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Review Article

Unlocking Nanosponges Potential: An Overview of Formulation Strategies, Assessment Approaches and Emerging Applications

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ABSTRACT

Nanotechnology, a multidisciplinary field, has emerged as a transformative force in various industries, particularly medicine. Among its innovations, nanosponges stand out as a promising class of nanomaterials, distinguished by their porous, sponge-like structures. Typically synthesized through the cross-linking of cyclodextrins, nanosponges exhibit remarkable capabilities in drug administration and diagnostics because of their capacity to encapsulate diverse molecules. These properties enable enhanced solubility, controlled release, and targeted delivery. Nanosponges are fabricated using various techniques, such as quasi-emulsion solvent diffusion, ultrasound-assisted synthesis, and melt methods, each influencing their particle size, surface charge, and drug-loading capacity. These methods ensure reproducibility, scalability, and compliance with regulatory standards. Evaluation methods like thermo-analysis, microscopy, zeta potential, and particle size determination further affirm their efficiency and compatibility. They also find applications in diagnostics, serving as biosensors and imaging agents, and in theranostics for simultaneous disease detection and treatment. Additionally, they hold potential in gene delivery, tissue engineering, and vaccine development. Future research aims to address these issues and explore novel applications, positioning nanosponges as a pivotal tool in advancing healthcare and biomedical technologies.

INTRODUCTION

The manipulation of matter at the nanoscale, typically ranging from 1 and 100nm, is the main emphasis of the multidisciplinary field of nanotechnology. Its potential to transform a number of industries, including health, has drawn a lot of interest [1]. Nanomaterials with advantages in size, surface area and functionalization like nanoparticles, Nanosponges and nanorods, been investigated for a range of biological purposes [2]. A distinct class of nanomaterials known as nanosponges is distinguished by its porous, sponge-like structure. In order to create a three-dimensional network, they are usually created by cross-linking cyclodextrins, a family of cyclic oligosaccharides, with different chemical agents [3-4]. Because nanosponges are porous, a wide range of compounds, for example, medications, proteins, and nucleic acids, can be encapsulated and effectively transported to particular bodily locations [5]. Nanosponges are adaptable carriers in drug delivery applications because the cross-linking agents they contain can be changed to alter their stability, drug release profile, and interaction with biological systems [6].

Enhanced solubility of poorly water-soluble medicines, controlled release, and targeted distribution to particular tissues or cells are just a few of the many benefits that nanosponges provide in drug administration [7]. Additionally, by functionalizing nanosponges with targeting ligands, precision distribution to disease sites—like tumors—is made possible, lowering the possibility of off-target effects and enhancing therapeutic results [8]. In addition to drug delivery, nanosponges have demonstrated potential in diagnostic applications, including contrast agents for imaging, disease detection biosensors, and materials for wound healing [9-10].

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This review will comprehensively explore the formulation techniques of nanosponges, focusing on the methods used to prepare and evaluate their properties, such as particle size, surface charge, and drug-loading capacity [11].This review will also highlight emerging applications of nanosponges in various fields, such as drug delivery systems, diagnostics, and wound healing, illustrating their potential to revolutionize biomedical therapies [12].

The Benefits of Nanosponges

- By allowing components to become trapped, nanosponges lessen negative impacts.
- Stays stable at pH values between 1 and 11.
- They are resistant to temperatures as high as 1300°C.
- Due to their tiny pore size of 0.25 m, which inhibits germs from penetrating, they function as self-sterilizers.
- They are free-flowing and inexpensive.
- They increase the solubility of drugs that are difficult to dissolve.
- They improve the drug's bioavailability.
- They are more elegant, more stable, and have better formulation flexibility [13].

The Drawbacks of Nanosponges

- Only small molecules can be encapsulated by nanosponges, rendering larger molecules unsuitable.
- Dosage dumping is possible [14].

