# A Review On Nano-sponges in Enhancing the Solubility, stability and Bioavailability of Pharmaceutical Compounds.

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## ABSTRACT

The development of nanoscale drug delivery systems that work to deliver medications at the target place is the result of advances in pharmaceutical research. For the purposes of disease detection, prevention, and treatment, nanosized carriers are being researched. Because of their distinct structural characteristics, nanosponges, a subset of nanotechnology, have gained popularity. It is a little sponge with large spaces between its organic and inorganic components. They can become stuck in the structure and have both hydrophobic and hydrophilic properties. They have the benefits of improved absorption, less toxicity, and a prolonged release profile. The structural characteristics, several generations, preparation methods, characterization techniques, and application of nanosponge formulation are briefly discussed in this review.

***Key words:*** *Improved Solubility, Small Size, and Controlled Delivery, Nanosponges*

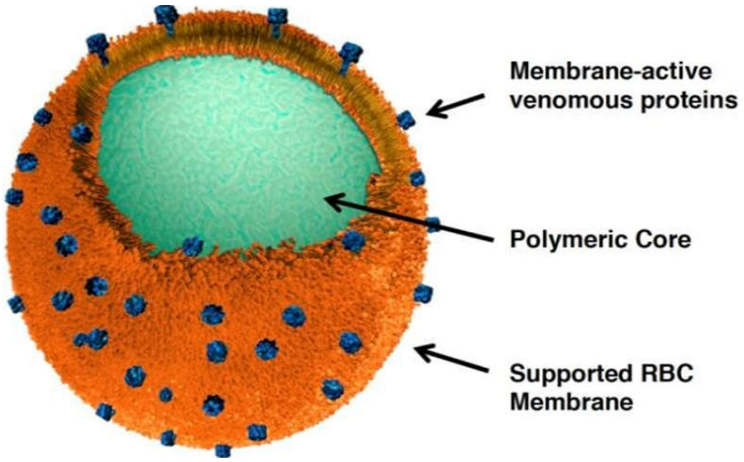
## INTRODUCTION

The latest developments in nanotechnology are called nanosponges. The original purpose of the nanosponge delivery technology was topical medicine delivery. These days, water-soluble and bio erodible polymers can also be employed to administer medications orally. Nanosponges are porous materials that are roughly the size of a virus, with an average diameter of less than 1µm.

Nanosponges can bind to poorly soluble medications and increase their bioavailability because of their small size and porous nature. These nanosponges can move throughout the body and interact with target sites. Numerous methods, including the melt method, solvent diffusion method, solvent method, ultrasound assisted method, and sonication, are documented to produce nanosponges. (1)

Colloidal carriers known as nanosponges have been created and suggested for drug delivery. Nanosponges are microscopic structures that resemble meshes. They are small, spherical, spongy porous polymeric structures that release the medication in a predictable and regulated way. Nanosponge has an average diameter of less than 1µm.By creating inclusion and non-inclusion complexes, nanosponges can contain a variety of molecules. Both hydrophilic and lipophilic compounds can be cared for by these particles. (2,3)

These tiny sponges can move throughout the body until they meet a particular target place, adhere to the surface, and begin to release medication in a regulated way. They are self-sterilizing, free-flowing, economical, and stable at pH 1–11 and temperatures up to 130°C.




**Basic Structure of Nanosponges**

**Advantages of Nanosponges** (4,5)

1. Targeted medicine delivery to specified sites.
2. Less detrimental adverse effects.
3. The pH range of 1 to 11 is stable for these formulations.
4. These mixtures remain stable at temperatures as high as 130°C.
5. It can be used to turn liquids into solids and cover off offensive flavors.
6. Biodegradable.
7. By altering the ratio of cross linker to polymer, particles can be made smaller or larger Consistent release.
8. Enhanced flexibility, elegance, and stability in the formulation.

**Disadvantages of nanosponges**

1. NSs have ability to include only small molecules.
2. They could be either paracrystalline or in crystalline form.
3. Paracrystalline NSs can show different loading capacities.

