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A Review on Nanosponges

Nanosponges as approach in rapid onset of action of Medicaments

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Abstract : The long-standing ambition of developing efficient, personalized medicine delivery systems has faced significant setbacks due to the complex chemistry involved in creating these new systems. A key development in addressing these challenges is the creation of nanosponges. These tiny sponges, comparable in size to viruses, can hold various medications. They can travel through the body until they reach a specific target area, where they attach to the surface and begin to release the drug in a controlled and predictable manner. Known as solid porous particles, nanosponges can load medications and other active compounds into their nanocavity and can be designed for oral use.

IndexTerms **- Nanosponges, Medicaments, routes of administration**

- **Introduction** Cross-linkers with a specific affinity for areas of polyester are utilized to create nanosponges, which form into spherical structures featuring numerous pockets or cavities suitable for drug storage. These polyesters are predictably biodegradable, allowing for controlled drug release as they decompose in the body. The nanosponges act as encapsulating nanoparticles, trapping drug molecules within their core. They can be categorized into encapsulating, complexing, and conjugating nanoparticles, with nanosponges and nanocapsules representing the encapsulating type. For instance, alginate nanosponges are porous nanoparticles with many holes that can carry drug molecules, while poly(isobutyl-cyanoacrylate) (IBCA) nanocapsules can hold drugs within their aqueous core. Complexing nanoparticles utilize electrostatic attraction for binding, whereas conjugating nanoparticles attach to drugs via covalent bonds.

These nanosponges, often derived from natural sources, exhibit unique properties, being insoluble in both water and organic solvents, porous, non-toxic, and stable at temperatures up to 300°C. Their three-dimensional structure features nanometric cavities with tunable polarity, enabling them to capture, transport, and selectively release a wide range of substances. Importantly, they can be easily regenerated through eco-friendly treatments, contributing to their application in various fields, including cosmetics and pharmaceuticals.

Nanosponges can enhance the aqueous solubility of lipophilic drugs, protect fragile molecules, and facilitate drug delivery across multiple administration routes aside from oral methods. The straightforward chemistry involved in their preparation lends itself well to scalable production. Though water-soluble, nanosponges do not chemically degrade in water; instead, they blend with it and serve as a transport medium. They can mask unpleasant flavors and convert liquids into solid forms, with chemical linkers allowing them to preferentially bind to target sites. However, a limitation is their capacity to encapsulate only small molecules.

Nanosponges can exist in paracrystalline or crystalline forms, with their loading capacity influenced by the degree of crystallization, as paracrystalline variants can exhibit varying loading abilities. By adjusting the ratio of cross-linker to polymer, nanosponges can be synthesized to specific sizes for timed drug release. Their engineering advantage lies in the relatively simple chemistry of the polyesters and cross-linking peptides used, compared to other nanoscale drug delivery systems. Additionally, these nanosponges can be magnetized when prepared with magnetic compounds, making them suitable for pulmonary and venous delivery due to their tiny size.

Regarding synthesis, various polymers such as hyper cross-linked polystyrenes and cyclodextrins, along with a range of cross-linkers, are utilized to create nanosponges, which significantly improve the aqueous solubility of lipophilic drugs.

Advantages of Nanosponges

- Enhance the solubility of lipophilic drugs in water.
- Protect molecules and facilitate the development of drug delivery systems for various routes of administration. They blend with water to serve as a medium for transporting fluids and can mask undesirable tastes.
- Their chemical linkers allow nanosponges (NSs) to specifically target the desired site.
- The simplistic chemistry of polyesters and crosslinking peptides contributes to the engineering capabilities of NS.

Key Features of Nanosponges

Nanosponges come in varying dimensions (1 µm or smaller) and have cavities with adjustable polarity.

