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Nanosponges: Versatile Nanocarriers for Enhanced Drug Delivery

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Abstract:

Achieving a successful targeted drug delivery system for an extended duration remains an aspiration, primarily hindered by the intricate chemical reactions involved in developing the latest drug delivery systems. However, a newly devised colloidal system known as nanosponges holds significant potential in addressing challenges such as drug toxicity, diminished bioavailability, and erratic drug release. Nanosponges exhibit adaptability to both hydrophilic and hydrophobic types of drugs. Described as miniature sponges capable of circulating within the body, nanosponges aim to reach specific sites, binding to the surface of affected areas to release drugs in a controlled, sustained, and predictable manner. With a porous structure, nanosponges can entrap drug moieties, ensuring a desired and controlled release. The Nanosponge Drug Delivery System (NSDDS) emerges as one of the highest encouraging fields in pharmaceutical. This review aims to provide comprehensive insights into nanosponges, covering their preparation techniques, evaluation, and applications in healthcare.

Keyword: Nanosponge, Novel drug delivery system, Polyvinyl alcohol, Nanotechnology

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Introduction:

The field of nanomedicine heralds a revolutionary advancement in medical sciences, leveraging nanotechnology to enhance and develop medicines. Utilizing nanoscale materials, this approach proves valuable in monitoring, controlling, constructing, and repairing biological systems.[1]

Pharmaceutical scientists have been increasingly investigating nanotechnology in recent years for the development of temporal and targeted drug delivery systems.[2]

Various nanocarrier combination, similarly metallic nanoparticles, polymeric nanoparticles, nano-suspensions, nano-tubes, and nanosponges, have been widely employed for the efficient treatment of infectious diseases, along with their commercial applications in consumer products. Studies indicate that utilizing nanoparticles loaded with apremilast enhances drug solubility, bioavailability, and efficacy in the management of psoriasis.[3]

Topical medication administration entails localised distribution via the skin, vaginal, ophthalmic, and rectal channels to different parts of the body. Nevertheless, there are problems with this approach, including allergic responses, permeability problems, and skin irritation. The skin's barrier layer is blamed for many medications' restricted topical bioavailability. Another strategy is to formulate current pharmacological molecules using new nano-carrier systems and add them to gels that may be used topically to increase their therapeutic efficacy. An inventive class of encapsulating nanoparticles known as nanosponges has shown great promise for regulated medication delivery, especially in topical formulations. These solid nanoparticles including colloidal range and nanosized voids are part of these hyper-crosslinked polymer-based colloidal formations. Nanosponges are tiny sponges that range in size from 100 to 150 nm. They are mostly used to passively target medicament molecules to the skin. Benefits of this method include lowering the dosage, keeping the dosage form on the skin for a longer duration of time, and preventing systemic absorption. Controlled drug release is made possible by the porosity nature of nanosponges, which allow them to encapsulate a wide variety of drug molecules within their holes. Furthermore, their potential to increase the solubility of poorly soluble medications is enhanced by their nanometric size.[4,5,6]

The concept of "miniaturization" holds a pivotal role in the realm of nanotechnology research and innovation, carrying substantial implications for advancements in treatments, diagnostics, and healthcare-related research.[7]

Nanoscale-sized drugs, made feasible through nanotechnology, enhance their effectiveness across various dosage forms.[8]

However, the low viscosity of nanosponges makes them unsuitable for topical medication administration. The rheological behaviour of nanosponges has been modified by biodegradable gels with weak contacts with polymers, improving their stability properties. Various gel matrices have been used to increase the viscosity of nanosponges for topical distribution, such as carbomer 940, carrageenan gum, xanthan gum, and spray-dried silica.[9,10] Consequently, combining nanosponges with a gel matrix appears to be a better method for topical administration than using nanosponges alone. Moreover, the incorporation of nanocarriers inside a gel matrix dispenses with the need for chemical penetration enhancers—

a critical need for topical delivery systems. Chemical boosters can be hazardous to use because most of them are poisonous and irritants, especially when used over an expanded duration of time. Because they are nanosized, nanocarriers—like nanosponges—able conveniently permeate the demis without the use of extra permeation enhancers.[11,12,13]
Research and reports have explored topical gels that incorporate nanosponges. For instance, topical gels containing nanosponge carriers of lemongrass oil demonstrated notable antifungal activity, while topical gels incorporating isoniazid nanosponges exhibited sustained drug delivery.[14,15]

