derivatives such as Methyl-cyclodextrin (-CD), alkyloxy carbonyl cyclodextrins, 2-hydroxy propyl-CDs, and copolymers such as poly (Valero lactoneallylvalero lactone) and poly (Valero lactone-allyl Valero lactone oxepanedione), Hyper cross-linked polystyrenes, ethyl cellulose and PVA are among the polymers used to make nanosponges.[13]

2. Cross linking agents

The cross-linking agent can be selected based on the structure of the polymer and the medicine that will be synthesized. Depending on the type of cross linkers used, water soluble or insoluble nanosponge structures are created.

Examples: Diphenyl Carbonate, Diarylcarbonates, Di-Isocyanates, Pyromellitic anhydride, Carbonyl-di-Imidazoles, Epichloridrine, Glutaraldehyde, Carboxylic acid dianhydrides, 2,2-bis(acrylamido) Acetic acid and Dichloromethane. [14]

FACTORS AFFECTING FORMULATION OF NANOSPONGES[15, 16, 17]

1. Type of Drug
2. Type of Polymer used
3. Temperature
4. Method of preparation nanosponge
5. Degree of substitution

1. Type of Drug

The therapeutic molecules that will be used in incision and non-incision nanosponge complexes should have the following characteristics:

1. The drug molecule's structure should not include more than five condensed rings.
2. The drug's melting point should be less than 250°C.
3. In water, drug solubility should be less than 10 mg/ml.
4. The molecular weight of drug should be between 100 and 400 gm/mole.

2. Type of Polymers Used

The type of polymer employed in nanosponge formulation can have an impact on the nanosponge formation and performance. The polymer utilised in the formulation determines the size of the nanosponge cavity and drug complexation.

3. Temperature

The drug/nanosponge complexation can be affected by temperature changes. Reduces the perceived stability's magnitude by a factor of two. The constant increase in temperature of the Drug/Nanosponge complex could be related to the likely lowering of drug/Nanosponge contact forces as temperature rises.

4. Method of Preparation Nanosponges

The loading of a drug into a nanosponge has the potential to change the nanosponge/drug complexation. In any instance, the success of a method is determined by the nature of the drug and polymer. Freeze drying has proven to be the most effective way for drug complexation in many cases.

5. Degree of Substitution

The type, amount, and placement of the substituent on the parent molecule can all affect the ability of nanosponge to complex.

METHOD PREPARATION OF NANOSPONGES

There are several methods of preparation of Nanosponges:

(ⅰ) Solvent method

(ⅱ) Ultrasound-assisted synthesis

(ⅲ) Emulsion solvent diffusion method

(Ⅳ) From Hyper crosslinked β-Cyclodextrin.

Solvent method

The polymer is combined with a suitable solvent, preferably a polar aprotic solvent such as dimethylformamide or dimethyl sulfoxide. This mixture is applied to an excess of crosslinker, preferably in a 4 to 16 molar ratio of crosslinker to polymer. The reaction is carried out at temperatures ranging from 10 °C to the solvent's reflux temperature for 1 to 48 hours. Carbonyl compounds are preferred cross linkers (dimethyl carbonate and carbonyl diimidazole).[18]

Following the completion of the reaction, the solution is allowed to cool to room temperature before being added to a substantial amount of distilled water, filtered under vacuum, and purified using a long Soxhlet extraction with ethanol. The product is vacuum dried and pulverised in a mechanical mill to produce a homogenous powder.[19]

Ultrasound-assisted synthesis

Nanosponges can be made using this process, which involves reacting polymers with cross-linkers in the absence of a solvent and sonication. The nanosponges produced will be spherical, homogenous in size, and less than 5 microns in diameter. The cross-linker in this approach is di-phenyl carbonate (or) pyromelitic anhydride. Place the flask in a water-filled ultrasonic bath and heat it to 90°C. For 5 hours, sonicate the mixture.[20]

