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Review Article

# Nanosponge Innovations: Revolutionizing Targeted Drug Delivery

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## A B S T R A C T

Nanosponges emerge as sophisticated nanoporous platforms, engineered through crosslinking of polymers like cyclodextrins, ethylcellulose, and polyvinyl alcohol to form stable, three-dimensional matrices with submicron cavities ideal for entrapping diverse drug molecules. These structures excel in overcoming solubility barriers for BCS Class II/IV compounds, leveraging non-covalent interactions, hydrogen bonding, vander Waals forces, and inclusion complexesto achieve loading efficiencies up to 33%, while enabling pH-responsive, sustained release via polymer hydration and diffusion.

Diverse fabrication techniques, including emulsion-solventdiffusion, ultrasound-assisted synthesis, microwave irradiation, and melt methods, offer flexibility in tuning porosity, particle size (<1 µm, optimal 200-300 nm for dermal routes), and zeta potential (>±30 mV for stability). Rigorous characterization employs DLS, SEM/TEM, FTIR, helium pycnometry for porosity, and UV spectroscopy for entrapment, confirming biocompatibility, thermal stability to 300°C, and self-sterilizing properties due to 0.25 µm pores.

Broad applications encompass oncology (paclitaxel, doxorubicin), antifungals (itraconazole, voriconazole), and topicals, with marketed formulations like Tamodex 20 and Piroxicam-20 validating clinical translation. Advantages include cost-effectiveness, biodegradability, taste-masking, and reduced side effects, though limitations persist, burst release risks, exclusion of macromolecules >400 Da, and scale-up challenges. Future prospects focus on magnetic targeting, greener solvents, and hybrid systems for personalized medicine.

**Key words:** Nanosponges, Porous, Polymer, Micrometer, Particle size, Ligands, Cross linkers.

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## INTRODUCTION

The pharmaceutical and health sectors extensively employ nano-scale materials to address various physical, chemical, and biological challenges associated with disease treatment. Nanotechnology has significantly contributed to advancement of drug delivery systems, diagnostic tools, and therapeutic strategies. Since the 1950s, it has emerged as key technology in modern pharmaceutical and medical research.[1]

Medical researchers have long faced challenges in delivering drugs effectively within the human body. Two major obstacles include directing the drug to the intended site of action and controlling its release rate[2]. Advances in modern therapy increasingly depend on targeted drug delivery systems, which aim to enhance therapeutic efficacy while minimizing adverse effects and optimizing dosing regimens. Targeted drug delivery involves selectively transporting the active pharmaceutical ingredient to specific tissues or pathological sites, ensuringoptimal local drug concentrations with minimal distribution tonon-target organs. By concentrating the drug at desired site, this approach improves treatment outcomes, enhances patient safety, and maximizes the therapeutic index of the drug.[3]Nanotechnology has created new possibilities in pharmaceutical development by carriers such as nanoparticles, nano capsules, nanospheres, nanosuspension, nanocrystal, nanosponges, and nano

ethosomes. These systems are designed to enhance drug solubility, protect active compounds from degradation, improve bioavailability, and enable site-specific delivery, thereby increasing therapeutic effectiveness while minimizing unwanted side effects.[4]In recent years, nanosponges have become a growing focus in scientific research because they offer wide versatility and can be produced using simple, cost-effective methods.[5]

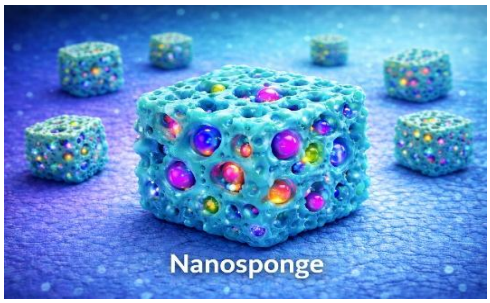



**Figure** 1: Nanosponge

## NANOSPONGE

Nanosponges are nanoscale, three-dimensional porous structures made up of spherical particles within the colloidal size range. They generally have an average particle size of less than 1 µm and exhibit a consistent size distribution, forming slightly cloudy (opalescent) dispersions when mixed with water. Due to their highly porous nature, nanosponges are remarkably stable and capable of carrying large amounts of substances, allowing them to encapsulate both water-soluble and water-insoluble compounds. These properties help improve the solubility and stability of drugs that dissolve poorly in water, ultimately enhancing their bioavailability. In addition, nanosponges have been widely investigated for various uses, such as drug delivery, enzyme immobilization, gas storage, and the removal of toxic materials.[6]

## Types of Nanosponges

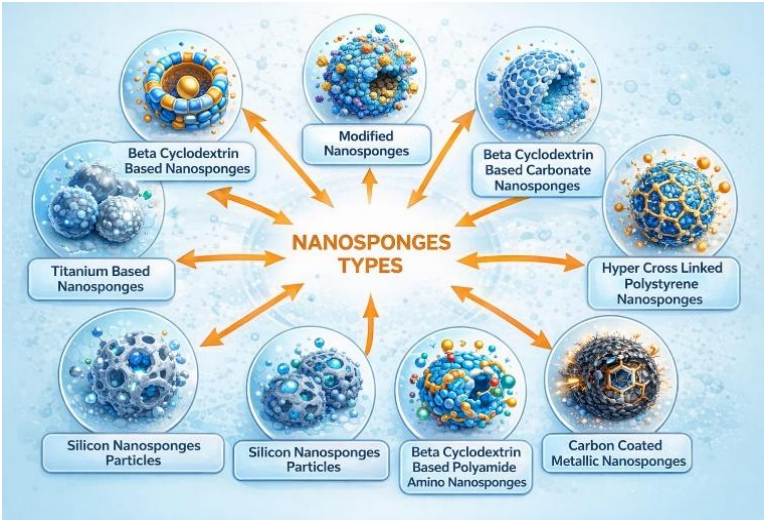



**Figure 2:** Types of Nanosponges

## Composition of Nanosponges

### Polymer

Choosing the right polymer is essential for the successful development and functionality of nanosponges. This choice depends largely on the characteristics of the drug being incorporated and the desired release profile. The selected polymer must contain appropriate functional groups that support efficient cross-linking and ensure the formation of a stable nanosponge structure. Moreover, it should be capable of interacting with specific ligands, which facilitates targeted delivery and enables controlled release of the drug.

### Cross-Linking Polymer

Choosing a suitable cross-linker mainly depends on the type of polymer being used and the characteristics of the drug involved.

