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Review on Nanosponges: An Innovative Frontier in Drug Deliver

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ABSTRACT

Nanosponges are an innovative class of nanocarriers characterized by their porous, sponge-like structures. They offer numerous advantages in drug delivery, including controlled release, enhanced stability, and targeted delivery. This review explores the synthesis, characterization, and applications of nanosponges in various fields, with a particular emphasis on pharmaceutical and biomedical applications. We discuss the different methods of fabrication, including solvent evaporation and ultrasound-assisted synthesis, and highlight the various materials used, such as cyclodextrins and hyper-crosslinked polymers. The chapter also delves into the mechanisms of drug release from nanosponges, their biocompatibility, and safety profiles. Finally, we examine the current challenges and future prospects in the development of nanosponge-based drug delivery systems.

Keywords: Nanosponges, Drug Delivery, Controlled Release, Cyclodextrins, Biocompatibility, Hyper-crosslinked Polymers, Biomedical Applications

1. Introduction to Nanosponges

Nanosponges are a type of nanomaterials that are relatively recent and are known for their distinctive sponge-like porous structures. These formations have the ability to encase a range of materials, allowing for diverse uses in various contexts. Originally created for environmental purposes like water treatment, nanosponges have become widely utilized in the pharmaceutical industry for delivering drugs. The attractive option for pharmaceutical applications lies in their capacity to enhance the stability, solubility and bioavailability of drugs.

Nanosponges are usually made up of interconnected polymers that can be manipulated to regulate the pores dimensions. This characteristic is essential for customizing their medication release patterns. Moreover, nanosponges surface can be altered to improve their ability to target specific tissues or cells, resulting in more effective delivery of therapeutic substances [1].

Initially, Nanosponge drug delivery system was limited to topical use, but in the 21st century, Nanosponges can now be given orally or through intravenous (IV) route as well. Nanosponge is a type of contemporary material composed of minuscule particles that contain a small cavity only a few nanometers wide. Different kinds of substances can be used to fill up these narrow spaces [2].

The capability of nanosponges to encase drugs that are both water-soluble and water-insoluble increases their versatility. Nanosponges are especially advantageous for improving the solubility of hydrophobic drugs. Enclosing drugs inside nanosponge pores shields them from deterioration, enhancing their durability and storage time.

The significant advantage of nanosponges is their ability to deliver targeted delivery. By altering the surface of nanosponges with ligands or antibodies, they can be guided to certain tissues or cells, decreasing side effects and improving treatment efficiency. This focused strategy is particularly advantageous in cancer treatment, as it is essential to reduce harm to non-cancerous tissues.

Nanosponges also have uses in diagnostics and imaging, aside from drug delivery. Their permeable makeup can be filled with substances or dyes that improve the visualization of tissues and cells. Nanosponges are highly versatile and can be utilized effectively in various therapeutic and diagnostic applications [1].

1.1. Advantages

- 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.[3]

1.2. Disadvantages

- They include only small molecule.
- They depend only upon the loading capacities.[3].

2. Methods of Nanosponges

Nanosponges can be created through different techniques, each providing distinct benefits and impacting the characteristics of the end product. Some commonly used methods for synthesis include:

2.1 Solvent Evaporation Method

This method involves combining the drug and polymer in an oil-in-water emulsion to create a mixture. The organic solvent evaporates, leading to the formation of nanosponges. By adjusting variables such as polymer concentration and evaporation rate, the dimensions of the nanosponges can be controlled.

The drug and polymer are initially dissolved in an organic solvent, such as dichloromethane or acetone, in the process of solvent evaporation. Next, the mixture is blended with a surfactant in a water-based solution to create a stable emulsion. The polymer precipitates and nanosponge particles form as the organic solvent evaporates gradually.

By adjusting the polymer concentration, organic solvent volume, and evaporation rate, it is possible to regulate the dimensions and

shape of the nanosponges. Increased levels of polymer usually result in bigger nanosponges, whereas quicker evaporation rates can lead to smaller, more evenly sized particles [4].

