IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.53
Volume 4, Issue 2, January 2024

Nano Sponges: Applications and a Specific Drug Delivery System

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Abstract: *Nano sponges have emerged as a promising paradigm in the realm of drug delivery systems, offering unprecedented advantages in targeted and controlled drug release. This review encapsulates the synthesis methodologies, structural features, and the myriad applications of nano sponges as a versatile platform for drug delivery. The porous nanostructure of these materials provides an ideal reservoir for encapsulating diverse therapeutic agents, facilitating precise and sustained release at specific target sites. The unique physicochemical properties of nano sponges, including their biocompatibility and tunable surface functionalities, contribute to enhanced drug stability and bioavailability. Furthermore, the ability to tailor the size and composition of nano sponges allows for customization, optimizing their performance for various therapeutic scenarios. This review comprehensively explores the applications of nano sponges in treating diverse diseases, such as cancer, infectious diseases, and inflammatory disorders, showcasing their potential to revolutionize the landscape of modern medicine. The integration of nano sponges as a targeted drug delivery system holds promise for minimizing side effects, improving patient compliance, and maximizing the therapeutic efficacy of pharmaceutical agents, marking a significant stride towards personalized and precision medicine.*

Keywords: Nano sponges; Targeted dug delivery; Solubility enhancement; Controlled drug delivery

I. INTRODUCTION

Nanosponge technology is an emerging and innovative approach to targeted drug delivery, facilitating controlled release at specific sites[1]. Nano sponges, characterized by their tiny sponge-like structure with narrow cavities measuring a few nanometers and an average diameter below 1µm, are a class of materials at the forefront of this advancement. These structures are formed by cross-linking segments of polyester, resulting in a spherical shape with numerous cavities capable of storing drugs.The narrow cavities of nano sponges offer versatility, accommodating various substances[2]. This includes the ability to carry both hydrophilic and lipophilic drug substances, enhancing the solubility of poorly water-soluble drugs. This technology presents a novel and efficient method for controlled drug delivery, particularly for topical use.Nanosponge technology provides several advantages, including the entrapment of ingredients, leading to reduced side effects, improved stability, increased elegance, and enhanced formulation flexibility. The unique features of nano sponges position them as a promising avenue in pharmaceutical research, offering precise and targeted drug administration with improved therapeutic outcomes.Nanosponges, a subtype of encapsulating nanoparticles, employ various association methods to encapsulate drug molecules within their core[3,4]. Classifiable into encapsulating, complexing, and conjugating nanoparticles, nanosponges distinguish themselves by their insolubility in both water and organic solvents. Primarily existing in solid form, they are versatile and can be formulated for oral, parenteral, topical, or inhalation dosage forms.Extensively studied for proteins, peptides, genes, anti-cancer agents, and biomolecules, nanosponges within the nanoparticulate system exhibit the potential to mitigate undesired effects and enhance efficacy[5]. In oral administration, nanosponges may disperse within matrices of excipients, diluents, lubricants, and anticaking agents, making them suitable for capsule or tablet formulations. For parenteral administrations, nanosponges can be mixed with saline, other aqueous solutions, or sterile water. This versatile and innovative approach positions nanosponges as promising contributors to advanced drug delivery systems[6].

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Advantages Nanosponges

- Efficient entrapment of ingredients and reduced side effects.
- Improved stability, increased elegance and enhanced formulation flexibility.
- These formulations are stable up to a temperature of 130°c.
- These formulations are compatible with most vehicles and ingredients.
- These are self-sterilizing as their average pore size is 0.25µm which makes the bacteria unable to penetrate.
- These are free flowing and can be cost effective.
- These formulations modify the release of the drug.
- They increase the solubility of poorly soluble drug.
- It can be used to mask flavours and to convert liquid substance to solids.
- These formulations increase the bioavailability of the drug.
- They are non-irritating. Non mutagenic, nontoxic and non-allergic.
- It has an extended release which provide continuous action up to 12 hrs.
- Easy scale up for commercial production
- Biodegradable
- The material used in this system can provide a protective barrier that shields the drug from premature destruction within the body[7,8,9].

