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Research Article

Nanosponges

Nanosponges: A Novel Class of Versatile Drug Delivery System – Review

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Nanotechnology advancements have resulted in the creation of tailored medicine delivery systems. However, properly targeting a molecule to a specific region with a drug delivery system necessitates using a specialized drug delivery system. The development of nanosponge has become a crucial step in solving some challenges such as drug toxicity, low bioavailability, and predictable drug release. Many drug delivery methods, such as nanoparticles, nanoemulsions, nanosuspensions, and nanosponges, have been developed via nanomedicine technology. Nanosponges are little sponges like the size of a virus that may be loaded with a vast range of medications. Nanosponges serve an essential function in regulated medication delivery. These mini sponges may flow throughout the human body until they reach the same target region. They adhere to the surface and begin to release the medicine in a regulated and predictable way. The outside surface is often porous, which allows for regulated medication release. The important feature of these sponges is their aqueous solubility, which makes them appropriate for medications with low solubility. Their molecular architecture is often composed of several polymer chains that can generate unique microdomains suited for co-encapsulating two medicines with different chemical structures. When used to release insoluble medications, nanosponges also shield the active components from physicochemical deterioration. Nanosponges can be made into a number of dosage forms, including parenteral, aerosol, tablets, topical, and capsules, thanks to their small size and spherical structure. This study focuses on the techniques of synthesis and applications of nanosponges in the realm of medication delivery.

Keywords: Nanosponges, Nanomedicine, Parenteral, Aerosol, Topical, Bioavailability

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Introduction

To achieve the desired outcome, targeting drug delivery systems has been an aspiration for an extended period of time. The Nanosponge medication delivery device was initially only accessible as a topical delivery method. However, Nanosponges can now be used intravenously and orally in the twenty-first century (IV)1.

A modern kind of substance called a "nanosponge" consists of tiny molecules, a mini-scale void, and a few manometers. Various shorts of substances can be utilized to fill these narrow pouches. These small molecules have the capability to transport both non-polar and polar medicinal materials, which makes lipophilic drug substances or molecules2 more stable. The nanosponges are a 3D scaffold (backbone) or matrix of polyester that can break down naturally. These polyesters are combined with a cross linker in a mixture to form Nanosponges. Polyester disassemble moderately in the body because it usually is biodegradable. When the scaffold of nanosponges opens up, it releases the drug molecules loaded in a derogatory fashion.

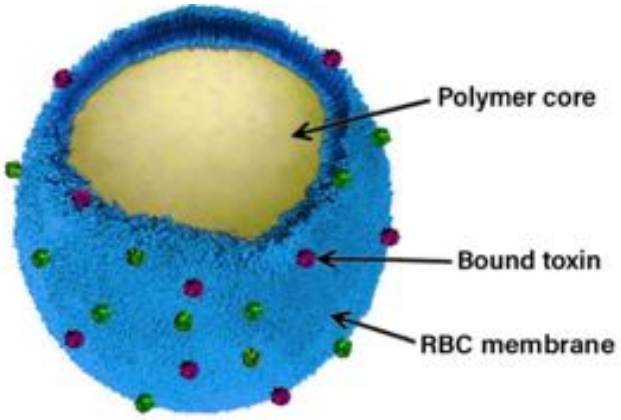

Figure 1: Structure of Nanosponge

Advantages

1. These compositions can be utilized with most vehicles and additives. 3

2. They improve the drug's bioavailability. 4

3. These formulas remain stable in the pH range of 1 to 11.

4. Entrapment of chemicals and a reduction in adverse effects are also features of this technology. 5

5. They improve a drug's low solubility.

6. These compositions are stable up to 1300C.

7. The average pore size is 0.251 mm, meaning that bacteria cannot pass through them, making them self-sterilizing.

8. Nanosponges allow precise control over the drug molecules' release rate.

9. Decreasing the dosage frequency.

10. Nanosponges can be used as a safe, non-allergic, and non-toxic drug delivery system.

11. Nanosponges assist in removing noxious and harmful compounds from the body.

12. Improved patient compliance.

Disadvantage of Nanosponges-

1. Sometimes, there may be dose dumping.6

2. Purely rely on loading capacities

3. Only small molecules are found in nanosponges.7

Methods of Preparation

Solvent method

Primarily, a polar aprotic solvent like dimethyl formamide or dimethyl sulfoxide is used to mix the solvent and polymer. then a surplus amount was put at a ratio of 4:16 to the cross-linker. (8)

The reaction should continue for 1 to 48 hours at a temperature of 10 oC to reflux the solvent's temperature. Following completion of the reaction, the mixture is cooled to room temperature.