### Drug Substance

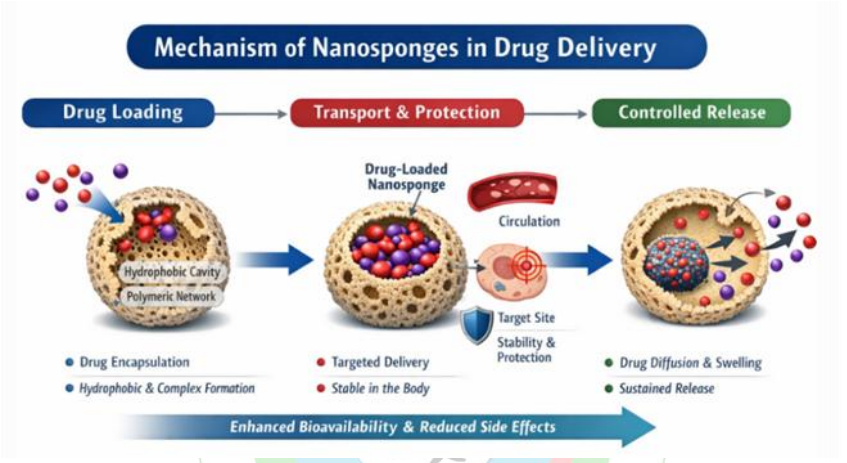
Certain characteristics of drug compounds are essential for their incorporation into nanosponges:

- Ideally, the drug should have a molecular weight in the range of 100 to 400 daltons for effective incorporation into nanosponges.
- The drug molecule should not be too complexin structure generally,it should have maximum of five condensed rings, since excessive rigidity can hinder entrapment.
- For effective incorporation into nanosponges, the drug should have low water solubility, typically less than 10 mg per milliliter.[7]

| POLYMER | COPOLYMER | CROSSLINKER | POLAR SOLVENTS |
|---|---|---|---|
| 1. HyperCrosslinked Polysterene Cyclodextrin | 1. poly (Valerolactone Allyl valerolactone) | 1. Carbonyl Diimidazole(CDI) | 1. Ethanol |
| 2. Cyclodextrin(alkoxy Carbonyl CD) | 2. poly(Valerolactone 3. Allyl oxypanedione) | 2. Diarylcarbonates | 2. Dimethylacetamide |
| 3. Methylβ-CD | 4. Ethylcellulose | 3. Dichloromethane | 3. Dimethylformamide |
| 4. Hydroxy propylβ-CD | 5. Polyvinylalcohol | 4. Diisocynates | ---------- |
| 5. Poly-Valerolactone | ---------- | 5. Glutaraldehyde | ---------- |
| 6. Eudragit RS100 | ---------- | 6. Pyromellitic anhydride | ---------- |
| 7. Acrylic polymer | ---------- | 7. 2,2bis(acrylamide) Acetic acid | ---------- |

## Mechanism of Nanosponges

Nanosponges are nano-sized, porous carriers made from cross-linked polymers that trap drug molecules within their internal cavities. Drugs are incorporated through hydrophobic forces, hydrogen bonding, and inclusion interactions, which enhance both solubility and stability. Once administered, these carriers convey the drug toward the desired site of action. When exposed to biological fluids, the polymer structure becomes hydrated, allowing the drug to escape gradually through diffusion and matrix expansion. This controlled release maintains prolonged therapeutic levels, improves bioavailability, and minimizes adverse effects.[8]




## Features of Nanosponges

1. The size distribution of nanosponges is relatively uniform, and the average diameter is less than 1 micron.[9]
2. The parenteral route could be used to administer nanosponges with mean sizes of 200–300 nm.
3. Drugs that are hydrophilic or hydrophobic can be transported by nanosponges.
4. They occur in both crystalline and paracrystalline forms depending on the processing conditions, and this feature can be exploited to calculate the drug loading capacity.
5. These result in a steady suspension without aggregation because of their high zeta potential.
6. They are insoluble in both water and organic solvents. They have thermal stability up to 300°C and are porous and nontoxic.
7. Drugs can be trapped in nanosponges using inclusion complexes such as β-CD and non-inclusion complexes.
8. 3D construction with adjustable porosity cavities, polarity, and stability throughout a broad pH range of 1-11.[10]
9. After formulation, magnetic particles can be incorporated to impart magnetic characteristics.[11]
10. Chemical linkers facilitate more effective adhesion of nanosponges to the target site.
11. In water, they create a clear, opalescent suspension.
12. They can be developed via microwave, ultrasonic, solvent extraction, and basic thermal desorption techniques.[12]

## Advantages

1. **Sterility and Compatibility:**Nanosponge are compatible with a wide range of carriers and excipients. They are self-sterilizing due to 0.25 µm pore size, no microbial penetration.
2. **Cost-effective and easy-going:** These can be cheap and flexible.
3. **Extended Release:** NS can release for up to 12 hours, offering more flexibility and a smoother formulation.
4. **Improved Stability and Fewer Side Effects:** These topical oil control agents adjust medication release profiles for better systemic exposure while also providing lower doses, better stability, and fewer side effects.
5. **Versatility:** Nanosponges can improve the physical, chemical, and thermal stability of formulations and develop new product forms.
6. **Taste Masking and Formulation Improvement:** NS may improve the solubility and stability of poorly water-soluble medications, mask undesirable tastes, and transform immiscible liquids into solid dosage forms.
7. **Biodegradable and non-toxic:** The Nanosponges is biodegradable and non-toxic. It is also completely free from allergens, mutagens, and irritants.

8. **Better products:** The Carries drug in the system improves the therapeutic index and the duration of action. It is a better product.
9. This platform can transport both polar and non-polar molecules. It increases their dissolution and uptake in the body while slowing their release to achieve prolonged therapeutic action.[13]

## Disadvantages

1. Performance is influenced only by the extent of its loading capability.
2. Only low-molecular-weight compounds participate, rather than bulky macromolecules.
3. An uncontrolled burst of drug may take place.
4. The liberation of the drug may occur at a slower rate.
5. These carriers are capable of encapsulating low-molecular-weight compounds, whereas larger molecules cannot be efficiently incorporated.[14]

## Factors affecting nanosponges

### Nature of polymer and crosslinker

The choice of polymer in the creation of nanosponges can impact both their pre-formulation and development processes. The internal cavity of a nanosponges should be sufficiently large to fit a drug molecule of a specific size for effective complexation. The efficacy of nanosponges is shaped by the specific polymer utilized in their formulation. Active crosslinkers transform nanoporous molecular structures into three-dimensional (3D) frameworks. Target molecules can become entangled by hydrophilic or hydrophobic segments produced during this process. modifying the level of crosslinking. Based on the properties of the crosslinkers, nanosponges that are either soluble in water or insoluble can be created. Using epichlorohydrin as a crosslinker results in the formation of hydrophilic nanosponges. These can enhance the absorption of drugs across biological membranes and function as efficient drug carriers. Crosslinkers such as diphenylcarbonate, pyromellitic anhydride, and diisocyanates were utilized to develop hydrophobic nanosponges. These hydrophobic nanosponges can be used to deliver hydrophilic drugs, including peptides and proteins, for prolonged periods.[16]

### Drug and medium used for interaction

1. Drug molecules must have the following characteristics in order to combine with nanosponges:
2. The drug molecule should ideally have a molecular weight between 100 and 400 daltons to ensure effective incorporation into nanosponges.
3. The structure of a medicine molecule should consist of no more than five compacted rings.
4. The melting point of the drug must be lower than 250˚C.
5. Less than 10mg/ml drug should dissolve in water.

The type of crosslinker and polymer used, as well as the nature of the drug being incorporated, may all have an effect on the preparation of nanosponges. To be successfully entrapped in nanocavities, drug molecules require specific properties. Molecules having molecular weight ranging from 100 to 400 Da, melting points below 250 °C, limited than five condensed rings, and low water solubilitycan all be effectively trapped by a nanocavity.

Due to the tendency of these compounds to decrease in stability once incorporated into nanosponges, it is unfeasible for substances with higher melting points to establish stable complexes with pharmaceuticals and nanosponges. Fluctuations in temperature influence a complex's stability constant. Moreover, because of the complex's structural rigidity, heating it to elevated temperatures results in reduced drug loading. In hydrophilic environments, organic guest molecules are driven to enter hydrophobic cavities, while organic solvents tend to release the organic molecules confined within the nanosponges. The medium plays a significant role in shaping the interactions between targeted molecules and the Nanosponge cavity.[17]

### Temperature

The way a drug or nanosponge complexes can be affected by temperature changes. The stabilityof the medication or the nanosponge complex is frequently weakened by increasing the temperature. This could be as a result of the hydrophobic and van der Waals forces between the drug and nanosponges weakening with increasing temperature.