Disadvantages of Nanosponges

- They include only small molecule.
- They depend only upon the loading capacities[10].

Characteristic Features of Nanosponges

- **Nanostructure:** Nanosponges exhibit a nanoscale structure, often resembling tiny sponges with porous and interconnected networks[11].
- **Porous Architecture:** They possess a porous architecture with narrow cavities, providing a high surface area and space for encapsulating various substances, including drugs[12].
- **Material Composition:** Nanosponges are typically made of materials that can be cross-linked, such as polymers or other biocompatible substances, forming a stable structure.
- **Insolubility:** In general, nanosponges are insoluble in both water and organic solvents, contributing to their stability and versatility in different applications.
- **Solid State:** Nanosponges are commonly found in a solid state, allowing for easy formulation into different dosage forms, such as oral, parenteral, topical, or inhalation forms[13,14].
- **Encapsulation Capability:** One of the primary features is their ability to encapsulate a variety of substances, including hydrophilic and lipophilic drug molecules, proteins, peptides, genes, anti-cancer agents, and biomolecules.
- **Drug Delivery System:** Nanosponges serve as a drug delivery system, enabling controlled and targeted release of encapsulated substances.
- **Biocompatibility:** When designed using biocompatible materials, nanosponges can be compatible with biological systems, minimizing adverse reactions or immune responses.
- **Customizability:** The size, composition, and surface properties of nanosponges can often be tailored to meet specific requirements, allowing for customization based on the intended application[15,16].
- **Reduction of Side Effects:** Nanosponges may contribute to reducing undesired effects associated with drug delivery by providing a controlled and localized release of therapeutic agents.
- **Improved Stability:** The encapsulation within nanosponges can enhance the stability of the loaded substances, protecting them from degradation.

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- **Formulation Flexibility:** Their versatility allows for different formulation approaches, making them suitable for various pharmaceutical dosage forms[17,18].

Composition of Nanosponges

Polymer

The selection of polymer can influence the formation along with the performance of Nano sponges. The cavity size must be suitable to incorporate the particular drug molecule. The polymer selection is based upon the required release and drug to be enclosed. The selected polymer should have the property to attach with specific ligands[19].

Cross linking agent

The cross linking agent selection can be carried out depending upon the structure of polymer and the drug which is to be formulated. The different examples include Diphenyl carbonate, Dichloromethane, Diaryl carbonates, Diisocyanates[20].

Drug substance

Molecular weight between 100 and 400 Daltons.
Drug molecule consists of less than five condensed rings.
Solubility in water is less than 10 mg/ml.
Melting point of substance is below 250 °C [21,22].

Method of Preparation

Nano sponges made from hyper cross-linked β-cyclodextrins

Nanosponges crafted from hyper-cross-linked β-cyclodextrins involve a process where β-cyclodextrins undergo hyper-cross-linking with a specific agent under controlled conditions. This results in the creation of nanoscale sponges with a porous structure. The hyper-cross-linking imparts stability and rigidity to the β-cyclodextrins, forming a three-dimensional network. These nanosponges, characterized by their porous nature, can encapsulate various substances, making them versatile for drug delivery applications. The method allows for size control and customization of the nanosponges, ensuring adaptability to specific biomedical needs. The biocompatibility of the chosen cross-linking agents is considered, making these nanosponges suitable for biomedical applications where controlled drug release and enhanced stability are essential. This synthesis method provides a platform for the development of nanosponges with tailored properties, particularly beneficial for improving drug solubility, stability, and targeted delivery in the field of pharmaceuticals[23].

