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AN OVERVIEW OF NANOSPONGES

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ABSRACT

Effective targeted drug delivery systems have been a dream for a long time, but it has been largely frustrated by the complex chemistry that is involved in the development of new systems. The invention of nano sponges has become a significant step toward overcoming these problems. Nano sponges are a novel class of nanomaterials characterized by their sponge-like structure, offering high surface area, porosity, and functional versatility. Nano sponges are tiny sponges with a size of about a virus, which can be filled with a wide variety of drugs. These tiny sponges can circulate around the body until they encounter the specific target site and stick on the surface and begin to release the drug in a controlled and predictable manner. Because the drug can be released at the specific target site instead of circulating throughout the body it will be more effective for a particular given dosage. Another important character of these sponges is their aqueous solubility; this allows the use of these systems effectively for drugs with poor solubility. Nano sponges, a recently created colloidal system, have the potential to overcome issues with medication toxicity, decreased bioavailability, and drug release over a wide area because they can be modified to work with both hydrophilic and hydrophobic types of drugs. Recent advancements in nano sponges have focused on optimizing their design for targeted therapy, minimizing side effects, and overcoming biological barriers. This review focused on definitions, types, advantages, disadvantages, polymers used, suitable characteristics of polymers, including the outline of preparation of nano sponges and the evaluation.

KEYWORDS: Targeted drug delivery system, Nano sponges, hydrophilic, hydrophobic drug, solubility, bioavailability.

INTRODUCTION

Targeted medication delivery has been a primary focus of medical research for years, aiming to direct drugs to affected tissues or organs while minimizing exposure to healthy cells. This approach enhances treatment efficacy and reduces the risk of adverse effects. Nano sponges hold great promise in this area, as their design and composition can be tailored to selectively target specific cells or tissues.[1] Nano sponges are mesh – like minute structures that can be encapsulate a large variety of substances and medication molecules and offers a promising solution. They are like a 3D network having a backbone of long chain polyesters present in the solution along with crosslinkers that connect different parts of the polymer. These materials minimize drug carrier size, enhancing the solubility and bioavailability of hydrophobic medications ultimately improving their therapeutic effectiveness. Nano sponges represent a cutting-edge advancement in drug delivery technology, offering a versatile platform for creating intricate drug delivery systems.[6]

These nanocarriers are designed to encapsulate a wide range of therapeutic agents, including both hydrophilic (water-soluble) and hydrophobic (water-insoluble) compounds, within their porous structures. This unique capability enhances their utility, particularly in overcoming the limitations associated with conventional drug delivery methods. Research has demonstrated that nano sponges can increase the concentration of medications such as doxorubicin within tumor, resulting in enhanced effectiveness of the treatment. Nano sponges are being explored not only for cancer therapy but also for their potential in wound healing. By releasing growth factors and antimicrobial agents in a controlled manner, they can enhance tissue regeneration and protect against infections, making them ideal for advanced wound dressings. Additionally, during the COVID-19 pandemic.[9] Researchers have investigated their use in antiviral formulations and vaccines, show casing their versatility in addressing various medical challenges. Compared to other nanoparticles, they possess some advantages as they are easily reproducible using different treatments such as washing with environmentally friendly solvents, stripping with relatively innocuous hot gases, gentle heating, or changing pH or ionic strength. They are used in different fields. They are shown to be risk-free for both oral and invasive routes, making them a viable medication delivery vehicle.[2,3] Nano sponges can be delivered through the lungs and veins because of their microscopic size. To make

capsules or tablets for oral administration, the complexes may be dispersed in a matrix containing diluents, lubricants, excipients & anticaking agents. This step is necessary for the manufacturing process.[4]