The complexity of nanosponges is affected by temperature variations. The stability of a medication or nanosponge complex frequently decreases with temperature. This might result from a decrease in contact forces like vander waals and hydrophobic forces.[18]

### Degree of substitution

The complexation capacity of nanosponges is significantly influenced by the type, number, and spatial arrangement of substituents on the parent molecule. Likewise, the nature, quantity, and position of substituents on the polymeric molecule are crucial factors in determining the efficiency of nanosponge complex formation.[19]

### Method of preparation

The way the drug is loaded into the nanosponge can affect the bond between the drug and the nanosponge. However, the type of drug and polymer determines how well a procedure works. Often, freeze drying has proven to be the most effective for drug bonding.[20]

### Examples of drug molecules that have been successfully incorporated into nanosponges.

| Drugs | Nanosponge vesicle |
|---|---|
| Paclitaxel | βcyclodextrine |
| Tamoxifen | βcyclodextrine |
| Resveratrol | βcyclodextrine |
| Temozolamide | Poly(valerolactoneallylerolactone)and poly(valerolactoneallylerlactoneoxepanedione)Ethyl cellulose, polyvinyl alcohol |
| Econazole nitrate | Ethyl cellulose, Polyvinyl alcohol |

| | |
|---|---|
| Intraconazole | βcyclodextrin:CDI<br>βcyclodextrine |
| Antisense | sodium alginate |
| Dexamethasone | βcyclodextrine |
| Camptothecin | βcyclodextrine |
| Ferulic acid | cyclodextrinnanosponges |
| carboplatin | ethylcellulose |
| oxyresveratro1 | cyclodextrin |
| Doxorubicin | βcyclodextrin, DPC<br>βcyclodextrin:PMA |
| Temoporofin | βcyclodextrin |
| Voriconazole | ethylcellulose, PVA, polymethylmethacrylate |
| Celecoxib | βcyclodextrin, NNmethylene bisacrylamide |
| Dithranol | Diphenylcarbonate, βcyclodextrin |
| Flubiprofen | βcyclodextrin, DPC |
| Nelfinavir mesylate | βcyclodextrin,dimethylcarbonate |
| Gamma-oryizanol | βcyclodextrin, DPC |
| 5-Fliurouracil | βcyclodextrin |
| Acetylsalicylic acid | βcyclodextrin, PMDA |
| curcumin | βcyclodextrin, dimethylcarbonate |
| miconazole nitrate | βcyclodextrin, Diphenylcarbonate<br>PVA, ethylcellulose, βcyclodextrin, Dichloromethane<br>Methylcellulose, sodium carboxy methyl cellulose, HPMC |
| Celecoxib | βcyclodextrin, N,N-methylene bisacrylamide |
| L-dopa | βcyclodextrin |
| Fenofibrate | Maize starch, SDS |
| Nifedifine | βcyclodextrin |
| Glypizide | βcyclodextrin |
| Ibuprofen | Ethylcellulose and PVA |
| Telmisartan | Carbonated crosslinker |
| Nelfenavir Mesylate | βcyclodextrin |
| Fluconazole | PVA, HPMC, Eudragit RS 100, Ethyl cellulose |
| Metformin | Ethyl cellulose, ethanol:DCM, PVA |
| Etodolac | EC, PVA, DCM, Acetone |
| Sulfasalazine | βcyclodextrin, DPC |
| Curcumin and Voriconazole | PVA, EC, DCM |
| Butenafine | EC, PVA |
| Tacrolimus | EC, PVA, DCM |
| Gliclazide | Eudragit |
| Insulin | βcyclodextrin:PMA |
| Artemether+lumefan | HP βcyclodextrin+ βcyclodextrin:CDI |
| Terbinafine hydrochloride | EC |
| Febuxostat | βcyclodextrin:DPC |
| Paracetmol+caffeine | βcyclodextrin:DMC |
| Sulfamethoxazole | βcyclodextrin:CDI |
| Bortezomib | βcyclodextrin:CDI |
| α-Mangostin | Ethyl cellulose |
| Curcumin+Caffeine | βcyclodextrin:DMC |
| Griseofulvin | βcyclodextrin |
| Irbesartan | βcyclodextrin:PMA<br>βcyclodextrin:DPC |
| Indomethacin | Ethylcellulose |
| Clobetasol Propionate | βcyclodextrin:DPC |
| Sesamol | βcyclodextrin:DPC |
| Limonene essential | βcyclodextrin:DPC |
| Voriconazole | Pluoronic F-68 |
| Flutamide | βcyclodextrin:CDI |
| Lansoprazole | Ethyl cellulose |
| Thyme essential oil | βcyclodextrin:DPC |

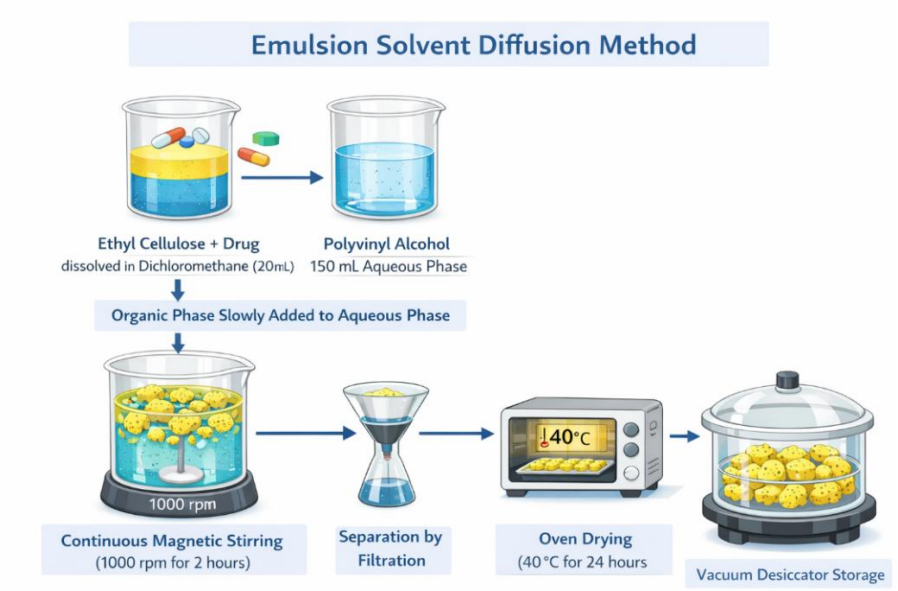
## Marketed preparation of nanosponges

| Drug | Marketed Formulation |
|---|---|
| Dexamethasone | Dexamethasone Sodium Phosphate tablet |
| Alprostadil | Alporstadil injection IP |
| Piroxicam | Piroxicam-20 |
| Tamoxifen | Tamodex 20 |
| Iodine | Mena-gargle Solution |

