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Review Article

Nanosponges in Modern Pharmaceutics: A Comprehensive Review on Structure, Functionality, and Future Directions

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A B S T R A C T

Nanosponges (NSs) are an emerging class of porous polymeric nanocarriers that have revolutionized the field of drug delivery by offering enhanced solubility, stability, and controlled release of therapeutic agents. Structurally, they consist of three-dimensional hyper-cross-linked polymer networks with nano-sized cavities capable of encapsulating both hydrophilic and lipophilic drugs. Cyclodextrin-based NSs, in particular, have gained prominence due to their ability to form inclusion complexes, improving drug bioavailability and reducing adverse effects. These carriers provide significant advantages such as biocompatibility, biodegradability, non-toxicity, and high loading efficiency, making them superior to traditional nanocarriers.Various synthesis techniquesincluding solvent evaporation, ultrasound-assisted synthesis, melt method, and quasi-emulsion solvent diffusionenable tunable physicochemical properties for desired drug delivery applications.NSs have demonstrated promising potential in oral, topical, transdermal, pulmonary, and targeted drug delivery systems. Their ability to provide sustained and site-specific release makes them particularly valuable in cancer therapy, antifungal treatments, and antimicrobial drug formulations. Furthermore, the incorporation of NSs into hydrogels or composite systems has opened new possibilities for wound healing and cosmetic formulations. Current research is directed toward developing stimuliresponsive and ligand-functionalized NSs to achieve smart, targeted delivery.The future scope of NSs lies in the development of herbal NS systems, multi-drug delivery platforms, and environmentally responsive nanocarriers for precision therapeutics.

Keywords –Nanosponges, Drug Delivery System, Cyclodextrin, Controlled Release, Bioavailability, Targeted Therapy, Polymeric Nanocarriers etc.

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INTRODUCTION

Nanosponges (NSs) represent an innovative class of drug delivery systems composed of minute spherical nanoparticles with porous cavities capable of encapsulating a wide variety of therapeutic agents [10]. These sponge-like microscopic structures, typically a few nanometers in size with cavities smaller than one millimeter, function as porous polymeric colloidal networks similar in scale to viruses [11]. Their distinctive structure allows the entrapment of both hydrophilic and lipophilic drugs, thereby enhancing the versatility and efficiency of drug delivery [3].

The main objective of any drug delivery system is to transport an effective dose of the drug to the desired site within the body and to maintain the therapeutic concentration for a specified duration [3]. NSs, being insoluble porous materials with nanometric pores, exhibit exceptional adsorption and complexation capabilities. They are synthesized using either organic or inorganic components, depending on the desired application [2].

Structurally, NSspossess a three-dimensional, sponge-like framework with nanosized cavities or voids that encapsulate drug molecules. These carriers circulate through the body,

locate their specific target site, attach to the surface, and gradually release the drug. They have demonstrated up to five times greater efficiency in delivering drugssuch as anticancer agents for breast cancercompared to conventional systems, and are non-toxic, non-irritating, non-mutagenic, and non-allergenic [5].

Being polymeric hyper-cross-linked colloidal structures, NSsoffer a highly porous surface suitable for efficient drug loading [6]. Their design allows for improved aqueous solubility and enhanced bioavailability of poorly soluble drugs. Cyclodextrins (CDs) play a crucial role in forming inclusion complexes with drug molecules, which enhances solubility, masks undesirable properties, and improves photostability and aqueous stability in pharmaceutical formulations. CD-based NSsare synthesized by hyper-crosslinking CD molecules using crosslinkers such as carbonyl or carboxylate compounds, resulting in polymeric structures capable of swelling, chemical inclusion, and efficient controlled release of active ingredients [9].

A significant advantage of NSsover conventional nanoparticles lies in their easy regeneration. They can be reused through simple processes such as washing with eco-friendly solvents, heating, or modifying the pH or ionic strength. Due to these favourable properties, NSshave found broad applications across pharmaceutical and cosmetic industries [7].

Recent research from Vanderbilt University and Emory University introduced a controlled-release NSsystem for the delivery of anticancer drugs. These nanoparticles circulate in the bloodstream, recognize tumors cell surfaces, adhere to them, and release the drug in a controlled and predictable manner, thereby improving therapeutic efficacy and minimizing side effects [8].

