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RESEARCH ARTICLE
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DRUG DESIGN AND CHARACTERIZATION OF NANOSPONGES FOR ENHANCED SOLUBILITY OF POORLY SOLUBLE DRUGS

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Abstract:
Nanosponges (NSs) represent a novel class of nanomaterials that have gained significant attention for their unique structural and physicochemical properties, particularly in the field of drug delivery. Aim of this study to provide a comprehensive overview of nanosponge-based drug delivery systems, focusing on their fundamental concepts, methods of preparation, and evaluation techniques. It further explores the current challenges encountered in both research and industrial-scale manufacturing. NSs are nano-sized, porous structures capable of encapsulating a wide variety of therapeutic agents—including proteins, enzymes, hydrophilic and lipophilic drugs, vaccines, and antibodies—enhancing their solubility, stability, bioavailability, and providing controlled or extended release. These systems can be synthesized using both organic and inorganic materials, offering several advantages such as biocompatibility, cost-effectiveness, improved stability, taste masking, and reduced side effects. This review also discusses various types of nanosponges, their synthesis methods, diverse applications, and characterization approaches. Overall, NSs show immense promise as multifunctional carriers, with the potential to significantly advance the field of nanomedicine.
Conclusion: Nanosponges significantly enhanced the solubility and release profile of the drug, suggesting a potential oral delivery platform for hydrophobic therapeutics.

Keywords: Nanosponges, β-Cyclodextrin, Poorly Soluble Drugs, Solubility Enhancement, Drug Delivery, Ibuprofen, Cross-linking.

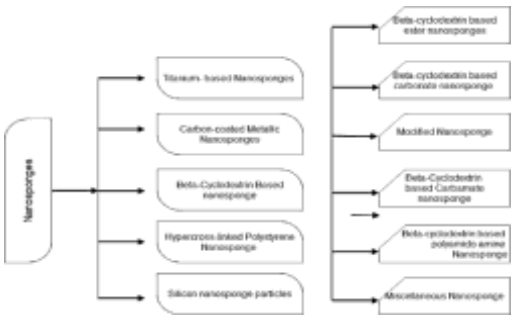
1. Introduction

Poor aqueous solubility is a critical factor limiting the bioavailability of many therapeutic agents, particularly those in BCS Class II and IV. Traditional solubility enhancement techniques have limited effectiveness for such drugs. Nanosponges, a novel nanoscale delivery system formed by crosslinked cyclodextrins, offer high surface area, tunable porosity, and stability to improve drug solubility and stability. This study investigates the formulation and characterization of β-cyclodextrin-based nanosponges for enhancing solubility and modifying release behavior of a model hydrophobic drug. Nanosponges can harden compounds and mask taste, making it 5 times better for breast cancer drugs than conventional methods and treating various diseases [1]. Nanosponges a type of nanoparticle, can be regenerated through light heating, inert gases, solvents, and pH adjustments, with applications in flower culture, flame retardancy, pharmaceuticals, and cosmetics. NS, a type of nanoparticle, can be regenerated through light heating, inert gases, solvents, and pH adjustments, with applications in flower culture, flame retardancy, pharmaceuticals, and emetics [2]. Poly(isobutyl-cyanoacrylate) nanocrystals with hydrophilic cores

absorb medicinal molecules via electrostatic contact, offering higher entrapment efficiency and resistance to molecular degradation [3]

TYPES OF NANOSPONGE

NS can be developed into various types based on polymer, concentration, and production method. Cyclomaltoheptaose-based NS is a common type. Metal Organic Frameworks (MOFs) offer flexibility in design and synthesis, using methods like deployment, precipitation gelation, electrochemical deposition, and solvothermal gelation [4] figure shows the classification of nanosponges



Aim:

To design, formulate, and characterize nanosponges as novel drug delivery systems to enhance the solubility, stability, and bioavailability of poorly soluble drugs.

Objectives:

1. To identify and select a model poorly soluble drug for incorporation into nanosponge formulations based on physicochemical properties and clinical relevance.
2. To design and optimize Nanosponges formulations using appropriate polymers (e.g., cyclodextrins, ethyl cellulose) and cross-linking agents through techniques such as solvent evaporation or emulsion solvent diffusion.
3. To evaluate the physicochemical characteristics of nanosponges, including particle size, surface morphology, zeta potential, and encapsulation efficiency.
4. To assess the solubility enhancement of the poorly soluble drug in nanosponge formulations compared to its pure form.
5. To perform in vitro drug release studies to determine the release kinetics and mechanism of drug delivery from nanosponges.