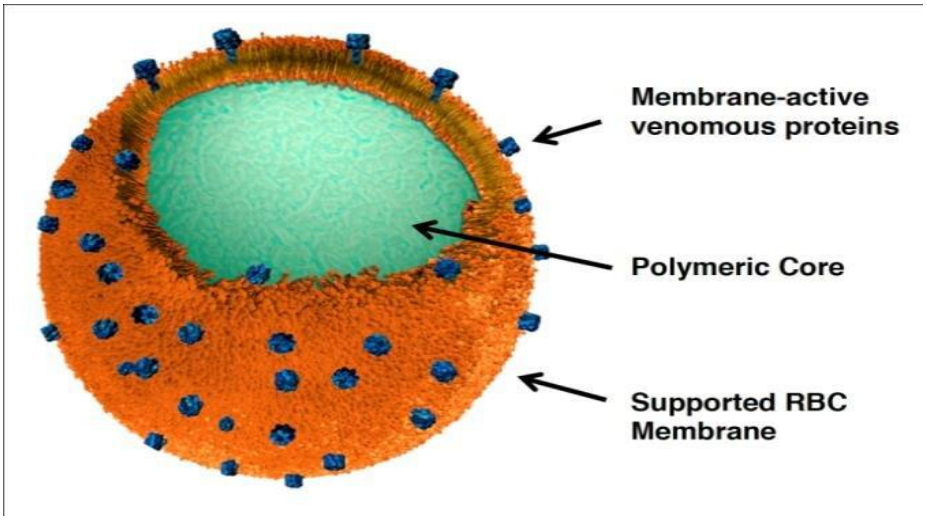


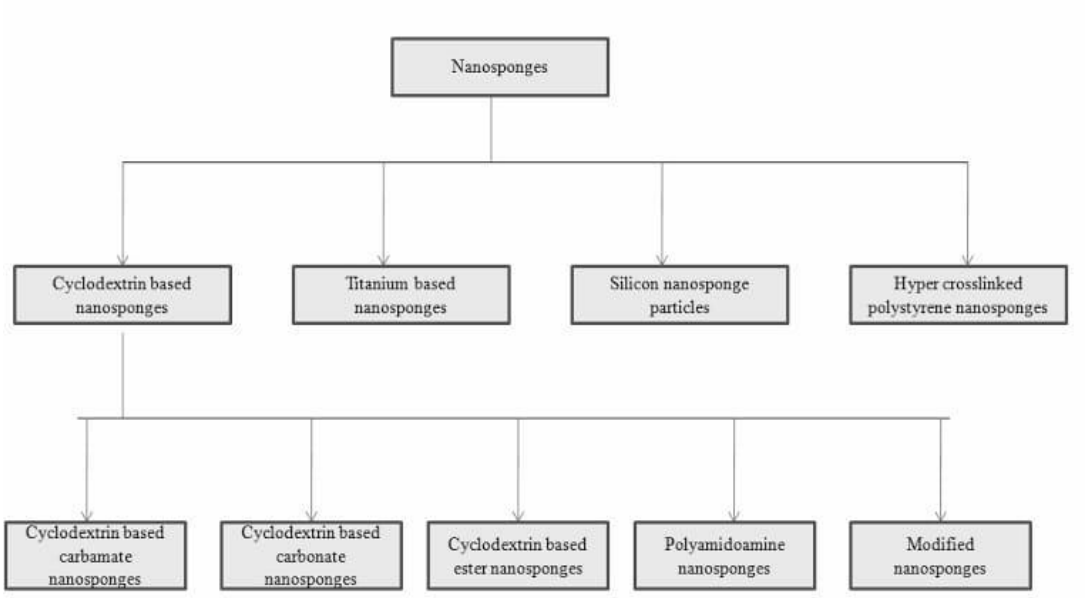
Fig. 1: Structure of nanosponges.