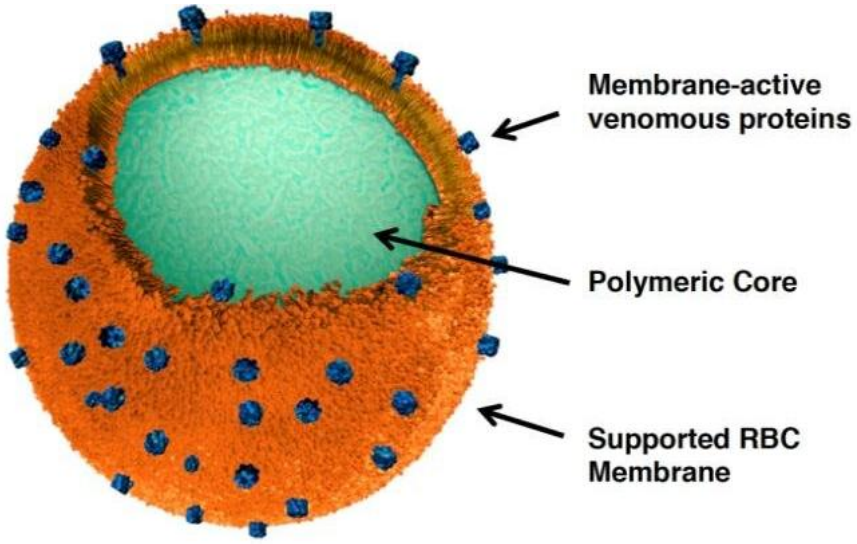

Figure 1: Nanosponges

ADVANTAGES

1. NSsdrug delivery system is non-irritating, non-mutagenic and non-toxic.
2. NSshelp to remove the toxic and venom substance from the body.
3. NSsdrug delivery system minimizes side effect.
4. Increase formulation stability and enhance the flexibility of the formulation.
5. Reduce dosing frequency.
6. Better patient compliance. [12]
7. Biodegradable.[13]
8. These formulations are free flowing. [14]
9. NS are versatile, can create new product forms and enhance physical, chemical and thermal stability of formulations.[15]
10. Improved bioavailability.[16]
11. Protecting the medicine against deterioration.
12. Drugs are passively targeted to macrophages in liver and spleen.[17]

DISADVANTAGES

1. NSsinclude only small molecules.
2. Depend only upon loading capacities. [12]
3. Dose dumping may occur at times.
4. The particulate nature of NSs designed for topical use and the inconvenience associated with their direct application over the skin, are significant limitations.
5. The loading ability of NSs rests on degree of crystallization. [18].