Emulsion solvent diffusion method

Different concentrations of ethyl cellulose and polyvinyl alcohol can be used to make nanosponges. To optimise drug loading and achieve a customised release, several drug-to-polymer ratios are used. The dispersed phase with drug and polymer dissolved in 20 mL dichloromethane, is slowly added to a specific amount of polyvinyl alcohol in 100 mL of aqueous external phase using a magnetic or mechanical stirrer at 1000-1500 rpm for 3-5 hours. The generated nanosponges are filtered and dried in an oven at 40°C for 24 hours before being placed in a container.[21]

Hypercrosslinked β-Cyclodextrin

Cross connecting different types of cyclodextrins (CD's) with a carbonyl or dicarboxylate chemical as a cross linker can produce nanosponges. To optimise drug loading and obtain a customised release profile, the ratio of CD's can be changed during preparation. β -cyclodextrin nanosponges are generated by placing 100 ml of Dimethyl Formamide (DMF) in a round bottomed flask and adding 17.42g of anhydrous β -CD to accomplish complete dissolution. The solution is then added to 9.96 g of carbonyl di-imidazole (61.42 mmol) and allowed to react for 4 hours at 100°C. The transparent block of hyper cross linked cyclodextrin is roughly crushed once condensation polymerization is done, and an excess of deionized water is added to remove DMF. Finally, by using Soxhlet extraction with ethanol, any leftover byproducts or

unreacted chemicals are totally eliminated. The resulting white powder is dried in a 60°C oven overnight before being ground in a mortar. Water is used to disperse the fine powder that had been obtained. The colloidal part of the solution that remained suspended in water is extracted and lyophilized. The resulting nanosponges are sub-micron in size and spherical in shape.[22.23]

CHARACTERIZATION OF NANOSPONGES

Thermo-analytical methods

Thermo-analytical methods evaluate whether the drug substance changes before the nanosponge is thermally degraded. Melting, evaporation, breakdown, oxidation, and polymorphic transition are examples of drug substance changes. The presence of a change in the drug substance implies the creation of a complex. Broadening, shifting, and the emergence of new peaks or the elimination of certain peaks can be detected in the thermogram acquired by DTA and DSC. Changes in weight loss can also be used as evidence for the establishment of inclusion complexes.[24,25]

Microscopy studies

The microscopic characteristics of the medication and a nanosponge formulation can be studied using scanning electron microscopy (SEM) and transmission electron microscopy (TEM). The morphology of nanosponges is studied using SEM. The contrast in crystallization state of the raw materials used to manufacture nanosponge and the final formulation, as examined under electron microscope, demonstrates the formation of inclusion complexes.[26]

Zeta potential

The zeta potential is used to determine the surface charge and type of nanosponges using the zeta sizer device. The study will benefit from a possible charge of around 30Mv.[27]

Particle size determination

The particle size of Nanosponge is an important parameter in the process of nanosponge optimization. The drug's particle size can have an impact on its release as well as its solubility. The instrument, laser light diffractometry, or a Zeta sizer can be used to determine particle size. To investigate the effect of particle size on drug release, the cumulative percentage drug release from nanosponges of various particle sizes can be plotted versus time. Particles bigger than 30 m can have a gritty feel, hence particles between 10 and 25 m are preferable for topical medication administration.[28]

In vitro release studies

Using a multi compartment rotating cell with dialysis membrane, the drug release from the optimized nanosponge formulation may be investigated. In distilled water, drug-loaded nanosponge complexes are present in both the donor and receptor phases. After a set amount of time, the receptor phase is removed, diluted with distilled water, and examined with a UV spectrophotometer.[29]

X-ray diffractometry and single crystal X-ray structure analysis.