**Classification of nanosponges** (6)

**1.Nanoparticle encapsulation**

Nanosponges serve as a representation of the encapsulating nanoparticles. Drug molecules are carried in the aqueous core of sponge-like nanoparticles called nanosponges, which have many pores.

**2.Complexing nanoparticles**

They use electrostatic charge to draw molecules to them.

**3. Conjugating nanoparticles**

These nanoparticles attach to medications via covalent bonds.

**Materials Used**

| | | |
|---|---|---|
| 1 | Polymers | Hyper cross-linked polystyrene, cyclodextrin & its derivatives like methyl B-cyclodextrin, hydro propyl B- cyclodextrin, Eudragit RS 100 |
| 2 | Cross linkers | CH-Diphenyl carbonate, Diarylcarbonete, pyromellitic anhydride, Diisocyanates, Carbonildiimidazoles, Epicloridrine, Glutaraldehyde, Carboxylic acid, Acetic acid, Dicloromethane. |
| 3 | Co-polymer | Ethyl Cellulose, Polyvinyl Alcohol |
| 4 | Polar a protect solvent | Dimethyl Sulfoxide, Dimethyl Formamide, Ethanol |

## TYPE OF NANOSPONGES

### The process for creating nanosponges

### 1.Melt Method

Cyclodextrin and a cross-linker react to creating nanosponges. Numerous cross-linkers are available, including the commonly used 2,2-bis(acrylamido) acetic acid, dimethyl carbonate, diphenyl carbonate, diisocyanates, diaryl carbonates, carbonyl diimidazoles, and carboxylic acid anhydrides. After thoroughly mixing all the ingredients, they are put in a 250 ml flask and heated to $100^0$C. A magnetic stirrer was used to evenly mix the reaction mixture during the several hours that the reaction was conducted. The product broke down by allowing the mixture to cool. To get rid of any remaining unreacted excipients, the final product was cleaned using an appropriate solvent. For instance, Ibuprofen, Naproxen, Miconazole nitrate, and so forth. (7)

### 2.Solvent Method

A polar aprotic solvent, such as dimethyl formamide or dimethyl sulfoxide, will be needed. The aprotic solvent dissolves polymer. The cross linker is mixed with the polymer-aprotic solvent combination. It is necessary to employ an excessive amount of cross linker. It is preferred that the cross linker/molar ratio be between 4 and 16. The reaction is carried out over a period of 1 to 48 hours at a solvent reflux temperature. After the reaction is finished, the solution is let to reach room temperature. After adding too much double-distilled water, the resultant product is filtered using a vacuum filter. Soxhlet extraction with ethanol is used to further purify the result. The product is next vacuum-dried and ground into a uniform powder in a mechanical mill. such as Ciprofloxacin, Flurbiprofen, etc. (8)

### 3.Loading of drugs into Nanosponges

Drug loading Into Nanosponges to keep the mean particle size of the resulting nanosponges below 500 nm, pretreatment is necessary. After being suspended in water and sonicated to prevent the formation of aggregates and particles, the nanosponges were centrifuged to extract the colloidal fraction. Following the separation of the supernatant, the material was frozen and dried. The next step involves creating an aqueous suspension of nanosponges and dispensing excess medication to keep the suspension constantly stirred for a predetermined amount of time. Once complexation is complete, the undissolved drug (also known as the un complex condition) is separated from the complexed drug using centrifugation. Through solvent evaporation or freeze drying, this method aids in the development of solid nanosponge crystals. Crystal nanosponges are crucial for drug complexation. When compared to crystalline nanosponges, para-crystalline nanosponges showed varying loading capacities. Poorly crystalline nanosponges acted as a mechanical mixture rather than an inclusion complex when loading drugs. (9)

### 4.Ultrasound Assisted Synthesis

Without a solvent, the interaction between the polymer and cross linkers is permitted. The interaction is caused by the ultrasonic waves. The size produced by this method will be

homogeneous and spherical. Important factors that must be optimized include the ratio of polymer to crosslinker, water bath temperature, and sonication duration. (10)