CLASSIFICATION OF NANOSPONGES

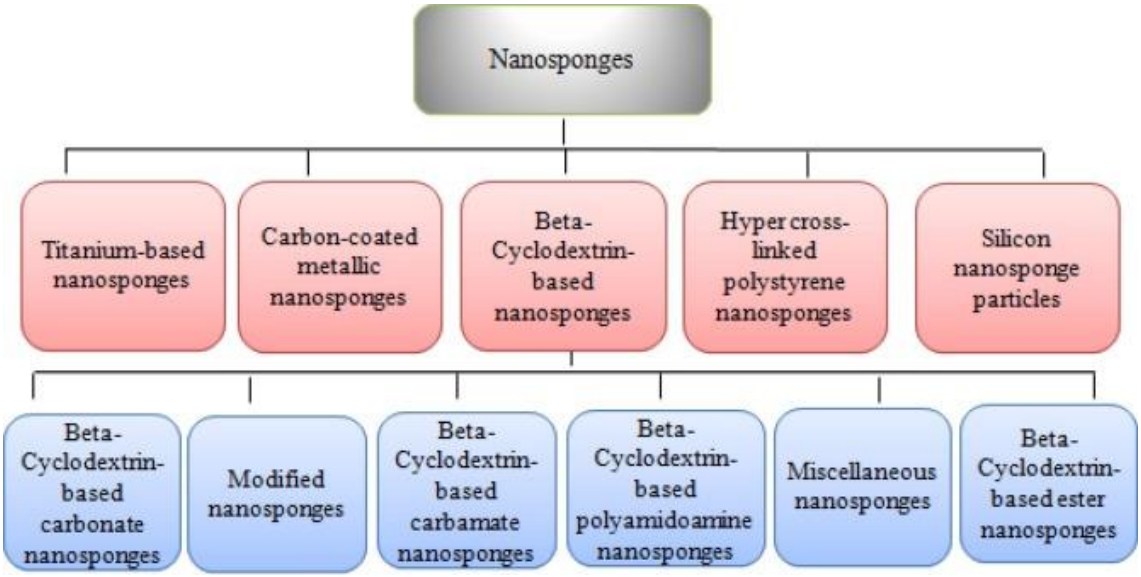

Figure 2: Classification of Nanosponges

COMPOSITIONS OF NANOSPONGES

1. Polymer

The polymer selected can have effect on the manufacture and performance of NSs. The cavity must be large enough to accommodate the drug molecule. The polymer is selected based on the desired release and medicine which is encapsulated. The polymer of choice must be able to bind to the selected ligands.

2. Agent for cross-linking

These cross-linking agents can be chosen on the basis of the polymer structure and the medicament to be prepared. Diaryl carbonates, dichloromethane, diphenyl carbonates & Di isocyanates are some examples.

3. Drug Content

- Between 100 and 400 Daltons are the ranges of molar mass.
- A pharmacological molecule is made up of no more than five compacted rings.
- Lower than 10 mg/ml of solubility is required in water.
- The substance's melting point is less than 250 °C.
- Procedure for the Preparation of Nano-sponges.
- Procedure for the Preparation of Nano-sponges. [3]

Table 1: Composition of Nanosponges

Polymer	Hyper cross-linked polystyrene, Cyclodextrin and its derivatives like β-Cyclodextrin, Alkyloxy Carbonyl Cyclodextrin, 2-Hydoxy Propyl β-Cyclodextrin, Methyl β- Cyclodextrin.
Co-Polymer	Poly(valerolactone-allylvalerolactone),Poly(valerolactone-allylvalerolactone oxepanedione), Ethyl cellulose, Polyvinyl alcohol.
Cross linker	Carbonyl diimidazoles,Carboxylic acid dianhydrides, Diphenyl carbonate, Diaryl carbonates, Disocyanates, Pyromellitic anhydride, Epichloridine, Glutaraldehyde, 2,2- bis(acrylamido), Acetic acid and Dichloromethane
Vehicle	Dimethyl Sulfoxide (DMSO), Dimethyl formamide (DMF).

LOADING OF DRUG IN NANOSPONGES

Nanosponges possess a porous framework in which the active drug molecules are encapsulated within the carrier structure. In the formulation of NSsfor drug delivery, the process typically begins with pretreatment to ensure the particles attain an average size of less than 500 nm. Following this, the NSsare dispersed in water and exposed to sonication to prevent particle aggregation and maintain a uniform suspension [22].

Once sonication is complete, the resulting suspension is centrifuged to isolate the colloidal fraction. The supernatant obtained from this step is collected, and a sample is subjected to freeze-drying to yield a dry NSpowder. Subsequently, an aqueous suspension of the NSsis prepared, and an excess amount of the desired drug is added. This mixture is continuously stirred for a specific period to facilitate complex formation between the drug and the NSs. Finally, any uncomplexed or undissolved drug is removed by centrifugation, leaving behind a purified NSdrug complex ready for further characterization or use [23].

MECHANISM OF RELEASE OF NANOSPONGES

The sponge-like structure of NSsthe active substance to move freely in and out of their porous network, maintaining a dynamic equilibrium. When the formulation is applied topically to the target tissue, the active ingredient within the vehicle is absorbed by the tissue, which disturbs this equilibrium. As a result, the drug begins to diffuse from the sponge particles into the surrounding vehicle and then into the tissue itself. This process continues until the vehicle is completely depleted or fully absorbed. Additionally, the sponge particles that remain on the surface of the tissue provide a controlled and sustained release of the active ingredient over time, ensuring prolonged therapeutic action [3].

FACTORS INFLUENCE NANOSPONGES

1. Type of Polymer

The nature of the polymer used plays a crucial role in determining the structure, formulation, and performance of NSs. The pore diameter of the NSmust be appropriately sized to accommodate the drug molecule and enable effective complexation between the drug and the polymeric matrix [19].

2. Type of Drug

For successful complexation with NSs, the drug molecule must meet certain physicochemical criteria. Ideally, it should have a molecular weight between 100 and 400 Da and contain fewer than five condensed rings. The drug should exhibit limited aqueous solubility (less than 10 mg/mL) and possess a melting point below 250°C. These properties ensure optimal interaction between the drug and the NSframework [20].