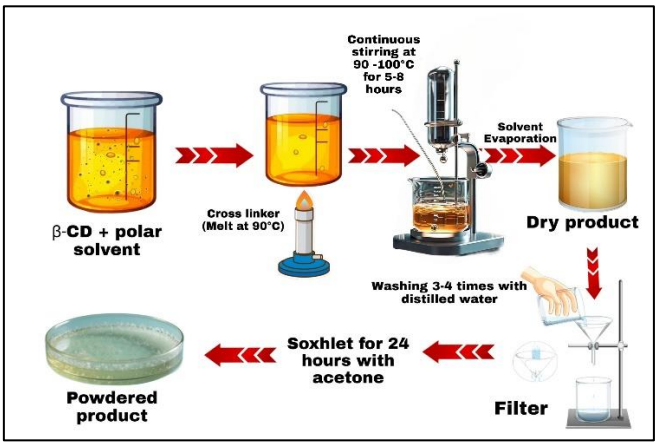

Fig 1: SOLVENT EVAPORATION METHOD

2.2 Ultrasound-Assisted Synthesis

Ultrasound waves are employed to create nano-sponges by causing cavitation in a polymer solution. This method is advantageous because of its simplicity and ability to produce nanosponges with a limited size range. Ultrasonic energy helps create consistent pores in nanosponges, leading to even drug loading and release benefits.

During ultrasound-enhanced synthesis, a polymer solution is exposed to high-frequency ultrasonic waves. Ultrasonic energy produces cavitation bubbles in the solution, leading to the formation of intense localized heat and pressure when they collapse. This procedure results in the creation of nanosponges that have clearly defined pore formations.

Adjusting the frequency, power, and duration of the ultrasound can control the size and porosity of the nanosponges. This technique is especially effective for creating nanosponges with a uniform size range, crucial for reliable drug release patterns.[4]

2.3 Emulsion Solvent Diffusion Method

In this method, both the drug and polymer are mixed in a volatile organic solvent and then dispersed in a water-based solution. Nanosponges are created as the solvent diffuses away. This technique enables efficient drug loading and the creation of nanosponges with a controlled release pattern.

The process of emulsion solvent diffusion includes forming an oil-in-water emulsion that contains the drug and polymer dissolved in an organic solvent, like ethyl acetate. The organic phase is next emulsified in a water phase that includes a surfactant. When the organic solvent moves out into the aqueous phase, the polymer solidifies, creating nanosponge particles.

By adjusting the polymer concentration, organic solvent volume, and solvent diffusion rate, one can regulate the dimensions and shape of the nanosponges. This technique is especially handy for creating nanosponges with excellent drug loading efficiency and precise release characteristics.[5]

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Fig 2: EMULSION SOLVENT DIFFUSION METHOD

3. Factors influencing in the formulation of nanosponges

3.1 Nature of polymer

The type of polymer utilized in making nanosponges can impact both their creation and the pre-formulation process. The nanosponge cavity must be sufficiently large to fit a specific drug molecule for complexation [6].

3.2 Drug:

In order to work with nanosponges, drug molecules need to meet certain criteria:

- The drug's molecular weight must be between 100-400 Daltons.
- It should have no more than 5 condensed rings in its structure.
- The drug should have a water solubility of <10 mg/ml and a melting point of <250 ˚ C [7].

3.3 Temperature:

Variation in temperature can impact the binding of drug molecules or nanosponges. Rising temperature usually lowers the stability constant of the drug or nanosponge complex, possibly because the interaction forces like hydrophobic and Van der Waals forces between the drug/nanosponges decrease as the temperature increases[8] .