**5.β-Cyclodextrin (βCD) NS acts as a drug carrier**

Due to the truncated cone structure, cyclodextrins can be easily utilized for drug ensnarement. NS are formed by reacting cyclodextrin and a suitable cross-linking agent like carbonyl diimidazole, diisocynates. The average diameter of developed NS is less than 1 micrometer. Various cross-linking agents modify crucial characteristics of the final nan-porous polymer such as swellability and hydrophilicity & hydrophobicity. (11)

**6.Emulsion solvent diffusion method**

Emulsion solvent diffusion is a two-step method that uses polyvinyl alcohol and ethyl cellulose. Ethyl cellulose & Drug is dissolved in dichloromethane is continues phase then the aqueous solution of polyvinyl alcohol is added to it by keeping the mixture at a magnetic stirrer at a speed of 1000 rpm for 2 hours. After stirring thorough the reaction is completed and NS are collected by filtration and drying at $40^0$C. (12)

**7.Quasi-emulsion solvent method**

In this method, different quantities of NS can be developed by using the polymer. Eudragit RS 100 is used to prepare the internal phase and added to a reasonable dissolvable. The drug to be incorporated is prepared as a solution and ultrasonicated at 35°C to dissolve it. This inner phase is then added to an external phase that contains polyvinyl alcohol, which acts as an emulsifying agent. The mixture is then blended at 1000–2000 rpm for three hours at room temperature before being dried for 12 hours in a hot air oven at 40°C. (13,14)

**Factors Influencing nanosponges Formulation**

**Type of polymer**

Type of polymer used can affect the formation along with the performance of Nanosponges. For complexation, the cavity size of nanosponge should be capable to take in a drug molecule of size.

**Type of drugs**

Drug compounds that are to be complexed with nanosponges must possess specific properties.

- The drug's molecular weight should fall between 100 and 400 Dalton's.
- Water solubility is less than 10 mg/ml.
- The number of condensed rings in a drug molecule should be less than five.
- The material has a melting point below 250°C. (15)

**Temperature**

Drug/Nanosponge complexation can be altered by temperature changes. As a result of potential decreases in drug/nanosponge contact forces, such as van der Waal forces and hydrophobic forces, the distinct stability constant of the drug/nanosponge complex generally decreases as the temperature rises.

**Method of preparation**

Loading drug into nanosponge can alter Nanosponge/drug complexation. Anyhow, the efficacy of a method based on the nature of the drug and polymer, in numerous cases freeze drying was built to be most effective for drug complexation.

**Degree of substitution**

The complex capacity of the nanosponge may be much influenced by kind, amount, and placement of the substituent on the parent molecule (16).

**EVALUATION OF NANOSPONGES**

**Solubility studies**

Several commonly utilized methods to learn inclusion complexation is the stage solubility process reported by Higuchi and Connors, which inspect the result of a nanosponge, on the solubility of drug. stage solubility figures show the degree of complexation (17).

**Infra-Red spectroscopy**

Infra-Red spectroscopy is utilized to guess the interaction in the middle of the drug molecules and nanosponges in the solid state. Nanosponge bands frequently change only moderately upon complex formation and if the fragment of the guest compound encapsulated in the complex is lower than 25%, bands which could be allocated to the incorporated part of the guest molecules are smoothly cover up by the bands of the spectrum of nanosponges. The method is not normally acceptable to determine the inclusion complexes and is fewer purifying than other approaches (18).

**Loading efficiency**

The loading efficiency of nanosponges can be resolved by the numerical estimation of drug loaded into nanosponges by HPLC and UV spectrophotometer methods.

**Microscopy studies**

Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM) can be utilized to study the microscopic characteristics of the drug, nanosponges and by-product (drug/nanosponge complex). The variation in crystallization state of the basic material and by product observed lower electron microscope shows the formation of the inclusion complexes. (19)

**Particle size, polydispersity and Zeta potential**

The particle size can be decided by energetic light scattering utilizing 90 Plus particle sizer equipped with MAS OPTION particle sizing software. From this the mean diameter and polydispersity index can be established. Zeta potential is an estimation of surface charge. It can be estimated by utilizing extra electrode in particle size instruments (19).