FEATURES OF NANOSPONGES

1. An important character of these sponges is their aqueous solubility; this allows the use of these systems effectively for drugs with poor solubility.
2. The nano sponges are capable of carrying both lipophilic and hydrophilic drugs.
3. They have been used for removal of organic impurities in water, as nano – carriers for biomedical applications.
4. Nano sponges are non-irritating and non-mutagenic, non- allergic and non-toxic.
5. Nanosponges can disperse at molecules level, highly insoluble principles, stabilizing and protecting their structures, from chemicals, light, oxygen etc.[5]

TYPES OF NANOSPONGES

The most common types of NS which are prepared and have been diversely used are beta Cyclodextrin-based Nanosponges. The formulation aspect for beta-Cyclodextrin nanosponges is a relatively simple process and there are relatively multiple modifications that are possible.[6]



ADVANTAGES

- Increase aqueous solubility of the poorly water-soluble drug.
- Nanosponges can release the drug molecules in a predictable fashion.
- Because of their tiny pore size (0.25 µm), bacteria cannot penetrate the nanosponges and they act like a self-sterilizer.
- Nanosponges drug delivery system is non-irritating, non-mutagenic and non-toxic.
- Nanosponges help to remove the toxic and venom substance from the body.
- Nanosponges drug delivery system minimizes side effect.
- Increase formulation stability and enhance the flexibility of the formulation.
- Reduce dosing frequency.
- Better patient compliance.[7]
- Nanosponges complexes are stable over wide range of pH (i.e. 1-11) and a temperature of 130 °C.

Disadvantages of nanosponges

- Nanosponges have the capacity of encapsulating small molecules, not suitable for larger molecules.
- Dose dumping may occur at times.[8]

MECHANISM

The active ingredient is given to the vehicle in an encapsulated form since nanosponges have an open structure and lack a continuous membrane around them. From the particles into the

vehicle, the encapsulated active ingredient can travel freely until the vehicle becomes saturated and equilibrium is reached. The vehicle carrying the active ingredient becomes unsaturated as soon as the product is applied to the skin, disrupting the balance. Thus, until the vehicle is either absorbed or dried, active compounds from nanosponge particles start to flow into it. The release of active substance to skin continues for a considerable amount of time even after the retention of the nanosponge particles on the stratum corneum of the skin. The nanosponges are encapsulated in various routes of drug administration such as topical, inhalational, parenteral or oral dosage forms. In oral route, they are consumed as tablets or capsules in which there may be a matrix of lubricants, excipients, diluents and anticaking agents. In parenteral route, the drugs may be composed of aqueous solutions, saline, and sterile water.[9]

METHOD OF PREPARTION

1. Solvent method

Suitable solvents, like dimethylformamide and dimethyl sulfoxide which are polar aprotic solvents, were used in the process. To this, polymer was added and properly blended. The crosslinker/polymer ratio of 8:2 is ideally used into which the above mixture was added. The mixture got from the above mixing, was then left to react for 48 hours and in a temperature range of 10 °C and up to solvent's reflux temperature. On completion of the reaction, the solution was cooled until it reached the room temperature. Excess amount of bi-distilled water was added to obtain the product from the above-cooled solution and the product was recovered under vacuum filtration.[10]

2. Ultra sound – assisted method

The ultrasound-assisted method of synthesis utilizes polymer ultrasonics junction. Crosslinking is got without using any solvent, and polymer crosslinking occurs due to ultrasonic waves. In a flask, polymer and crosslinker were combined at a reasonable molar ratio. During the ultra-sonication process, ultrasound bath was used to place the flask, at a temperature of 90 °C and for a time period of 5 h. The temperature of the collected mixture was reduced after sonication, and the product was split harshly and cleaned to extract unreacted polymer and reagents with an excess volume of water.

The washed solid was purified with ethyl alcohol by Soxhlet extraction. The filtered NSs acquired were vacuum dried and processed correctly until further loading of drugs.[10]

Melt method

The crosslinker and the polymer are melted together in the melting process. All the ingredients were finely homogenized. NSs were collected by washing the acquired product repeatedly with a suitable liquid. Cleaning the product, extracts the waste polymer and reagents which are unreacted and divides the product into the form of NSs. Such blank NSs were further exposed to the encapsulating of narcotics.[11]

Bubble electrospinning method

A conventional and typical electrospinning configuration consists primarily of a syringe, syringe pump, as defined in many literatures, a high-voltage power, and a grounded collector. But one of the major limitations that limits their applications is the amount of output of nanofibers.

