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NANOSPONGES: A NOVEL STRATEGIC APPROACH FOR DRUG DELIVERY

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ABSTRACT
Pharmaceutical nanotechnology, the most recent field of pharmaceutical sciences, offers new tools, prospects, and scope that are intended to have major implications in disease diagnostics and therapies. Pharmaceutical nanotechnology is made up of nanoscale materials that can be altered in a variety of ways to improve their properties. Nanosponge is one of the nanoformulations. 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. These can transport both hydrophilic and hydrophobic medications. Nano sponge technology is frequently used to deliver controlled and predictable drug delivery to the target region. Nano sponges also have the ability to increase the solubility of drugs that are poorly water soluble. Nanosponges have been examined in this review in terms of their benefits, composition, preparation process, evaluation, and application.

KEYWORDS: Nanotechnology, Nanosponges, solubility.

INTRODUCTION
The pharmaceutical and health-care industries have been developing and employing nano-scale materials to solve a variety of physical, biological, and chemical issues connected to disease treatment. The hydrophobic nature of the majority of the pharmaceuticals makes in vivo delivery difficult. The efficacy of such medications has been greatly improved by shrinking materials to nano size. A variety of polymers have been investigated and employed in the development of novel medication delivery methods. [1]

An optimal medication therapy achieves effective drug concentration at the target site for a given amount of time while reducing both general and local side effects. The correct dose of medicine should be used to get the desired therapeutic effect. Targeted drug delivery refers to the distribution of a drug to a receptor, organ, or other portion of the body to which it is specifically intended. Medical specialists have long grappled with how to deliver medication to the correct spot within the frame while also managing the release of the medication to avoid overdose. Nanosponges, a fresh new and complicated molecule, have the potential to solve this problem.[2]

Nanosponges are small particles with a few nanometer-wide cavities that can encapsulate a wide rage of compounds. These particles contain both lipophilic and hydrophilic compounds, increasing the solubility of molecules that are poorly water soluble. Nanosponges, which are tiny mesh-like structures, may revolutionise the treatment of numerous diseases, according to research. Early trials suggest that this technology is up to five times more successful at delivering medications for breast cancer than traditional approaches.[3]

Nanosponges are encapsulating nanoparticles with therapeutic molecules encapsulated within their core. Nanoparticles are divided into three categories based on how they associate with drugs: encapsulating nanoparticles, conjugating nanoparticles, and complexing nanoparticles.[4] They are insoluble in both water and organic solvents, porous, non-toxic, and stable at high temperatures up to 300°C, compared to other nanoparticles. Because of their unique 3D structure, which includes nanometric-sized voids and variable polarity, they can capture, transport, and selectively release a wide range of chemicals.[5]

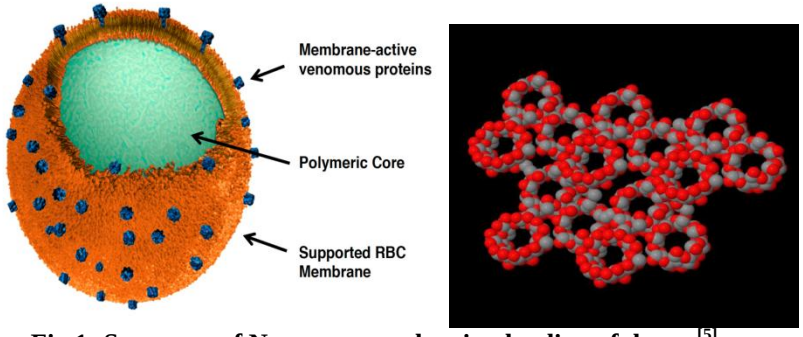

Fig 1: Structure of Nanosponges showing loading of drugs.[5]

Fig 2: Molecular structure of cyclodextrin cavity for carbonates nanosponge.[5]

Advantages[6]

- Ingredient entrapment is more efficient, and adverse effects are decrease.
- Improved stability, increased elegance and enhanced formulation flexibility
- These compositions are temperature stable up to 130°C.
- Most vehicles and chemicals are suitable with these formulations.
- These are self-sterilizing because the average pore size is 0.25m, preventing bacteria from penetrating.
- These are cost-effective and free-flowing.
- These are inexpensive and easy to use.
- They improve the solubility of drugs that are poorly soluble.
- It can be used to mask flavours and solidify liquid substances.
- These formulations improve the drug's bioavailability.
- They do not irritate the skin. Non-mutagenic, non-toxic, and allergy-free.
- It features a long-acting formula that lasts up to 12 hours.
- Commercial production is simple to scale up.
- The substance utilised in this technique can act as a protective barrier, preventing the medicine from being destroyed prematurely within the body.