**The structure and chemistry of nanosponges**:

Cyclodextrin NSs often exhibits monodispersed particles with an average diameter of less than 1 μm and a very low polydispersity index. With high, typically negative, zeta potential values and swelling characteristics that really on the cross-linker utilized during synthesis and the ratio of cyclodextrin to the cross-linker, the NSs are extremely stable. The NSs swelling properties are also influenced by the cross-linker's branching and the attachment of basic and acidic groups. The porosity and surface area can be affected by the cross-linker concentration. The cyclodextrin-based NSs exhibit distinct peaks in FTIR spectroscopy and are thermally stable up to $300^0$C.

In a different study, tiny mesh-like structures made of porous three-dimensional nano-catalysts were created to determine the uses of β-cyclodextrin NSs. Several aromatic aldehydes with activated methylene compounds, such as thiobarbituric acid, 4-hydroxy-6-methyl-2-pyrone, dimedone, 4-hydroxycoumarin, and nucleophiles including amines and indole, were subjected to a one-pot condensation process with three components. When 1,1′-carbonyldiimidazole and the β-cyclodextrin monomer interacted, cross-linked NSs were produced, to which 3-substituted indole moieties were added. The synthesis of 3-substituted indole moieties was carried out using the Yonemitsu-type condensation reaction, which involved the reaction combination of indole (0.117gr, 1 mmol), 2-chloro benzaldehyde (0.14 gr, 1 mmol), and dimedone (0.14 gr, 1 mmol).

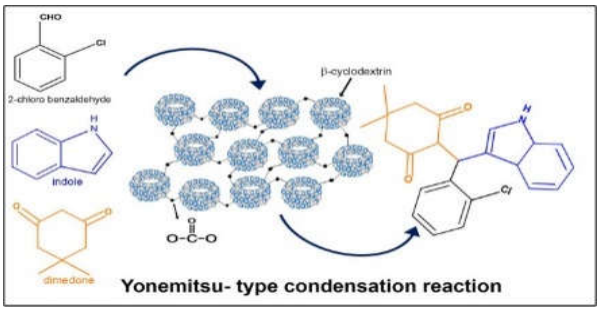



Fig no.1. Yonemitsu-type condensation reaction

**Drug loading into nanosponges**

The size of the particle, which should be less than 500 nm, is the primary determinant of drug transport into NSs. The produced NSs were suspended in the aqueous phase; they were sonicated and centrifuged for the colloidal fraction to stop the particles from aggregating. The supernatant was then separated and dried using a freeze-dryer. The aqueous suspension was separated to create NSs. After adding the extra medication, they were continuously stirred for a while until a complex formed. The undesirable medication was now eliminated by centrifugation**.** Lastly, either solvent evaporation or freeze-drying the solid crystals produced the NSs. The complexation between the medication and the NSs crystal structure is crucial. Compared to crystalline NSs, Para-crystalline

NSs have higher loading capabilities. In crystalline forms, drug loading takes place as an inclusion complex; in weak crystalline NSs, drug loading takes place as a mechanical mixing.

## Applications of Nanosponges

### Nanosponges as a sustained delivery system

It is one of the largely utilized as antiviral agent for the treatment of herpes simplex virus infection. Nanosponge absorption in the Gastrointestinal tract is prolonged and uncomplete and highly wavering. The in vitro release profile of the acyclovir from dissimilar types of Nano sponges appeared sustained release of the drug.

