Nanosponges as a revolutionary platform in delivery of drugs

[1] Dr.A.Seethadevi, [2]Kodali kousalya
[1] Professor, [2]M.Pharmacy Student
[1]Department of Pharmaceutics
[1] Gokaraju rangaraju collage of pharmacy, Hyderabad, India
[1]seethadevi8090@grcp.ac.in, [2] kodalikousalya@gmail.com

Abstract – Nano-sponges have emerged as a cutting-edge class of nano-carriers that hold the potential to revolutionize traditional drug delivery methods. These nanoscale systems are distinguished by their porous, sponge-like architecture and extensive surface area, typically achieved by cross- linking Cyclodextrin or other environmentally friendly polymers with appropriate cross-linking agents. Their versatile structure allows for the incorporation of a broad spectrum of therapeutic agents, including both water-soluble and insoluble compounds, thereby significantly improving drug solubility, stability, and therapeutic efficiency. Their structural versatility makes nanosponges highly adaptable, enabling modifications that can control drug release rates, improve surface properties, and introduce site-specific targeting features. Different fabrication techniques such as solvent evaporation, ultrasonic-assisted methods, and emulsion solvent diffusion can be used to fine-tune particle size, porosity, and drug loading capacity. The mechanisms by which nanosponges capture drugs include entrapment within internal cavities, surface adsorption, and the formation of inclusion complexes. Upon administration, they can deliver medications in a controlled, sustained, or stimulus-responsive manner, enhancing therapeutic outcomes while reducing potential side effects. Nanosponges have demonstrated exceptional promise in various therapeutic fields, including oncology, infectious disease treatment, dermal and transdermal delivery, and formulations for poorly soluble drugs. Recently, the incorporation of herbal and plant-based bio actives into nanosponge systems has gained momentum, offering a novel approach to overcome the stability and bioavailability challenges associated with many phytochemicals. This review explores the fundamental aspects of nanosponge design, synthesis techniques, drug loading and release mechanisms, as well as their broad spectrum of biomedical applications. It also examines safety profiles, biocompatibility, and the evolving regulatory landscape. Together, these attributes establish nanosponges as a highly promising platform in the development of next-generation drug delivery systems aimed at addressing both current limitations and future clinical challenges.

Index Terms **- Nano-sponges, Drug delivery, Herbal drug delivery.**

A. OVERVIEW OF NANOSPONGES

I. Introduction

The pharmaceutical industry has witnessed a paradigm shift with the integration of nanotechnology into drug delivery systems. Among the various nanoscale carriers explored, nano-sponges have emerged as a novel and highly promising platform due to their unique physicochemical properties, such as high porosity, tunable surface chemistry, and the ability to encapsulate both hydrophilic and hydrophobic drugs [1]. Nano-sponges are a class of hyper-cross linked polymeric structures that form three-dimensional porous networks capable of hosting a wide range of bioactive compounds. Typically ranging from 100 nm to 1 µm in size, these nanoscale carriers were initially developed using cyclo dextrins and cross linkers such as carbonyl di imidazole (CDI) or dimethyl carbonate (DMC) to enhance drug solubility and stability [2]. Their sponge-like structure enables the entrapment of poorly water-soluble drugs, thereby improving bioavailability and allowing for sustained and controlled release profiles [3]. What distinguishes nano-sponges from conventional carriers is their ability to release drugs in a controlled and predictable manner, often triggered by physiological stimuli such as pH, temperature, or enzymatic activity. This makes them particularly advantageous for targeted delivery, minimizing systemic toxicity while maximizing therapeutic efficacy [4]. Furthermore, nano-sponges offer excellent physicochemical stability, biocompatibility, and ease of functionalization, making them suitable for a broad spectrum of pharmaceutical applications, including oral, topical, ocular, and transdermal drug delivery. Their potential extends beyond synthetic drugs to natural products and phytochemicals, protecting labile compounds from degradation and enhancing their therapeutic performance [5]. Given these versatile properties, nano-sponges represent a cutting-edge advancement in drug delivery science, holding immense potential for future clinical applications and commercialization. As research continues to evolve, there is growing interest in exploring multifunctional and stimuli-responsive nano-sponge systems for precision medicine.

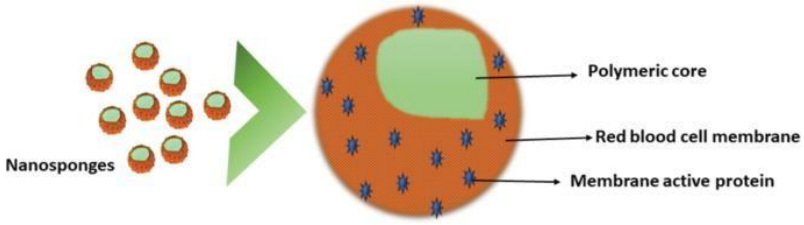

Figure 1: Structure of Nano-sponges

II. Classification of nano-sponges

Nano-sponges are highly versatile nano-carriers that can be classified based on different criteria, including the nature of the polymeric material**,** structural morphology, and functional response to external stimuli**.** These classifications not only determine their physical and chemical properties but also influence their drug loading capacity, release behaviour, and suitability for specific therapeutic applications.

1. Based on material composition

The choice of base material plays a significant role in the physicochemical behaviour, biodegradability, and biocompatibility of Nano sponges. Common material-based classifications include:

1.1. Cyclodextrin based nanosponges

Cyclodextrins (CDs), cyclic oligosaccharides obtained from starch, are widely used as the base material for nanosponge synthesis due to their hollow, hydrophobic cavities and hydrophilic outer surfaces. Crosslinking CDs with agents like dimethyl carbonate (DMC) or carbonyl di imidazole (CDI) results in a three-dimensional network capable of encapsulating both lipophilic and hydrophilic drugs (6). These nanosponges exhibit good biocompatibility, low toxicity, and high encapsulation efficiency for various drugs.

1.2. Polymer – based nanosponges

Natural and synthetic polymers such as gelatin, ethyl cellulose, polylactic acid (PLA), and hyper-cross linked polyesters are also used to prepare nanosponges. These polymers offer enhanced mechanical strength and tunable biodegradability. The use of synthetic polymers can tailor the nanosponge properties for prolonged circulation, pH sensitivity, or site-specific targeting (7).

1.3. Silica-based nanosponges

Silica nanosponges are inorganic porous nanocarriers synthesized using sol-gel processes. They offer higher chemical and thermal stability, making them suitable for encapsulating volatile or thermolabile substances. Their rigid matrix can also be functionalized with ligands for active targeting (8).

1.4. Based on crosslinking agents

Nanosponges can also be classified by the type of crosslinking agents used during synthesis:

- **Organic Crosslinkers**: Such as dimethyl carbonate (DMC), carbonyldiimidazole (CDI), and glutaraldehyde. These are commonly used for CD-based nanosponges and contribute to network formation.
- **Inorganic Crosslinkers**: Include agents like silica or borate compounds, often used in developing inorganic nanosponges for high thermal stability.

The choice of crosslinker impacts the Nano sponge's porosity, drug encapsulation capacity, and biodegradation rate (9).

2. Based on functional behavior

With the advancement of smart drug delivery systems, nanosponges can be engineered to respond to various physiological triggers. This functionality-oriented classification includes:

2.1 pH-responsive nanosponges

These nanosponges are designed to swell or degrade at specific pH levels, commonly found in the gastrointestinal tract or tumor microenvironments. Such systems are ideal for oral or cancer drug delivery, releasing drugs selectively at the target site (10).

2.2 Temperature responsive nanosponges

Incorporating thermo-sensitive polymers like poly(N-isopropylacrylamide) (PNIPAM) into the nanosponge matrix allows drug release in response to changes in body temperature. This property is particularly useful in hyperthermia-based therapies (11).