3.4 Degree of substitution

The ability of nanosponges to complex may be greatly influenced by the number, location, and nature of the substituent on the main molecule. [8]

4. Materials Used in Nanosponge

Nanosponges are commonly created using different materials, with each material impacting the characteristics of the nanocarrier as a whole. Important materials are:

4.1 Cyclodextrins

Cyclodextrins are circular oligosaccharides recognized for their capacity to create inclusion complexes with hydrophobic compounds. Their biocompatibility and capacity to improve the solubility of drugs make them highly utilized in nanosponge

synthesis. Cyclodextrins consist of glucose units connected by α-1,4-glycosidic bonds, creating a donut-shaped structure with a water-attracting outer surface and a water-repelling inner core. Cyclodextrins special design enables them to trap hydrophobic molecules inside their space, improving their solubility and stability.

During the creation of nanosponges, cyclodextrins are connected together using appropriate cross-linking agents like diphenyl carbonate or pyromellitic dianhydride. This procedure forms a porous three-dimensional framework that can trap various types of medications.

Cyclodextrin-based nanosponges are highly effective in enhancing the solubility and bioavailability of drugs that have low water solubility. The solubility of hydrophobic drugs is increased through inclusion complexation with cyclodextrins, and a controlled release mechanism is achieved by the porous structure of nanosponges.[9]

4.2 Hyper-crosslinked Polymers

These polymers are known for their large surface area and porous nature. Hyper-crosslinked polymers offer a stable framework for drug encapsulation and are beneficial for developing nanosponges with controlled release characteristic.

Hyper-crosslinked polymers are usually made by polymerizing monomers with a cross-linking agent to form a densely cross-linked structure that has high surface area and porosity. This framework offers a stable structure for enclosing drugs and enables the controlled discharge of the enclosed medications.

The large surface area of hyper-crosslinked polymers enables them to hold a large amount of drug, and the porous structure allows for controlled drug release. Adjusting the cross-linking density and the size of the pores can regulate the rate at which the encapsulated drugs are released.

Hyper-crosslinked polymers are highly beneficial for producing nanosponges that have controlled release capabilities, rendering them appropriate for a variety of pharmaceutical uses. These polymers' stability contributes to the extended shelf life and effectiveness of the enclosed drugs [9].

4.3 Biodegradable Polymers

Poly (lactic-co-glycolic acid) (PLGA) is frequently utilized in creating nanosponges for medical purposes, as they are biodegradable polymers. These polymers break down into harmless substances, making them suitable for use inside the body.

Biodegradable polymers play a vital role in creating nanosponges for medical uses. These polymers break down into harmless substances like lactic acid and glycolic acid, which the body naturally processes. This guarantees the secure and effective removal of the nanosponges from the body once their therapeutic effects have finished.

PLGA is a popular biodegradable polymer often utilized in creating nanosponges. A polymer with adjustable degradation rates is formed by combining lactic acid and glycolic acid through copolymerization. The rate of PLGA degradation can be modified by changing the proportion of lactic acid to glycolic acid, enabling the controlled release of drugs within it [9].

5. Mechanisms of Drug Release from Nanosponges

The release of drugs from nanosponges can occur through various mechanisms, including:

5.1 Diffusion

Drug molecules have the ability to gradually move out of the nanosponge matrix. The size of the pores and the type of polymer utilized both impact the rate of diffusion.

The release of drugs from nanosponges is primarily driven by diffusion. Within the nanosponge matrix, drug molecules enclosed in the pores are released gradually. Several factors such as pore size, polymer type, and drug properties affect the rate of diffusion.

The pores' size is crucial in determining the speed of diffusion. Reduced pore size leads to a decreased release rate, whereas larger pores enable quicker diffusion of drug molecules. The diffusion rate is also affected by the polymer's nature, with hydrophilic polymers resulting in a quicker release compared to hydrophobic ones[10] .

5.2 Swelling

Certain nanosponges expand when they come into contact with biological fluids, enabling the drug contained within them to be released. The extent of this swelling behaviour can be adjusted by changing the polymer's cross-linking density.

In nanosponges, swelling is another significant process for drug release. In this process, the nanosponges increase in size when they come into contact with biological fluids, which helps in releasing the enclosed drug. Modifying the polymer's cross-linking density can customize the swelling of the nanosponges.