Formulation Techniques

Since they affect the quality, functionality, and suitability of these delivery systems for medications and other materials, effective and repeatable formulation techniques are essential in the creation of nanosponges. Such techniques are crucial for maintaining regulatory compliance, guaranteeing end-user safety, and producing consistent product attributes. The capacity to increase output and guarantee consumer confidence in these cutting-edge materials is strongly impacted by the formulation procedures' dependability [15].

Materials Used in Nanosponges Preparation

Depending on the kind of nanosponges that are desired and the level of crosslinking that is needed, a variety of chemicals have shown encouraging results and can be used to create them. The quantity of crosslinking, which depends on the concentration of the crosslinker, is an essential part of nanosponges since it has an impact on both drug encapsulation and drug release patterns [16].

Different components used in Nanosponges are discussed below:

Table 1: Materials Used in Nanosponge Formulation [16]

Materials	Examples
Polymer	Acrylic polymers, Eudragit RS100, hyper crosslinked polystyrene, cyclodextrin and its derivatives, etc.
Polymer Blends	Ethylcellulose, PVA, polyvalerolactone, allylvalerolactone, etc.
Crosslinkers	Dichloromethane, diphenyl carbonate, glutaraldehyde, carboxylic acid dianhydrides, carbonyl diimidazoles, etc.

Specific Techniques

Various methods are employed for the preparation of Nanosponges, including emulsion solvent evaporation, ultrasonication, and thermal cross-linking. These techniques enable the synthesis of Nanosponges with desired characteristics, tailored for specific applications like drug delivery, environmental remediation, and catalysis.

Solvent Diffusion in Quasi-Emulsions

The aqueous and organic phases are used in varying ratios in this technique to make Nanosponges. PVA utilizes the aqueous phase., whereas a drug and polymer solution are used in the non-aqueous phase. The medication is dissolved in a suitable organic solvent after the polymer has been selected, and the solution is then progressively added to the aqueous phase. At 1000 rpm, the final resolution is stirred for over two hours. Filtration, washing, and drying are done on the prepared nanosponges (Fig. 1) [17].

Ultrasound-assisted Synthesis

This method involves sonicating a reaction between polymers and crosslinkers without the need of a solvent to create the nanosponges. This approach creates spherical, uniformly sized nanosponges. This process involves mixing the polymer with crosslinkers like pyromellic anhydride or di-phenyl carbonate in a flask at a particular molar ratio. Following cooling, the liquid in the flask reached 90 degrees Celsius in a water-filled bath with ultrasonic waves. To remove the excess nonreacted polymer, then, water is used to wash the mixture. The mixture that has been improved using a lengthy process of soxhlet extraction using ethanol (Fig. 2) [18].