2.3 Enzyme responsive nanosponges

These are fabricated using materials that degrade or change structure in the presence of specific enzymes, such as proteases or lipases, commonly found in diseased tissues. This ensures a site-specific release mechanism (12)

3. Based on morphology and structure

The morphology of nanosponges also determines their classification and potential applications:

3.1 Spherical Nanosponges: Typically formed during emulsion-solvent diffusion techniques, ideal for topical or injectable applications.

3.2 Porous Nanosponges: Exhibit high surface area and pore volume, suitable for sustained release formulations.

3.3 Layered or Core-Shell Nanosponges: Designed for dual drug delivery or targeted release, often functionalized with ligands or surface coatings.

These structural variants are identified and optimized using techniques like SEM, TEM, and BET surface analysis (13).

4. Based on Drug Loading Mechanism

Nanosponges can also be categorized based on how they encapsulate drug molecules:

- **Inclusion Complex Nanosponges**: Encapsulation within the cavities of cyclodextrin units, ideal for hydrophobic drugs.
- **Non-Inclusion Nanosponges**: Drug molecules are adsorbed on the surface or within the polymeric matrix, suitable for large or hydrophilic molecules.

The interaction between drug and carrier through hydrogen bonding, van der Waals forces, or hydrophobic interactions determines the release kinetics and efficiency (14).

III. SYNTHESIS AND FABRICATION METHODS OF NANO SPONGES

Nano sponges are synthesized using a variety of chemical and physical techniques that aim to produce porous, nanoscale, three-dimensional networks capable of entrapping and releasing therapeutic agents in a controlled manner. The selection of a suitable synthesis method depends on the nature of the drug to be loaded, the choice of polymer and cross linker, desired particle size, and intended route of administration. The most commonly used techniques for nano sponge fabrication include the solvent method, emulsion solvent diffusion, ultrasound-assisted synthesis, and microwave-assisted synthesis.

1. Solvent Method

The solvent method is one of the earliest and most widely adopted techniques for synthesizing cyclodextrin-based nano sponges. In this method, a cyclodextrin (such as β-cyclodextrin) is reacted with a suitable crosslinking agent— such as dimethyl carbonate (DMC), carbonyldiimidazole (CDI), or diphenyl carbonate—in a polar aprotic solvent like di methyl formamide (DMF) or dimethyl sulfoxide (DMSO). The mixture is heated under reflux, usually at 90– 100 °C for several hours, resulting in crosslinking and nano sponge formation (15).

Once the reaction is complete, the mixture is cooled and the nano sponges are recovered by filtration or centrifugation, washed thoroughly to remove unreacted materials, and dried under vacuum.

Advantages: Simple, cost-efective, scalable

Limitations: Requires post-synthesis purification to eliminate solvent residues.

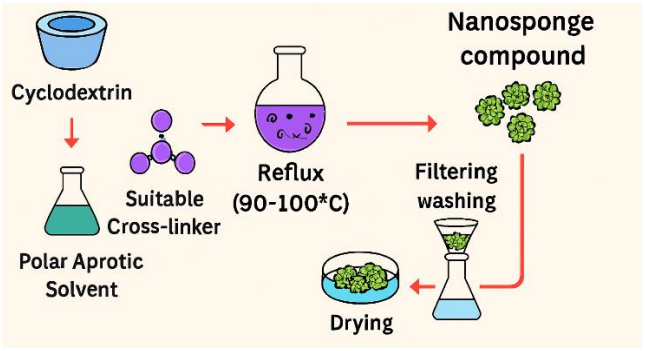

Figure 2: Schematic image representing solvent method

2. Emulsion Solvent Diffusion Method

The emulsion solvent diffusion method is particularly useful for producing spherical nano sponges with controlled particle size. In this method, the polymer and drug are dissolved in a volatile organic solvent (such as dichloromethane or ethyl acetate), which is then emulsified in an aqueous phase containing a stabilizer like polyvinyl alcohol (PVA) under high-speed stirring (16).

As the organic solvent diffuses into the aqueous phase, it induces nanoparticle formation. The resulting nano sponges are solidified by solvent evaporation, filtered, and lyophilized.

Advantages: Produces uniform particles with high drug encapsulation efficiency.

Limitations: Requires the use of organic solvents and surfactants.

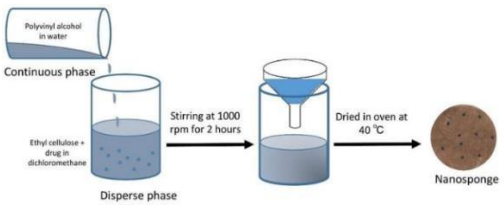

Figure-3 Schematic image representing Emulsion solvent diffusion method

3. Ultrasound-Assisted Synthesis

This method involves exposing a polymer–cross linker mixture to ultrasonic energy to facilitate the formation of nano sponges. The ultrasonic waves promote cavitation, which enhances the crosslinking efficiency and results in nano sponges with smaller particle sizes and uniform distribution (17).

This approach is suitable for thermos labile drugs and materials, as the process typically occurs at lower temperatures than traditional heating methods.

Advantages: Energy efficient, time saving and produce smaller, uniform particles.

Limitations: Requires specialized ultrasonic equipment.

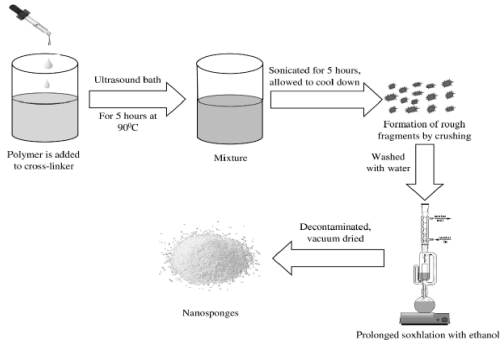

Figure-4 Schematic image representing Ultrasound-Assisted synthesis method

4. Microwave-Assisted Synthesis

Microwave irradiation is an advanced method used to accelerate chemical reactions by uniform heating at the molecular level. In this method, cyclo dextrin and cross linker are exposed to microwave radiation, leading to rapid synthesis of nano sponges within minutes (18).

This method eliminates the need for external heating and significantly reduces the reaction time compared to conventional methods.

Advantages: Rapid, energy-efficient, and eco-friendly.

Limitations: Limited scalability and specialized equipment needed.

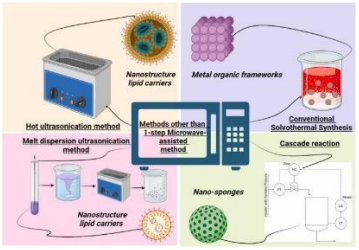

Figure-5 Schematic image representing Microwave-Assisted synthesis method

5. Freeze-Drying and Spray Drying

Post-synthesis drying methods such as freeze-drying (lyophilization) or spray drying are often employed to convert nanosponge suspensions into a stable, dry powder. These powders can be stored, formulated into solid dosage forms, or reconstituted for use. Freeze-drying is particularly favoured for preserving structural integrity and drug stability.

6. Influence of Crosslinking Agent and Polymer Selection

The type and concentration of crosslinking agents significantly impact the final properties of nanosponges. For example:

- Dimethyl carbonate (DMC) and carbonyldiimidazole (CDI) are non-toxic, green crosslinkers commonly used in pharmaceutical applications (19).
- Glutaraldehyde, a bi functional aldehyde, offers strong crosslinking but must be used cautiously due to potential toxicity if not properly removed (20).
- The polymer matrix, such as gelatin, β-cyclodextrin, or polylactic acid, determines biodegradability, compatibility, and drug release behaviour.

IV. CHARACTERIZATION TECHNIQUES OF NANO SPONGES

Characterization of nano sponges is essential to determine their physicochemical properties, drug loading capacity, surface morphology, stability, and drug release behaviour. A variety of analytical techniques are employed to confirm the successful synthesis and functionality of nano sponges. Each technique provides unique insights into specific attributes such as particle size, surface area, chemical interactions, porosity, and structural morphology. Below is a detailed description of the commonly used characterization techniques for nano sponges:

1. Fourier transform infrared spectroscopy (FTIR)

Purpose: FTIR is used to investigate the chemical interactions between the drug and the nano sponge matrix and to confirm successful crosslinking during synthesis.