Emulsion solvent method

The emulsion solvent method for nanosponges involves dissolving a chosen polymer, often cyclodextrins, in a solvent to create a polymer solution. If intended for drug delivery, the drug is incorporated into this solution. The emulsion is formed by introducing the polymer solution into an immiscible phase, typically an oil phase, resulting in droplets of the polymer solution dispersed in the oil. Cross-linking agents are added to initiate the solidification of the polymer and form nanosponges within the emulsion droplets. As cross-linking progresses, nanosponges with a porous structure are created. After solidification, nanosponges are isolated from the emulsion, typically through centrifugation or filtration, and are then dried to remove any residual solvent. Characterization analyses are performed to assess particle size, surface morphology, and drug loading. This method is valued for its simplicity, scalability, and ability to produce nanosponges with controlled properties for diverse applications, particularly in drug delivery systems[24].

Solvent used method

The above used polymer can be used along with some suitable polar aprotic solvent such as Dimethylformamide, dimethylsulfoxide and mix proportionally. Then to this mixture, cross-linkers available are added with a ratio of 4: 16. A temperature is maintained from 10°C for reaction of polymers for 2 days. Most of the carbonyl cross linkers (Dimethyl carbonate and Carbonyl diimidazole) are used. After the reaction is complete the product kept to cool at room temperature, then add the mixture with distilled water for recovering and filtered under air oven and purification

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is done by soxhchlet apparatus added with ethanol for further extraction. Again go for drying under vacuum and and powdered mechanically to get a homogeneous white powder[25].

Ultrasound-assisted synthesis

- **Selection of Materials:** Choose the appropriate polymer and solvent for nanosponge synthesis. Common polymers include cyclodextrins.
- **Polymer Dissolution:** Dissolve the selected polymer in a suitable solvent to create a polymer solution.
- **Drug Incorporation (Optional):** If drug delivery is the goal, incorporate the drug into the polymer solution.
- **Ultrasound Irradiation:** Expose the polymer solution to ultrasound irradiation. Ultrasound waves generate cavitation bubbles in the solution, causing localized heating, pressure changes, and intense shear forces.
- **Emulsion Formation:** If needed, introduce the polymer solution into an immiscible phase, typically an oil phase, to form an emulsion. The ultrasound waves contribute to emulsion stability and particle size reduction.
- **Cross-Linking:** Initiate the cross-linking process during or after ultrasound irradiation. This step solidifies the polymer and forms nanosponges.
- **Nanosponge Formation:** The combination of ultrasound and cross-linking results in the formation of nanosponges with a porous structure.
- **Solidification:** Complete the cross-linking process until the nanosponges are solidified. Additional purification or washing steps may be performed.
- **Isolation:** Separate and isolate the nanosponges from the solution or emulsion using methods such as centrifugation or filtration.
- **Drying:** Remove any remaining solvent or water by drying the isolated nanosponges.
- **Characterization:** Perform characterization analyses to assess particle size, surface morphology, and other relevant properties[26,27].

Factors influencing nano sponge formulation

- **Polymer Selection:** The choice of polymer is crucial in nanosponge formulation. Different polymers, such as cyclodextrins, can affect the solubility, biocompatibility, and drug-loading capacity of the nanosponges.
- **Cross-Linking Agents:** The type and concentration of cross-linking agents used during synthesis impact the structural integrity, porosity, and stability of the nanosponges.
- **Solvent System:** The selection of solvents affects the dissolution of polymers, as well as the overall stability and compatibility of the nanosponge formulation. The choice of a solvent can influence drug encapsulation efficiency and release characteristics[28].
- **Drug Loading:** The nature and amount of the drug incorporated into the nanosponges influence drug loading capacity, release kinetics, and the therapeutic efficacy of the formulation.
- **Surfactants:** Surfactants play a role in emulsion stability and particle size control during nanosponge synthesis. The type and concentration of surfactants impact the formulation's physicochemical properties[29].
- **Method of Synthesis:** The chosen synthesis method, whether it's emulsion solvent, ultrasound-assisted, or other techniques, affects the size, morphology, and porosity of the nanosponges.
- **Process Parameters:** Factors like temperature, reaction time, and pH during synthesis can significantly influence the final characteristics of the nanosponge formulation[30].
- **Particle Size and Distribution:** Controlling the particle size and distribution of nanosponges is essential for optimizing their performance, especially in drug delivery applications where smaller particles often lead to enhanced bioavailability.
- **Stabilizers and Excipients:** Additional stabilizers and excipients may be added to the formulation to enhance stability, shelf life, and the overall performance of nanosponges.
- **Biocompatibility:** Consideration of the biocompatibility of all components is essential, especially if the nanosponges are intended for biomedical or pharmaceutical applications[31].