Disadvantages[7,8]

- They only contain tiny molecules.
- They are solely dependent on the loading capacity.
- Dose dumping may occur at times

Characteristics[9]

- By altering the crosslinker to polymer ratio, nanosponges of specific sizes can be created.
- They're nontoxic, porous particles that are insoluble in most organic solvents and can withstand temperatures of up to 300°C. They are pH stable between 1 and 11.
- They can be recreated using simple thermal desorption, solvent extraction, microwaves, and ultrasounds.
- Chemical linkers allow nanosponges to bind to the target location more effectively.
- Nanosponges can produce inclusion and non-inclusion complexes by combining with certain substances.

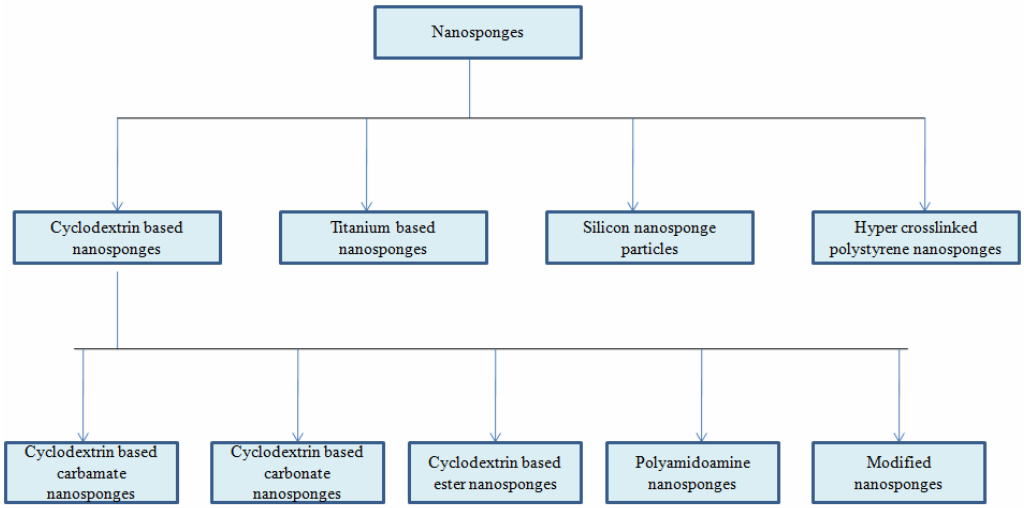

Fig 3: Types of Nanosponges.

Chemicals used for the nanosponge formulation

Polymers	copolymers	Cross linkers
Hyper cross linked polystyrenes cyclodextrines and its derivatives like Methyl β-Cyclodextrin, Alkyloxycarbonyl cyclodextrins, Hydroxy propyl β- cyclodextrin	Poly (Valerolactone - allylvalererolactone oxepanedione), Poly vinyl alcohol, Ethyl cellulose, poly (Valerolactone - allylvalererolactone)	Carboxylic acid dianhydrides, carbonlyl diimidazoles, Diarylcarbonates, Epichloridine, Diisocyanates, Gluteraldehyde

Factors influence Nanosponge formulation

Type of polymer

The type of polymer utilised can have an impact on Nanosponge creation and performance. The cavity size of the nanosponge should be large enough to admit a drug molecule of a specific size for complexation.[10]

Type of drugs

Certain characteristics of drug molecules that will be complexed with nanosponges are listed below.

- The drug's molecular weight should be between 100 and 400 Daltons.
- Less than five condensed rings make up a drug molecule.
- Water solubility should be less than 10 mg/ml.
- The substance's melting point should be less than 250°C.[11]

Temperature

Drug/Nanosponge complex can be affected by temperature fluctuations. In general, rising temperature reduces the magnitude of the apparent stability constant of the Drug/Nanosponge complex, which could be owing to a reduction in drug/nanosponge contact forces like van-der waal forces and hydrophobic forces.