Principle: This technique analyzes the vibrational transitions of chemical bonds in a sample when exposed to infrared radiation. The appearance, disappearance, or shifting of characteristic peaks in the spectrum indicates the presence of new functional groups or interactions.

Application in Nano sponges: For example, in β-cyclodextrin-based nano sponges cross linked with carbonyldiimidazole (CDI), FTIR shows the disappearance of the OH peak and the appearance of ester or carbonate peaks, confirming crosslink formation (21). Additionally, drug-loaded nano sponges are compared with pure drug spectra to detect drug-polymer interactions.

2. Scanning electron microscopy (SEM)

Purpose: SEM provides detailed images of the surface morphology and texture of nanosponges.

Principle: A focused beam of electrons scans the sample surface, producing high-resolution images based on electron-sample interactions.

Application in Nanosponges: SEM analysis reveals the porous, spongy nature of nanosponges, validating their structural characteristics. The images help to evaluate particle shape, size distribution, and surface roughness. In cyclodextrin-based nanosponges, SEM confirms a highly porous network necessary for drug entrapment (22).

3. Transmission electron microscopy (TEM)

Purpose: TEM provides insights into the internal structure and core morphology of nanosponges at the nanoscale.

Principle: A beam of electrons is transmitted through an ultra-thin section of the sample, generating images based on electron absorption.

Application in Nanosponges: TEM enables visualization of the internal porous architecture and confirms the spherical or sponge-like structure of nanosponges. It is often used to verify the nanoscale size and uniformity of particles in colloidal nanosponge systems (Shah et al., 2020).

4. Dynamic Light Scattering (DLS)

Purpose: DLS is used to determine the average particle size, size distribution, and poly dispersity index (PDI) of nano sponge particles in suspension.

Principle: This technique measures the scattering of light from particles undergoing Brownian motion. The fluctuation in scattered light intensity is used to calculate particle size.

Application in Nano sponges: DLS helps in optimizing formulation parameters like surfactant concentration and stirring speed during nanosponge synthesis. Smaller particle sizes and low PDI values indicate uniform dispersion and better drug delivery potential (Ansari et al., 2011).

5. X-ray Diffraction (XRD)

Purpose: XRD is used to study the crystalline or amorphous nature of nanosponges and their drug-loaded forms.

Principle: XRD detects the diffraction of X-rays through a crystal lattice, producing a diffraction pattern unique to crystalline substances.

Application in Nanosponges: A decrease in drug crystallinity in the nanosponge formulation (compared to the pure drug) is often observed, indicating successful entrapment in an amorphous matrix. This leads to improved solubility and bioavailability (Shah et al., 2020).

6. Brunauer–Emmett–Teller (BET) Surface Area Analysis

Purpose: BET analysis measures the surface area, pore size, and pore volume of nanosponges, essential for evaluating drug loading capacity.

Principle: Based on nitrogen gas adsorption-desorption isotherms, BET theory provides quantitative measurements of surface characteristics.

Application in Nanosponges: Cyclodextrin-based nanosponges have been reported to possess high surface areas and mesoporous structures ideal for encapsulating hydrophobic drugs. BET analysis confirms the porosity required for efficient drug loading (Trotta et al., 2014).

7. Differential Scanning Calorimetry (DSC)

Purpose: DSC is used to study the thermal behavior of nanosponges, including melting point, glass transition temperature, and thermal stability.

Principle: The technique measures heat flow into or out of a sample as it is heated or cooled.

Application in Nanosponges: A shift or disappearance of the drug's endothermic peak in the DSC thermogram indicates its molecular dispersion in the nanosponge matrix. This suggests successful drug entrapment and improved physical stability (Swaminathan et al., 2010).

8. Zeta Potential Analysis

Purpose: Zeta potential measurement is used to evaluate the surface charge and stability of nanosponges in suspension.

Principle: It determines the electric potential at the slipping plane of particles using electrophoretic light scattering.

Application in Nanosponges: Nanosponges with a zeta potential greater than ±30 mV are considered stable due to electrostatic repulsion, which prevents aggregation. Surface charge also plays a key role in cellular uptake and biodistribution (Kuthati et al., 2015).

V. DRUG LOADING AND RELEASE MECHANISMS OF NANO SPONGES

Nanosponges, owing to their unique porous architecture and high surface area, offer diverse avenues for drug loading and controlled release. The drug entrapment can be passive or active, while the release is governed by physicochemical properties of both the drug and the nanosponge matrix. The versatility of nanosponges stems from the variety of synthetic polymers, crosslinking agents, and stimuli-responsive designs used during their preparation. Understanding these mechanisms at a deeper level is crucial for the rational design of advanced drug delivery systems.

1. Advanced Drug Loading Techniques

1.1 Incubation (Equilibrium) Method

Mechanism Overview:

The incubation or equilibrium method relies on the diffusion of drug molecules into the nanosponge matrix from a solution under passive conditions. The process is driven by a concentration gradient and relies heavily on the compatibility between the drug and the nanosponge's internal cavities.

Detailed Process:

- The nanosponge is first pre-synthesized and purified.
- It is dispersed in an aqueous or hydro-alcoholic solution of the drug at a known concentration.
- The suspension is agitated at controlled temperature (25–37°C) for 12–48 hours.
- The system reaches a thermodynamic equilibrium where the drug molecules partition preferentially into the hydrophobic or hydrophilic pores of the nanosponge depending on their solubility characteristics.
- After loading, the mixture is centrifuged or filtered to separate unbound drug. (Trotta, F., et al. 2009).

Influencing Factors:

- Drug solubility and partition coefficient (log P).
- pH of the solution (especially for ionizable drugs).
- Temperature, as it affects drug diffusivity and nanosponge flexibility.
- Surface functional groups on the nanosponge.

Advantages:

- Simple, non-destructive technique.
- Suitable for temperature-sensitive and protein-based drugs.
- Enables high drug loading for hydrophobic drugs.

Limitations:

- Inefficient for drugs with poor affinity for the nanosponge matrix.
- May require long incubation times.

1.2. Solvent Evaporation Method

Mechanism Overview:

This technique exploits the solubility of both the drug and nanosponge in a common organic solvent. Upon evaporation of the solvent, the drug gets entrapped within the collapsing sponge-like matrix due to capillary forces and polymer-solid interactions.

Detailed Process:

- A volatile organic solvent such as ethanol, acetone, or dichloromethane is selected.
- The drug is dissolved completely in the solvent.
- Nanosponges are added to the solution and stirred or sonicated to form a homogeneous suspension.
- The solvent is gradually evaporated under reduced pressure using a rotary evaporator or vacuum oven.
- The solid mass obtained is collected, dried, and ground into a fine powder. (Swaminathan, S., et al. 2010).

Key Insights:

- Solvent type influences drug loading efficiency: non-polar solvents favour hydrophobic drugs.
- This method can entrap drugs inside inner cavities (not just on the surface), enhancing stability.

Advantages:

- Rapid and efficient entrapment.
- Suitable for both hydrophilic and hydrophobic drugs depending on solvent selection.
- Allows co-loading of multiple drugs.

Challenges:

- Residual solvent traces need to be removed.
- Not suitable for thermolabile drugs.

1.3. Ultrasonication-Assisted Loading

Mechanism Overview:

Ultrasonication improves drug loading efficiency by breaking agglomerates, increasing wettability of nanosponges, and enhancing diffusion of drug molecules through microjet and cavitation forces generated by ultrasound waves.

Detailed Process:

- Nano sponges are suspended in a drug solution or dispersion.
- The suspension is sonicated using a probe or bath sonicator at specific frequency (typically 20–40 kHz) and amplitude for a defined time.
- Acoustic cavitation results in high shear forces and microbubble collapse, forcing drug molecules into the nano pores.
- The mixture is cooled and allowed to stand before recovering drug-loaded nano sponges via centrifugation. (Ansari, K. A., et al. 2011).