The outcome is included in the bidistilled water. To create a uniform powder, the product is vacuum-dried and then crushed in a mill (9).

Synthesis using ultrasound

Polymer and cross linkers are reacted without adding a solvent to produce nanosponges while maintaining sonification. This approach yields nanosponges that are spherical and uniform in size(10).

The polymer is combined with cross-linkers in a uniform ratio in a flask. Then the flask is positioned in a molar ratio in a water-filled ultrasonic bath. The temperature is kept at 90oC for 5 hours before the mixture is sonicated (11). The Product Is Vacuum Dried At 25oc Before Being Used (12).

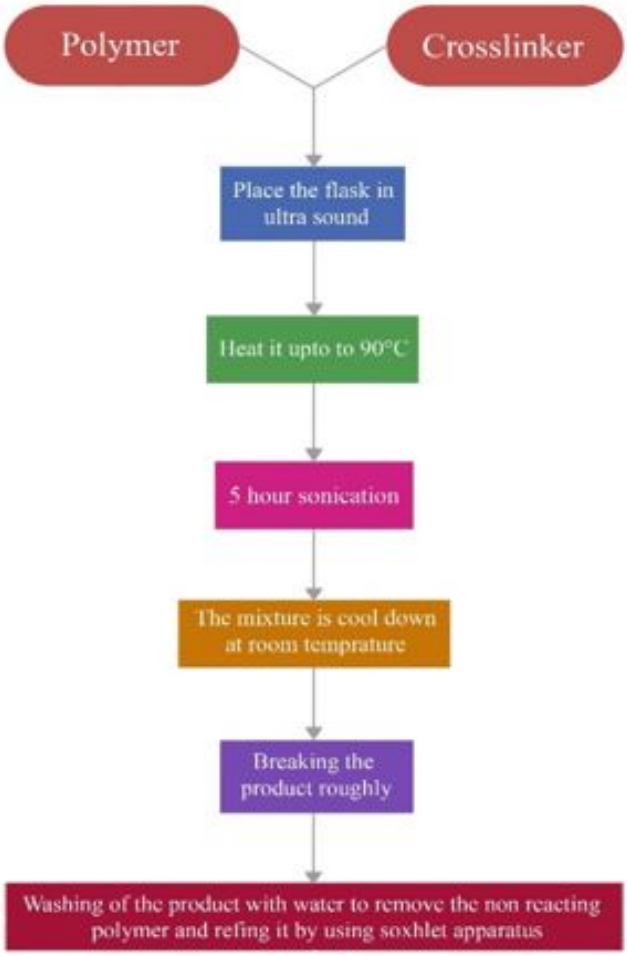

Fig 2. Flow Diagram for The Synthesis of Nanosponges by using Ultra Sound

Drug loading in the nanosponges: The resulting nanosponges should be processed to keep the average particle size below 500nm. Nanosponges were submergred in water to get the colloidal fraction. Then sonicated to remove aggregates and particles. Next, centrifuged to obtain the colloidal fraction. The supernatant was then removed, and the sample was dried by freezing and drying. (13) Nanosponges' solid crystals are acquired either through solvent evaporation or freeze drying. (14, 15) This Solid Crystal constructs of nanosponges plays a crucial role in drug complexation. When compared to crystalline nanosponges, paracrystalline nanosponges possess lower drug-loading capacity. The drug is loaded mechanically into the weakly crystalline nanosponges. (16)

Emulsion solvent diffusion method: In this process, different ratios or amounts of ethyl cellulose and polyvinyl alcohol are mixed to create nanosponges. Dispersed phase and continuous phase are the two phases of this method. The dispersion phase is composed of the Medicine and ethyl cellulose. The constant phase is created by combining the components from the dispersion phase with 20 ml of dichloromethane and some polyvinyl alcohol (PVA) (aqueous). After that, the solution is treated at 1000 rpm for around two hours. To collect the nanosponges as a result, filtering is used. After that, the product is dried in an oven at 400 °C. (17)

Drug release from nanosponges: Mechanism: Since the nanosponges have an open structure and lack a continuous membrane around them, the active molecule is introduced to the vehicle in an enclosed form. The encapsulated active component can move freely between the particles and the vehicle until equilibrium is attained and the vehicle reaches saturation. The carrier of the active substance becomes unsaturated once the product is applied topically, upsetting the delicate balance. Thus, active components from nanosponge molecules begin to seep into the epidermis of the vehicle until the vehicle is either absorbed or dried. Even when the nanosponge particles are kept on the stratum corneum of the skin, the release of active ingredients to the skin continues for a substantial amount of time.