In bubble electrospinning, polyvinyl alcohol can also be used as polymer. By addition of distilled water into it, the solution of polymer (10%) was organized, which was then moved at 80–90 °C for 2 h to obtain a one-phase mixture. It was then left to achieve at room temperature with the polymer solution and then used to prepare nanoporous fibers.[11]

Emulsion solvent diffusion method

Two steps are used in this technique to vary the level of natural and aqueous (ethyl cellulose and polyvinyl liquor). In dichloromethane (20 ml) and an unmistakable measure of polyvinyl liquor added to 150 ml of fluid ceaseless process, the scattered stage with ethyl cellulose and moiety is dissolved. At this point, for 2 hours at 1000 rpm, the blend is thoroughly blended. The required NSs were collected by the filtration method and held for drying in an oven at 40 °C for 24 h. Dried NSs have been put away in desiccators and the evacuation of remaining solvents is assured.[12]

Nanosponges made from hyper cross-linked β-cyclodextrins

Nanosponges are made from materials that make non-porous molecules that are carriers called cyclodextrins for drug release. These cyclodextrins are hyper-cross-linking substances that create several nanoscale networks or can even take the form of a sphere with countless networks of protein channels, pores, etc. Based on the chemicals they contain, these cross linkers stabilise the sponge and give it a certain surface charge density, porosity, and pore size. Cross linkers aid in maintaining Nano sponges at various acidic and even neutral pH levels.[14]

Quasi emulsion solvent method

The NSs were arranged in different sums using the polymer. Using Eudragit RS 100, the inner stage is prepared and added to a fair dissolvable stage. The drug used produced a response and broke down at 35 °C under ultra-sonication. As an emulsifying operator, this internal process used in the outside phase containing polyvinyl alcohol goes around. At room temperature, the blend is blended at 1000–2000 rpm for 3 h and dried for 12 h in an air-warmed oven at 40 °C.[13]

EVALUTION

1. Solubility studies: The most widely used approach to study inclusion complexation is the phase solubility method described by Higuchi and Connors, which examines the effect of a nanosponges, on the solubility of drug. Phase solubility diagrams indicate the degree of complexation.

II. Loading Efficiency/ Entrapment Efficiency: Weighed amount of loaded nanosponges complexes is to be dissolved in suitable solvent, sonicated to break the complex, diluted suitably and then analysed by UV spectrophotometer or HPLC methods.[15]

III. Poly dispersity Index And particle Size: The particle size can be determined by dynamic light scattering using 90 Plus particle size equipped with MAS OPTION particle sizing software. From this, the mean diameter and polydispersity index can be determined. The particle size can be determined by scanning electron microscopy (SEM), transmission electron microscopy (TEM), atomic force microscopy (AFM), and freeze fracture electron microscopy (FFEM).[16]

IV. Zeta Potential Determination: Zeta potential measurements can be made by using an additional electrode in particle size instruments. Also, Laser Doppler anemometry, zeta potential meter can be used.

V. Infra-Red Spectroscopy: Infra-Red spectroscopy is used to estimate the interaction between nanosponges and the drug molecules in the solid state. Nanosponges bands often change only slightly upon complex formation and if the fraction of the guest molecules encapsulated in the complex is less than 25%, bands which could be assigned to the included part of the guest molecules are easily masked by the bands of the spectrum of nanosponges. The technique is generally not suitable to detect the inclusion complexes and is less clarifying

than other methods. The application of the Infra-red spectroscopy is limited to the drugs having some characteristic bands, such as carbonyl or sulfonyl groups. Infrared spectral studies give information regarding the involvement of hydrogen in various functional groups. This generally shifts the absorbance bands to the lower frequency, increases the intensity and widens the band caused by stretching vibration of the group involved in the formation of the hydrogen bonds. Hydrogen bond at the hydroxyl group causes the largest shift of the stretching vibration band.[17]

VI. In Vitro Release Studies: The release of the drug from the optimized nanosponges formulation can be studied using multicompartment rotating cell with dialysis membrane (12,000 Da). The donor phase consists of drug-loaded nanosponges complex in distilled water. The receptor phase also contains the same medium. The receptor phase is withdrawn completely after fixed time intervals, suitably diluted with distilled water and then analyzed by UV spectrophotometer. Also, USP II can be used in many cases depending upon the formulation.