## Method of Preparation

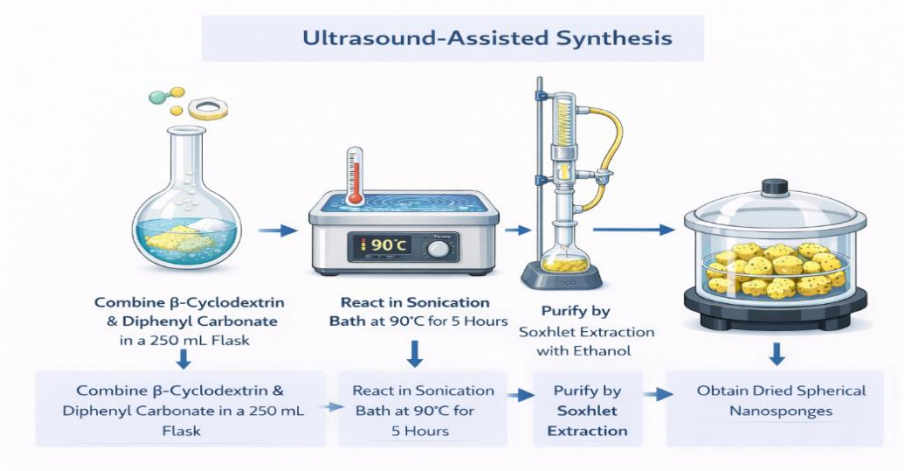
### Emulsion Solvent Diffusion Method

Nanosponges were made using different ratios of ethyl cellulose (EC) and polyvinyl alcohol (PVA). First, we prepared the dispersed phase by dissolving ethyl cellulose and the drug in 20 mL of dichloromethane. We then slowly added this organic phase to 150 mL of an aqueous continuous phase with a set concentration of polyvinyl alcohol while stirring constantly. The mixture was stirred at 1000 rpm for 2 hours to help form nanosponges through solvent diffusion and evaporation. We separated the resulting nanosponges by filtration and dried them in an oven at 40 °C for 24 hours. Finally, we stored the dried nanosponges in a vacuum desiccator to completely remove any leftover solvent..[21]



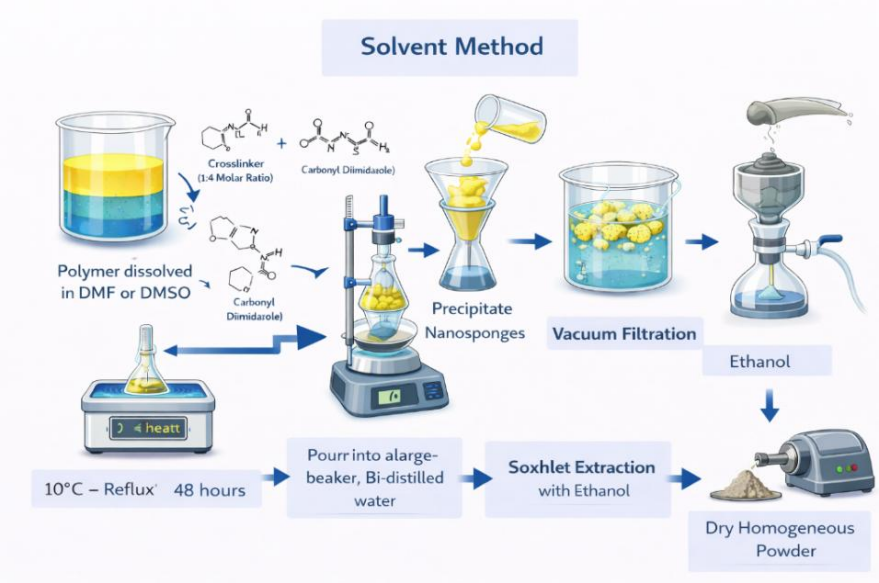

## Ultrasound Assisted Synthesis

Nanosponges can be made using the ultrasonication method, which involves a reaction between polymers and crosslinking agents without using organic solvents. This technique produces spherical nanosponges with a relatively uniform particle size. In this process, the polymer is mixed with a suitable crosslinker, such as diphenyl carbonate or pyromellitic anhydride, in a specific molar ratio. The mixture is then placed in a water-filled ultrasonic bath and heated to about 90 °C while being continuously sonicated. The ultrasonic energy helps form a cross-linked nanosponge structure. Once the reaction is complete, the mixture is cooled and washed with water to remove any unreacted polymer. The product is further purified using Soxhlet extraction with ethanol to get rid of impurities. For instance, anhydrous β-cyclodextrin and diphenyl carbonate can react under sonication at 90 °C for about 5 hours. The resulting nanosponges are then crystallized and purified similarly to melt or solvent-based methods. This method is beneficial because it avoids using organic solvents, making it a safer and more environmentally friendly way to prepare nanosponges.[22]




## Solvent method

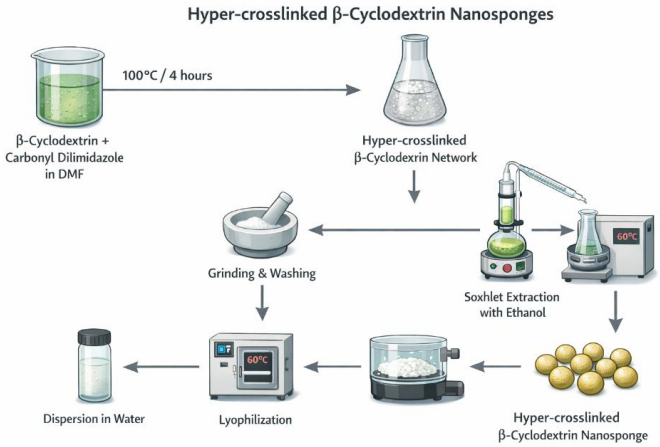
The polymer is initially dissolved in a correct solvent, commonly A polar aprotic solvent like dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) can be used. The prepared polymer solution is then mixed with an excess amount of cross-linking agent. A typical molar ratio of polymer to crosslinker is maintained at approximately 1:4. Crosslinking agents such as dimethyl carbonate or carbonyl diimidazole are normally used for this reaction. The reaction mixture is maintained at temperatures ranging from about 10 °C to the reflux temperature of the selected solvent. The reaction is allowed to proceed for a period ranging from 1 to 48 hours to ensure adequate cross-linking. After achievement of the reaction, the mixture is cooled to room temperature and poured into a large volume of bi-distilled water to precipitate the product. The precipitated nanosponges are collected by vacuum filtration, purified through prolonged Soxhlet extraction with ethanol, dried under vacuum, and finally ground to obtain a uniform powder.[23]




## From hyper-crosslink β-cyclodextrin

Nanosponges are three-dimensional polymeric networks consisting of nearly spherical structures produced by cross-linking cyclodextrins with suitable agents such as di-isocyanates, diaryl carbonates, dimethyl carbonate, or carbonyl diimidazole. These porous structures contain internal cavities and channels comparable in size to proteins, allowing them to encapsulate drug molecules effectively. The pore size and overall dimensions of the nanosponges can be regulated by correcting the degree of cross-linking during the synthesis process. Such nanocarriers are particularly beneficial for incorporating poorly water-soluble or highly hydrophobic drugs and enhancing their solubility. Additionally, a lower degree of cross-linking generally promotes a faster drug statement from the nanosponge matrix.