Increased intermolecular connections lead to a stiffer arrangement, leading to reduced expansion and a delayed release pace. A less dense cross-linking results in a more bendable framework, enabling increased swelling and quicker release. The expansion of the nanosponges may also be impacted by the type of polymer and the existence of hydrophilic or hydrophobic groups. [11]

5.3 Degradation

Biodegradable nanosponges release the drug they hold when the polymer matrix degrades. This system is particularly advantageous for applications that necessitate managed and extended drug administration.

Degradation plays a vital role in the release of drugs from biodegradable nanosponges. The nanosponges polymer matrix degrades as time passes, causing the drug inside to be released. By changing the composition and cross-linking density of the polymer, one can regulate the rate at which the polymer degrades.

Biodegradable polymers like PLGA break down into harmless substances, guaranteeing the safe removal of the nanosponges from the body. By changing the proportion of lactic acid to glycolic acid, the degradation speed of PLGA can be controlled to achieve a sustained and regulated release of the drug enclosed within.[12].

6. Evaluation of nanosponges

6.1 Microscopic studies:

Nano sponge, a drug product, can be analysed using Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) to investigate its microscopic characteristics. The discrepancy in the state of crystallization suggests the development of inclusion complexes [13].

6.2. Loading efficiency:

The amount of drug loaded into the nanosponge can be calculated through quantitative estimation using either a UV spectrophotometer or HPLC method. Loading efficiency can be determined through calculations [14].

$$\text{Loading efficacy} = \frac{\text{Actual drug content in nanosponge} \times 100}{\text{Theoretical drug content}}$$

6.3. Solubility studies

The method most commonly used is the phase solubility method, as described by Higuchi and Connors, which assists in assessing the impact of nanosponge on the drug's solubility [15].

6.4 Thin layer chromatography

The drug molecule's Rf values decrease significantly in thin layer chromatography, aiding in the detection of complex formation between the drug and nanosponge formulation [16].

6.5 Particle size and polydispersity

Dynamic light scattering can be used with a 90 plus particle sizer equipped with MAS OPTION particle sizing software to determine the particle size of a nanosponge formulation. The mean diameter and polydispersity index can be calculated using the collected data [17].

6.6 Zeta potential

Surface charge is determined by measuring zeta potential. An extra electrode can be utilized to measure it in particle size apparatus [18]

6.7 Production yield

The production yield is determined by measuring the initial weight of raw materials and the final weight of nanosponges [19].

$$\text{Product yield} = \frac{\text{Practical mass of nanosponges} \times 100}{\text{Theoretical mass}}$$

7. Characterization of Nanosponges

Understanding the characteristics of nanosponges is essential for grasping their properties and performance. Important methods for defining characteristics are:

7.1 Scanning Electron Microscopy (SEM)

SEM is employed for observing the external appearance of nanosponges, offering information on their dimensions, structure, and porousness.

SEM is a strong method for analyzing the surface structure of nanosponges. SEM produces detailed images of the nanosponges' surface, enabling scientists to observe their dimensions, configuration, and permeability. The SEM images offer important information on how the nanosponges are synthesized and fabricated. [20]

7.2 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR is useful for determining the chemical bonds and functional groups in the nanosponge, verifying the effective inclusion of drugs or changes to the polymer.

Fourier transform infrared spectroscopy (FTIR) is a useful method for analyzing the chemical makeup of nanosponges. FTIR offers insights into the chemical bonds and functional groups in the nanosponges, verifying the effective integration of medications or changes to the polymer. Comparing the FTIR spectrum of the nanosponges with that of the pure drug and polymer can verify the presence of the encapsulated drug. [20]

7.3 Differential Scanning Calorimetry (DSC)

DSC is used to analyse the thermal characteristics of nanosponges, such as their melting and crystallization patterns, which can impact the release of drugs.