3. Temperature

Temperature variations can significantly affect the formation and stability of the drugNScomplex. At higher temperatures, intermolecular forces such as van der Waals and hydrophobic interactions may weaken, leading to a reduction in the apparent stability constant of the complex. Maintaining an optimal temperature is therefore essential for effective complexation.

4. Method of Preparation

The technique used to load the active drug into NSscan influence the overall stability and efficiency of the complex. The choice of method largely depends on the characteristics of both the drug and the polymer. Among the various approaches, freeze-drying has been identified as one of the most effective techniques for achieving efficient drug encapsulation and stable NSformation.[30]

5. Degree of Substitution

The ability of NSsto form complexes is also affected by the type, number, and position of substituents present on the parent polymer molecule. A higher degree of substitution generally leads to increased porosity, thereby improving the drug-loading capacity of the NSs[21]. Ultimately, the selection of the preparation method and polymer type depends on the nature of the drug and the desired therapeutic effect of the developed NSformulation [5].

METHODS OF PREPARATION

1. Emulsion Solvent Diffusion Method

This method involves two phases a dispersed phase and a continuous phase. The dispersed phase is prepared by dissolving ethyl cellulose and the drug in 20 ml of dichloromethane. Meanwhile, the continuous (aqueous) phase is made by adding a certain amount of polyvinyl alcohol (PVA) to 150 ml of water. The two phases are then combined and stirred at 1000 rpm for about 2 hours. After stirring, the formed NSsare collected by filtration. Finally, they are dried in an oven at 40°C for 24 hours and stored in a desiccator to ensure complete removal of any residual solvent.

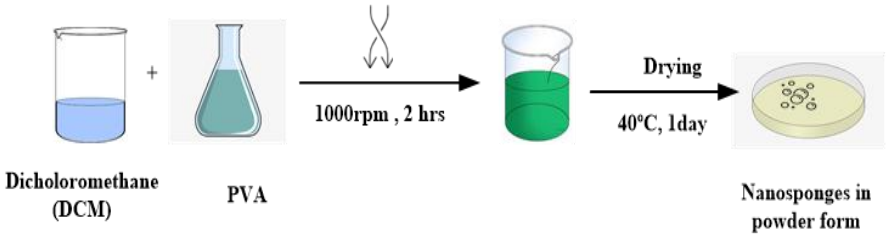

Figure 3: Emulsion Solvent Diffusion Method

2. Ultra Sound Assisted Synthesis

The polymers are reacted with cross-linking agents in a solvent-free flask. This flask is then placed in an ultrasonic bath containing water, which is heated to 90°C. The mixture is sonicated for about 5 hours to facilitate the reaction. After completion, the mixture is cooled to room temperature, and the solid product is broken into smaller pieces. Any unreacted polymer is removed by washing the product with water, followed by purification using a Soxhlet apparatus with ethanol as the solvent. The purified product obtained from this process is the NS.

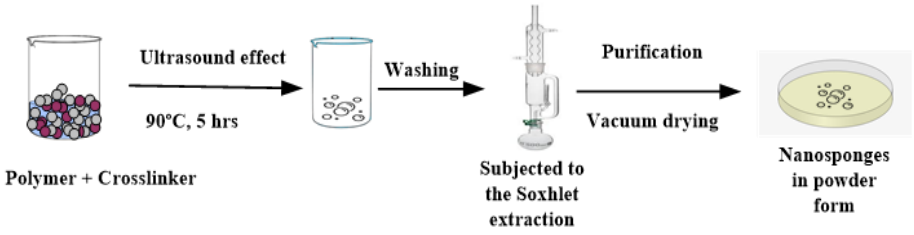

Figure 4: Ultrasound-assisted synthesis

3. Melt Method

NSsare synthesized by reacting cyclodextrin with a suitable cross-linking agent such as dimethyl carbonate, diphenyl carbonate, diisocyanates,diarylcarbonates, carbonyl diimidazoles, carboxylic acid anhydrides, or acetic acid 2,2-bis(acrylamide). All the components are thoroughly mixed and placed in a 250 ml flask, which is then heated to 100°C. The reaction is maintained for about 5 hours using a magnetic stirrer. After completion, the mixture is allowed to cool, and the resulting solid product is broken into smaller pieces. The product is then washed with an appropriate solvent to remove any unreacted materials and impurities.[24]