Factors Influencing Nanosponge Formation

Type of polymer- The kind of polymer utilized can impact how successfully Nanosponges develop and function. The pore size of a nanosponge should be adequate to fit a drug molecule of a particular size for complexation. (18)

Type of drugs: The following qualities for drug molecules that will be combind with nanosponges should be present (19).

1. Between 100 and 400 molecular weight

2. There are less than five condensed rings in a drug's molecule.

3. Less than 10 mg/mL of solubility in water

4. The melting point of the substance is lower than 250°C.

Temperature: Temperature changes may influence drug/Nanosponge complexation. It is probable that decreasing drug/nanosponge contact forces, such as van der Waal forces and hydrophobic forces with a temperature rise, is the cause of the apparent stability constant of the drug/nanosponge complex decreasing with temperature (20).

Method of preparation

Drug/Nanosponge complexation may be impacted by how the drug is loaded into the nanosponge. However, the medicine and polymer type will determine how effective a procedure is. Freeze drying was consistently proven to be the most effective method for drug complexation. (20).

Degree of substitution

The number, type, and position of the substitutes on the parent molecule may significantly impact the nanosponge's capacity for complexation(20).

Physicochemical Characterization of Nanosponge

Thin layer chromatography (TLC)

The Rf values of a therapeutic molecule are significantly decreased by thin-layer chromatography, which helps identify the intricate interactions between the drug and nanosponge. (21)

Microscopic analysis

Scanning and transmission electron microscopes can be used to analyse nanoparticles and medicines. The difference in crystallisation state between the raw materials and the end product, as seen under an electron microscope, demonstrates the creation of the inclusion complexes. (22,21)

Swelling and water uptake

By soaking the manufactured nanosponges in an aqueous solvent, the amount of water that a swellable polymer, such as polyamidoamine, will absorb may be calculated (23). Equations can be used to determine swelling and water absorption-

$$\%SWELLING = \left\{\frac{Marking\ of\ cylinder\ at\ a\ specifid\ timepoint)}{initial\ marking\ before\ soaking}\right\} * 100$$

$$\%WATER\ UPTAKE = \left\{\frac{Mass\ of\ hydrogen\ after\ 72\ hrs}{Initial\ mass\ of\ dry\ polymer}\right\} * 100$$

Loading efficiency

The quantitative determination of the amount of drug loaded into nanosponges utilizing UV spectrophotometer and HPLC techniques may be employed to assess the loading efficiency of nanosponges.

$$LOADING\ EFFICIENCY = \left\{\frac{ACTUAL\ DRUG\ CONTENT\ IN\ NANOSPONGES}{THEORITICAL\ DRUG\ CONTENT}\right\} * 100$$

Particle size and polydispersity

Photon correlation spectroscopy (PCS) is used to assess particle size using the 90Plus particle size determination program. Photon correlation spectroscopy (PSC) is a procedure for determining the mass distribution profile of nanoparticles. This allows for the calculation of the polydispersity index and means diameter. (22)

Zeta potential: The zeta potential quantifies surface charge. Zeta sizing can be used to estimate the surface charge of nanosponges. (24) The zeta potential can be measured by connect an electrode to particle size analysis equipment or a zeta seizer. A colloidal dispersion becomes more stable as the zeta potential value rises.

Permeation studies

To analyze the dissolution release of the manufactured nanosponge across a cellophane membrane, diffusion experiments can be conducted in a Franz diffusion cell. Diffusion assay on a nanosponge sample (0.5g) in a cellophane membrane was conducted at 37°C using 250 ml phosphate buffer (pH 7.4) as the dissolving medium. At intervals of 1, 2, 3, 4, 5, 6, 7, and 8 hours, 5 ml of each sample can be withheld, and each sample will be replaced with an equal amount of new dissolving media. (25)

Infrared spectroscopy

It is possible to evaluate how drugs and nanosponges interact in the solid state using infrared spectroscopy. During the creation of complexes, nanosponge bands may alter. The scope of nanosponges can readily hide the drug spectrum in complexes with a few guest molecules attached that make up less than 25% of the total. The methodology is different from the other methods for identifying the inclusion complex. (26)

Solubility enhancement

The phase solubility technique proposed by Higuchi and Connors studies the influence of a nanosponge on drug solubility. It is the most extensively used strategy for studying inclusion complexation. The degree of complexation is indicated by phase solubility diagrams (14, 20). Itraconazole nanosponges based on cyclodextrin have improved the drug's solubility. For example, when compared to a ternary dispersion system, the solubility rose by 50 times. (21)

Application of Nanosponges

Nanosponges are biocompatible and versatile. They can now be used in a wide range of medicinal applications as a result. Nanosponges can be used as an excipient in the pharmaceutical industry to create tablets, topical dosage forms, granules, pallets, capsules, suspensions, and solid dispersions.