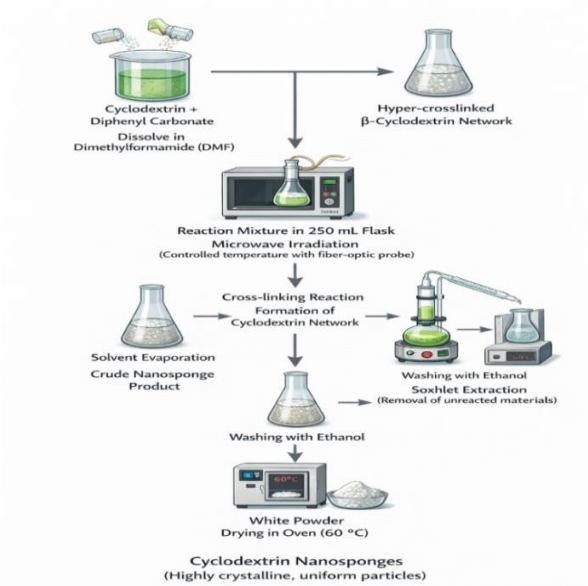
β-Cyclodextrin nanosponges can be synthesized by reacting β-cyclodextrin dissolved in dimethylformamide with carbonyl diimidazole at about 100 $^{0}$C for approximately four hours. The condensation polymerization results in the formation of a transparent, highly cross-linked cyclodextrin network. The obtained product is ground and washed with deionized water to remove the residual solvent and is extra purified with Soxhlet extraction with ethanol to eliminate unreacted reagents. Finally, the purified material is dried at 60 °C overnight, dispersed in deionized water, and the colloidal fraction is recovered and lyophilized to obtain sub-micron spherical nanosponges.[24]




## Microwave Irradiation method

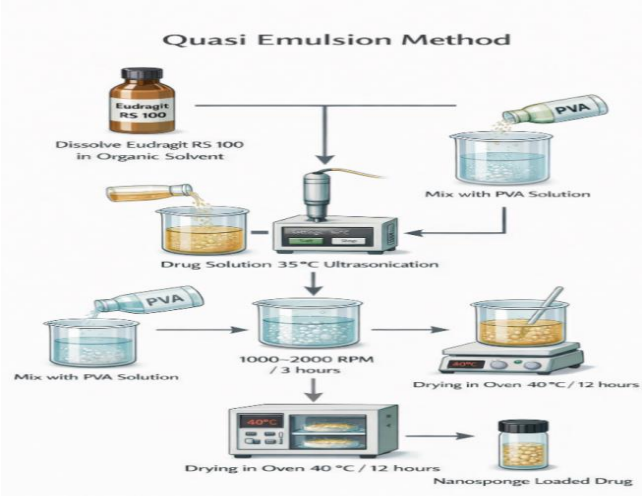
Microwave-assisted synthesis of nanosponges was carried out using a Cata Scientific microwave system. The temperature of the reaction mixture was monitored using a fiber-optic probe inserted into the reaction vessel. Diphenyl carbonate was used as the cross-linking agent, while dimethylformamide (DMF) served as the solvent for preparing cyclodextrin-based nanosponges. A 250 mL flask containing a mixture of cyclodextrin and diphenyl carbonate in DMF was subjected to microwave irradiation for a specific period under controlled conditions. During the process, the solvent gradually evaporated and the reaction progressed to form the nanosponge network. The obtained product was purified by washing with ethanol followed by Soxhlet extraction to remove any unreacted substances. The purified material appeared as a white powder and was further dried in an oven at 60 °C. A study by Singireddy et al. reported that microwave-assisted heating was more

efficient than conventional heating methods for nanosponge synthesis. The results exposed that microwave synthesis increased the drug-loading capacity of the model drug by about 50%. Additionally, high-resolution show electron microscopy revealed that nanosponges produced by microwave irradiation were more crystalline and exhibited a narrower particle size distribution.[25]



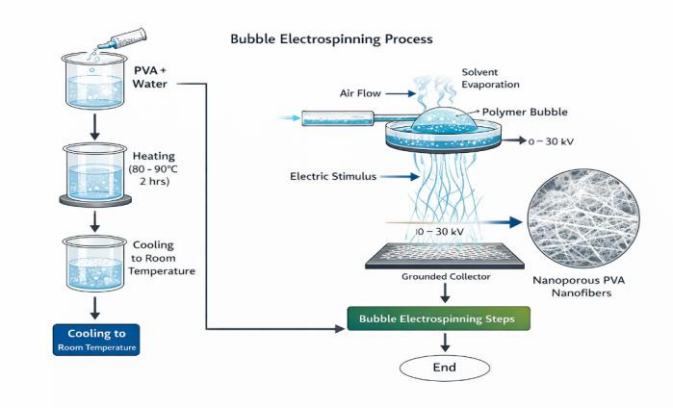

## Quasi Emulsion Method

Nanosponges were prepared using different polymer concentrations. The internal phase was formulated using Eudragit RS 100, which was then incorporated into a suitable organic solvent to form a dissolvable phase. The drug was melted in this phase with the help of ultrasonication at approximately 35 °C to ensure complete dispersion. This internal phase was subsequently added to an outside aqueous phase containing polyvinyl alcohol (PVA), which acted as an emulsifying agent. The mixture was stirred continuously at 1000–2000 rpm for about 3 hours at room temperature to allow proper emulsification and formation of nanosponges. After completion of stirring, the resulting dispersion was dried in a hot-air oven at 40 °C for 12 hours to obtain the final nanosponge product.[26]




## Bubble electrospinning method

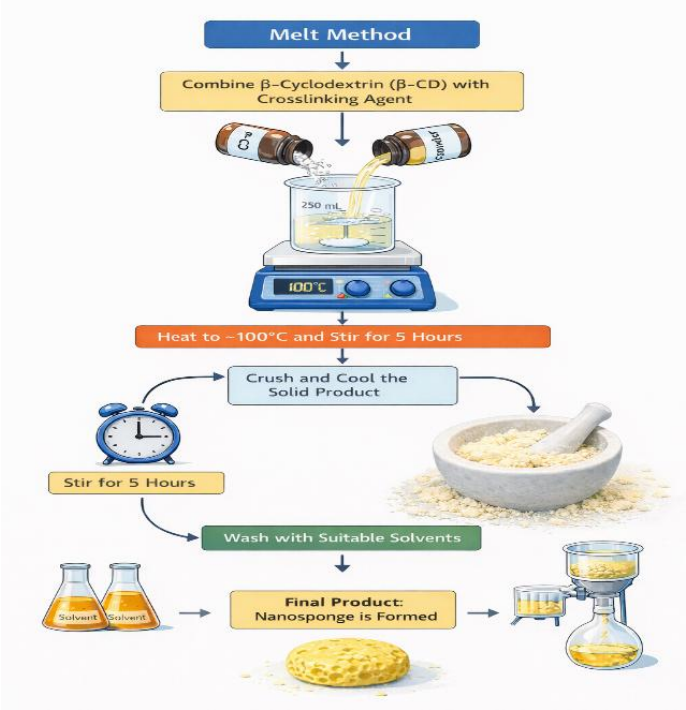
A conventional electrospinning system generally consists of four essential components: a high-voltage power supply, a grounded collector, a syringe pump, and a syringe containing the polymer solution. Despite its effectiveness in producing nanofibers, the traditional electrospinning technique is limited by its relatively low nanofiber production rate.