MATERIALS USED IN THE PREPARATION OF NANOSPONGE

Chemicals used in synthesizing NS depend on the type and extent of crosslinking, which affects drug release and encapsulation patterns and is influenced by the concentration of crosslinkers used.[5] CDs combine with active pharmaceuticals to form complexes, increasing water solubility, concealing undesirable qualities, reducing adverse effects, and enhancing photographic stability. CD-based nanocarriers have high drug-loading capacity.[6]

METHODS OF PREPARATION OF NANOSPONGE

Hyper-crossed linked β-CD method

Hyper-crosslinked β-CD NS are synthesized from the reaction between the β-CD of any type with a variety of cross-linking reagents, such as epichlorohydrin, diphenyl carbonate, or citric acid, in any polar or nonpolar solvents, like water, Dimethylformamide, or Dimethyl sulfoxide. The formation between 3D β-CD molecules is through covalent bonds. The product is washed, purified, and dried as NS characterized by high surface area.

Ultrasound-assisted synthesis of nanosponge

This method makes small, round NS of the same size. It does this by mixing a polymer and a crosslinker in a flask, heating it to 90°C, and breaking it into smaller pieces. The To conduct stability studies under ICH guidelines to evaluate the shelf-life and robustness of the nanosponges formulations.

product is rinsed, cleaned using Soxhlet extraction with ethanol, and dried in a vacuum. These NS are good for delivering drugs and soaking up other substances.[7]

Solvent Method of Nanosponge preparation

The method involves using dimethylacetamide and acetonitrile as solvents, combining them with a polymer, and optimizing the crosslinker/polymer ratio. The mixture is then heated for 48 hr, cooled, and a surplus of bi- distilled water is added to extract the product. The product is vacuum-filtered and recovered.[8]

Melt method of nanosponge preparation

The melt procedure involves melting both β- CDs and the crosslinker. After finely combining the remaining components, put them to a 250 mL jar that has been heated to 100°C. Following that, the reaction is performed for 5 hr using attractive magnetic mixing. Allow to cool and break down, then wash with solvents to remove byproducts and excess.[9]

Microwave synthesis of nanosponge preparation

In the microwave synthesis approach, this polymer, along with crosslinkers, can be mixed in an appropriate solvent. The mixture is then exposed to microwave irradiation, which rapidly heats up the components and accelerates the cross-linking process, developing a porous three-dimensional NS structure. The product then undergoes purification by washing and can be dried in a vacuum. This method will, therefore, provide faster, energy-efficient synthesis of uniform NS with a higher surface area for different applications.

Zeta potential

Zeta potential measures surface charge, and can be used in particle size measurement devices. NS samples are diluted with KCl and placed in an electrophoretic cell with 15 V/cm electric field.

Polydispersity Index (PDI) and particle size

Dynamic light scattering measures particle size using a 90 Plus particle sizer and MAS OPTION program, calculating mean diameter and PDI, which indicate the variation in particle size distribution between monodisperse and polydisperse samples.

Scanning Electron Microscopy (SEM)

SEM is used to analyse morphological structures of NS, characterizing detailed particle structures. Samples are vacuum- sealed and coated with palladium or gold using a scanning electron microscope sputter coater unit at 15 kV acceleration voltage (Subramanian *et al*., 2012).

Fourier Transform Infrared spectroscopy (FTIR)

The NS formulation was optimized using potassium bromide and NS in a 1:90 ratio, compressed under 15 tons of pressure, and recorded using FTIR spectra in the 4000-400 cm^{-1} wavelength region, observing changes in optimized primary peaks over time.

X-ray Diffractometry structure analysis (X-RD)
XRD is crucial for identifying solid-state inclusion complexes in drug molecules, with changes in diffraction patterns indicating new structures. Powder X-ray Diffraction (PXRD) patterns show solid phase formation, and complexes may produce additional peaks.[10]

Thin layer chromatography
Thin-layer chromatography was used to determine the R*f* values in these NS complex pharmaceutical molecules. The lower Rf value confirmed the presence of a complex between the NS and the drug molecule.

APPLICATIONS OF NANOSPONGE
Sustained drug delivery
Pharmaceuticals and Medical Devices Agency (PMDA) created insulin NS, sensitivity to pH, and efficacy in glipizide release after 12 hr, acyclovir for sustained release due to slow absorption in the gastrointestinal system.

NS as a carrier for gas delivery
In order to serve as gas carriers for gases like carbon dioxide and oxygen. The CD-based NS with improved penetration profiles. This allowed for a slower and more prolonged release of oxygen for topical administration.