Enhancements:

Surface area accessibility increases.

Reduced agglomeration leads to better dispersion and uniform drug loading.

Applications:

Particularly useful for poorly water-soluble drugs and protein therapeutics.

1.4. Detailed Drug Release Mechanisms

Drug release from nanosponges is influenced by pore architecture, polymer composition, and the release medium. The release mechanisms may be passive (diffusion-based) or stimuli-responsive.

1.5. Diffusion-Controlled Release

Mechanism Overview:

This is the most common release pathway where drug molecules diffuse through the interconnected pores and tunnels of the nanosponge matrix into the surrounding fluid.

Mathematical Models:

Higuchi model: Describes square root time-dependent release.

Korsmeyer-Peppas model: Defines release mechanism (Fickian or non-Fickian) based on the release exponent (n) (Trotta, F., et al. 2014).

Formulation Considerations:

Tighter crosslinking = slower diffusion.

Larger pores = faster drug egress.

Hydrophilic drugs diffuse faster in aqueous media.

1.6. Swelling-Controlled Release

Mechanism Overview:

Certain nanosponges, especially those based on swellable polymers (e.g., chitosan, gelatin), expand upon hydration. This swelling opens the matrix and facilitates drug release. (Cavalli, R., et al. 2010).

Steps Involved:

- Water absorption into polymer matrix.
- Swelling-induced stress opens microchannels.
- Drug diffuses out through the expanded structure.

Key Factors:

- Swelling index and water uptake capacity.
- Environmental pH and ionic strength.
- Crosslinker concentration.

1.7. Enzyme-Triggered Release

Mechanism Overview:

This mechanism leverages the biodegradability of natural or synthetic polymers used in nanosponges. Specific enzymes present at disease sites degrade the polymeric matrix, enabling localized drug release. (Krishna, S., et al. 2022).

Applications:

- Cancer therapy: Use of MMP (matrix metalloproteinase)-sensitive linkers.
- Wound healing: Protease-sensitive gelatin nanosponges.

Design Considerations:

- Polymer selection must match enzyme substrate.
- Degree of crosslinking must allow partial digestion.

1.8. pH-Responsive Release

Mechanism Overview:

Nanosponges can be designed to release drugs at specific pH values by incorporating pH-sensitive polymers that undergo swelling, dissolution, or charge reversal in response to acidic or basic environments (Kuthati, Y., et al. 2015).

Examples:

Tumor-targeted delivery (acidic pH ~6.5).

Colon-targeted delivery (pH > 7.0).

Gastric retention (pH < 2.0).

Mechanism:

Protonation or deprotonation alters solubility or porosity.

Polymer may collapse or swell at trigger pH.

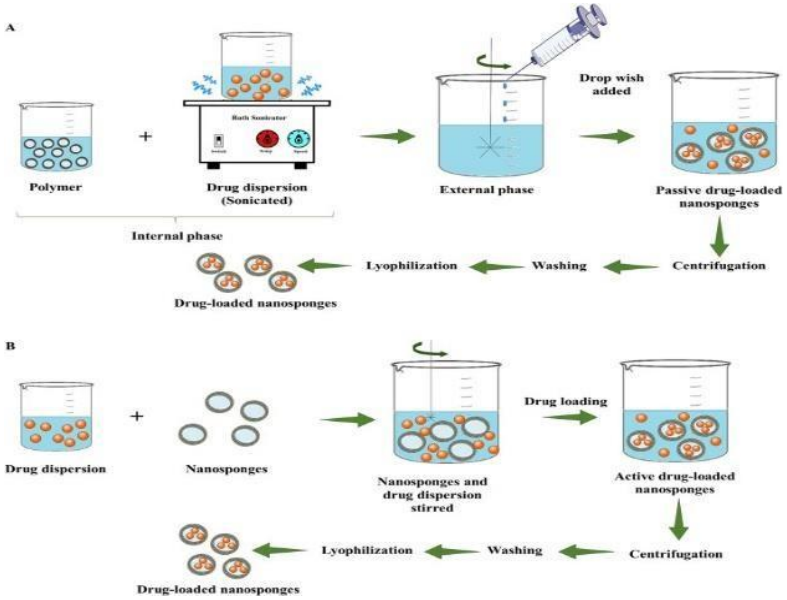

Figure-6 Drug loading into Nanosponges

VI. Applications of nanosponges in drug delivery

Nanosponges have revolutionized the field of drug delivery due to their porous nanostructure**,** large surface area**,** high entrapment efficiency**,** and ability to offer controlled and targeted release of a wide variety of therapeutic agents. Their structural versatility allows the encapsulation of drugs with diverse physicochemical characteristics, such as hydrophilic, hydrophobic, and amphiphilic molecules. Furthermore, the ability to modify their surface with ligands for targeted delivery makes them ideal carriers for site-specific drug action.

The following are the major therapeutic areas where nanosponges have demonstrated significant potential in drug delivery:

1. Oncology: Cancer Drug Delivery

One of the most impactful applications of nanosponges is in cancer therapy**,** where they serve as carriers for chemotherapeutic agents, minimizing systemic toxicity and enhancing drug accumulation at tumor sites.

Key Benefits:

- Prolonged circulation time in blood due to nanoscale size.
- Passive targeting via Enhanced Permeability and Retention (EPR) effect.
- Capability to bypass multidrug resistance mechanisms by controlled release.

Example:

Trotta et al. developed β-cyclodextrin-based nanosponges to deliver paclitaxel, a poorly water-soluble anticancer drug. The nanosponge formulation significantly improved drug solubility and showed sustained release properties, thereby reducing cytotoxicity to normal cells while maintaining efficacy against cancer cells [Trotta et al., 2014].

2. Dermatology: Topical Drug Delivery

Nanosponges have shown exceptional promise in topical drug delivery**,** especially in treating skin conditions such as acne, psoriasis, fungal infections, and eczema**.**

Advantages:

- Enhanced drug retention at the skin surface**.**
- Reduced skin irritation due to controlled release.
- Compatibility with gels, creams, and lotions**.**

Example:

Swaminathan et al. formulated fluconazole-loaded nanosponges in a gel base for the treatment of fungal infections. The system provided prolonged antifungal activity and better skin retention compared to conventional creams [Swaminathan et al., 2010].

3. Antiviral Drug Delivery

The delivery of antiviral drugs poses challenges due to poor solubility, low bioavailability, and systemic toxicity. Nanosponges can encapsulate antiviral agents and enhance their stability and therapeutic index.

Example:

A study by Darandale and Vavia (2013) demonstrated acyclovir-loaded nanosponges**,** showing a sustained release profile and improved bioavailability. The nanosponge system reduced the dosing frequency and enhanced patient compliance in the management of herpes simplex virus infections. (Darandale, S. S., & Vavia, P. R. 2013).

4. Antibacterial Therapy

The emergence of antibiotic resistance has prompted the need for novel drug delivery strategies. Nanosponges can protect antibiotics from enzymatic degradation and release them in a controlled manner.

Example:

Kumar et al. developed vancomycin-loaded nanosponges and demonstrated improved antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MRSA), indicating the potential for overcoming bacterial resistance [Kumar et al., 2020].

5. Oral Drug Delivery

Nanosponges can protect orally administered drugs from acidic degradation in the stomach**,** improve solubility**,** and prolong gastrointestinal retention**,** thereby enhancing oral bioavailability**.**

Example:

Ansari et al. designed nifedipine-loaded nanosponges to enhance the solubility of this poorly water-soluble antihypertensive drug. The study revealed a significant improvement in oral bioavailability and sustained plasma concentrations [Ansari et al., 2011].

6. Peptide and protein delivery

The delivery of peptides, proteins, and enzymes poses challenges such as enzymatic degradation and immunogenicity. Nanosponges can entrap these sensitive biomolecules within their network, providing protection and controlled release**.**

Example:

Cavalli et al. developed enzymatically degradable nanosponges for the delivery of therapeutic enzymes, showing prolonged activity and reduced immunogenic response in in vivo models [Cavalli et al., 2010].

