AN OVERVIEW ON DRUG DELIVERY SYSTEM USING NANOSPONGES

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ABSTRACT

Advancements in nanotechnology have ushered in nanosponges, biodegradable polyester structures with nanometer-sized cavities, designed for targeted drug delivery. Initially developed for topical applications, these nanosponges have evolved to be administered orally and intravenously. They exhibit a porous structure for controlled drug release, addressing issues like toxicity and poor bioavailability. Capable of carrying both hydrophilic and lipophilic drugs, nanosponges serve as versatile carriers for substances like enzymes, proteins, vaccines, and antibodies. Their characteristics include size and polarity control, crystalline forms, non-toxicity, stability in various conditions, suspension and regeneration capabilities, and a 3D structure for targeted capture and release. The composition involves a polymer, a cross-linking agent, and specific drug criteria. Advantages encompass targeted delivery, flavor masking, reduced side effects, water solubility, adjustable particle size, and easy commercial production. Disadvantages include limited encapsulation for larger molecules. The mechanism involves an open structure allowing prolonged release. Various types based on cyclodextrin offer unique properties. Factors affecting nanosponges include polymer nature, drug characteristics, complexation temperature, and degree of substitution. Preparation methods include solvent, ultrasound-assisted, melt, bubble electrospinning, and emulsion solvent diffusion methods. Comprehensive characterization includes drug entrapment efficiency, saturation state interaction, in vitro release studies, porosity measurement, and spectroscopic techniques. Applications span solubility enhancement, sustained delivery, oral and topical systems, protein delivery, protection from degradation, pollutant removal from water, cancer treatment, antiviral applications, enzyme immobilization, and modulation of drug release.

Keywords: Drug Delivery System, Nanosponges, Nanotechnology, Biodegradable Polyester Structures, Protein Delivery, Antiviral Applications, Enzyme Immobilization.

INTRODUCTION

Advancements in nanotechnology have paved the way for targeted drug delivery systems. The need for specialized drug delivery systems to effectively target molecules to specific locations has been a long-standing ambition. Initially designed for topical delivery, nanosponges have evolved to be administered orally and intravenously in the 21st century.

Nanosponges, a modern material category consisting of

tiny particles with nanometer-sized cavities, can carry both hydrophilic and lipophilic drug substances. Comprising a three-dimensional biodegradable polyester, nanosponges can naturally degrade, releasing loaded drug molecules in a controlled manner (Bhoumik et al., 2018).

This discovery is a significant stride in addressing issues such as drug toxicity, poor bioavailability, and predictable drug release. Nanosponges with porous structure allow them to entrap drug moieties, offering controlled and desired release. Formulated through crosslinking cyclodextrin with carbonyl or di-carboxylate, nanosponges find wide applications in oral, topical, and parental drug administration, serving as carriers for enzymes, proteins, vaccines, and antibodies. This paper emphasizes their preparation, characterization, and potential applications in drug delivery systems (Arshad et al., 2016).

1. Characteristic Features of Nanosponges

- *Size and Polarity Control:* Nanosponges exhibit dimensions of 1μm or less, and their cavity polarity is tunable. Specific sizes and adjustable polarities can be synthesized by varying the cross-linker to polymer ratio.
- *Crystalline Forms:* Depending on process conditions, nanosponges may be para-crystalline or crystalline. The crystal structure influences their complexation with drugs, and drug loading capacity depends on the degree of crystallization.
- *Non-Toxic and Stability:* Nanosponges are non-toxic, porous particles insoluble in most organic solvents, and stable at temperatures up to 300 $^{\circ}$C.
- *Stability in pH and Temperature:* Nanosponges remain stable over pH ranges of 1 to 11 and temperatures up to 130 $^{\circ}$C.
- *Suspension and Regeneration:* They can be regenerated through thermal desorption, solvent extraction, microwaves, and ultrasounds. They form transparent, opalescent suspensions in water.
- *3D Structure for Capture and Release:* The 3D structure enables the capture, transportation, and selective release of various substances. They can be targeted to different sites due to their linkability with different functional groups.
- *Chemical Linkers:* Nanosponges utilize chemical linkers to bind preferentially to target sites.
- *Formation of Complexes:* They form both inclusion and non-inclusion complexes with different drugs.
- *Magnetic Properties:* Magnetic properties can be imparted to nanosponges by adding magnetic particles into the reaction mixture.

2. Composition of Nanosponges

2.1 Polymer

- The choice of polymer significantly influences nanosponge formation and performance.
- Polymer selection is based on the desired release profile and the nature of the drug to be encapsulated.
- The selected polymer must have the capability to interact with specific ligands.