In the solid state, X-ray diffractometry can be used to identify inclusion complexation. When a drug molecule is liquid and does not exhibit its own diffraction pattern, the newly created substance diffraction pattern obviously differs from that of uncomplexed nanosponges. The difference in diffraction patterns shows the creation of an inclusion complex. When the drug component is solid, a comparison between the diffractograms of the assumed complex and a mixture of drug and polymer molecules must be made. Diffraction patterns are altered as a result of the drug's complex creation with nanosponges, as well as the drug's crystalline structure. The complicated creation causes existing peaks to sharpen, the appearance of a few new peaks, and the shifting of some summits.[30]

Solubility studies

Higuchi and Connors' phase solubility method, which investigates the influence of a nanosponge on drug solubility, is the most extensively used method for studying inclusion complexation. The degree of complexation is indicated by phase solubility diagrams.[31]

Thin Layer Chromatography

The Rf values of a drug molecule decrease significantly in Thin Layer Chromatography, which aids in recognizing the complex formation between the drug and nanosponge.[32]

APPLICATIONS OF NANOSPONGES

Nanosponges for drug delivery

Nanosponges can transport water-insoluble medicines due to their nanoporous properties. Nanosponge can speed up the dissolution of medications, improve their solubility and stability, hide undesirable flavours, and convert liquids to solids. Nanosponges made of cyclodextrin are said to transport drugs to the target place more effectively than direct injection. Nanosponge can be formed into oral, parenteral, topical, or inhalation dosage forms due to its solid structure. They could be mixed with excipients, diluents, lubricants, and anticaking agents to make capsules or tablets for oral delivery. They can be transported in sterile water, saline, or other aqueous solutions for parenteral delivery. They can be mixed into a topical hydrogel for topical delivery.[33]

Nanosponges for cancer therapy

Because of their low solubility, anticancer medication distribution is one of the most difficult jobs in the pharmaceutical industry today. According to one study, the nanosponge combination is three times more effective than direct injection in suppressing tumour growth. A specific peptide is firmly linked to a top layer of radiation-induced cells on the tumour receptor after a complex loading of the nanosponge with a medication. When the

nanosponges come into contact with a cancer cell, they adhere to its surface and begin to release medication molecules. Targeting medicine administration has the advantage of achieving a more effective therapeutic impact at the same dose with fewer side effects.[34]

The role of nanosponges in fungal infection treatment

One of the most serious diseases in the world is fungal skin infections. Topical therapy is a promising therapeutic option for skin infections because it has a number of advantages, including the ability to target medications directly to the infection site and lowering systemic side effects. Itraconazole is an antifungal medicine classified as a class II biopharmaceutical, with a slow dissolution rate and low bioavailability. Itraconazole nanosponges is found to boost its solubility and alleviated the bioavailability problem. The solubility of itraconazole can be increased in these nanosponges if -cyclodextrin is utilised as a carbon cross linked and loaded with itraconazole.[35]

In the treatment of blood poisoning as an absorbent

By absorbing the toxin, nanosponges can remove the hazardous poisonous chemical from our blood. Instead of utilising antidotes, we can use nanosponges to absorb toxins by injecting them into the bloodstream. The nanosponge imitates a red blood cell in the bloodstream, leading toxins to assault and absorb it.[36]

To improve the poor solubility of drugs

One of the most important issues to address throughout the design and development of materials is poor solubility. The efficacy of a formulation can be harmed by medication solubility issues. Nanosponge serves as a carrier for molecules, encapsulating them in its core and attempting to improve the formulation's solubility. The current way for increasing solubility is using a -cyclodextrin nanosponge.[37]

Table 1: List of drugs given as Nanosponges[38, 39, 40]

SL.no	Drug	Category	Polymer used	Method of preparation
1.	Clotrimazole	Antifungal	Ethyl cellulose	Emulsion solvent diffusion
2.	Lornoxicam	NSAIDs	Ethyl cellulose	Emulsion solvent evaporation
3.	Dapsone	Antibacterial	Ethyl cellulose	Solvent evaporation
4.	ketoconazole	Antifungal agents	Diphenyl carbonate	Cross linking

CONCLUSION

The nanosponges will retain either lipophilic or hydrophilic medicines and release them in a controlled and predictable manner at the target spot. They can consistently administer medications to the desired region via a variety of methods including oral, topical, and parenteral. Nanosponges have been proved to be a safe and efficient delivery mechanism for pharmaceuticals and other applications in addition to medication delivery.

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