7. Ocular Drug Delivery

In ophthalmic drug delivery, nanosponges can provide sustained release and improve ocular residence time**,** overcoming issues like rapid tear drainage and poor corneal penetration.

Example:

A recent study formulated dexamethasone-loaded nanosponges in an ophthalmic hydrogel, achieving sustained anti- inflammatory activity with reduced dosing frequency [Gade et al., 2022].

8. Pulmonary Drug Delivery

Inhalable nanosponges can be used for pulmonary drug delivery to treat respiratory conditions like asthma, COPD, and tuberculosis**,** ensuring deep lung penetration and extended drug retention. Kuthati, Y., et al. (2015).

Example:

Kuthati et al. (2015) prepared nanosponges for pulmonary delivery of isoniazid and rifampicin in tuberculosis treatment. The nanocarrier improved deposition in alveolar regions and reduced the dosing frequency.

9. Targeted Drug Delivery Using Ligand-Conjugated Nanosponges

Surface-modified nanosponges with targeting ligands (e.g., folic acid, antibodies, aptamers) enhance cell-specific uptake**,** especially in cancer and inflammatory diseases.

Example:

Ligand-modified nanosponges carrying **doxorubicin** demonstrated selective delivery to breast cancer cells overexpressing folate receptors, improving therapeutic efficacy and reducing cardiotoxicity [Zhang et al., 2020].

VII. ADVANTAGES OF NANOSPONGES IN DRUG DELIVERY SYSTEMS

Nanosponges are a novel class of hyper-crosslinked, porous polymeric carriers that have gained immense popularity in recent years for pharmaceutical and biomedical applications. Their ability to encapsulate both hydrophilic and hydrophobic drugs**,** along with properties such as controlled release**,** targeted delivery**,** and biocompatibility**,** places them at the forefront of next-generation drug delivery systems. The unique architecture of nanosponges, consisting of nanometer-sized cavities and tunable porosity, provides several technological and therapeutic benefits over conventional carriers.

1. High Drug Loading Efficiency

Nanosponges have a high surface area and internal porous structure that allow efficient encapsulation of various drugs, especially poorly water-soluble compounds. Their cavities provide microenvironments where drugs can be entrapped via hydrophobic interactions, hydrogen bonding, and van der Waals forces**.** (Trotta, F., et al. 2009).

2. Enhanced Solubility and Bioavailability

One of the primary challenges in oral drug delivery is the poor solubility of many active pharmaceutical ingredients (APIs). Nanosponges improve drug aqueous solubility and dissolution rate by reducing crystallinity and maintaining drugs in an amorphous or molecularly dispersed state**.** (Swaminathan et al. 2010)

3. Controlled and Sustained Drug Release

Nanosponges enable sustained and prolonged release of encapsulated drugs, which helps in maintaining therapeutic plasma concentrations over extended periods and reduces dosing frequency. This is especially beneficial for chronic conditions requiring long-term therapy. Cavalli, R., et al. (2010).

4. Targeted Drug Delivery

Surface modification of nanosponges using ligands, antibodies, peptides**,** or aptamer**s** allows for active targeting of specific cells or tissues, minimizing off-target effects and increasing therapeutic efficacy.

Example:

Folic acid-modified nanosponges have shown enhanced uptake in cancer cells overexpressing folate receptors. (Zhang, J., et al.2020).

5. Biocompatibility and Biodegradability

Nanosponges are often synthesized from GRAS (Generally Recognized as Safe) polymers like cyclodextrins, polyesters, or cellulose derivatives, making them non-toxic**,** non-immunogenic**,** and biodegradable**.** Their degradation products are usually non-harmful and easily excreted from the body. (Ansari, K. A., et al. 2011)

6. Versatile Drug Loading (Hydrophilic and Hydrophobic Drugs)

Unlike liposomes or micelles, nanosponges can incorporate both lipophilic and hydrophilic molecules due to their flexible 3D polymeric structure. This broadens their applicability across a range of therapeutic molecules, including small drugs, proteins, peptides, and even gases. (Begines, B., et al. 2020).

7. Protection of Labile Drugs

Nanosponges protect labile or sensitive drugs such as peptides, proteins, enzymes, or drugs prone to hydrolysis or photodegradation by encapsulating them inside their inner cavities. This improves shelf life and in vivo stability**.**

Example:

Cavalli et al. encapsulated dexamethasone in nanosponges to protect it from premature enzymatic degradation.

8. Reduced Toxicity and Side Effects

Because of their targeting capabilities and controlled release profiles, nanosponges minimize drug accumulation in non- target tissues, significantly reducing systemic toxicity and side effects**,** which is particularly crucial in oncology and antibiotic therapies**.** Gul, R., et al. (2021).

9. Multi-route Administration Compatibility

Nanosponges can be administered via oral**,** topical**,** parenteral**,** ocular**,** nasal, and pulmonary routes**,** making them flexible for different dosage forms and clinical requirements. Their mucoadhesive and bioadhesive properties also enhance their residence time at the site of action. Choudhary, N., & Rathi, R. (2013).

10. Potential for Stimuli-Responsive Delivery

Modern nanosponges can be engineered to release drugs in response to specific physiological triggers**,** such as pH**,** temperature**,** enzymes, or redox potential**.** These smart nanosponges provide precise control over drug delivery in complex disease conditions like cancer and inflammation. (Yang, J., et al. 2018).

ADVANTAGE	DESCRIPTION
Improved solubility & bioavailability	Enhanced dissolution of poorly soluble drugs
Controlled drug release	Maintains therapeutic levels, reduces dosing frequency
Targeted delivery	Surface functionalization for site-specific release
Biocompatibility	Made from safe, biodegradable polymers
Dual hydrophilic/lipophilic loading	Flexible carrier for various types of drugs
Drug protection	Shields labile drugs from environmental degradation
Low toxicity	Reduces systemic exposure and side effects
Multi-route administration	Suitable for oral, topical, nasal, and parenteral routes
Stimuli-responsive delivery	Responsive release under pathological conditions

Table-1 Advantages of Nanosponges

VIII. DISADVANTAGES OR LIMITATIONS OF NANOSPONGES IN DRUG DELIVERY

While nanosponges offer significant benefits as innovative drug delivery carriers, several limitations and challenges hinder their broad clinical translation. These disadvantages range from formulation complexities to regulatory concerns, and biological interactions that require critical evaluation.

1. Limited Drug Loading of Highly Hydrophilic Drugs

Although nanosponges can encapsulate both hydrophilic and hydrophobic compounds, they generally favor lipophilic drug entrapment due to the hydrophobic nature of their polymeric core. Hydrophilic drugs may demonstrate poor encapsulation efficiency unless additional surface functionalization or co-formulation strategies are employed. (Trotta & Cavalli, 2012)

2. Challenges in Large-Scale Manufacturing and Reproducibility

Nanosponges are often synthesized using complex cross-linking processes**,** involving multiple variables like polymer ratios, solvents, temperature, and reaction time. Maintaining batch-to-batch consistency and scaling up production under GMP (Good Manufacturing Practices) conditions is challenging. (Minelli et al., 2020)

3. Potential for Cytotoxicity and Biodegradation Issues

Although composed of biocompatible materials (e.g., cyclodextrins, polyesters), the crosslinkers used—such as diphenyl carbonate**,** glutaraldehyde**,** or carbonyldiimidazole—may leave toxic residues if not thoroughly removed. Also, incomplete or slow degradation of the polymer matrix may lead to bioaccumulation in tissues. (Swaminathan et al., 2013)

4. Complex Characterization Requirements

Comprehensive characterization of nanosponges involves multi-technique validation such as FTIR, SEM, TEM, DSC, PXRD, and NMR to assess morphology, drug loading, surface chemistry, and crystallinity. These analyses are cost- intensive and require advanced instrumentation and expertise**,** limiting accessibility in many research settings. (Ansari et al., 2011)