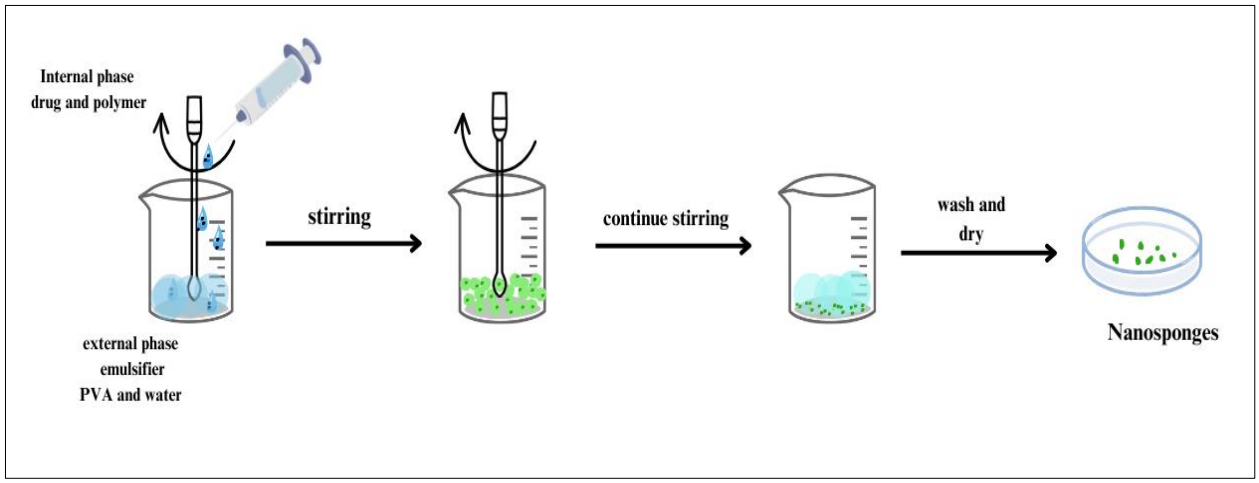

Figure 1: Emulsion solvent diffusion technique

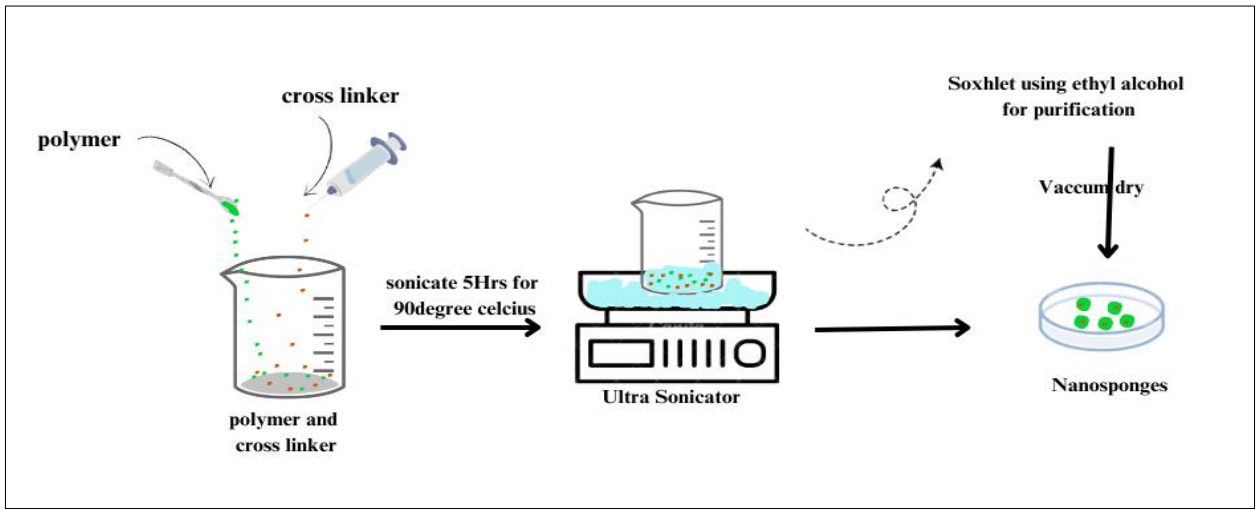

Figure 2: Ultrasound assisted technique

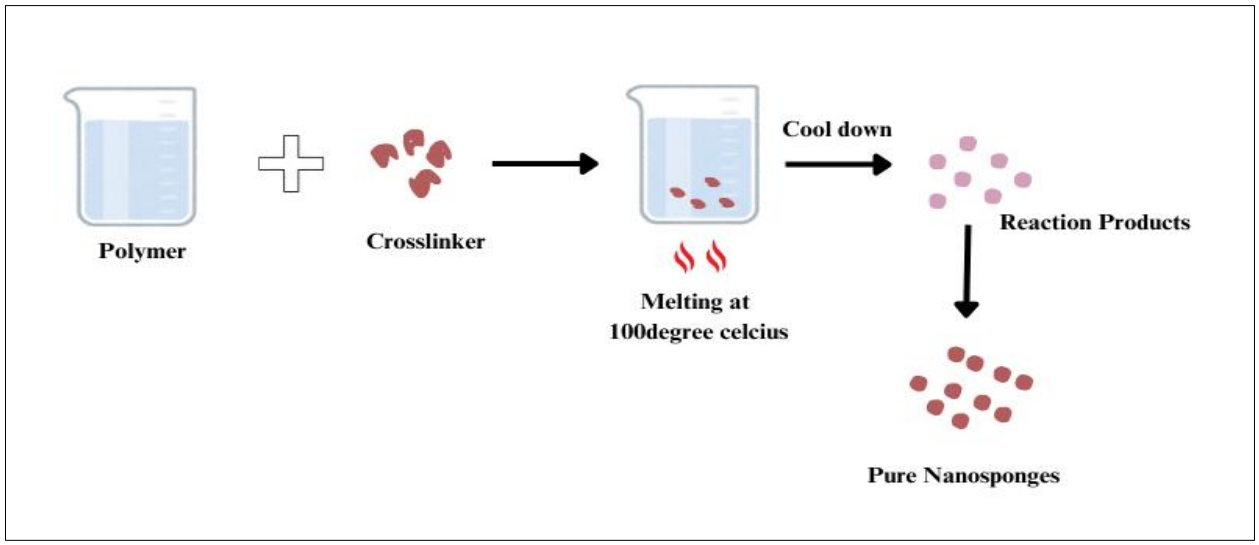

Figure 3: Melt Method

Melt Method

Acrylamido 2, 2-bis acetic acid is an example of a cross-linker., dimethyl carbonate, diphenyl carbonate, diisocyanates, diaryl carbonates, carbonyl diimidazoles, and carboxylic acid anhydrides is reacted with cyclodextrin to create nanosponges. After thoroughly mixing all the components, they are heated to 100°C in a 250 mL flask. Using a magnetic stirrer, the reaction was conducted for approximately five hours. The product was broken down by allowing the mixture to cool. To get rid of any remaining unreacted substances and byproducts, the final product was cleaned using an appropriate solvent (Fig. 3) [19].

Other Methods

It covers additional methods for creating nanosponges, such as the solvent method [20] and the microwave irradiation method [21].

Factors Influencing Nanosponges' Formulation

- **Drug Type:** The medicinal compounds utilised in both incisional and non-incisional procedures, the following qualities should be present in nanosponge complexes:
  - Five condensed rings is the maximum number that should be present in the structure of the medication molecule.
  - The MP of the drug should be below 250°C [22].