Differential scanning calorimetry (DSC) is a useful method for examining the thermal characteristics of nanosponges. DSC gives details on how the melting and crystallization characteristics of the nanosponges can impact their drug release patterns. The characteristics of the nanosponges' heat conduction abilities can be impacted by the type of polymer, the existence of the contained medication, and the level of cross-linking [20].

7.4 Drug Loading and Encapsulation Efficiency

The quantity of drug trapped in the nanosponges and how effectively it is trapped are important factors. These are commonly identified using spectroscopy or chromatography methods.

The drug loading and encapsulation efficiency of nanosponges are important factors that impact their effectiveness in treatment. Drug loading is the quantity of drug contained in the nanosponges, while encapsulation efficiency is the percentage of the original drug effectively encapsulated. Usually, these factors are established through spectroscopic or chromatographic methods like UV-visible spectroscopy or HPLC. [20]

8. Applications of Nanosponges

Nanosponges have a wide range of applications, particularly in the field of drug delivery. Some notable applications include:

8.1 Cancer Therapy

Nanosponges can transport chemotherapy drugs straight to cancer cells, improving treatment effectiveness and reducing unwanted side effects. Their capacity to contain both water-soluble and water-insoluble medications makes them flexible vehicles for mixed treatments.

The use of nanosponges shows great potential in cancer treatment. Nanosponges can transport chemotherapy drugs directly to cancer cells, increasing treatment effectiveness and reducing side effects. The selective delivery abilities of nanosponges enable the targeted delivery of chemotherapy drugs to cancer cells, reducing side effects and improving treatment effectiveness.

Nanosponges' versatility in carrying combination therapies is due to their capability to encapsulate both hydrophilic and hydrophobic drugs. Combination treatments, which administer several drugs at the same time, can improve the effectiveness of cancer therapy by focusing on various pathways that are crucial for tumor development and survival [21].

8.2 Antiviral and Antibacterial Agents

The nanoporous nature of nanosponges enables the continuous delivery of antiviral and antibacterial substances, resulting in prolonged treatment benefits. This is especially beneficial for addressing long-term infections.

Nanosponges have the ability to transport antiviral and antibacterial agents, resulting in extended therapeutic benefits. The porous nature of nanosponges enables the continuous release of the enclosed substances, keeping their medicinal concentrations stable for long durations. This extended release is especially beneficial for treating long-term infections, where the pathogens need prolonged exposure to the drugs to be eliminated [21].

8.3 Gene Delivery

Nanosponges can be designed to transport genetic material, like DNA or RNA, to particular cells. This app shows potential for gene therapy and managing genetic disorders.

Using nanosponges for gene delivery shows great potential as well. Nanosponges can be designed to transport genetic material, like DNA or RNA, to particular cells. This specific delivery method can improve the effectiveness of gene therapy and the management of genetic conditions. The permeable design of nanosponges offers a sheltered space for the genetic material, improving its durability and delivery effectiveness. [21]

8.4 Cosmetic Applications

Nanosponges are utilized in the beauty sector to transport active components in skincare items. Their capacity for controlled release aids in preserving the effectiveness of the active components for prolonged durations.

Nanosponges are utilized in the beauty sector to transport active substances in skincare items. Nanosponges can sustain the effectiveness of active ingredients for long durations due to their controlled release capabilities. This extended release can boost the effectiveness of skincare products, delivering lasting advantages to the skin. [21]

9. Biocompatibility and Safety of Nanosponges

The biocompatibility and safety of nanosponges are critical for their use in biomedical applications. Studies have shown that:

9.1 Cytotoxicity Studies

Experiments are carried out to assess the possible harmful impacts of 2nanosponges on different cell types in vitro. These research studies assist in establishing the appropriate concentration ranges for safe therapeutic application.

Assessing the biocompatibility and safety of nanosponges involves conducting imperative cytotoxicity studies. Cytotoxicity studies conducted in vitro assess the potential toxic effects of nanosponges on different cell lines. These studies assist in establishing the appropriate concentration levels for medicinal purposes so that the nanosponges do not harm normal cells.[22]

9.2 In Vivo Studies

Animal experiments are carried out to evaluate how nanosponges are distributed in the body, how they are processed by the body, and how safe they are. These studies offer insights on the behavior of nanosponges within a living organism.