5. Regulatory Uncertainty and Approval Delays

Due to their nano-size range and complex formulation, nanosponges fall under nanotechnology-based therapeutics**,** which face rigorous regulatory scrutiny**.** Currently, there is no standardized regulatory framework specifically dedicated to nanosponges, leading to delays in market approval and commercialization. (Rani et al., 2021

6. Possible Immunogenic or Inflammatory Responses

Some nanosponges, especially those administered via parenteral routes**,** may trigger immune responses depending on their size, charge, surface chemistry**,** and degradation byproducts. Although rare, such immune stimulation can result in cytokine storms**,** allergic reactions, or chronic inflammation in sensitive individuals. (Elsabahy & Wooley, 2013)

7. Difficulty in Surface Functionalization for Targeting

Although nanosponges can be functionalized with targeting ligands, the process involves chemically modifying surface groups, which can be technically demanding and may alter the core structure or drug release profile. Improper ligand attachment may lead to reduced targeting specificity**.** (Elsabahy & Wooley, 2013**)**

8. Short Shelf Life of Aqueous Dispersions

Nanosponges, especially in suspension or gel form**,** can be prone to physical instability such as agglomeration, sedimentation, or changes in particle size over time. This reduces shelf life and may affect the consistency of dosing. (Ghumman et al., 2021)

9. Limited Clinical Data and Lack of Human Trials

Most research on nanosponges is still at the preclinical or early-stage development level. A major limitation is the lack of large-scale clinical trials validating their safety and efficacy in humans, which delays translational potential. (Jain et al., 2020)

10. Economic Limitations for Low-Income Settings

The overall cost of materials**,** instrumentation**,** and synthesis procedures for nanosponges can be prohibitive in resource- limited environments**,** making them less feasible for widespread use in developing countries unless cost-effective alternatives are developed. (Pandey et al., 2021)

Limitation	Explanation
Low hydrophilic drug loading	Limited entrapment due to hydrophobic core
Complex synthesis & scalability	Difficult large-scale production with reproducibility issues
Toxic crosslinkers or residues	Risk of cytotoxicity from glutaraldehyde or CDI
Costly characterization	Requires FTIR, SEM, TEM, PXRD, DSC, etc.
Regulatory hurdles	Lack of specific global regulatory pathway
Immunogenicity potential	Possible immune activation in vivo
Difficult surface modification	Technical challenges in ligand attachment
Stability issues in storage	Particle agglomeration or size shifts over time
Sparse clinical evidence	Few human studies validating safety and efficacy
Cost concerns for developing nations	Economic burden due to synthesis and analytical complexity

Table-2 Limitations of Nano-sponges

B. NANOSPONGES FOR HERBAL AND NATURAL PRODUCTS: A PROMISING PLATFORM FOR PHYTOPHARMACEUTICAL DELIVERY

I. Introduction

The integration of nanotechnology into herbal medicine has brought a paradigm shift in the delivery of bioactive compounds derived from natural sources. Natural products, especially those derived from medicinal plants**,** are rich in phytochemicals such as flavonoids, terpenoids, alkaloids, and polyphenols. These molecules possess a wide range of pharmacological effects including antioxidant, anti-inflammatory, anticancer, and antimicrobial activities. However, the clinical translation of these compounds is often hindered by poor aqueous solubility**,** low membrane permeability**,** rapid metabolism**,** and instability in biological systems (Patel & Patel, 2020). Nanosponges, a class of hyper-cross-linked polymeric nanostructures, offer a unique and promising solution to these challenges. Their porous, sponge-like structure allows the encapsulation of both hydrophilic and lipophilic compounds, offering a platform for controlled, targeted, and efficient delivery of herbal therapeutics (Trotta et al., 2012).

II. Structural Advantages of Nanosponges for Phytochemical Encapsulation

Nanosponges are typically composed of biodegradable polymers such as β-cyclodextrins**,** ethyl cellulose**,** or polyvinyl alcohol**,** cross-linked with agents like carbonyldiimidazole or glutaraldehyde. These cross-linked networks form nano- sized cavities that can physically trap bioactive compounds or chemically interact with them through hydrogen bonding**,** Van der Waals forces**,** or host-guest inclusion complexes**.**

This unique architecture enables:

- Improved solubility and dispersion of hydrophobic herbal constituents like curcumin and resveratrol.
- Protection from enzymatic degradation and oxidative stress**.**
- Sustained and controlled drug release**,** reducing dosing frequency.
- Improved cellular uptake due to the nanoscale size. (Trotta, F., et al. (2012).

III. Examples of Herbal Actives Delivered via Nanosponges

1. Curcumin

Curcumin, a principal component of *Curcuma longa*, is a potent antioxidant and anti-inflammatory agent. However, it's extremely low oral bioavailability (due to poor water solubility and first-pass metabolism) limits its therapeutic application. When encapsulated in β-cyclodextrin nanosponges, curcumin exhibits significantly enhanced solubility, better plasma concentration, and sustained therapeutic effects. (Jain, R., & Jain, S. (2018).

2. Resveratrol

Resveratrol, a natural polyphenol found in grapes and red wine, exhibits cardioprotective and anticancer properties. However, it is photosensitive and unstable in aqueous environments. Nanosponges protect it from light degradation, enhance systemic absorption, and provide a controlled release profile. (Shah, R. R., & D'Souza, A. A. (2017).

3. Berberine

Berberine is an alkaloid known for its anti-diabetic and antimicrobial effects. Nanosponges encapsulating berberine have demonstrated improved stability in the gastrointestinal tract**,** better permeability, and reduced systemic toxicity. (Mishra, V., et al. (2019).

IV. Methods for Formulating Herbal Nanosponges

The encapsulation of herbal bioactives in nanosponges typically involves the following techniques:

1. Emulsion-Solvent Diffusion Method

This method is widely used for lipophilic phytoconstituents. The drug and polymer are dissolved in a volatile organic solvent (e.g., dichloromethane), emulsified in an aqueous phase containing a surfactant, followed by solvent evaporation. This results in nano-sized spongy particles encapsulating the herbal compound.

2. Ultrasonic-Assisted Synthesis

Ultrasound energy facilitates nucleation and polymerization during the mixing of cross-linker and polymer in the presence of herbal compounds. This method allows the formation of uniform and thermodynamically stable nanosponges**.**

3. Freeze Drying

After encapsulation, the nanosponge suspension is subjected to lyophilization**,** preserving the structure and enhancing shelf life. This technique is especially suitable for temperature-sensitive herbal molecules**.** (Kavitha, K., et al. (2020).

V. Mechanisms of Herbal Drug Release from Nanosponges

The drug release mechanism depends on several factors such as polymer type, cross-linking density, and interaction with the encapsulated molecule.

- **Diffusion-Controlled Release**: Phytochemicals slowly diffuse out of the polymer matrix into the surrounding medium.
- **Swelling-Controlled Release**: In aqueous environments, nanosponges swell, triggering the release of the active compound.
- **Stimuli-Responsive Release**: Some nanosponges respond to pH, temperature, or enzyme concentrations, allowing site-specific delivery**,** especially in cancer or inflammatory conditions. (Swaminathan, S., et al. (2010).

VI. Benefits of Nanosponges for Herbal Drug Delivery

- Enhanced solubility and bioavailability of poorly soluble natural compounds.
- Minimized degradation and metabolic breakdown**.**
- Targeted and prolonged drug release**,** reducing frequency and improving compliance.
- Feasibility of topical, transdermal, oral, and parenteral formulations**.**
- Biocompatible and non-toxic polymers**,** suitable for long-term use. (Patel, H., & Patel, J. K. (2020).

VII. Challenges and Limitations

- Lack of large-scale clinical data on herbal-loaded nanosponges.
- Regulatory challenges in classifying nanoscale herbal formulations.
- Variability in herbal extract composition**,** affecting reproducibility and standardization.
- Potential polymer-herbal interactions requiring thorough toxicity studies. (Kesarla, R., et al. (2021).