In the bubble electrospinning method, polyvinyl alcohol (PVA) is frequently selected as the polymer material. To prepare the polymer solution, a 10% aqueous PVA solution is heated at a temperature between 80°C and 90°C for around two hours until a homogeneous β-phase solution is obtained. After the heating process, the solution is allowed to cool to room temperature before it is further processed to fabricate nanoporous fibers.[27]

## Melt Method

In the melt method, β-cyclodextrin (β-CD) is combined with a appropriate crosslinking agent to form the nanosponge structure. The mixture is transferred into a 250 mL reaction vessel and heated to approximately 100 °C to simplify the reaction. The contents are continuously stirred using a magnetic stirrer for about five hours to ensure proper interaction between the components. After completion of the reaction, the mixture is allowed to cool to room temperature. The resulting solid product is then crushed into a fine powder and thoroughly washed with appropriate solvents to remove unreacted substances and residual by-products, yielding purified nanosponges.[28]




## Evaluation Tests

### Physical appearance

The physical appearance of the prepared nanosponges was evaluated through visual observation. The obtained product appeared as a white, porous, sponge-like powder. The spherical morphology of the nanosponges is influenced by the viscosity of the polymer solution used during formulation, where appropriate viscosity facilitates the formation of uniform spherical structures.[29]

### Solubility studies

The solubility of the pure drug was determined with the shake-flask method. An extra quantity of the drug was added to separate test tubes containing 10 mL of different solvents, namely ethanol (95%), methanol, and distilled water, to ensure saturation in each medium. The mixtures were vortexed for around 15 minutes to facilitate proper mixing and then allowed to stand undisturbed for one hour to achieve equilibrium saturation. After equilibrium was attained, Any undissolved drug was removed from the mixture through filtration, and the resulting clear liquid was then collected for further analysis.[30]

### FTIR

Infrared spectroscopy is widely used to examine potential interactions between a solid drug and the nanosponge carrier system. Its effectiveness, however, is primarily associated with drugs that possess functional groups such as carbonyl or sulfonyl moieties. This analytical technique helps in identifying various functional groups present in the formulation and in assessing the role of hydrogen bonding in drug–polymer interactions.

Fourier Transform Infrared (FTIR) spectroscopy is therefore commonly applied to determine the compatibility between the drug and the polymer used in nanosponge formulations. During analysis, samples are typically scanned within the range of 400–4000 $cm^{-1}$. The resulting spectra allow for the detection of characteristic absorption peaks corresponding to specific functional groups, as well as the identification of any possible chemical interactions between the drug and the polymer matrix.[31]

## Porosity

Porosity analysis is performed to estimate the presence and extent of nanochannels and nanocavities formed within the nanosponges. The porosity of the nanosponge formulation is commonly determined using a helium pycnometer, as heliumgas can easily penetrate both interparticle and intraparticle pores within the material. In this method, the helium movement technique is employed to measure the true volume of the sample. The difference between the bulk volume and the true volume is used to calculate the percentage porosity of the material. The percent porosity is determined using the following equation:[32]

$$\text{Porosity (\%)} = \frac{\text{Bulk Volume} - \text{True Volume}}{\text{Bulk Volume}} \times 100$$

## Polydispersity Index and Particle size

Dynamic light scattering (DLS) was employed to determine the particle size using a 90 Plus particle size analyzer equipped with the MAS OPTION software. This technique calculates the average particle diameter and the polydispersity index (PDI), which reflects the uniformity of the particle size delivery and helps distinguish between monodisperse and polydisperse systems.

In addition to dynamic light scattering (DLS), particle size can also be determined using sophisticated imaging techniques such as freeze-fracture electron microscopy, transmission electron microscopy (TEM), scanning electron microscopy (SEM), and atomic force microscopy (AFM). These advanced methods provide in-depth information about particle morphology, including their shape, structural characteristics, and surface features.

$$\textbf{Polydispersity Index} = \frac{\Delta d}{davg}$$

| SR No | PDI | Type of Dispersion |
|---|---|---|
| 1 | <1 | Single dispersion standard |
| 2 | 0.1-0.25 | Nearly single disperse |
| 3 | >0.1 | Mid-range Multi dispersity |
| 4 | >0.5 | Very Multi disperse |

d-Average particle size shown mV(nm); davg-Represents the breadth of the distribution.[33]

## Zeta potential

Zeta potential analysis is performed to determine the surface charge of the prepared nanosponges using a Malvern Zeta Sizer. Zeta potential is defined as the electrical potential alteration between the dispersion medium and the stationary layer of fluid attached to the surface of dispersed particles. It is considered an important parameter for evaluating the stability of colloidal systems. A higher magnitude of zeta potential generally indicates stronger electrostatic repulsion between particles, which contributes to better stability of the dispersion. For analysis, the nanosponge samples are appropriately dispersed in double-distilled water and transferred into a clear disposable zeta cell. In aqueous systems, a zeta potential value of approximately ±30 mV is typically regarded as an indicator of good colloidal stability.[34]

## Microscopy Study

Zeta potential measurement is carried out to evaluate the surface charge of prepared nanosponges, commonly using instruments such as a Malvern Zeta Sizer. It represents the electrical potential difference between the dispersion medium and the immobile layer of fluid that surrounds the surface of dispersed particles. This parameter plays a crucial role in assessing the stability of colloidal systems.

Generally, a higher absolute value of zeta potential indicates stronger electrostatic repulsion among particles, which helps prevent aggregation and enhances dispersion stability. For analysis, nanosponge samples are suitably diluted with double-distilled water and placed in a transparent disposable zeta cell. In aqueous dispersions, a zeta potential value around ±30 mV is typically considered sufficient to ensure good colloidal stability.[35]

## Entrapment Efficiency

Entrapment efficiency refers to the proportion of drug that is successfully incorporated within the nanosponge particles. It is an important parameter used to evaluate the drug-loading capacity of the nanosponge formulation. The entrapment efficiency is commonly determined by centrifugation of the nanosponge dispersion with methanol at 10,000 rpm for 30 minutes. After centrifugation, the concentration of the drug present in the supernatant is analyzed using a UV–visible spectrophotometer. The percentage of drug entrapped within the nanosponges is then calculated using an suitable formula.[35]

$$\textbf{Entrapment efficacy} = \frac{\textbf{actual drug content}}{\textbf{therotical drug content}} \times 100$$

## Thermoanalytical method

Thermoanalytical methods are employed to investigate possible physical or chemical changes in a drug substance before the thermal degradation of the nanosponge formulation occurs. These techniques help identify alterations such as melting, evaporation, decomposition, oxidation, or polymorphic transitions of the drug. The presence of such changes may suggest the formation of a drug–nanosponge inclusion complex. Thermal behavior is typically analyzed using techniques such as Differential Thermal Analysis (DTA) and Differential Scanning Calorimetry (DSC). The resulting thermograms are examined for variations including peak broadening, peak shifting, the emergence of new peaks, or the disappearance of characteristic peaks associated with the pure drug. Furthermore, differences in weight loss patterns may also provide secondary evidence for the successful formation of drug–nanosponge inclusion complexes.[36]

## In-Vitro Drug Release

The in-vitro drug release from the optimized nanosponge formulation can be evaluated using Franz diffusion cells with a diffusional area of 2.26 cm², as well as a multi-compartment rotating cell fitted with a dialysis membrane. The donor compartment contains the drug-loaded nanosponge gel, while the receptor section is filled with the pH 7.4 buffer medium. At predetermined time intervals, samples are withdrawn completely from the receptor compartment, diluted appropriately with distilled water, and analyzed using a UV spectrophotometer. The drug release apparatus is further analyzed using GraphPad Prism software, which applies non-linear curve fitting to determine the model that best describes the experimental data.[37]