Nanosponges can accommodate both polar and non-polar drug molecules, specifically those that are classified as biopharmaceutical substances (BCS-class II) and the hydrophabic medicament. (27)

Antiviral application

Both the nasal and pulmonary routes are used to give nanosponges. By using nanocarriers, it is possible to selectively deliver antiviral medications based on RNA to the nasal or pulmonary pathways for viruses. It may result in RTI infections from viruses such the flu and the rhinovirus. Two drugs used as nanocarriers include zidovudine and saquinavir. (28)

Absorbent for treating blood toxicity

Nanosponges can eliminate harmful poison from our blood since they are absorbent in treating poison in the blood. We can absorb toxins rather than antidotes by injecting nanosponges into the bloodstream. The nanosponges mimic a RBC in the bloodstream to lure poisons into attacking it, which it then absorbs. Each nanosponge has a unique capacity to absorb harmful substances. (29)

Nanosponges for drug delivery

Nanosponges are advantageous for carrying medications that are not soluble in water because of their nonporous nature (Biopharmaceutical Classification System class-II drugs). These complexes can mask bitter flavors, turn liquid substances into solids, and boost the solubility and stability of medications. (22)

Nanosponges in cancer treatments

The administration of anticancer medications is one of the most challenging difficulties the pharmaceutical industry is currently dealing with due to their poor solubility. According to one study, the nanosponge substance is three times as effective at reducing tumour growth as direct injection.

A drug is loaded onto the complex of the nanosponge, which also reveals a targeting peptide that securely clings to a radiation-induced cell top layer on the tumour receptor. With a single injection, nanosponges have been utilised to treat a range of cancer cells, such as breast cancer and glioma of the fast-acting array (30).

Targeting drug delivery can lessen negative effects while increasing therapeutic impact at the same dose. (31)

Nanosponges for delivery of protein

Nanosponges can improve protein stability when used to deliver proteins like Bovine Serum Albumin (BSA) that have a cyclodextrin base.

Bovine serum albumin (BSA) was employed as a model protein to research the encapsulating ability of β-cyclodextrin-based nanosponges. The protein solution of bovine serum albumin (BSA) is unstable, so it is kept in lyophilized form. Denaturation of proteins may occurs from the lyophilisation of proteins from their original structures. Maintaining its original structure and long shelf life before and after synthesis is a significant issue for formulating and developing proteins. Protein encapsulation, controlled delivery, stabilization, and enzyme immobilization have all been achieved using nanosponges. (32)

Fungal infections are treated with nanosponges

One of the most deadly medical problems in the world is a fungus infection of the skin. (33) Due to a number of benefits, such as a reduction in systemic adverse effects and the direct administration of medication to the site of infection, topical treatment is a popular choice for treating conjunctivitis. Athlete's foot, jock itch, and tinea pityriasis Versicolor are all conditions that can be treated with econazole nitrate (imidazole), a topical antifungal or pharmaceutical fungicide.

It also works to cure ringworm and vaginal thrush. Products containing econazole nitrate are sold as solutions, creams, lotions, and ointments.

Since econazole nitrate does not permeate the skin efficiently, a sufficient quantity of other active drugs must be taken in addition for the treatment to be successful. Using the emulsion solvent approach, econazole nitrate nanosponges were made. (34- 35)

Table 1. Chemicals used for the synthesis of nanosponges

Crosslinkers	Diarylcarbonates, Diisocyanates, Diphenyl Carbonate, Carbonyldiimidazoles, Glutarldehyde, 2,2-bis(acrylamido) Acetic acid and Dichloromethane, Pyromellitic anhydrideEpichloridrine, Carboxylic acid dianhydrides
Polymers	Alkyloxycarbonyl Cyclodextrins, Hyper cross linked Polystyrenes, Cyclodextrines and its derivatives like Methyl β-Cyclodextrin, 2-Hydroxy Propyl β-Cyclodextrins and Copolymers like Poly(valerolactone-allylvalerolactone) & Poly(valerolactone-allylvalerolactoneoxepanedione) and Ethyl Cellulose & PVA