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- **Targeted Application:** The intended application of nanosponges, whether for drug delivery, environmental remediation, or other purposes, influences the formulation requirements.
- **Regulatory Requirements:** Adherence to regulatory standards and guidelines is critical, especially in pharmaceutical applications, to ensure the safety and efficacy of nanosponge formulations[32].

Application of nanosponges

- **Drug Delivery Systems:** Nanosponges are extensively used in drug delivery to improve the solubility, stability, and controlled release of pharmaceutical agents. They can carry both hydrophilic and lipophilic drugs, reducing side effects and enhancing therapeutic efficacy.
- **Cancer Therapy:** In cancer treatment, nanosponges can be employed to encapsulate anti-cancer drugs, providing targeted delivery to tumor sites while minimizing the impact on healthy tissues.
- **Biomedical Imaging:** Nanosponges can be functionalized with imaging agents, making them suitable for biomedical imaging applications. This includes magnetic resonance imaging (MRI), fluorescence imaging, and other diagnostic techniques[33,34].
- **Gene Delivery:** Nanosponges can serve as carriers for gene delivery, protecting genetic material from degradation and facilitating controlled release. This is particularly relevant in gene therapy applications.
- **Wound Healing:** In wound care, nanosponges can be loaded with therapeutic agents to enhance wound healing processes. Their porous structure allows for the sustained release of healing compounds.
- **Environmental Remediation:** Nanosponges can be utilized for the removal of pollutants and contaminants from water and other environmental matrices. The porous structure enables efficient adsorption of contaminants.
- **Food Industry:** In the food industry, nanosponges can be employed for the encapsulation of flavors, colors, and nutrients. This enhances the stability and controlled release of these components in food products.
- **Cosmetics:** Nanosponges are used in cosmetics for the encapsulation and controlled release of active ingredients. This helps improve the stability and effectiveness of cosmetic formulations[35].
- **Antibacterial Applications:** Nanosponges loaded with antibacterial agents can be used to combat bacterial infections. The controlled release of antimicrobial substances contributes to their efficacy.
- **Vaccine Delivery:** Nanosponges can be designed to carry vaccine antigens, offering a controlled and targeted delivery system. This is particularly relevant in the development of novel vaccine formulations.
- **Oil Spill Cleanup:** In environmental cleanup efforts, nanosponges can be utilized to adsorb and remove oil and hydrophobic pollutants from water surfaces, contributing to oil spill remediation.
- **Sensory Applications:** Nanosponges can be employed in sensors for their high surface area and ability to encapsulate sensing agents, enhancing the sensitivity and selectivity of the sensor[36,37].

Evaluation of nanosponges

Microscopic studies

To study the microscopic aspects of a drug, Nano sponge, or the product it can be subjected to Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM). The difference in the crystallization state indicates the formation of inclusion complexes

Loading efficiency

It can be determined by quantitative estimation of the drug which is loaded into the nanosponge using either by UV spectrophotometer or HPLC method. The loading efficiency can be calculated by

$$Loading\ efficiency = \frac{Actual\ drug\ content\ in\ nano\ sponge}{Theoretical\ drug\ content} \times 100$$

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Solubility studies

The most frequently used method include phase solubility method described by Higuchi and Connors which helps to determine the effects of nanosponge upon the solubility of the drug. The degree of complexation was indicated by phase solubility diagram.