Protein delivery
Lyophilization can cause permanent denouement, requiring long-term stability for pharmaceutical production. Cross-linking β- CD with 2,2-bis-acrylamidoacetic acid or polyamido-amine chains creates stable, complex able poly(amidoamine) NS.[11]

Solubility and bioavailability enhancer
The solubility of hydrophobic medications may be improved by using NS in CD cavities. This can result in lower dosages, better treatments, fewer adverse effects, and more patient compliance. This has been used to treat cancer, including the creation of paclitaxel.[12]

Nanosponge in cancer therapy
Tumours can be treated using anticancer drugs delivered by NS, which focuses on peptides attaching to radiation-activated cell surface receptors, potentially enhancing the solubility of camptothecin, thereby circumventing its limitations.[13]

Stability enhancer
NS enhances soluble, stable, and efficient dissolution of compounds like volatile oils, medications, Bovine Serum Albumin (BSA) proteins, and resveratrol, while genetic engineering improves enzyme stability, economy, and specificity.

Drug delivery
There are several ways to employ NP, including topical, parenteral, aerosol, tablet, and capsule forms. They are useful nanocarriers for the treatment of cancer because they increase the solubility of medications including TEL, paclitaxel, and econazole nitrate.[14]

Enzyme entrapment
Enzyme entrapment is a significant challenge for lipases, impacting stability, enantion selectivity, and reaction speeds. A new, solid basis is needed for enzyme development, and Pseudomonas fluorescence lipase exhibits exceptional catalytic activity.[15]

Severe Acute Respiratory Syndrome (SARS)-CoV-2 inhibition
NS, or nanoparticles, can treat and prevent serious illnesses like SARS and Zika by imitating host cells to capture and kill SARS- CoV-2, using Angiotensin-Converting Enzyme 2 (ACE2)-containing plasma membranes.

Diagnostic test
β-CD is extensively employed in the formulation of multiple diagnostic products. CD-NS are favored for their excellent biocompatibility, prolonged circulation time in the blood, consistent particle size distribution that enhances permeability, and their efficient ability to reach specific targets.[16]

Cosmetics
NSs are used in the cosmetics industry to protect photosensitive components by prolonging the release of volatile oils and absorbing unpleasant bodily odours. They also subtly eliminate volatile substances, leaving oral cosmetics fresh for longer, and providing a long-lasting appearance in rouge and lipsticks.[17]

DRUG RELEASE MECHANISM AND PHARMACOKINETIC STUDIES
Nanosponges release drugs in a controlled release mechanism, where the medication migrates towards the skin's stratum corneum until fully absorbed, resulting in a pseudo- zero order pattern of drug release.[18]

RELEASE PROFILE
A rotating multicompartment cell with a dialysis membrane is used to test NS *in vitro* release. The donor phase contains drug- loaded NS complexes, while the receptor phase is removed and diluted. The USP Apparatus II can be used in various applications. The release data helps understand drug release mechanisms. First and zero-order models are fitted, and data analysis software like GraphPad Prism is used to find optimal nonlinear functions and parameters.[19]

Emerging Trends and Future Research Areas in NS Technology
NSs are being developed as a promising drug delivery platform for cancer therapy, infectious disease control, and environmental remediation. They can be used in stimuli- responsive drug delivery systems that respond to environmental triggers such as pH, temperature, or light to release drugs. They allow for site-specific delivery of drugs, which avoids side effects and improves the treatment outcome. Studies have also been done using NSs with dual-mode therapy, where a combination of chemotherapy with photothermal or photodynamic therapy degrades the tumor effectively. They are also of interest for oral delivery of biologics, where there is a problem of degradation within the gastrointestinal tract

CONCLUSION
This study highlights nanosponges as a potent nanocarrier system for poorly soluble drugs, enhancing solubility and enabling controlled drug delivery. These findings support further development for oral dosage forms, with additional in vivo evaluation warranted. NS can deliver both hydrophilic and lipophilic drugs via several routes, including oral, transdermal, rectal, and parenteral routes. In particular, β-NS Improves the solubility of drugs classified as BCS Class II. which is useful for certain drug delivery techniques. The formulation design, applications, characterization techniques, synthesis methods, and modifications of NS are discussed in this extensive review. Human health has already improved owing to recent approvals of drug delivery systems based on NS technology. At the same time, ongoing research continues to explore new pharmaceuticals that will help improve therapeutic outcomes. The safety and effectiveness of such medications delivered through NS as an innovation are expected to encourage pharmaceutical

companies to adopt them.

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