Studies are done in living organisms to assess nanosponges' safety and effectiveness in animal models. These research projects analyze the biodistribution, pharmacokinetics, and general safety of nanosponges, offering understanding of their behavior within a living organism. Conducting studies in living organisms is essential to comprehend the therapeutic benefits of nanosponges and to verify their safety for human consumption.[23]

9.3 Immunogenicity

The potential immunogenicity of nanosponges, or their ability to provoke an immune response, is also evaluated. This is crucial for ensuring that nanosponges do not cause adverse immune reactions when administered.

Immunogenicity studies are conducted to evaluate the potential of nanosponges to provoke an immune response. These studies are crucial for ensuring that nanosponges do not cause adverse immune reactions when administered. The biocompatibility and immunogenicity of nanosponges are critical factors in determining their safety and efficacy for therapeutic use.[24]

10. Challenges and Future Prospects

Despite their potential, nanosponges face several challenges that need to be addressed for their widespread use. These include:

10.1 Scalability

Developing scalable and cost-effective methods for the large-scale production of nanosponges remains a significant challenge.

Scalability is one of the major challenges in the development of nanosponges. Developing scalable and cost-effective methods for the large-scale production of nanosponges is crucial for their widespread use. Current synthesis methods, such as solvent evaporation and ultrasound-assisted synthesis, may not be suitable for large-scale production. Researchers are exploring new synthesis methods and process optimization techniques to overcome this challenge.[25]

10.2 Stability

Ensuring the long-term stability of drug-loaded nanosponges is essential for maintaining their efficacy during storage and use.

Stability is another important challenge in the development of nanosponges. Ensuring the long-term stability of drug-loaded nanosponges is essential for maintaining their efficacy during storage and use. Factors such as the nature of the polymer, the presence of the encapsulated drug, and the storage conditions can influence the stability of nanosponges. Researchers are investigating new materials and formulations to enhance the stability of nanosponges.[26]

10.3 Regulatory Approval

Navigating the regulatory landscape for the approval of nanosponge-based drug delivery systems can be complex and time-consuming.

Regulatory approval is a significant challenge for the development of nanosponge-based drug delivery systems. Navigating the regulatory landscape for the approval of nanosponges can be complex and time-consuming. Regulatory agencies require extensive data on the safety, efficacy, and quality of nanosponges before granting approval. Researchers and manufacturers must work closely with regulatory agencies to ensure compliance with regulatory requirements.[27]

10.4 Future Directions

Research is ongoing to address these challenges and explore new applications for nanosponges. Advances in materials science and nanotechnology are expected to drive the development of next-generation nanosponges with enhanced properties and functionalities.[28]

The future of nanosponges is promising, with ongoing research addressing the current challenges and exploring new applications. Advances in materials science and nanotechnology are expected to drive the development of next-generation nanosponges with enhanced properties and functionalities. Researchers are investigating new materials, synthesis methods, and applications to unlock the full potential of nanosponges.[29]

11. Conclusion

Nanosponges represent a promising frontier in drug delivery and other applications. Their unique properties, such as controlled release, high drug loading capacity, and versatility, make them attractive candidates for various therapeutic and industrial uses. Continued research and development are essential to overcome current challenges and unlock the full potential of nanosponges.[30] In conclusion, nanosponges are an innovative class of nanocarriers with unique properties and potential for a wide range of applications. Their controlled release capabilities, high drug loading capacity, and versatility make them attractive candidates for drug delivery, cancer therapy, antiviral and antibacterial treatments, gene delivery, and cosmetic applications. Despite the challenges in scalability, stability, and regulatory approval, ongoing research and development are addressing these issues and exploring new applications for nanosponges. The future of nanosponges is promising, with advances in materials science and nanotechnology expected to drive the development of next-generation nanosponges with enhanced properties and functionalities.

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