The size and polarity can be controlled by altering the ratio of cross-linkers to polymer. They can exist in either para-crystalline or crystalline forms based on production conditions. The crystal structure significantly influences their drug complexation capability. The drug loading capacity is largely determined by the level of crystallization present, with para-crystalline nanosponges exhibiting varied drug loading capacities. They are non-toxic, porous, and insoluble in many organic solvents, maintaining stability at elevated temperatures (up to 300 °C). Additionally, nanosponges remain stable across a pH range of 1 to 11 and up to 130 °C. They form clear and opalescent suspensions in water and can be regenerated through thermal desorption or extraction with solvents, microwaves, and ultrasounds. Their three-dimensional structure enables the capture, transport, and selective release of a wide array of substances. Nanosponges can be directed to specific sites by linking them with different functional groups,

allowing them to form inclusion and non-inclusion complexes with various drugs. They can also possess magnetic properties.

Composition of Nanosponges

Polymer:

The choice of polymer impacts the formation and performance of nanosponges. The cavity size should be suitable for the drug molecule being incorporated. Polymer selection considers the required drug release profile and the drug itself, with the polymer needing to have properties that facilitate attachment to specific ligands.

Cross-Linking Agent:

The selection of cross-linking agents depends on the polymer's structure and the drug formulation. Examples include diphenyl carbonate, dichloromethane, diaryl carbonates, and diisocyanates.

Drug Substance:

Ideal drug molecules have a molecular weight between 100-400 Daltons, contain fewer than five condensed rings, have a solubility in water of less than 10 mg/ml, and a melting point below 250 °C.

Methods of Preparation

Nanosponges from Hyper-Cross-Linked β-Cyclodextrins:

These nanosponges utilize non-porous compounds, specifically cyclodextrins, as carriers for drug release. Hyper-cross-linking these agents creates numerous interconnected networks, which can form spherical shapes with protein channels and pores. These cross-linkers stabilize the nanosponges, affecting their surface charge density, porosity, and pore sizes.

Emulsion Solvent Method:

This involves the use of ethyl cellulose and polyvinyl alcohol in various proportions. An ethyl cellulose and drug mix is added to dichloromethane, followed by a gradual addition of polyvinyl alcohol dissolved in water. The mixture is stirred at 1000 rpm for approximately 2 hours, after which the nanosponges are collected, filtered, dried, and stored.

Solvent Method:

In this approach, suitable polar aprotic solvents like dimethylformamide or dimethylsulfoxide are used along with the previously mentioned polymer. Cross-linkers are added in a specific ratio and allowed to react at controlled temperatures for two days. After cooling, distilled water is added for recovery, followed by airfiltering and purification using a soxhlet apparatus with ethanol. The final product is vacuum-dried and ground into a fine powder.

Ultrasound-Assisted Synthesis:

This method yields nanosponges by combining polymers with carbonyl cross-linkers in the absence of solvents, followed by sonication. The resulting nanosponges are uniform in shape. After reaction conditions involving heating and sonication, the final product is washed, purified, and dried.

Loading Drugs into Nanosponges

To deliver drugs effectively, nanosponges must first be pre-treated to achieve a mean particle size under 500 nm. The nanosponges are then suspended in water and sonicated to prevent aggregation. The resulting suspension is centrifuged to isolate the colloidal fraction, with the supernatant separated and freeze-dried. Alternatively, a suspension may be prepared and mixed continuously until solid crystals form through solvent evaporation or freeze-drying. The crystal structure is crucial for drug complexation, with higher drug loading achieved in crystalline nanosponges compared to their para-crystalline counterparts. Nanosponges with poor crystalline structures tend to present drug loading as a mechanical mixture rather than forming complex inclusions.

Factors Affecting Nanosponge Formulation

Polymer Type:

The choice of polymer is crucial for both the formation and effectiveness of the nanosponge. The size of the cavities or pores within the nanosponge must be appropriate for housing drug molecules of a compatible size.

Drug Type:

The molecular weight of the drug should fall between 100 to 400 Daltons, with a structure that contains no more than five condensed rings. Additionally, the drug should have a solubility of less than 10 mg/ml and a melting point lower than 250 °C.