2.2 Cross-Linking Agent

- Selection of the cross-linking agent depends on the polymer's structure and the drug being formulated.
- Examples include diphenyl carbonate, dichloromethane, diaryl carbonates, and di isocyanates.

2.3 Drug Substance

- Molecular weight should be between 100 and 400 Daltons.
- The drug molecule should consist of less than five condensed rings.
- Solubility in water should be less than 10 mg/ml.
- The melting point of the substance should be below 250 $^{\circ}$C (Ravi et al., 2019).

3. Advantages of Nanosponges

- Targeted site-specific drug delivery.
- Masks unpleasant flavors and odors, and converts liquids to solids.
- Reduced harmful side effects due to minimal contact with healthy tissue.
- Soluble in water, allowing encapsulation of hydrophobic drugs.

- Adjustable particle size for versatility.
- Improved patient compliance and reduced dosing frequency.
- Acts as a self-sterilizer due to its tiny pore size.
- Easy scale-up for commercial production.
- Efficient capture of substances with minimized side effects.
- Enhanced safety, gloss, and formulation flexibility.

4. Disadvantages of Nanosponges

- Limited encapsulation capacity for larger molecules.
- Potential for dose dumping.
- Possibility of delayed release.
- Dependence on loading capacities.
- Limited incorporation of only small molecules.
- Varied transparency or crystalline structure.
- Loading capacity is influenced by the degree of crystallization (Lakshmi et al., 2021).

5. Mechanism of Nanosponges

Nanoparticles, acting as sponges, possess an open structure, allowing the active ingredient to freely move in and out, establishing equilibrium. In topical applications, upon skin application, the active in the vehicle is absorbed, disrupting equilibrium. This prompts a continuous flow of the active from the sponge particles to the vehicle and then to the skin until the vehicle is depleted. Even after, retained sponge particles on the skin surface gradually release the active, ensuring prolonged release over time (Salunke et al., 2019).

6. Types of Nanosponges

Cyclodextrin (CD) based Nanosponges can be classified into:

6.1 CD-Based Carbonate Nanosponges

- Derived from local β-cyclodextrin and dynamic carbonyl mixtures like carbonyl di-imidazole.
- Gas encapsulation demonstrated with gases like 1-methylcyclopropene, oxygen, and carbon dioxide.
- Oxygen-filled nanosponges can supply oxygen to hypoxic tissues for biomedical applications.

6.2 Carbamate Nano Sponges

- Prepared by reacting cyclodextrins with cross-linkers like hexamethylene di-isocyanate and toluene di-isocyanate.
- Initially developed for water treatment, including the removal of dissolved organic carbon.
- Used for encapsulating substances like steroids, dyes, and dextromethorphan.

6.3 Anhydride Nanosponges

- Produced by a solvent method with bases like pyridine or triethylamine, using cross-linkers such as pyromellitic dianhydride.
- Cross-linking molar ratios range from 1:2 to 1:8.
- Used to encapsulate drugs like doxorubicin, meloxicam, ibuprofen, and acetyl salicylic acid.

6.4 Epichlorohydrin Cyclodextrin Nanosponges

- Prepared by dissolving cyclodextrins in a basic medium like sodium hydroxide using cross-linking agents.
- More hydrophilic, exhibiting high chemical resistance and flexible expanding capacity.
- Used for encapsulating drugs like creatinine and captopril, enalapril, and cilazapril.

6.5 Cyclodextrin-Based Nanosponges

- Utilize a specific dianhydride, like pyromellitic anhydride, as a crosslinking agent.
- Rapid heat release during crosslinking at normal temperature.
- These nanosponges have both anionic and cationic nature with free carboxylic acidic groups.

6.6 Polyamide Nanosponges

- Produced by reacting to acrylamide for 94 hours at normal temperature.
- Bulge in an aqueous solution and remain stable in both basic and acidic solutions.
- Transparent gel formation in contact with water solution, stable for 80 hours.
- High entrapment efficiency for proteins like albumin, with sustained release over 24 hours (PD et al., 2022).

7. Factors Affecting Nanosponges

7.1 Nature of Polymer

- The choice of polymer in nanosponge preparation influences its development and design.
- The cavity size of the nanosponge should be large enough to accommodate a drug.