VII. Thermo -Analytical Method: Thermo-analytical methods determine whether the drug substance undergoes some change before the thermal degradation of the nanosponge. The change of the drug substance may be melting, evaporation, decomposition, oxidation or polymorphic transition. The change of the drug substance indicates the complex formation. The thermogram obtained by DTA and DSC can be observed for broadening, shifting and appearance of new peaks or disappearance of certain peaks. Changes in the weight loss also can provide supporting evidence for the formation of inclusion complexes.[18]

IX. Fourier Transformer Infrared Spectroscopy: Fourier transformer infrared spectroscopy (FTIR) analysis is a primary tool for structure confirmation of NS. Cross-linking in CD moieties can be evaluated using FTIR. The FTIR spectra of β-CD show characteristic peak of non-hydrogen-bonded O-H stretching at 3450 cm-1 due to presence of primary alcoholic groups. Absence of this peak in NS advocates that all free primary alcoholic groups of β-CD are utilized in the cross-linking process. In case of CD-NS prepared using diphenylcarbonate as cross-linking agent, the characteristic peak given by the carbonate group in DPC (1775 cm-1) shifts to 1750 cm-1 and other characteristic peaks of CD-NS are observed in the range of 1460–1600 cm-1 and 1270–1290 cm-1. On loading drugs into NS, the FTIR spectra shows broadening or shifting of drug peak due to molecular interaction between the drug and NS.

VIII. Scanning Electron Microscopy And Transmission Electron Microscopy: The average particle size of NS can be assessed using SEM and TEM. Further the porosity can also be evaluated. Through TEM/SEM it was observed that CD-NS, prepared using the ultrasound-assisted method mentioned earlier, showed average diameter of 400–500 nm while the Para crystalline particles were 900–1300 nm in size. The SEM image of oxygen encapsulating β-CD nano- sponges.[19]

APPLICATIONS OF NANOSPONGES

Topical agents

Nanosponges delivery system is a unique technology for the controlled release of topical agents of prolonged drug release and retention of drug form on skin. Local anaesthetics, antifungal and antibiotics are among the category of the drugs that can be easily formulated as topical nanosponges. Rashes or more serious side effects can occur when active ingredients penetrate the skin. In contrast, this technology allows an even and sustained rate of release, reducing irritation while maintaining efficiency. A wide variety of substances can be incorporated into a formulated product such as gel, lotion, cream, ointment, liquid, or powder. Econazole nitrate, an antifungal used topically to relive the symptoms of superficial candidiasis, dermatophytosis, versicolor and skin infections available in cream, ointment, lotion and solution. Adsorption is not significant when econazole nitrate is applied to skin and required high concentration of active agents to be incorporated for effective therapy. Thus, econazole nitrates Nanosponges were fabricated by emulsion solvent diffusion method, and these Nanosponges were loaded in hydrogel as a local depot for sustained drug release.

Enhanced solubility

The nanosponge system has pores, that increase the rate of solubilisation of poorly soluble drug by entrapping such drugs in pores. Due to nano size surface area significantly increased and increase rate of solubilisation1. BS class-2 drugs having low solubility, and a dissolution rate limited poor bioavailability. However, when formulated with Nanosponge they demonstrate enhanced solubilisation efficiency, with desired drug release characteristics.