Introducing nanosponges into the body, loaded with medication and equipped with specific chemical "linkers" designed to selectively bind to a characteristic unique to the surface of cancer cells, introduces a new class of miniature sponges comparable in size to a virus. These microscopic sponges motion around the body until they come into contact with the surface of a cancer cell, when they either adhere to the cell or become entangled in it. Then, they carefully and precisely release their powerful medication. The structural basis of nanosponges is mostly made up of long polyester fibres and has the appearance of a three-dimensional network or scaffold. Cross-linkers combine with the solution to form a framework by functioning as tiny grappling hooks. Drug molecules might be contained inside the net effect created by the spherically shaped particles that fill the voids in this framework. The polyester degrades within the body over time since it is biodegradable. Depending on the nanosponge framework, the diameter of the particles may be changed by varying the cross-linker to polymer ratio. Because of their minuscule, mesh-like architecture, nanosponges hold great promise for transforming the way that many illnesses are treated. This technology facilitates a fivefold improvement in the distribution of cancer medication compared to conventional methods.[16]

The objective of the current review is to examine nanosponge-based gels, aiming to boost topical bioavailability, minimize side effects, and improve applicability and permeation potential within the skin.

Advantages of Nanosponge:

- Nanosponge creates complexes that are not harmful.
- They shield the drug with protective layers.
- They maintain stability across a broad pH range.
- They exhibit surface functionalization capabilities.
- They demonstrate the flexibility in the formulation.
- They can effectively decrease drug irritation without compromising their efficacy.
- The nanosponge is biodegradable, offering an environmentally friendly solution for various applications.
- Enhancing patient compliance by extending dosing intervals through the use of nanosponge technology.[17,18,19,20]

Disadvantages of Nanosponges:

- In the nanosponge occasional instances of dose dumping may occur.
- The release of the drug may be delayed in the nanosponge.
- Loading capacities are the sole determinant.

Components Employed in the Fabrication of Nanosponges:

Here are the key components typically employed in the fabrication of nanosponges:

1. **Polymers:** Polymers form the primary scaffold of nanosponges, providing the structural framework necessary for their porous architecture. Commonly used polymers include:
   Cyclodextrins: Cyclic oligosaccharides that are widely used due to their ability to form inclusion complexes with guest molecules.
   Polyesters: Such as poly(lactic acid) (PLA) and poly(glycolic acid) (PGA), known for their biodegradability.
   Polyurethanes: Offering flexibility and robustness.
   Hyper-crosslinked Polymers: Known for their high surface area and porosity.
2. **Crosslinkers:** Crosslinkers are critical for stabilizing the polymer structure and enhancing the mechanical properties of nanosponges. Common crosslinkers include:
   Dianhydrides: Such as pyromellitic dianhydride.
   Epichlorohydrin: Widely used for crosslinking cyclodextrin-based nanosponges.
   Carbonyl Diimidazole: Useful for forming stable amide bonds in polymer networks.
3. **Organic Solvents:** Solvents are used during the synthesis process to dissolve the polymers and crosslinkers and to control the reaction environment. Typical solvents include:Dimethylformamide (DMF), Dimethyl sulfoxide (DMSO), Tetrahydrofuran (THF).
4. **Functionalization Agents:** To impart specific functionalities to the nanosponges, various agents can be introduced during or after the fabrication process. These agents can modify surface properties, enhance biocompatibility, or introduce specific binding sites. Examples include:**Amino Groups:** For enhanced interaction with biomolecules.
   Carboxyl Groups: To increase hydrophilicity and provide reactive sites for further conjugation.
   Alkyl Chains: To modify hydrophobicity.
5. **Template Agents:** In some fabrication methods, templates are used to define the pore structure and size. After the sponge is formed, the template is removed, leaving behind a porous network. Common templates include:Silica Nanoparticles, Polymer Beads.