### Enhancement of Solubility

Nanosponges can be used to improve the aqueous solubility and dissolution profile of poorly soluble by drugs by forming the inclusion complex while ac encapsulation. The insoluble nature of nanosponges prevents supersaturation and promotes the protection of entrapped drugs from agglomeration and precipitation. Nanosponges can incorporate both hydrophobic and hydrophilic drugs. The hydrophobic drugs are associated with the interior hydrophobic cavities whereas hydrophilic drugs occupy the external hydrophilic cavities. Lower drug crystalline and higher thermodynamic energy result in increased drug dissolution and bioavailability. In the study, Vavia and co-workers successfully increased the solubility of Itraconazole by about 20-fold by entrapping the drug into the nanosponge formulation. Phase solubility study copolyvidonum, nanosponge, and their combination was performed to compare the solubility efficacy of nanosponge formulation (13). Besides, Itraconazole other BCS class II drugs in which this approach has been successfully applied include Doxorubicin, Paclitaxel, Flurbiprofen, and Dexamethasone, etc.

### Cancer Therapy

Since NS productions are three to five times more effective than direct injection of medications at reducing tumor development, they play a significant role in drug delivery, especially in the treatment of cancer. The sponges were then injected into the body, where they interact with the cancer cells, adhere to their surface, and become part of the cell. From there, they release their medication at a steady pace. As a result, anticancer medications loaded with NS were exhibiting enhanced anticancer activity.

### Topical Agents

NS is an essential technology for the prolonged and regulated release of medications that are retained in the skin. Traditional personal care and dermatological products typically include active ingredients in quite high concentrations, but they also have very short half-lives. These recur frequently, for example, with a brief overdose followed by a prolonged underdose. Rashes and other adverse effects may result from the active components' penetration of the skin. In contrast to

this technology, the NS-based drug delivery system reduces discomfort while maintaining efficiency by enabling a consistent and constant rate of drug release.

**Protein Delivery**

NS serves as the vector for delivering proteins, enzymes, antibodies, and vaccinations in drug delivery systems to aid in diagnosis resolution. The most common NSs for adsorbing proteins, macromolecules, enzymes, and enzymes are cyclodextrin-based NSs. These carriers may help protect the protein in vivo by altering its pharmacokinetics, enhancing its stability, and halting its degradation. The pH, temperature, and series of reactions of some enzymes may be extended, their activity can be conserved, they can withstand the behavior of continuous flow methods, and they are efficient. Proteins and other macromolecules, including the useful industrial enzymes trypsin, alpha amylase, cellulase, and pectinase, were encased in cyclodextrin NS. Proteins have problems with long-term preservation and maintain their natural structure during manufacturing.

**Nanosponge as Chemical Sensors**

In a recent work, nanoparticle-based NS was used to examine the fluorometric detection of environmental pollutants, such as volatile organic compounds (VOCs) like xylene. The NS sensor, which is composed of polythiophene and nanoparticles, was able to detect xylene at levels as low as 7 parts per million.

**In Agriculture**

The technique used to grow the plant plays a significant effect in how it looks, in addition to the climate. In agriculture, the development of functionalized nanosponges (FNS) has improved plant growth and appearance by providing the right number of micronutrients and active chemicals, which are critical for the plants' healthy development.

**The cosmetics industry**

For components in cosmetics that are susceptible to photodegradation, NSs offer good protection. It can catch up and extend the volatile oil leak, dude. Sweating produces an unpleasant bodily odor that can also be absorbed. It can gradually release volatile chemicals, giving oral cosmetics a persistently fresh feel. For a longer-lasting effect, it can also be used on lipsticks and rouge.

**Conclusion**

Nanotechnology has minimized all the processes at the nanometric scale. The multifaceted approach of nanotechnology has led to the development of many formulations that are advantageous over the other conventional formulations. The application of technology has led to the utilization of many software used for the optimization of formulations. The obstacles in formulation development such as the burst effect, stability problems, and drug loading issues can be overcome by employing these miniature systems as drug delivery carriers. The degree of crosslinking is varied to optimize the viscoelasticity of the desired formulation. The stimuli-activated nanosponges and molecularly imprinted nanosponges can be employed for effective drug targeting. Nanosponges find their applications as the carriers of both lipophilic and hydrophilic

drugs, carriers of protein, peptides and enzymes, biomarkers, and, purifiers also in the field of cosmetics. The future research goals must be to reduce the cost of synthesis of nanosponges on a large scale and also to avoid the adverse effects of the polymers employed.

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