Table 2. Biopharmaceutical Classification System Class II drugs (36)

Antibiotics	Azithromycin, Sulfamethoxazole, Ofloxacin, Ciprofloxacin, Erythromycin
Anticonvulsants	Carbamazepine, Primidone, Clonazepam, Oxycarbazepine, Felbamate,
Antiarrhythmic agents	Amiodarone hydrochloride
Antianxiety drugs	Lorazepam
Anticoagulant	Warfarin
Antihistamines	Terfenadine
Antidiabetic and Antihyperlipidemic drugs	Atorvastatin, Troglitazone, Fenofibrate, Lovastatin, Glibenclamide, Glipizide,
Antipsychotic drugs	Chlorpromazine Hydrochloride
Antifungal agents	Econazole nitrate, Vericonazole, Griseofulvin, Lansoprazole, Itraconazole, Ketoconazole
Antiepileptic drugs	Phenytoin
Antihypertensive drugs	Nifedipine, Nicardipine, Felodipine, Nisoldipine
Antineoplastic agents	Camptothecin, Irinotecan, Docetaxel, Tamoxifen, Etoposide, Exemestane, Temozolamide, Flutamide, Paclitaxel, Raloxifene, Topotecan
Antioxidants	Resveratrol
Anthelmintics	Albendazole, Praziquantel, Mebendazole
Antiretrovirals	Indinavir, Ritonavir, Saquinavir, Nelfinavir,
Antiulcer drugs	Omeprazole, Lansoprazole
Diuretics	Spironolactone, Chlorthalidone
Cardiac drugs	Carvedilol, Talinolol, Digoxin,
NSAIDs	Dapsone, Diclofenac, Piroxicam, Diflunisal, Etodolac, Etoricoxib, Oxaprozin Flurbiprofen, Ibuprofen, Nimesulide, Indomethacin, Ketoprofen, Mefenamic acid, Naproxen,
Gastroprokinetic agent	Cisapride
Immunosupressants	Cyclosporine, Tacrolimus, Sirolimus
Miscellaneous	Atovaquone, Phenazopyridine, Melarsoprol, Ziprasidone,
Steroids	Dexamethazone, Danazol,

Table 3. Examples of nanosponges

Drug	Nanosponge vehicle	Indication	Study	In vitro / in vivo / Mathematical model	Reference
Camptothecin	β-Cyclodextrin	Cancer	Haemolytic activity Cytotoxicty	Diluted blood HT-29 cell line	22, 37
Paclitaxel	β-cyclodextrin	Cancer	Bio- availability Cytotoxicty	Sprague Dawley rats MCF7 cell line	38 39
Itraconazole	Polyvinylalcohol β-Cyclodextrin& copolyvidonum	Antifungal	Saturation solubility study	Higuchi Model	40
Dexamethasone	β-Cyclodextrin	Brain tumors	Drug release experiment	Dialysis bag technique in vitro	15
Antisense oligonucleotides	Sodium alginate Poly L-lysine	Cancer therapy Viral infections Pathologic disorders	Pharmacokinetic studies	Mice	41
Resveratrol	β-Cyclodextrin	Inflammation, Cardiovascular diseases, Dermatitis, Gonorrhea, Fever and Hyperlipidemia	Cytotoxicty Accumulation of drug in the buccal mucosa of rabbit Ex-Vivo Study Permeation study	HCPC-I cell line Rabbit buccal mucosa Pig skin	42
Tamoxifen	β-Cyclodextrin	Breast cancer	Breast cancer	MCF-7 cell line	14
Temozolamide	Poly (valerolactone-allylvalerolactone) and poly (valerolactone-allylvalerolactone – oxepanedione)	Brain tumors	Drug release study	In vitro and in vivo studies	43
Econazole nitrate	Ethyl cellulose Polyvinyl alcohol	Antifungal	Irritation study	Rat	44,45

Conclusion

Nanosponges are extremely small web-like structures that may change how different diseases are treated. When compared to conventional methods, this procedure is five times more successful at delivering cancer drugs. Nanosponges are employed in numerous dosage forms, including parenteral, aerosol, topical, tablets, and capsules, due to their small size and rounded structure. The medications can be included into the nanosponges in both lipophilic and hydrophilic forms, and they will release in a regulated and predictable manner at the desired area. Topical nanosponge can improve patient compliance and provide adequate patient benefits by reducing repeated doses and side effects. Nanosponge can be successfully incorporated into topical drug delivery systems

To maintain the dosage form on the skin. Consequently, based on the findings.

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