X ray diffraction studies

For the solid state, powder X ray diffractiometry can be used to determine the inclusion complexation. When the drug molecule is liquid and liquid have 0 diffraction pattern of their own the diffraction pattern of a newly formed substance clearly differs from that of uncomplexednanosponge. This difference in the diffraction pattern indicates the complex formation. When the drug compound is a solid substance, a comparison has to be made between the diffractogram of the complex and that of mechanical mixture of the drug and polymer molecules. A diffraction pattern of physical mixture is often the sum of those of each component, while the diffraction pattern of complexes are apparently different from each constituent and lead to a new solid phase with different diffractograms. Diffraction peaks for a mixture of compounds are useful in determining the chemical decomposition and complex formation. The complex formation of drug with nanosponge alters the diffraction pattern and also changes the crystalline nature of the drug. The complex formation leads to sharpening of the existing peaks and shifting of certain peaks.

II. FUTURE SCOPE

- **Advanced Drug Delivery Systems:** Continued advancements in nanosponge technology are expected to enhance drug delivery systems further. This includes the development of nanosponges for specific diseases, targeted drug delivery, and personalized medicine.
- **Cancer Therapy:** Nanosponges hold great potential in improving cancer therapy by optimizing drug delivery to tumor sites, reducing side effects, and enhancing the efficacy of anti-cancer drugs. Future research may focus on tailoring nanosponges for specific types of cancer and exploring combination therapies.
- **Gene Delivery and Therapy:** Nanosponges can play a significant role in gene delivery and gene therapy. Future developments may involve designing nanosponges to efficiently deliver genetic material for therapeutic purposes, addressing genetic disorders, and facilitating gene editing techniques.
- **Immunotherapy:** Nanosponges may contribute to the field of immunotherapy by enhancing the delivery of immunomodulatory agents, vaccines, and other immune system modulators. This could lead to improved treatments for various diseases, including infectious diseases and autoimmune disorders.
- **Neurological Disorders:** Research into the use of nanosponges for the treatment of neurological disorders, such as Alzheimer's and Parkinson's disease, is an emerging area. Nanosponges could potentially assist in delivering therapeutic agents across the blood-brain barrier and improving drug efficacy in the central nervous system.
- **Antimicrobial Applications:** Nanosponges with antimicrobial properties could find applications in combating drug-resistant infections. Future developments may focus on designing nanosponges for efficient antimicrobial drug delivery and wound healing.
- **Environmental Remediation:** Nanosponges have the potential for environmental applications, such as the removal of pollutants from water sources. Future research may explore their use in cleaning up contaminated environments and addressing emerging environmental challenges.
- **Diagnostic Imaging:** Functionalizing nanosponges for diagnostic imaging purposes could be a future avenue. They may be engineered to carry imaging agents for enhanced visualization in various imaging modalities, contributing to early disease detection.
- **Personalized Medicine:** As nanosponge technology advances, there is a potential for the development of personalized medicine approaches. Tailoring nanosponges to individual patient characteristics and specific diseases could revolutionize treatment strategies.

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- **Integration with Other Nanotechnologies:** Nanosponges may be integrated with other nanotechnologies, such as nanosensors and nanorobots, to create multifunctional systems for diagnosis, drug delivery, and monitoring of physiological parameters.
- **Regulatory Approval and Commercialization:** The future may see increased efforts toward obtaining regulatory approval for nanosponge-based products and their commercialization. This involves addressing safety, efficacy, and manufacturing challenges.

III. CONCLUSION

Nanosponges exhibit tremendous potential due to their unique properties, including a porous structure and versatile applications. Their role in drug delivery, particularly in improving solubility and targeted release, shows promise for enhanced therapeutic outcomes. Nanosponges also hold potential in environmental remediation, addressing pollution challenges in water sources. As research progresses, nanosponges may find applications in gene delivery, immunotherapy, and personalized medicine. Despite their exciting prospects, addressing biocompatibility and regulatory considerations is crucial for responsible development. Overall, nanosponges represent a promising nanomaterial with diverse applications and ongoing innovation.

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