Method of preparation

Drug/Nanosponge complex can be affected by how the drug is loaded into the nanosponge. However, because the success of a method is dependent on the nature of the drug and polymer, freeze drying has been proven to be the most effective way for drug complexation in many circumstances.

Degree of substitution

The type, number, and position of the substituent on the parent molecule can affect the nanosponge's capacity to complex.[12]

Method of preparation of Nanosponges

- Solvent method
- From Hypercrosslinked β-cyclodextrin
- Ultrasound-assisted synthesis
- Emulsion solvent diffusion method

Solvent Method

Nano sponges are made by mixing polar aprotic solvents like Dimethyl sulfoxide (DMSO) and Dimethylformamide (DMF) with the polymer using the solvent technique. In a 1:4 ratio, a crosslinker is subsequently added to the mixture. The present reaction should be carried out at 10°C to reflux the solvent temperature for 1 to 48 hours. After the reaction is complete, the solution is allowed to cool to room temperature before being added to bi-distilled water. The product is recovered by filtering it under vacuum and refining it with ethanol soxhlet extraction and drying.[13,14]

From Hyper cross-linked β-cyclodextrins

Hyper cross linked cyclodextrin polymers nano organized to form 3-dimensional networks have recently been developed; a roughly spherical structure, about the size of a protein, with channels and pores inside. They're made by combining cyclodextrin with cross-linkers such di isocianates, diaryl carbonates, Dimethyl carbonate, diphenyl carbonate, carbonyl di-imidazoles, carboxylic acid dianhydrides, and 2, 2-Bis (acrylamido) acetic acid. To connect different molecules, sponges' surface charge density, porosity, and pore diameters can be adjusted. A low cross-linked nanosponge allows for rapid drug release.[15, 16]

Ultrasound-assisted synthesis

In this process, nano sponges are made by sonicating polymers with carbonyl cross linkers in the absence of solvent. The spherical dimension of these Nano sponges will be uniform. In a flask, combine the polymer and cross-linker in an appropriate amount. For ultrasonication, the flask is filled with water and heated to 90°C. For continuous sonication, the mixture is held for 5 hours. The combination is then cooled, and the result is rinsed with distilled water before being purified with a soxhlet extractor and ethanol. The final product is dried at 25^0C, and the whitish powder is collected and stored away from moisture.[17]

Emulsion solvent diffusion method

Ethyl cellulose and polyvinyl alcohol, in various quantities, are the major polymers employed in this process. The dispersed phase is created by combining ethyl cellulose with the available medication, which has been dissolved in 20ml of dichloromethane. The continuous phase drop wise addition is made by dissolving polyvinyl alcohol in 150 mL distilled water. Then the mixture is allowed to stir for 1000rpm for about 2 hrs. The obtained Nano sponges are collected, filtered

and dried in oven for around 1 day and stored in desiccators.[18]

Loading of drug into Nanosponges

The drug delivery nanosponges should first be pretreated to achieve a mean particle size of less than 500nm. The nanosponges are then suspended in water for some time and subjected to sonication so as to avoid the formation of aggregates. A colloidal fraction is obtained by centrifuging the obtained product suspension. The obtained supernantant is separated, and the sample is freeze dried. In other way a nanosponge aqeous suspension is prepared and dispersed it with constant stirring for a specific period of time. The nanosponge solid crystals are obtained by the solvent evaporation or either by freeze drying. The nanopsonge crystal structure plays a very important rule in the complexation with the drug. The drug loading is high in crystalline nanosponge than the paracrystalline one. In nanosponges which contain poor crystalline structure the drug loading occurs as a mechanical mixture rather than forming inclusion complex.[19]

Characterization Parameters of Nanosponges.[20-29]