- **Polymer Type and Crosslinker:** The performance of nanosponges is influenced by the kind of polymer used in their formulation. Nanoporous molecular structures are converted into three-dimensional (3D) structures through effective crosslinkers. By altering the Hydrophilic or hydrophobic sections can be produced depending on the degree of crosslinking to target molecules to become entangled. The development of Nanosponges that are insoluble or soluble in water is based on the characteristics of crosslinkers [23].
- **Temperature:** The complexation of nanosponges is affected by temperature variations. The medication or nanosponges complex's stability constant. Generally speaking, A falls with temperature, maybe as a result of a decrease in forces of contact such van der Waals and hydrophobic forces [24].
- **Level of Replacement:** The capacity of nanosponges to complex depends on the type of substituent, location and number of the polymeric molecule [25].

Evaluation Methods

Nanosponges, as advanced drug delivery systems, require comprehensive evaluation to ensure their efficiency, stability, and compatibility for biomedical applications.

Thermo-Analytical Methods

Before the nanosponge undergoes thermal degradation, thermo-analytical techniques assess If the drug's composition changes. Melting, evaporation, disintegration, oxidation, and polymorphic transition are examples of changes in drug substances. The presence of a change in the drug substance suggests the formation of a complex. The DTA and DSC thermograms may exhibit widening, shifting, the appearance of additional peaks, or the removal of specific peaks [26].