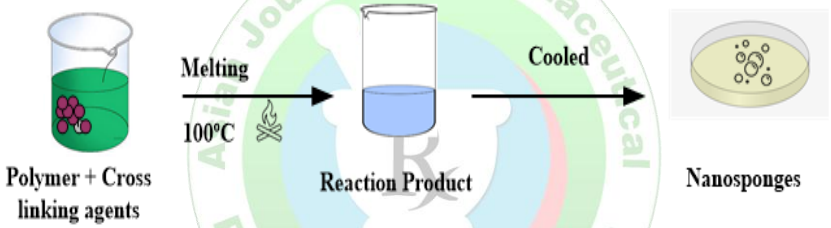

Figure 5: Melt Method

4. Quasi emulsion solvent method

NSscan also be prepared using the quasi-emulsion solvent diffusion method with varying amounts of polymer. In this process, Eudragit RS100 is first dissolved in an appropriate solvent to form the inner phase. The drug is then added to this solution and dissolved using ultrasonication at 35°C. This inner phase is gradually poured into an aqueous solution of polyvinyl alcohol (PVA), which serves as the outer phase. The mixture is stirred for about one hour, and the formed NSsare then collected by filtration. Finally, the NSsare dried in an air-heated oven at 40°C for 12 hours.[29]

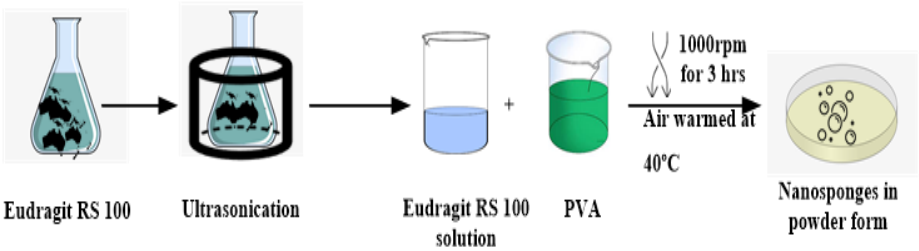

Figure 6: Quasi Emulsion Solvent Method

5. Solvent method

The polymer is first mixed with a suitable solvent, preferably a polar aprotic solvent such as dimethylformamide (DMF) or dimethyl sulfoxide (DMSO). This mixture is then added in excess to the cross-linker, maintaining an optimal cross-linker-to-polymer molar ratio of 1:4. The reaction is carried out at a

temperature between 100°C and the reflux temperature of the solvent, for a duration ranging from 1 to 48 hours. Commonly used cross-linkers include dimethyl carbonate and carbonyl diimidazole. Once the reaction is complete, the solution is cooled to room temperature, and the product is precipitated by adding it to a large volume of bi-distilled water. The NSsare then collected by vacuum filtration and purified using a prolonged Soxhlet extraction with ethanol. Finally, the purified product is vacuum-dried and ground in a mechanical mill to obtain a uniform fine powder.[25]

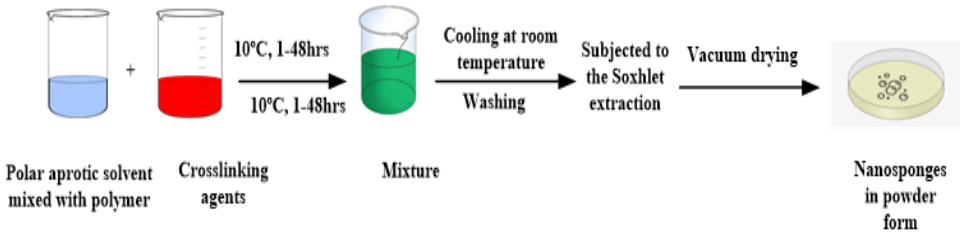

Figure 7: Solvent Method

6. Bubble electrospinning

A standard electrospinning setup typically includes four main components: a high-voltage power supply, a grounded collector, a syringe pump, and a syringe. However, a major limitation of this traditional system is its low yield of nanofibers.In the bubble electrospinning technique, polyvinyl alcohol (PVA) is commonly used as the polymer. To prepare the polymer solution, a 10% aqueous PVA mixture is heated at 80–90°C for about two hours, forming a uniform β-phase solution. After heating, the mixture is allowed to cool to room temperature before being processed to produce nano-porous fibers.[5]