Method of Preparation of Nanosponges:

Nanosponges are crafted through a variety of methods, as outlined below:

(A) Solvent Method: After dissolving the polymer in the proper solvent, add more cross-linker to it. The mixture should be refluxed for 48 hours at 10˚C. Then, let the mixture to come to room temperature, mix it with an excess of bi-distilled water, and strain the finished product. Use ethanol to purify using prolonged Soxhlet extraction. Then, dry the result and use a mechanical mill to homogenise it into a powder.[16]

(B) Ultrasound assisted synthesis of nanosponges: In order to create nanosponges, this method entails sonicating polymers with a cross-linker without a solvent. The resultant nanosponges are spherical in shape and have a consistent size. Mix the polymer and cross-linker in a flask according to a predetermined molar ratio. Place the flask in an ultrasonic bath filled with water and heat it to 90°C. After five hours of sonication, let the mixture cool before breaking it up coarsely. Before putting the

product through an extensive ethanol Soxhlet extraction for purification, wash it in water to get rid of any non-reacted polymers. When the finished product is ready for use, vacuum-dry it and store it at 25°C.[21,22,23]

Loading of drug into nanosponges:

Pre-treating nanosponges to get a mean particle size of less than 500 nm is crucial for preparing them for drug delivery. To stop aggregates from forming, initially suspend the nanosponges in water and sonicate them.[24]
Centrifuge the suspension thereafter to separate the colloidal fraction. After separating the supernatant, use freeze-drying to dry the sample.
Subsequently, prepare an aqueous solution of nanosponges, add an excess of the medication, and agitate the mixture constantly for the length of time needed for complexation. Centrifugation should be used to separate the complexed medicine from the uncomplexed (undissolved) drug after complexation. By either freeze drying or solvent evaporation, solid nanosponge crystals may be obtained. A crucial factor in the drug's complexation with nanosponges is their crystal structure. According to a study, crystalline and paracrystalline nanosponges have differing loading capabilities. When compared to paracrystalline nanosponges, crystalline nanosponges exhibit greater drug loading. Instead of creating an inclusion complex, drug loading happens as a mechanical mixing in weakly crystalline nanosponges.[25]

Variables influencing the liberation of drugs from nanosponges:[26]

The captured activities are influenced by the physical and chemical characteristics.

- Characteristics of the sponge system, including pore size, pore volume, and resilience, play a role.
- Vehicle characteristics impact the distribution of the sponges.
- Parameters like particle size, pore characteristics, and compositions are crucial considerations.
- Other important factors include external triggers, which include temperature, pressure, and the solubility of active ingredients.
- Pressure: Microsponges' active chemicals can be released onto the skin by pressing or rubbing them.
- Temperature: Some entrapped actives may exhibit increased flow rates with rising skin or environmental temperatures, facilitating drug release.
- Solubility: When water is present, sponges containing water-soluble compounds release the active ingredient; this is especially important for products like antiperspirants and antiseptics.[27]

Elements impact the formation of nanosponges:

- The choice of polymer in use can affect both the creation and effectiveness of nanosponges. In the case of complexation, the cavity size of the nanosponge must be appropriate to accommodate a drug molecule of specific dimensions.
- Specific characteristics are required for drug molecules intended for complexation with nanosponges.[28]

Characterization of Nanosponge:

1. **Particle Size:**During polymerization, particle size is carefully controlled to create free-flowing powders with desirable aesthetic characteristics. Particle size analysis of both

loaded and unloaded nanosponges is conducted using laser light diffractometry or Malvern Zeta Sizer. A cumulative graph is plotted, depicting particle size against time, to examine the impact of particle size on drug release. The average particle size of nanosponges ranged from 400 to 800 nm, and there was an increase in particle size as the amount of polymer decreased.[29]