Sl. NO	Characterization parameters	Objective	Refs
1	Solubility study	HPLC is used to determine the drug concentration.	[20]
2	Porosity	Performed to determine the number of nanochannels and nanocavities formed.	[21]
3	Loading efficiency	The amount of drug loaded into nanosponges is determined quantitatively.	[22]
4	Microscopic studies	Scanning electron microscopy and transmission electron microscopy are used to study the morphology and surface topography.	[23]
5	Particle size and polydispersity	The particle size is calculated by dynamic light scattering with a 90Plus particle size reequipped with 'MAS OPTION' particle sizing software. The polydispersity index and mean diameter are calculated using this method.	[23]
6	Thermo analytical methods	Before the thermal degradation of the nanosponge, this method evaluates whether the drug substance undergoes any changes (such as melting, evaporation, breakdown, oxidation, or polymorphic transition).	[24]
7	Zeta potential	The electric potential is examined during zeta potential measurement. The zeta potential is used to determine the stability of the formed nanosponges.	[24]
8	Swelling and water uptake	By soaking the prepared nanosponges in an aqueous solution, these can be determined.	[25]
9	Drug release kinetics	To identify the release pattern, drug release is computed.	[25]
10	X-ray diffractometry	In the solid state, it's utilised to identify inclusion complexation.	[26]
11	Infrared spectroscopy	It's utilised to figure out how nanosponges interact with drug molecules in the solid state.	[26]
12	Raman spectroscopy	It's used to figure out how molecular structures work.	[27]
13	Thin layer chromatography	It helps in the identification of the drug-nanosponge complex development.	[28]
14	Saturation state interaction	This study is carried out to find out the drug loading in a saturated state using UV-spectroscopy.	[29]

Application of Nanosponges

Drug	Indication	Reference
Camptothecin	Prostate tumor and thyroid cancer	[30,31]
Cefadroxil	Broad spectrum antibiotic	[32]
Alprostadil	Erectile dysfunction	[7]
Celecoxib	NSAID	[33]
Dexamethasone	Ocular infection, brain tumors	[34,35]
Heparin	Anticoagulant	[36]
Nifedipine	Angina pectoris	[37]
Gabapentin	Epilepsy	[38]
Quercetin	Anticancer	[39]
Rilpivirine	HIV	[40]
Tamoxifen	Breast cancer	[41]
Resveratrol	Inflammation, breast cancer	[22]

Paclitaxel	Cancer	[42]
Itraconazole	Antifungal	[43]

Solubility enhancement[44]

Nanosponges can help compounds that have a low water solubility enhance their wetting and solubility. The medications can be molecularly disseminated within the nanosponge structure before being released as molecules, eliminating the need for dissolution. As a result, the drug's perceived solubility can be boosted. Many formulation and bioavailability issues can be overcome by increasing a substance's solubility and dissolving rate, and nanosponges can significantly increase drug solubility.

Nanosponges for drug delivery[45]

The nanosponges are solid in nature and can be used in dose forms such as oral, parenteral, topical, and inhalation. The complexes may be disseminated in a matrix of excipients, diluents, lubricants, and anticaking agents suitable for the manufacture of capsules or tablets for oral delivery. The compound can be transported in sterile water, saline, or other aqueous solutions for parenteral delivery. They can be efficiently integrated into topical hydrogels for topical delivery.

In enzyme immobilization[46,47]

Immobilization enhances enzyme stability and alters features such as enantioselectivity and reaction speeds, which is particularly advantageous for lipases. As a result, there is a continuing demand for new solid supports that are suited for this family of enzymes. The remarkable catalytic efficiency of Pseudomonas fluoresces lipase adsorbed on a new type of cyclodextrin-based NSs was reported by Boscolo *et al.*

As a carrier for delivery of gases[48]

Gases are used extensively in medicine for diagnostic and therapeutic purposes. Hypoxia, or a lack of oxygen supply, is linked to a variety of diseases, ranging from inflammation to cancer. As a result, delivering oxygen gas in the proper form and quantity in clinical practise might be challenging at times. Cavalli *et al*., created NSs formulations as topical oxygen delivery systems with the potential to store and release oxygen slowly over time.

As a protective agent from light or degradation[49]

Gamma-oryzanol was enclosed in the creation of NSs, providing excellent photoprotection. With the gammaoryzanol-loaded NSs, an O/W emulsion and a gel were created. Gamma-oryzanol is a ferulic acid ester combination that has newly gained popularity as a natural antioxidant. It is commonly used to stabilise food and pharmaceutical raw materials, as well as a sunscreen in the cosmetics industry. Because of its high instability and photo degradation, its applicability is limited.