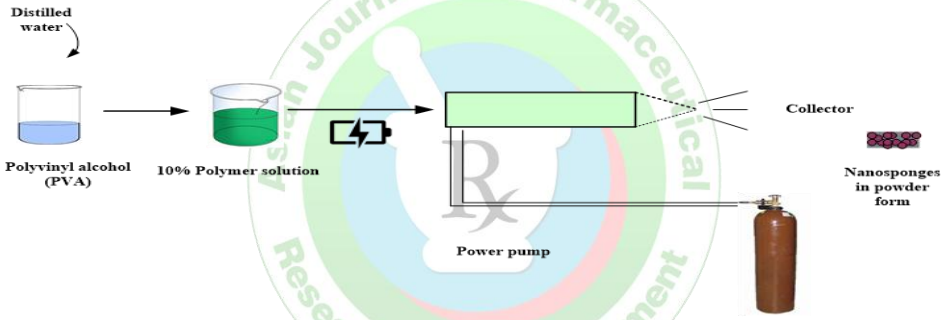

Figure 8: Bubble Electrospinning

EVALUATION OF NANOSPONGES

1. Particle Size and Morphology

The particle size of NSs is a key factor influencing their drug delivery efficiency and biodistribution. Smaller NS particles generally provide higher bioavailability because their larger surface area allows better interaction with biological membranes and easier penetration into tissues. The morphology and size of NSs are typically examined using scanning electron microscopy (SEM) and transmission electron microscopy (TEM), which provide detailed visualizations of their surface structure and shape.

2. Encapsulation Efficiency (EE) and Drug Loading Capacity (DLC)

Encapsulation efficiency refers to the proportion of the drug that is successfully entrapped within the NSmatrix, whereas drug loading capacity indicates the amount of drug that can be carried by the NSsrelative to the weight of the carrier material. High EE and DLC values are desirable, as they ensure efficient drug utilization and sustained therapeutic effects.[28]

3. Release Kinetics

Drug release kinetics describe how the active compound is released from the NSover time. An ideal NSformulation should offer controlled and sustained release, which helps maintain consistent drug levels in the body, minimizes side effects, and reduces the need for frequent dosing.

4. Stability Studies

Stability testing is crucial to ensure that NSformulations remain safe and effective throughout their shelf life. Instability may cause drug degradation, changes in particle size, or aggregation, all of which can impact therapeutic performance. Stability is usually evaluated under varying environmental conditions, including temperature, humidity, and light exposure [1].

5. Biocompatibility and Toxicity

Before clinical use, NSsmust be tested for safety. Biocompatibility refers to their ability to function within biological systems without causing adverse reactions, while toxicity studies determine whether the formulation induces any harmful biological effects. These assessments are essential to confirm the suitability of NSsfor medical applications.[27]

6. In Vivo Performance

In addition to laboratory (in vitro) testing, in vivo studies are essential for evaluating the actual therapeutic effectiveness of NSbased drug delivery systems in living organisms. Animal studies are commonly conducted to investigate parameters such as pharmacokinetics, biodistribution, and therapeutic outcomes [9].

APPLICATIONS OF NANOSPONGES

1. Targeted Drug Delivery

NSs can be modified with specific targeting ligands such as antibodies, peptides, or small molecules, allowing drugs to be directed precisely to particular tissues or cells. This targeted approach helps minimize systemic side effects while improving therapeutic effectiveness [1].

2. Combination Therapy

NSshave the unique ability to encapsulate and deliver multiple drugs simultaneously. This enables combination therapy, which can produce synergistic effects and help overcome multidrug resistance. Such co-delivery systems are especially valuable for treating complex conditions like cancer and infectious disease [2].

3. Oral Drug Delivery

NSscan protect sensitive drugs from the harsh gastrointestinal environment, thereby enhancing their stability and absorption. This is particularly advantageous for drugs that are easily degraded by stomach acid or digestive enzymes. Many poorly water-soluble drugs (BCS Class II/IV) show improved solubility and dissolution when incorporated into cyclodextrin-based NSs(CD-NS) or other porous polymeric systems. These NSsenhance solubility through inclusion complexation within the cyclodextrin cavity and adsorption into their porous networks, leading to improved oral bioavailability [3].