7.2 Drug Characteristics

- Drug molecules complexed with nanosponges should have specific attributes.
- Molecular weight between 100 and 400 Daltons.
- Drug molecule structure with no more than 5 condensed rings.
- Solubility in water less than 10 μg/mL.
- Melting point less than 250 °C.
- Changes in temperature can affect complexation, and increasing temperature generally reduces complexing due to decreased interaction forces.

7.3 Complexation Temperature

- The durability of a complex is influenced by temperature changes.
- Kinetics and heat increase in durability are inversely correlated.
- A rise in temperature decreases the strength of interactions between drugs or nanosponges, impacting complex stability.
- Maintaining a specific temperature is necessary for nanosponge preparation.

7.4 Degree of Substitution

- The number, type, and position of substitutions on the polymer material affects the chemical capacity of nanosponges.

The type of substitution is crucial, as cyclodextrin derivatives are available in various functional categories (Sabzi & Kiasat, 2018).

8. Methods of Nanosponge Preparation

8.1 Solvent Method

- Polar aprotic solvents like dimethylformamide and dimethyl sulfoxide are used.
- Polymer is blended with a crosslinker and polymer ratio of 8:2.
- Reaction occurs for 48 hours at temperatures ranging from 10 °C to the solvent's reflux temperature.
- Product is obtained by adding excess bi-distilled water, recovered by vacuum filtration (Pedrazzo et al., 2020).

8.2 Ultrasound-Assisted Method

- Synthesis utilizes ultrasound to achieve polymer crosslinking without a solvent.
- Polymer and crosslinker are combined in a flask at a reasonable molar ratio.
- Ultrasound bath is used during sonication at 90 °C for 5 hours.
- Product is split, washed, purified with ethyl alcohol, and vacuum dried (Tiwari & Bhattacharya, 2022).

8.3 Melt Method

- Crosslinker and polymer are melted together.
- Ingredients are homogenized, and nanosponges are collected by washing the product.
- Product is cleaned to extract unreacted polymers and reagents and then divided into nanosponges.

8.4 Bubble Electrospinning Method

- Polyvinyl alcohol is used as the polymer, and a solution is prepared with distilled water.
- Solution is heated, left to cool at room temperature, and used to prepare nanoporous fibers.

8.5 Emulsion Solvent Diffusion Method

- Two steps involve varying levels of organic and aqueous phases.
- Ethyl cellulose and polyvinyl alcohol are dissolved in dichloromethane.
- Mixture is blended, and nanosponges are collected by filtration, dried, and stored (Eldose et al., 2015).

9. Characterization and Evaluation of Nanosponges

Drug Entrapment Efficiency: Drug loading was measured by suspending cyclodextrin nano sponges in a high-concentration drug solution. The obtained portion was freeze-dried, and drug loading was calculated using UV-Visible spectroscopy and HPLC.

Saturation State Interaction: A UV-Spectrophotometer was employed to assess the shift in absorbance maxima (λ max) in spectra, comparing pure drug and NSs.

Phase Dissolution Studies: Enclosure complexion was studied using phase solubility diagrams. Excess drug moiety was used in suitable liquids, and blank NSs were added incrementally. Drug concentration was analyzed using HPLC.

In Vitro Release Studies: A multi-compartment rotating cell with a hydrophilic dialysis membrane was used to study the drug release pattern.

Porosity: The extent of voids in nanosponges was measured using a helium pycnometer.

Swell Index: The Brunauer–Emmett–Teller nanosponge testing method was employed to measure the swelling ratio.

Average Diameter and Polydispersity: A particle size analyzer and dynamic light scattering were used to determine the average diameter and polydispersity.

Fourier Transform Infrared Spectroscopy (FTIR): The sample was studied under FTIR to elucidate the presence of functional groups.

Powder X-Ray Diffraction: Powder X-ray diffraction was used to analyze chemical breakdown and encapsulation (Martí-Rujas, 2020).

Thermal Analysis: Differential scanning calorimetry and differential thermal analysis were utilized to study melting point, crystallization temperature, and thermal stability.

Nuclear Magnetic Resonance (NMR) Spectroscopy: NMR techniques were used to understand the structure of CD crosslinked polymers.

Zeta Potential: Zeta potential was measured to understand particle distribution and interaction.

Stability Studies: Nanosponges were subjected to accelerated conditions and photodegradation experiments for 3 months, with changes in appearance, size, and physical characteristics being analyzed.

Moisture Examination: Dynamic vapor absorption studies were conducted to examine the moisture absorbent role of NSs.