Cancer therapy[50]

A tumour delivery system is a device that transports tumours from one location to another. They claim that the procedure is three to five times more successful than injecting the medications directly into the tumour. The small nanosponges contain a drug load and expose a targeting peptide that binds to the tumor's radiation-induced cell surface receptors. When the sponges come into contact with tumour cells, they attach to the surface and release their cargo. Targeted drug delivery has several advantages, including more effective treatment at the same dose and fewer adverse effects. Animal studies with paclitaxel as the sponge load have been conducted so far.

Because of its poor aqueous solubility, lactone ring instability, and substantial side effects, camptothecin, a plant alkaloid and strong anticancer agent, has limited therapeutic usefulness. Cyclodextrin-based nanosponges are a new class of cross-linked cyclodextrin derivatives.

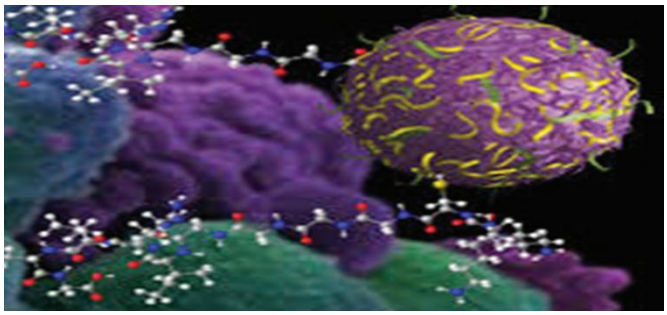

Fig 4: Nanosponge particles attach to a human breast cancer Cells.[50]

Topical agent[51]

The nanosponge delivery system is a one-of-a-kind device for the regulated release of topical medicines with long-term drug release and skin retention. Traditional dermatological and personal-care solutions often include active substances in high concentrations but for a short period of time. This could result in a cycle of short-term overmedication and long-term undermedication. When active substances permeate the skin, they might cause rashes or more serious side effects; a consistent rate of release that reduces discomfort while maintaining efficiency. A designed product can contain a wide range of components, including gel, lotion, cream, ointment, liquid, or powder.

Econazole nitrate is an antifungal cream, ointment, lotion, and solution that is used topically to relieve the symptoms of superficial candidasis, dermatophytosis, vesicular, and skin infections. When econazole nitrate is applied to the skin, adsorption isminimal, and substantial concentrations of active substances are necessary for effective therapy. Thus, by using the emulsion solvent diffusion approach, econazole nitrate Nanosponges were created, and these Nanosponges were placed into a hydrogel as a local depot for sustained drug release.

Name of the research	Title of project	Conclusion	Reference
Trotta F *et al.,*	Molecularly imprinted cyclodextrin nanosponges for the controlled delivery of L-DOPA: perspectives for the treatment of Parkinson's disease	MIP-NSs appear to be a good choice for L-DOPA storage and distribution management.	[52]
Arvapally *et al,.*	Formulation and in vitro evaluation Of Glipizide nanosponges	The optimized formulation's release kinetics was better suited to the Higuchi model, demonstrating zero-order drug release via the Fickian diffusion process.	[53]
Zainuddin R, *et al.*	Enhancement of oral bioavailability of Anti-HIV drug rilpivirine HCl through nanosponge formulation	The technique provides a suitable dosage range for AIDs patients, reducing the need to take medications just when they are fed.	[54]
Momin M, *et al*	Extended-release delivery of Erlotinib glutathione nanosponge for targeting lung cancer	Nanosponge can encapsulate high-efficiency anticancer medicines, which have a longer half-life and a stronger antiproliferative activity than free drugs, resulting in site-specific drug delivery and superior cellular drug absorption.	[55]
Wang *et al.,*	Nonviolent Self -Catabolic DNAzyme Nanosponges for Smart Anticancer Drug Delivery	The current DNAzyme NS framework could be used to demonstrate outstanding biomedical and bioengineering applications.	[56]

CONCLUSION

The nanosponges can transport the drug to the desired location in a regulated manner. They have the ability to transport both lipophilic and hydrophilic compounds. These can be created as many dose forms such as oral, parenteral, and topical treatments due to their small particle size and spherical shape. Nanosponge technology allows substances to be entrapped, resulting in fewer adverse effects, more stability, increased elegance, and higher formulation flexibility. As a result, Nanosponge technology delivers targeted drug administration and extends dosing intervals, enhancing patient compliance. The use of nanosponge formulations in the pharmaceutical industry could be the most effective way to address a variety of nano-related concerns.

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