Nanosponge as chemical sensors

Nanosponges which are the type of “metal oxides” act as a chemical sensor which is used in highly sensitive detection of hydrogen using nanosponge titania. Nanosponge structure initially have no point of contact so there is less hinderance to electron transport and it results in higher 3D interconnect nanosponges titania which is sensitive to H2 gas.[20]

Chemotherapy

The tiny sponges are filled with drug and expose a targeting peptide that bind to radiations induced cell surface receptor on tumor. When the sponge encounter tumor cell they stick to surface and triggered to release cargo. One of the important drugs formulated as nanosponge is paclitaxel, the active ingredient in the anti-cancer therapy Taxol.

Biomedical applications

Nanosponge can be used for contaminated water. Nanosponge have been used for the removal of organic impurities in water.

Oral delivery

For oral delivery as capsules or tablets, the complex can be disseminated in a matrix comprising diluents, excipients, lubricants and anti-caking agents. Nanosponges can increase the wetting and solubility of molecules that have low water solubility. The medications may be molecularly disseminated inside the nanosponge structure and subsequently released as molecules, eliminating the need for disintegration. As a result, the drug's perceived solubility can be boosted. Many formulation and bioavailability issues may be overcome by increasing a substance's solubility and dissolving rate, and nanosponges can significantly increase medication solubility. BCS class II medicines have relatively poor solubility and are thus great candidates for nanosponges. To produce nanosponges for use in an oral medication administration system, acetyl salicylic acid, a Nonsteroidal Anti-Inflammatory Drug (NSAID) classed as a BCS class II agent, was utilised. When taken orally, it creates a nanosponge system with holes that speed up the solubilization of medications with low water solubility by trapping them in the pores.[21]

FACTORS AFFECTING OGF NANOSPONGES

Degree of substitution

The complexation ability of the nanosponge may be strongly influenced by the kind, quantity, and location of the substituent on the parent molecule.

Method of preparation

The complexation may be impacted by the drug's loading into the nanosponge formulation. The complexation may be impacted by the type of the medication and polymer. Freeze drying has proven to be a more productive approach for pharmacological complexation in many instances.

Temperature

Drug complexation may be impacted by temperature changes. Due to a potential reduction in drug nanosponge contact forces, van der waals forces, and hydrophobic forces with rising temperature, the apparent stability of the nanosponge complex diminishes with temperature.

Type of drug

The following qualities for drug compounds that will be complexed with nanosponges should be present. Water solubility should be less than 10 mg/ml. No more than five condensed rings should be present in the medication molecule structure. Less than 250° should be the melting point. 100 to 400 Da is the required molecular weight range.

Type of polymer and crosslinkers

The choice of an appropriate polymer affects both the production and performance of nanosponge. The nanosponges cavity or pore size should be able to fit a medication molecule of the appropriate size. Crosslinkers aid in the formation of a 3D structure of nanosponges. The amount of crosslinker utilized affects drug entrapment as well as organ targeting. The crosslinker utilised determines whether the nanosponge is soluble in water or any other solvent. Epichlorohydrin will be used as a crosslinker to create hydrophilic nanosponges. The benefit of utilising hydrophilic nanosponges in drug delivery is that it enhances drug absorption across biological membranes and is a valuable transporter for pharmaceuticals in order to produce quick release formulations.[22,23]

CONCLUSION

Nanosponge are nano sized colloidal carrier so they easily penetrate through skin. Due to their small size and porous nature, they can bind poorly- soluble drugs within the matrix and improve their bioavailability of drug and they also increase the solubility of poorly soluble drugs. The nanosponges have the ability to incorporate many drugs and release them in a controlled and predictable manner at the target site. Topical nanosponge can be more patient compliant and provide sufficient patient benefits by reducing repeated doses and side effects. Nanosponge can be effectively incorporated into topical drug delivery system for retention of dosage form on skin. Nanosponges are tiny mesh like structures that may revolutionise the treatment of many diseases and this technology is five times more effective at delivering drugs for cancer than conventional methods. These are self-sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none.

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