Scanning Electron Microscopy (SEM) Analysis: The JEOL JSM-5610LV scanning electron microscope at 30 kV transmissions was utilized. Alterations between the initial materials' crystallization state and the resultant structures were observed under the electron microscope. The JEOL JFC-1600 auto fine coater was employed to cover the sample with a gold-palladium alloy, ensuring sample preparation for SEM analysis.

Transmission Electron Microscopy (TEM) Analysis: The TEM JEOL 1400 at transmissions of 60kV was used for higher resolution. Approximately 10µL of NS sample was diluted with Milli-Q water to 100µL. To visualize the sample, 5µL of the watery mixture was taken and placed on a network. The network was secured on a glass plate for microscope observation. The sample was microscopically observed and analyzed, providing insights into the detailed morphology and structural characteristics, particularly in the nanoscale range.

10. Applications of Nanosponges

- *Solubility Enhancement:* Nanosponges improve the solubility of poorly water-soluble drugs by molecularly dispersing them within the nanosponge structure, enhancing apparent solubility.
- *Sustained Delivery System:* Nanosponges offer prolonged drug release profiles, optimizing treatment regimens, reducing administered doses, and minimizing side effects.
- *Oral Delivery Systems:* Nanosponges address the dissolution rate limitations of solid drugs, improving oral bioavailability, especially for hydrophobic drugs.
- *Topical Delivery Systems:* Nanosponges provide even and sustained release in dermatological and personal care products, reducing irritation and maintaining efficacy (Patel & Oswal, 2012).
- *Protein Delivery:* Swellable cyclodextrin-based nanosponges are designed for protein delivery, showcasing sensitivity to the pH of the surrounding media.
- *Protection from Light or Degradation:* Nanosponges act as carriers to protect encapsulated molecules from light or degradation, improving stability and potency.

- *Removal of Organic Pollutants from Water:* β-cyclodextrin nano sponges impregnated in ceramic filters efficiently remove organic pollutants from water, demonstrating high purification efficiency (Khan et al., 2016).
- *Cancer Treatment:* Nanosponges enhance drug delivery for anticancer medications, improving cancer cell death and slowing tumor growth.
- *Antiviral Applications:* Nanosponges serve as carriers for antiviral drugs, contributing to effective drug delivery.
- *Enzyme Immobilization:* Studies show the efficient hydrolytic activity of enzymes when absorbed to cyclodextrin-dependent nanosponges.
- *Modulation of Drug Release:* Nanosponges enable controlled and slow release of drugs, overcoming the constant administration limitation of traditional drug delivery systems.
- *Absorbent in Treating Poison in Blood:* Nanosponges can absorb toxins in the bloodstream, acting as a potential treatment for poisoning.
- *Treatment of Fungal Infections:* Nanosponges are used for topical treatment of fungal infections, providing effective antifungal delivery.
- *Diagnostic Tool:* β-CD-based nanosponges serve as diagnostic agents, offering high biocompatibility and prolonged blood circulation.
- *Hydrogen Storage:* Nanosponges composed of long carbon chains linked by metal atoms show promise in hydrogen storage for future energy applications.
- *Cosmetics Industry:* Nanosponges protect cosmetic ingredients, absorb odors, release volatile oils slowly, and find applications in items like lipsticks for long-lasting effects.
- *Food Industry:* Nanosponges are employed in the food industry for masking, reduction, and elimination of bitter components from dietary products.

Conclusion

In conclusion, Nanosponges (NSs) offer a versatile and controlled platform for drug transportation and delivery to specific areas. They can encapsulate a broad range of medications, facilitating oral and topical administration, and are effective for both lipophilic and hydrophilic drugs. NSs are used in cosmetics, gas trapping, solubility increase, adsorption of toxicity, and diagnostics. Structural and chemical integrity assessments ensure product quality. The nanoscale revolution in medical science, facilitated by NSs, enables targeted and managed drug release, reducing toxicity and improving therapeutic outcomes. The critical role of NSs in therapeutics and nanotechnology growth is highlighted. Challenges include cost reduction, exploring new polymers and crosslinkers, and developing efficient production methods. Factors like particle size, synthesis, crystallinity, porosity, and crosslinking influence drug release. Ongoing research explores methods like bubble electrospinning and solvent evaporation. Despite simple preparation methods, addressing residual liquids is crucial to prevent toxic effects. Nanosponges, based on nano and polymer spheres, can be incorporated into various formulations, offering reduced side effects, enhanced stability, and increased formulation flexibility. They are particularly effective in topical and oral drug delivery systems, with potential applications in colon-specific and controlled-release delivery. The unique characteristics of nanosponges make them promise for future pharmaceutical innovations.

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