2. **Determination of loading efficiency:**The loading efficiency of the nanosponge is assessed by calculating the difference between the total drug amount and the portion that remains unentrapped. The entrapment efficiency of the drug is determined by isolating the unentrapped drug using an appropriate analytical method. The separation of unentrapped drug can be achieved through techniques such as gel filtration, dialysis, or ultra-centrifugation.The loading efficiency is calculated as: Loading efficiency = Actual drug content in nanosponge / Theoretical drug × 100.[30]
3. **Solubility studies:**The control of drug bioavailability and solubility is achieved through inclusion complex techniques. The investigation of inclusion complexes of nanosponges (NSs) typically employs solubility techniques. Phase solubility plots, commonly associated with the degree of completion, serve as a valuable means to assess the interactions. Solubility determination plays a crucial role in evaluating the pH of molecules, estimating factors influencing drug solubility, and outlining solubilization patterns.[31]
4. **Zeta potential analysis:**The surface electric charge of particles is determined by the Zeta Potential (ZP). ZP values serve as an indicator of the physical stability of colloidal systems. The assessment of ZP values involves determining the electrophoretic mobility of particles using ZP equipment from Malvern Instruments in Malvern, UK. Samples were introduced into transparent disposable zeta cells, and the results were subsequently recorded.[32]
5. **Microscopic analysis:**The examination of drug incorporation in nanosponges involves microscopic analysis using both scanning electron microscopy and transmission electron microscopy. The diversity observed in the crystallization state and the formulation's appearance under a microscope serve as indicators for the prepared complex.[33]
6. **Swelling studies:**The swelling capacity of the dehydrated nanosponge formulations was evaluated in distilled water. Specifically, 5 mg of the dried nanosponge were placed in a glass vial containing 5 ml of distilled water. The vials were maintained at a temperature of 37°C for a duration of 24 hours. Subsequently, the swollen nanosponge were filtered, blotted, and promptly weighed using an electronic balance.The percentage swelling of the nanosponge at equilibrium was determined using the following formula.
   % SW = We - Wo/ Wo 100
   where, SW is percent swelling of nanosponge,
   Wo is the initial weight of nanosponge,
   We isthe weight of nanosponge at equilibrium[34,35]
7. **Porosity:** The porosity research looks at the nanochannels and nanocavities that are present in nanosponges. A helium pycnometer is used to measure porosity by enabling helium gas to enter the material's intra- and inter-particular channels. The real volume of the substance is ascertained using the helium displacement technique.
   Percent porosity is given by the following equation:
   % Porosity Bulk volume Actual / volume Bulk volume 100.[36,37,38]

Applications of Nanosponges:

Nanosponges exhibit excellent biocompatibility and flexibility, making them highly versatile in various pharmaceutical applications. In the pharmaceutical business, they are frequently

used as excipients in the formulation of tablets, capsules, granules, pallets, suspensions, solid dispersions, and topical dosage forms. It is noteworthy that weakly water soluble medications as well as lipophilic and hydrophilic drug molecules, namely those categorised under the Biopharmaceutical Classification System (BCS-class II), can be efficiently hosted by nanosponges.

1. **Nanosponges for drug delivery:**Leveraging their nanoporous structure, nanosponges offer a distinct advantage in carrying water-insoluble drugs, particularly those categorized as Biopharmaceutical Classification System class-II drugs. These complexes play a crucial role in enhancing the dissolution rate, solubility, and stability of drugs. Additionally, they are utilized to mask undesirable flavors and transform liquid substances into solids. Notably, nanosponges based on β-Cyclodextrin have been documented to deliver drugs to the target site with three to five times greater efficiency compared to direct injection.[39]
   The solid nature of nanosponges allows for their formulation into various dosage forms such as Oral, Parenteral, Topical, or Inhalation. In the case of oral administration, these complexes can be dispersed within a matrix comprising excipients, diluents, lubricants, and anticaking agents. This formulation is well-suited for the preparation of capsules or tablets.[40]
   For parenteral administration, the complex can be conveniently conveyed in sterile water, saline, or other suitable aqueous solutions. In the case of topical administration, effective incorporation into a topical hydrogel is achievable.[41]
   Nanosponges for cancer therapy: Currently, one of the most formidable challenges in the pharmaceutical field involves delivering anticancer drugs, primarily attributed to their limited solubility.[42]
   The nanosponge complex exhibits a threefold increase in efficacy in impeding tumor expansion compared to direct injection. This complex, loaded with a drug, reveals a targeting peptide that securely binds to the outer layer of radiation-induced cells on the tumor receptor.[43]
   Upon encountering the tumor cell, nanosponges adhere to the surface of the tumor cell and commence the release of drug molecules. The advantage of targeted drug delivery lies in achieving a more effective therapeutic impact at the same dose while minimizing side effects.
2. **Treatment of fungal infections through nanosponges:**Globally, skin infections caused by fungi pose significant health concerns. Topical treatment stands as a widely accepted solution for addressing cutaneous fungal infections, offering numerous advantages such as targeted application of medication to the infection site and reducing systemic adverse effects.[43]
3. **Encapsulation of gases:**A Cyclodextrin-based carbonate Nanosponge was employed to create inclusion complexes with three distinct gases: 1-methylcyclopropene, oxygen, and carbon dioxide. The complexation of oxygen or carbon dioxide holds promise for various biomedical applications. Specifically, the oxygen-filled Nanosponge demonstrates potential in supplying oxygen to hypoxic tissues associated with various diseases. Due to its highly porous nature, the Nanosponge has also been investigated as an efficient gas carrier. The Nanosponge formulation exhibits the capability to store and release oxygen in a controlled manner, suggesting its future utility as a valuable tool for delivering essential gases.[44]
4. In medical treatment, gases play a crucial role, and the inadequacy of essential oxygen supply, known as Hypoxia, is associated with diverse Patho physiologies ranging from cancer to inflammation.[45]