VIII. Future Outlook

- The fusion of herbal pharmacology with nanosponge technology has the potential to revolutionize the nutraceutical and phytopharmaceutical industries. Future research should focus on:
- Developing standardized protocols for herbal nanosponge synthesis.
- In vivo studies and clinical trials to assess therapeutic efficacy.
- Creating multi-targeted nanosponge systems combining two or more phytochemicals.
- Green synthesis approaches to align with eco-friendly drug development.

IX. Conclusion

Nanosponges represent a versatile and transformative delivery system for herbal and natural products. By overcoming critical limitations such as poor solubility and instability, they enable a more effective, targeted, and patient-friendly delivery of phytochemicals. With ongoing research and regulatory advancements, herbal nanosponges may soon become mainstream in modern pharmaceutical and nutraceutical applications.

Herbal Compound	Source Plant	Therapeutic Use	Polymer Used	Cross-Linker	Method of Preparation	Benefits of Nanosponge Formulation
Curcumin	Curcuma longa	Anti-inflammatory, anticancer	β-Cyclodextrin	Diphenyl carbonate	Solvent evaporation	Improved solubility and bioavailability
Resveratrol	Vitis vinifera (Grape)	Cardioprotective, antioxidant	Ethyl cellulose	Glutaraldehyde	Emulsion solvent diffusion	Photostability and controlled release
Berberine	Berberis vulgaris	Antimicrobial, anti-diabetic	Polyvinyl alcohol	Carbonyldiimidazole	Ultrasound-assisted synthesis	Enhanced GI stability and absorption
Quercetin	Onion, Apple	Antioxidant, antihistamine	β-Cyclodextrin	Carbonyldiimidazole	Freeze drying	Better solubility and sustained plasma levels
Glycyrrhizin	Glycyrrhiza glabra	Anti-ulcer, anti-inflammatory	Cyclodextrin	Urea	Solvent evaporation	Targeted delivery and reduced toxicity

Table-3 Formulated Herbal Compounds Using Nano-sponges

X. Case Studies

Case Study 1: Curcumin Nanosponges for Oral Delivery

Background: Curcumin has poor aqueous solubility and is rapidly metabolized.
Approach: Cyclodextrin nanosponges synthesized via solvent evaporation.
Results: >5-fold increase in solubility, improved anti-inflammatory efficacy in rat models. (Jain, R. & Jain, S. (2018).

Case Study 2: Resveratrol-Loaded Nanosponges for Topical Use

Background: Resveratrol degrades upon light exposure and shows poor transdermal absorption.
Approach: Ethyl cellulose nanosponges prepared using emulsion-diffusion method.
Results: Enhanced skin permeation and antioxidant activity. (Shah, R. R., & D'Souza, A. A. (2017).

Case Study 3: Berberine Nanosponges for Diabetes Management

Background: Berberine has GI side effects and low oral bioavailability.
Approach: Polyvinyl alcohol nanosponges prepared via ultrasound-assisted synthesis.
Results: Better pharmacokinetics, lower blood glucose levels in diabetic mice. (Mishra, V., et al. (2019).

C. Toxicity and Biocompatibility of Nano - sponges in drug delivery systems

1. Introduction

Nanosponges (NSs), as nanocarrier systems with a 3D porous network, have revolutionized the landscape of modern drug delivery due to their ability to encapsulate and release both hydrophilic and lipophilic compounds in a controlled and sustained manner. While their benefits in terms of solubility enhancement, stability, and site-specific delivery are well- established, an essential concern remains: Are nanosponges safe and biocompatible? For nanosponges to move from bench to bedside, comprehensive evaluation of their toxicity and biocompatibility across biological systems is imperative.

Biocompatibility refers to the ability of a material to perform without eliciting any undesirable local or systemic effects in a host**,** whereas toxicity involves the potential of the material to cause harmful effects at the cellular, tissue, organ, or organism level. Both these aspects are critical for regulatory approval and long-term human use. (Fadeel, B., Feliu, N., et al. (2013).

2. Factors Influencing the Toxicity and Biocompatibility of Nanosponges

The toxicological behavior of nanosponges depends on multiple physicochemical characteristics:

2.1. *Polymer Type and Origin*

Natural polymers (e.g., β-cyclodextrin, dextran, gelatin): exhibit low immunogenicity and are generally considered safe.

Synthetic polymers (e.g., polycaprolactone, polyvinyl alcohol, ethyl cellulose): often used for mechanical stability but may require biocompatibility testing. β-Cyclodextrin-based nanosponges (CD-NSs) have been extensively studied for safety due to their non-toxic, GRAS (Generally recognized as safe) status granted by the FDA. (Trotta, F., Zanetti, M., & Cavalli, R. (2012).

2.2. *Type and Amount of Cross-Linker*

Cross-linkers like glutaraldehyde**,** carbonyldiimidazole (CDI)**,** and diphenyl carbonate are crucial in defining pore structure and mechanical strength. However, their residual presence may induce cytotoxicity.

Glutaraldehyde, though efficient, may cause membrane disruption and ROS generation if not adequately washed.

CDI is preferred due to its lower toxicity profile and clean decomposition by-products. (Adepu, S., & Ramakrishna, S. (2021).

2.3. *Surface Chemistry and Functionalization*

The zeta potential, surface charge, and functional groups impact cellular interactions:

Neutral or slightly negative surfaces are generally more biocompatible.

Positive surfaces**,** while improving uptake, may interact with negatively charged cell membranes, leading to toxicity.

PEGylation (attachment of polyethylene glycol chains) reduces immunogenicity and prolongs systemic circulation by avoiding recognition by RES (reticuloendothelial system). (Suk, J. S., Xu, Q., et al. (2016).

3. In Vitro Toxicological Evaluation

Standard in vitro assays are the initial step in nanotoxicity profiling:

3.1. *MTT/XTT Assay*

Evaluates mitochondrial dehydrogenase activity in viable cells. Nanosponges (especially β-CD-NSs) show >90% cell viability in HEK293, HepG2, and NIH-3T3 cells up to 100 μg/mL. (Swaminathan, S., et al. (2010).

3.2. *LDH Release Assay*

Assesses membrane integrity**.** Minimal LDH release confirms that nanosponges do not compromise cell membranes.

3.3. *Reactive Oxygen Species (ROS) Assay*

Some nanoparticles can induce oxidative stress. Nanosponges made from biodegradable polymers show no significant ROS generation at therapeutic doses.

3.4. *Hemocompatibility Testing*

Nanosponges do not induce hemolysis or red blood cell aggregation**,** indicating their safety for parenteral use. (Sonvico, F., et al. (2012).

4. In Vivo Toxicity and Biocompatibility Studies

Animal models provide a holistic view of systemic exposure**,** biodistribution, and organ-specific effects.

4.1. *Acute and Sub-chronic Toxicity*

- Mice/rats were administered with varying doses of blank and drug-loaded nanosponges (50–500 mg/kg).
- No significant changes in body weight, food intake, hematology, or organ histology were reported.
- **No** inflammation, necrosis, or immune infiltration was observed in liver, spleen, lungs, or kidneys. (Mishra, V., et al. (2019).

4.2. *Biodistribution and Clearance*

Fluorescent-labeled nanosponges showed:

- Accumulation in liver, spleen (typical RES organs).
- Slow but complete clearance over 48–72 hours.
- No prolonged tissue retention**,** suggesting a favorable excretion profile.

4.3. *Immunotoxicity*

Levels of TNF-α, IL-6, IL-10**,** and other inflammatory cytokines remained within normal ranges, indicating no immunostimulation or immunosuppression**.**

5. Regulatory Safety Considerations

Although nanosponges are still under preclinical development for most applications, they align with FDA and EMA guidelines for nanocarriers:

- Require standardized toxicity testing under GLP conditions.
- Must report long-term stability, leachable residues**,** and immunogenic responses**.**
- Batch reproducibility and scale-up synthesis without altering safety profiles is crucial for commercial translation. (European Medicines Agency. (2019).