4. Topical and Transdermal Drug Delivery

NSsimprove drug penetration through the skin, increasing the efficiency of topical and transdermal treatments. Their small particle size allows them to cross the skin barrier and deliver drugs to deeper layers. For antifungal, anti-inflammatory, and cosmetic formulations, NSsincorporated into gels or creams enable sustained drug release and enhanced local absorption, ensuring high drug concentration at the target site with minimal systemic exposure [4].

6. Pulmonary Drug Delivery

NSscan be developed into inhalable aerosols or dry powders for effective pulmonary delivery. Their porous structure allows for a high drug payload and efficient lung deposition, making them suitable for the treatment of respiratory disorders. Pulmonary or nasal administration of NSscan also offer rapid systemic absorption or direct nose-to-brain delivery, bypassing the blood–brain barrier for certain central nervous system drugs [1].

7. Nanosponges for Cancer Therapy

NSscan encapsulate chemotherapeutic drugs, reduce systemic toxicity while improvetumortargeting efficiency. When functionalized with specific ligands, they can selectively deliver anticancer agents to tumor cells, thereby increasing treatment efficacy and minimizing damage to healthy tissues [5].

8. Antimicrobial and Antiviral Therapy

NSsare also effective carriers for antimicrobial and antiviral agents. They provide sustained release of the active drug, enhance its solubility, and reduce the likelihood of developing resistance. This approach is particularly useful for treating localized infections such as skin infections, resistant biofilms, and mucosal infections. For example, NSssignificantly improve the solubility and therapeutic performance of hydrophobic antifungal drugs like itraconazole[6].

9. Vaccine Delivery

NSscan act as effective vaccine carriers by ensuring stable and controlled antigen release, leading to stronger and longer-lasting immune responses. Their porous structure also helps protect the antigen from degradation before administration [7].

10. Enzyme Immobilization

NSscan be used to immobilize enzymes, enhancing their stability and activity. This property makes them valuable not only for therapeutic applications but also in industrial biocatalysis where enzyme stability is crucial [8].

FUTURE PROSPECTIVES

A. Stimuli-Responsive Nanosponges

- Develop NSsthat release drugs in response to pH, temperature, or enzymes.
- Example: pH-sensitive itraconazole NSsfor fungal infections.

B. Hydrogel-Nanosponge Hybrid Systems

- Embed drug-loaded NSsinto hydrogels for topical or wound-healing applications.
- Example: Itraconazole NSsloaded hydrogel for antifungal therapy.

C. Targeted Drug Delivery

- Functionalize NSswith ligands or antibodies for cancer targeting.

D. Combination Therapy

- Load two or more drugs (e.g., antifungal + anti-inflammatory) to enhance therapeutic effect.

E. Herbal Nanosponges

- Use plant extracts or natural bioactive (like curcumin, quercetin) in NSsto improve delivery and stability.[26]

CONCLUSION

NSsrepresent a novel and versatile class of drug delivery systems that have shown immense potential to overcome the limitations of conventional pharmaceutical formulations. Their unique porous architecture, high surface area, and ability to encapsulate both hydrophilic and hydrophobic drugs enable improved solubility, enhanced bioavailability, and sustained drug release. Cyclodextrin-based and polymeric NSshave demonstrated notable efficiency in delivering a wide range of therapeutic agents, including antifungal, anticancer, anti-inflammatory, and antiviral drugs.The simplicity of their synthesis, combined with their biocompatibility and non-toxic nature, positions NSsas promising candidates for various routes of administration, including oral, topical, transdermal, and pulmonary drug delivery. Furthermore, their application extends beyond pharmaceuticals to cosmetics, enzyme immobilization, detoxification, and environmental remediation.Despite these advancements, several challenges remain, such as optimizing drug loading capacity, understanding long-term toxicity, ensuring scalability of production, and achieving regulatory acceptance. Future research should focus on the development of stimuli-responsive, targeted, and hybridNSsystems, which can release drugs selectively in response to physiological conditions. The integration of NSswith hydrogels, nanofibers, and smart biomaterials also holds potential to enhance therapeutic outcomes.In conclusion, NSsoffer a groundbreaking approach to controlled and targeted drug delivery. Continued innovation in their design, synthesis, and functionalization will cover the way for next-generation NSsbased therapeutics with improved efficacy, safety, and patient compliance.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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