Studies Using Microscopy

Two types of electron microscopy are scanning and transmission can be used to examine the microscopic properties of a nanosponge formulation and the drug. Using SEM, the morphology of nanosponges is examined. Under an electron microscope, the difference between the finished formulation and the raw materials utilised to make the nanosponge in terms of crystallisation state shows how inclusion complexes are formed [27].

Zeta Potential

The zeta sizer device uses the zeta potential to identify the type of nanosponges and their surface charge. A potential charge of about 30Mv will be advantageous to the study [28-29].

X-ray Structural Study of a Single Crystal

This technique is employed to ascertain the intricate structure of engagement and inclusivity. It is possible to identify the exact geometrical relationship and identify the interaction between the molecules that are both host and guest [30].

Particle Size Determination

One of the most crucial parameters in the nanosponge the particle size is the optimization procedure. Both the drug's solubility and release may be affected by the size of its particles. Particle size can be ascertained using the device, laser light diffractometry, or a Zeta sizer [31-35].

In-Vitro Drug Release Study

A diffusional region in a Franz diffusion cell of 2.26 cm^2 and a spinning cell with many compartments and a dialysis membrane can be utilised to investigate the drug release from the formulation of the optimised Nanosponges [36].

Kinetics of Drug Release

Higuchi, Korsemeyer-Peppas, zero order, and first order were used to analyse the release data, Makoid-Banakar, Kopcha, and Hixon Crowell models in order to look into the process of discharge of medication from the nanosponge. Software called the data can be analysed using Graph Pad Prism [37].

Diffractometry of X-rays and One Crystal X-ray Structure Analysis

It is possible to identify inclusion complexation in the solid-state using X-ray diffractometry. It is evident that the diffraction pattern of drug molecules and uncomplexed nanosponges are different. When it is liquid and doesn't exhibit a pattern of diffraction of its own. Both the drug's crystalline structure and the complex it forms with nanosponges change the diffraction patterns [38-39].

Emerging Applications of Nanosponges

Drug Delivery

Because of its special qualities—such as their huge surface area, high loading capacity, and capability to encapsulate both hydrophobic and hydrophilic drugs—nanosponges are receiving a lot of attention in the field of drug delivery systems. Their adaptability enables them to tackle a number of drug delivery issues, such as controlled release, bioavailability, and solubility.

Enhanced Solubility and Bioavailability

Many medications are poorly soluble in water, which reduces their effectiveness and absorption. These medications can be encapsulated in nanosponges to improve their solubility and absorption. Better therapeutic results and lower dosage needs may result from this [40].

Targeted Drug Delivery

Drugs can be delivered precisely to sick cells or tissues by functionalizing nanosponges with targeted ligands like peptides or antibodies. This method can lessen adverse effects and increase therapeutic efficacy [41].

Diagnostics

Biosensors

Highly sensitive and selective biosensors for the detection of a variety of illnesses, including infectious diseases and cancer, can be created using nanosponges [42].

Imaging Agents

Better visibility of tumours and other sick tissues is made possible by functionalizing nanosponges with contrast materials for computed tomography (CT) and magnetic resonance imaging (MRI), and other imaging modalities [43].

Theranostics

It is possible to identify and treat diseases at the same time by combining the diagnostic and therapeutic properties of nanosponges [43].

Other Biomedical Applications

Gene Delivery

As a safer and more effective substitute for viral vectors, nanosponges may be employed as non-viral gene delivery vehicles.

Tissue Engineering

By offering a favourable environment for cell development and differentiation, nanosponges can be employed as scaffolds for tissue regeneration.

Vaccine Delivery

By improving their stability, immunogenicity, and targeting properties, nanosponges can be utilised to create innovative vaccines [42].

CONCLUSION

Nanosponges offer transformative possibilities for the delivery of drugs and diagnostics due to their unique properties. By overcoming formulation and delivery challenges, they pave the way for safer, more effective therapies. Future advancements may expand their applications, establishing nanosponges as integral to modern medicine.

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