5. **Nanosponges for protection against photo degradation:**Nanosponges manufactured through the encapsulation of gamma-oryzanol exhibit effective protection against photodegradation.[46]
6. **Enhanced solubility:**The nanosponge system features pores that enhance the solubilization rate of poorly soluble drugs by entrapping them within these pores. The nano-sized surface area significantly augments, leading to an increased rate of solubilization. BCS class-2 drugs, characterized by low solubility and limited dissolution rates, often face challenges in achieving adequate bioavailability. However, when formulated with nanosponges, these drugs exhibit improved solubilization efficiency along with the desired characteristics of drug release.[47]
7. **Nanosponge in protein drug delivery:**Bovine serum albumin (BSA) protein, prone to instability in solution, is stored in lyophilized form. The stability of proteins, such as BSA, has been significantly improved through the use of swellable cyclodextrin-based poly (amidoamino) nanosponge. Nanosponges have found application in enzyme immobilization, protein encapsulation, and subsequent controlled delivery and stabilization.[48]
8. Nanosponges can transport biocatalysts and release enzymes, proteins, vaccines, and antibodies: It encompasses industrial processes interconnected with operational status. Insufficient yields arise from nonspecific reactions, requiring elevated temperatures and pressures in the downstream process, demanding substantial energy and cooling water usage.[49]One way to address this drawback is by employing enzymes as biocatalysts, as they operate efficiently at a rapid pace and under moderate environmental conditions.
9. **Modified drug release:**The primary drawback of traditional marketed formulations is the need for repetitive drug administration. However, in the nanosponge drug delivery system, the drug is loaded into the nanosponge, ensuring prolonged retention at the delivery site over an extended period.[50]
10. **Antiviral application:**Nanosponges find utility in ocular, nasal, and pulmonary administration routes. Nanocarriers play a crucial role in selectively delivering antiviral drugs or small interfering RNA (siRNA) to nasal epithelia and lungs, targeting viruses affecting the respiratory tract, including respiratory syncytial virus, influenza virus, and rhinovirus. Additionally, nanosponges can be applied in the treatment of HIV, HBV, and HSV. Currently employed nano delivery system drugs include zidovudine, saquinavir, interferon-α, and acyclovir.

Table: List of marketed preparations of nanosponges[51,52,53,54,55]

S. No.	Drug	Category	Polymer used	Method of preparation
1	Piroxicam	NSAID's	Ethyl cellulose	Cross linking
2	Clotrimazole	Antifungal	Ethyl cellulose	Emulsion solvent diffusion
3	Dapsone	Antibacterial	Ethyl cellulose	Solvent evaporation
4	Ketoconazole	Antifungal agents	Diphenyl carbonate	Cross linking
5	Lornoxicam	NSAID's	Ethyl cellulose	Emulsion solvent evaporation

Conclusion:

Since they are tiny and porous, nanosponges—colloidal transporters at the nanoscale—can easily permeate the skin. Their capacity to bind poorly soluble pharmaceuticals inside the matrix improves the drug's bioavailability while also making the poorly soluble medications

more soluble. Nanosponges, which are made of nanoscale polymer-based spheres, have the capacity to capture or suspend a wide variety of materials. These nanosponges may be easily included into manufactured goods such as liquids, powders, ointments, gels, lotions, and creams. This method makes it easier for components to get entrapped, which reduces adverse effects and improves stability, elegance, and formulation flexibility.

The incorporation of nanosponges into topical medication delivery systems in an efficient manner guarantees the dosage form's retention on the skin. Furthermore, bio-erodible polymers can be employed to administer drugs orally, particularly in the case of colon-specific delivery and controlled-release drug delivery systems. By offering a site-specific medication delivery mechanism, this method not only improves patient compliance but also increases dosing intervals.

Conflict of Interest: The authors have no conflict of interest.

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