## Swelling and water uptake

Water absorption in swellable polymers, such as polyamidoamine nanosponges, can be evaluated by immersing the prepared nanosponges in an aqueous medium. The extent of swelling and water uptake is then determined using the following expressions:[38]

$$\% \text{ Swelling} = \frac{\text{Final Marking after specified time}}{\text{Initial marking before soaking}} \times 100$$

$$\text{Water uptake} = \frac{\text{Mass of hydrogel after 72 hrs}}{\text{Initial mass of dry polymer}} \times 100$$

## Drug Release Kinetics

The drug release data from the nanosponge formulation were analyzed using various kinetic models, including zero-order, first-order, Higuchi, Korsmeyer–Peppas, Hixson–Crowell, Kopcha, and Makoid–Banakar models, to better understand the release mechanism. The analysis was achieved using GraphPad Prism software, which applies non-linear regression to estimate model parameters. The software identifies the best-fitting model by comparing how closely the experimental data align with the predicted values of each kinetic model.[39]

## X-ray diffraction studies

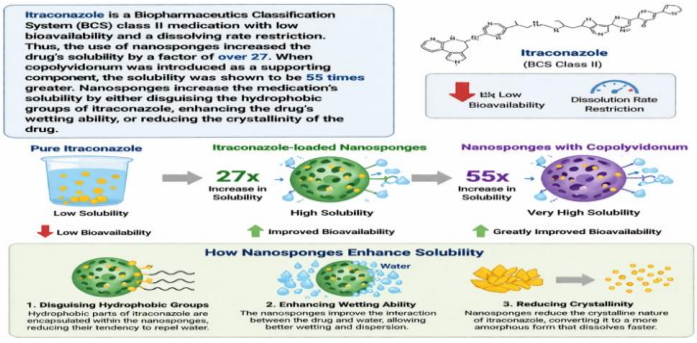
Powder X-ray diffractometry is widely used to evaluate inclusion complex formation in solid-state systems. When a drug is in liquid form and does not display its own diffraction pattern, the appearance of a new and distinct pattern compared to that of the uncomplexed nanosponge indicates successful complexation. In the case of solid drugs, the diffractogram of the prepared complex is compared with that of a simple physical mixture of the drug and polymer. A physical mixture typically shows a diffraction pattern that is the sum of the individual components, whereas a true inclusion complex produces a distinctly different pattern, suggesting the formation of a new solid phase. Additionally, analysis of diffraction peaks can provide insight into interactions such as complex formation or chemical changes. The formation of a drug–nanosponge complex often leads to modifications in the diffraction pattern, including changes in crystallinity, sharpening of peaks, and shifts in peak positions, all of which confirm the development of a new complexed structure.

## Single crystal x-ray structure analysis

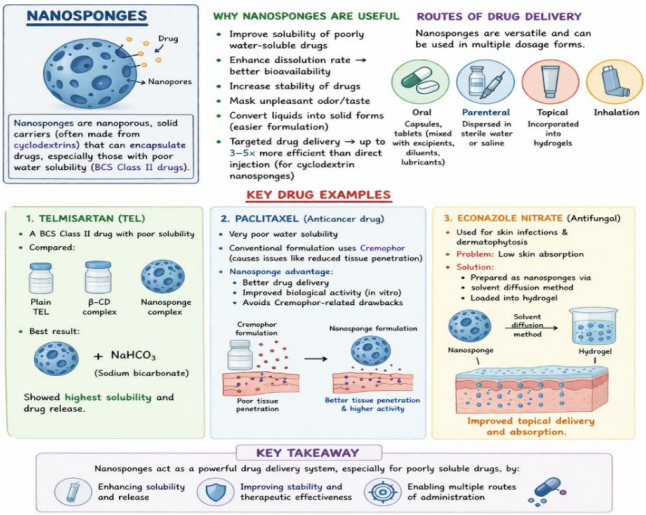
Single-crystal X-ray diffraction analysis is employed to elucidate the detailed structure of inclusion complexes. It enables the identification of interactions between host and guest molecules and allows for the accurate determination of their geometric relationships.[40]