6. Conclusion

Nanosponges, particularly those made from biodegradable and biocompatible polymers like cyclodextrins, show an impressive safety profile with minimal toxicity across in vitro and in vivo studies. The risk of toxicity is highly formulation- dependent**,** and controlling variables like cross-linker residuals, surface charge, and purification steps is critical. With rigorous characterization and regulatory alignment, nanosponges stand as a safe and effective delivery **s**ystem for a wide array of drugs, including challenging herbal and natural products.

Evaluation Type	Biological Model	Result Summary
MTT Assay	HEK293, HepG2	High cell viability (>90%) up to 100 µg/mL
LDH Assay	NIH-3T3	Minimal membrane damage; low LDH release
ROS Assay	HepG2	Negligible ROS production at therapeutic doses
Hemocompatibility	Human RBCs	No hemolysis; excellent blood compatibility
Acute Toxicity	Rats/Mice	No weight loss, organ damage, or mortality
Biodistribution	Rats	Liver and spleen uptake; cleared in 48–72h
Immunotoxicity	Mice	No increase in pro-inflammatory cytokines

Table-4 Evaluation types and their results

Nanocarrier	Toxicity Index	Toxicity Remarks
Nanosponges	1.2	Very low toxicity; biodegradable, low immune response
Liposomes	1.8	Biocompatible, but risk of rapid clearance and leakage
Dendrimers	3.5	Highly toxic at higher generations; cationic charge is risky
Gold NPs	4.0	Non-biodegradable; risk of accumulation and oxidative stress
PolymericNPs	2.2	Moderate toxicity, polymer-dependent

Table-5 Comparative Toxicity Chart Description

D. CHALLENGES AND FUTURE PERSPECTIVES OF NANOSPONGES IN DRUG DELIVERY

Nanosponges have shown immense promise as a novel drug delivery platform, especially due to their high loading capacity, stability, and ability to encapsulate both hydrophilic and hydrophobic drugs. However, despite their advantages, several challenges still limit their widespread clinical adoption and commercial scalability. Understanding these limitations is critical to guide future research and innovation in this field.

1. Challenges in nanosponges development

a. Lack of Standardization in Formulation

One of the major limitations in the field of nanosponges is the lack of standard protocols for their synthesis, functionalization, and evaluation. Different studies utilize varying cross-linkers, polymer concentrations, and fabrication techniques, which makes it difficult to compare results and establish robust benchmarks for therapeutic efficacy and safety (Swaminathan et al., 2013).

b. Scale-up and Manufacturing Limitations

While laboratory-scale synthesis of nanosponges has been relatively successful, translating these processes to large-scale manufacturing remains challenging. Issues such as batch-to-batch variability, high energy consumption during fabrication (e.g., ultrasonication, high-pressure homogenization), and difficulty in maintaining homogeneity at industrial scale impede commercialization (Begines et al., 2020).

c. Biodegradability and Long-Term Safety

Although many nanosponges are based on biodegradable polymers like cyclodextrins, polyesters, and gelatin, long-term biocompatibility studies are limited. There are concerns regarding the potential accumulation of non-degraded fragments in tissues and organs, which could elicit unforeseen toxicological responses (Krishnan & Muthusamy, 2022).

d. Drug Loading Efficiency and Release Control

Achieving consistent drug loading and controlled release is another major concern. Factors such as drug solubility, interaction with the sponge matrix, and environmental pH or enzymatic conditions can influence the drug loading capacity and release kinetics. For poorly soluble drugs, loading efficiency can still be suboptimal (Riva et al., 2011).

e. Regulatory and Approval Barriers

As with most nanotechnology-based products, nanosponges face rigorous scrutiny by regulatory agencies like the FDA and EMA. Their complex structure, dynamic release profiles, and diverse chemical compositions complicate the standard toxicity, pharmacokinetic, and efficacy assessments required for regulatory approval (Ventura et al., 2020).

f. Storage Stability and Shelf-Life

The physical stability of nanosponges during long-term storage is yet to be fully optimized. Factors such as humidity, temperature fluctuations, and polymer degradation can affect the morphology and efficacy of stored formulations, particularly when natural cross-linkers or bioactives are used (Shende et al., 2021).

2. Future perspectives and opportunities

Despite these challenges, nanosponges are poised to play a transformative role in drug delivery, especially when integrated with advanced biomedical and material science technologies.

a. Smart and Stimuli-Responsive Nanosponges

The integration of smart materials into nanosponge networks can result in stimuli-responsive drug delivery systems. These are designed to release their therapeutic payload in response to specific triggers like pH, temperature, magnetic field, or enzymatic activity. This could enhance site-specific targeting and reduce systemic side effects (Gul et al., 2020).

b. Multifunctional and Hybrid Nanosponges

Future research may focus on creating multifunctional nanosponges that combine diagnostic and therapeutic functions (theranostics). Incorporation of imaging agents, magnetic nanoparticles, or antibodies into the sponge matrix could allow for targeted therapy combined with real-time monitoring (Sharma & Pathak, 2021).

c. Application in Personalized Medicine

With the rise of precision medicine, nanosponges could be tailored to patient-specific needs based on genomic, proteomic, and metabolic profiles. Such customized therapies would require advanced computational modeling and AI-assisted formulation strategies, but hold great promise in increasing treatment efficacy (Patra & Mukhopadhyay, 2022).

d. Nanosponges in Natural and Herbal Drug Delivery

Given the instability and poor bioavailability of many herbal bioactives, nanosponges present an ideal vehicle for such compounds. Their ability to encapsulate volatile, photosensitive, or poorly water-soluble natural compounds can significantly enhance the therapeutic potential of traditional medicine (D'Souza & Devarajan, 2020).

e. Exploration beyond Human Health

Nanosponges also offer opportunities beyond human therapeutics. Their application in veterinary medicine, agriculture (e.g., controlled release of pesticides), and even environmental remediation (e.g., pollutant absorption) is a growing area of research (Liu et al., 2021).

3. Conclusion

While the journey from bench to bedside for nanosponge-based systems is still ongoing, the immense potential of these carriers to revolutionize drug delivery systems cannot be understated. Through collaborative research, interdisciplinary innovation, and stringent validation protocols, the existing barriers can be overcome. The integration of smart nanotechnology, AI-based design, and green chemistry principles will be instrumental in propelling nanosponges from experimental frameworks to clinically viable therapies.

CONCLUSION

- Nanosponges represent a groundbreaking advancement in the field of nanotechnology-driven drug delivery, offering a robust platform capable of overcoming many limitations associated with conventional delivery systems. Their distinctive porous architecture, tunable surface chemistry, and high loading efficiency make them suitable for a wide range of therapeutic agents including hydrophobic drugs, peptides, proteins, and phytochemicals.
- One of the most notable advantages of nanosponges lies in their ability to enhance solubility and bioavailability of poorly water-soluble drugs, a challenge that continues to hinder therapeutic outcomes in many pharmaceutical formulations. Moreover, the capability of nanosponges to offer sustained and controlled release profiles improves patient compliance and minimizes the risk of adverse effects due to drug overdose or frequent administration.
- Equally important is their demonstrated biocompatibility and low toxicity, which, when combined with their potential for targeted and stimuli-responsive delivery, positions them as ideal candidates for applications in oncology, dermatology, neurology, and even herbal medicine. The incorporation of biodegradable polymers, such as cyclodextrins and polyesters, further strengthens their clinical safety profile.
- Despite these compelling advantages, several obstacles remain before nanosponges can achieve widespread clinical and commercial success. These include challenges in large-scale production, long-term safety evaluations, regulatory standardization, and economic feasibility. However, ongoing research into smart, multifunctional nanosponges and advancements in personalized nanomedicine are expected to bridge these gaps.
- In summary, nanosponges offer a highly adaptable and efficient platform for modern drug delivery systems. With continued research and cross-disciplinary innovation, they are well-positioned to become a cornerstone technology in precision medicine, promising safer, more effective, and patient-friendly therapeutic options in the years to come.

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