***Temperature:**

Variations in temperature can influence the complexation of the drug. Higher temperatures may diminish the apparent stability of the nanosponge complex by potentially weakening the interaction forces, such as Van der Waals and hydrophobic forces, between the drug and the nanosponge.

Applications of Nanosponges:

Due to their biocompatibility and versatility, nanosponges have various applications in pharmaceuticals. They can be utilized as excipients in the formulation of tablets, capsules, pellets, granules, suspensions, solid dispersions, and topical products.

***Nanosponges as Sustained Delivery Systems:**

Acyclovir, a commonly used antiviral drug for herpes simplex virus infections, has slow and incomplete GI absorption. Studies on the release profile of acyclovir from various nanosponge types demonstrated sustained drug release, with approximately 22% and 70% of the drug released from carb-nanosponges and other nanosponges, respectively, after three hours, indicating no initial burst effect.

***Nanosponges for Solubility Enhancement:**

Itraconazole, a BCS class II drug with limited bioavailability due to poor dissolution rates, saw its solubility improve by more than 27-fold when formulated with nanosponges. The solubility increased to over 55-fold when copolyvidonum was included, achieved by masking the drug's hydrophobic groups or enhancing its wetting and reducing crystallinity.

***Nanosponges in Drug Delivery:**

They can be integrated into various dosage forms such as topical applications, parenteral solutions, aerosols, tablets, and capsules. For instance, Telmisartan (a class II drug with dissolution rate-limited bioavailability) was incorporated into a nanosponge formulation, resulting in enhanced solubility and release compared to plain Telmisartan. Similarly, nanosponges were effectively used to enhance the biological efficacy of Paclitaxel, which has poor solubility in water.

***Nanosponges in Enzyme Immobilization:**

Nanosponges are effective for stabilizing enzymes, preserving their catalytic efficiency, and aiding in the recycling of enzymes. The ability of cyclodextrin-based nanosponges to immobilize enzymes has been shown to enhance the performance of lipases used in various industrial processes.

***Nanosponges for Protein Delivery:**

Maintaining the structural integrity of proteins during formulation and storage is challenging. Research has shown that swellable cyclodextrin-based poly nanosponges significantly enhanced the stability and swelling capacity of proteins like bovine serum albumin.

***Nanosponges as Protective Agents:**

Gamma-oryzanol can be encapsulated in nanosponges, providing protection against photodegradation and extending its applications in food and pharmaceuticals.

***Nanosponges for Gas Delivery:**

For conditions like hypoxia, a nanosponge formulation for delivering oxygen has been developed. Studies confirmed its effectiveness and safety through various assessments.

***Evaluation of Nanosponges:**

- ***Microscopic Studies: Techniques such as Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) can reveal details about the nanosponge structure and confirm the formation of inclusion complexes.**

- **Loading Efficiency: This can be quantitatively assessed using UV spectrophotometry or HPLC to determine how much drug is incorporated into the nanosponge.**

- **Solubility Studies: The phase solubility method can illustrate how nanosponge formulations affect drug solubility, indicated by phase solubility diagrams.**

- **X-Ray Diffraction Studies: These help to identify complex formation by analyzing the diffraction patterns of nanosponge formulations in comparison to their uncomplexed states.**

- **Infrared Spectroscopy: This method assesses the interactions between the nanosponge and drug molecules. Changes in spectra upon complex formation can indicate successful encapsulation.**

- **Particle Size and Polydispersity: Dynamic light scattering can be employed to determine the size and distribution of nanosponge particles.**

- *Zeta Potential and Production Yield: Zeta potential indicates surface charge, while production yield can be calculated from the initial and final weights of materials involved in the formulation.

Conclusion: Nanosponge formulations can accommodate both lipophilic and hydrophilic drugs, enabling controlled and predictable drug release at targeted sites. By varying the polymer-to-cross-linker ratio, the size and release rate can be optimized. These characteristics allow nanosponges to incorporate insoluble drugs effectively while shielding active compounds from degradation, making them suitable for a variety of dosage forms, including parenteral, aerosol, topical, tablets, and capsules.

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