## Applications

## Solubility Enhancement[41]

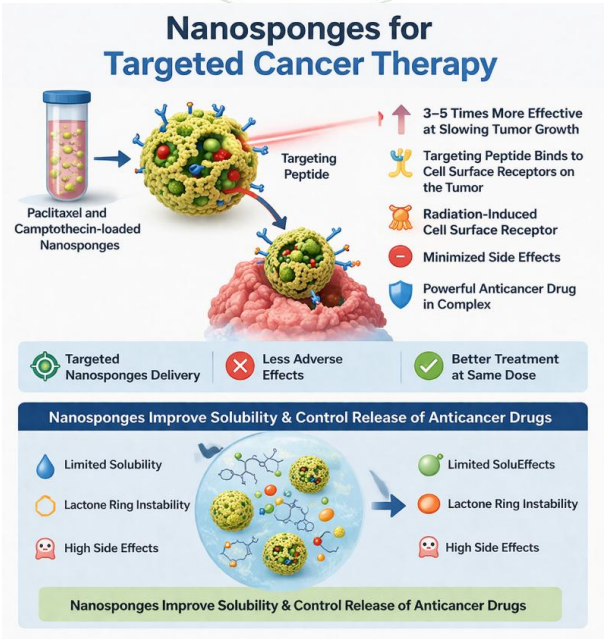


## Drug Delivery[42]

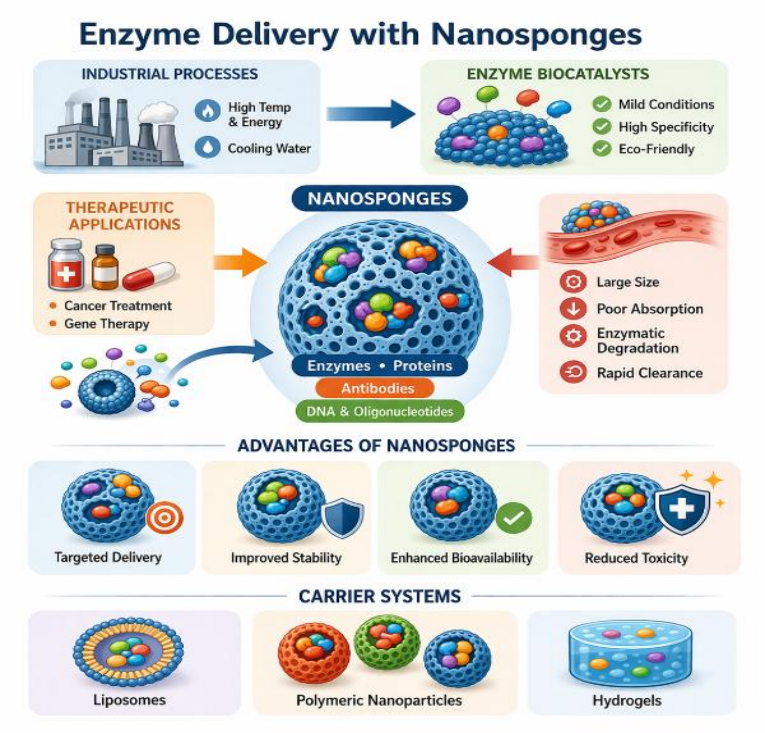



## Topical agents[43]

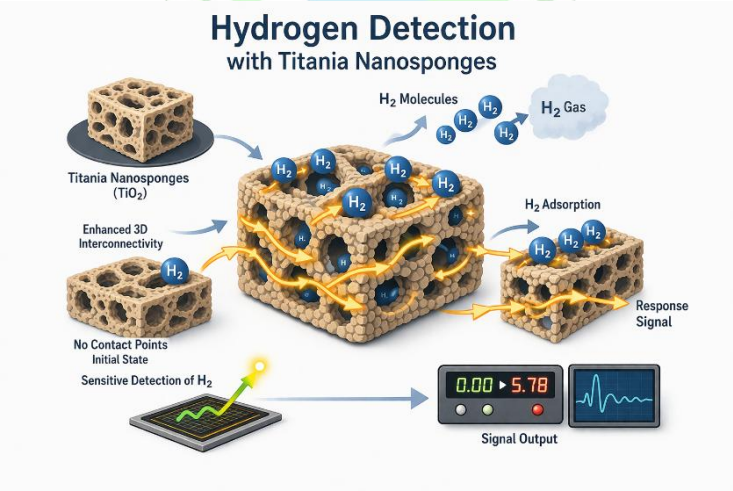

## Cancer Therapy[44]



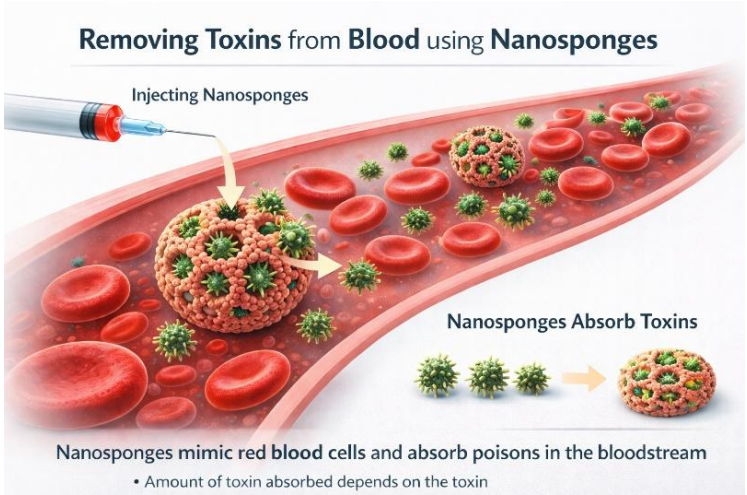
## Nanosponge as biocatalyst carrier [45]



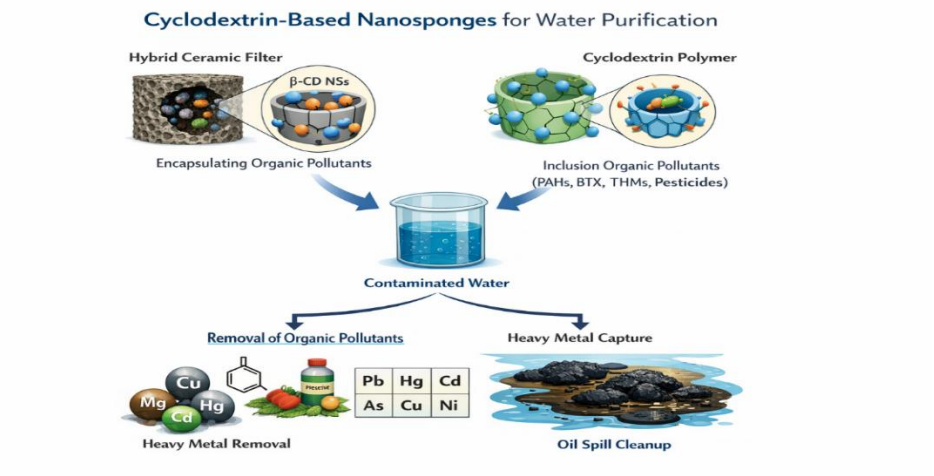

## Nanosponge as a chemical sensor[46]




## As a adsorbent treating poison in blood[47]



### Removal of organic pollutants of water[48]




## CONCLUSION

Nanosponges have emerged as an advanced and adaptable drug delivery system within the field of nanotechnology. Their porous, three-dimensional structure allows them to effectively encapsulate a wide range of drug molecules, including both water-soluble and poorly soluble compounds. This property significantly enhances drug solubility, stability, and overall bioavailability.

One of the key advantages of nanosponges is their capacity to deliver drugs in a controlled and targeted manner. This helps in maintaining consistent therapeutic levels of the drug in the body while reducing unwanted side effects. In adding, their physicochemical properties such as stability, biocompatibility, and non-toxic nature make them suitable for various pharmaceutical applications.

Different preparation techniques provide flexibility in designing nanosponge formulations based on specific drug requirements. Proper evaluation and characterization further ensure the quality, effectiveness, and duplicability of these systems.

However, certain limitations exist, including their reduced efficiency in encapsulating high molecular weight substances and the possibility of initial burst drug release. These challenges require careful optimization during formulation development.

In conclusion, nanosponges offer a promising stage for modern drug delivery with applications extending to cancer therapy, topical treatments, and environmental uses. Continuous research and development are expected to enhance their performance and expand their role in future pharmaceutical innovations.

### Future perspectives

Nanotechnology has significantly advanced medical research by enabling the development of materials at the nanoscale. Among these innovations, nanosponges (NS) are emerging as highly promising carriers due to their unique nanoporous structure.These structures enable them to trap a wide range of substances, especially drugs, which helps improve their therapeutic effectiveness.

Nanosponges play an important role in improving both the pharmacokinetics and pharmacodynamic properties of drugs. They help increase drug solubility and stability while also enabling controlled and targeted drug release. This controlled delivery reduces unwanted side effects and minimizes toxicity, making treatments safer and more effective.

In addition to pharmaceutical applications, nanosponges have potential uses in environmental and industrial fields. They can be explored for eliminating toxic substances from industrial waste and eliminating harmful organic vapors from the air. Their ability to trap undesirable compounds also makes them useful in masking unpleasant tastes in food and drug products.

Despite their advantage, several challenges remain. The cost of production needs to be reduced by identifying suitable polymers, cross-linking agents, and efficient synthesis methods. Current preparation techniques, such as conventional and ultrasound-assisted methods, require further optimization to achieve large-scale, cost-effective, and reproducible production. Another concern is the presence of residual solvents or by-products, which may cause toxicity. Therefore, the development of green chemistry approaches that avoid harmful solvents is essential.

Future research should also focus on understanding how factors such as particle size, porosity, crystallinity, and degree of cross-linking influence drug loading and release behavior. Additionally, the development of biodegradable and bioabsorbable nanosponges is important to ensure safe breakdown within the body without harmful effects.

Nanosponges also show promise in advanced medical applications such as cancer diagnosis and treatment. They can stabilize sensitive biomarkers and may be used in imaging techniques. Furthermore, combining nanosponges with targeting mechanisms, such as molecular transporters or magnetic guidance systems, could enhance their capability to deliver drugs precisely to specific tissues, including brain tumors.

Overall, nanospongesrepresent a versatile and innovative technology with applications across medicine, environmental science, and engineering. However, further

research is necessary to address challenges related to safety, cost, and scalability before they can be widely adopted in practical applications.[49]

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## Conflict of Interest

The authors declare that there is no conflict of interest regarding this study.

## Author Contributions

All authors have equally contributed to the research work and preparation of the manuscript.

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## Informed Consent Statement

Not applicable.

## Ethical Approval

Not applicable.

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