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A REVIEW ON NANOSPONGES: A REVOLUTIONIZING DRUG DELIVERY SYSTEM

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Abstract:
Nano sponges are minuscule sponges that have the ability to move throughout the body and adhere to the surface, therefore facilitating the regulated and predictable release of substances. The development of a medication delivery system based on nanosponges has been a major advancement in the treatment of some biopharmaceutical problems. A polymer-based sphere called a nanosponge may be used to apply medicine topically or orally. One important step in solving these issues is the development of nanosponges. Nanosponges are microscopic sponges that resemble viruses in size and may hold a broad range of medications inside them. Many different medications may be inserted into nanosponges for targeted drug delivery. Drugs that are hydrophilic or lipophilic may be added to nanosponge. Their aqueous solubility is another noteworthy characteristic that makes it possible to utilize them more often for medication with limited solubility, improving bioavailability, lowering drug toxicity, and halting drug breakdown. This work aims to elucidate the general introduction, properties, preparation process, characterization, and uses of nanosponges.
Keywords: Nanotechnology, nanosponge, bioavailability, drug delivery.

Introduction:

Nanotechnology is the study of materials containing nanometre-sized particles. The term "nano" is derived from the Latin word "dwarf" (1nm = 10-9m). Nanomedicine uses manmade nanostructures and devices to monitor, regulate, repair, and enhance the human biological system at the molecular level.[1] Drug delivery technology has rekindled interest in pharmaceuticals by enabling therapeutic targets. Researchers are now focused on addressing the challenge of targeted medicine delivery. Therapeutics will focus on target-oriented medication delivery to increase

efficacy, minimise negative effects, and optimise dose regimens.[2] (1)Nanoparticles come in various forms, such as polymeric, solid-lipid, nanoemulsion, nanosponges, carbon nanotubes, micellar systems, and dendrimers. The chemical is easily carried for parenteral administration in sterile water, saline, or other aqueous solutions. Topical hydrogels can effectively deliver them.[2] Nanosponges are nanoparticles that contain medicinal molecules inside their core. Nanoparticles may be categorised into three types based on their drug association: encapsulating, complexing, and conjugating. The first kind consists of nanosponges and nanocapsules. Alginate nanosponges are sponge-like nanoparticles with many pores to transport medicinal molecules. Poly(isobutyl-cyanoacrylate) (IBCA) Nano capsules can also encapsulate nanoparticles. They can hold medicinal molecules in their watery core. The second group is complexing nanoparticles, which attract molecules by electrostatic charges. The third kind is conjugating nanoparticles, which bind to medicines via covalent bonds.[3]

Nanosponges can enhance the water solubility of lipophilic medicines, preserve degradable molecules, and provide drug delivery methods beyond oral administration. Polymers and cross linkers have simple chemistry, making them easy to prepare and scale up to commercial manufacturing. Nanosponges are water-soluble yet do not dissolve chemically in water. They combine with water and serve as a transportation fluid. They may hide disagreeable flavours and transform liquids into solids. Chemical linkers allow nanosponges to preferentially connect to their target sites.[4]

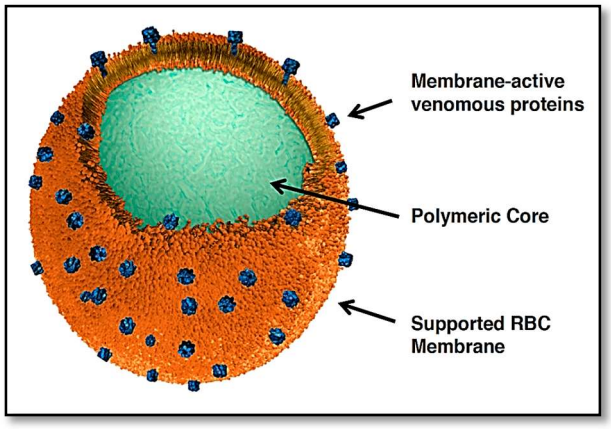


Figure 1: Structure of Polymer based Nanosponge

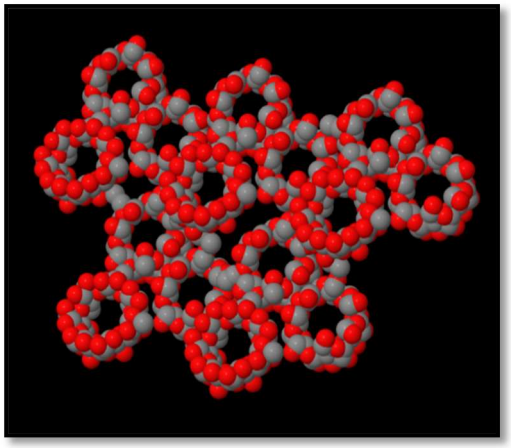


Figure 2: Molecular Structure of Cyclodextrin Based Nanosponge

Characteristics of Nanosponge: [5, 19]

- Nanosponges capture components, reducing harmful impacts.
- It stable over pH ranges from 1 to 11.
- It can endure temperatures up to 1300 °C.
- Their small hole size (0.25m) prevents germs from penetrating, making them self-sterilizers.
- They are cost effective and freely flowing.
- They enhance the solubility of poorly soluble medicines.
- They improve the bioavailability of drugs.

Merits of Nanosponges: [6]

1. It increases the surface area.
2. It improves solubility
3. Higher rate of disintegration
4. Increased oral bioavailability.
5. Reduces dosage and number of doses.
6. Protecting the medicine against deterioration
7. Faster start of therapeutic action
8. Successful drug targeting
9. Drugs are passively targeted to macrophages in liver and spleen.

Demerits of Nanosponges:

1. Nano sponges can only contain small molecules.
2. The degree of crystallization influences drug-loading capability. For example, crystalline and para-crystalline cyclodextrins have varying drug-loading capacities in the context of cafadroxil Nano sponge.

Various factors that affect the creation of Topical Nano sponges: [7]

Polymer:

The type of polymer impacts the creation of Nano sponge. To build a complicated cavity size of the polymer must be suitable to incorporate a medication molecule of a specified size. The particle size of the polymer should likewise be in nanometres size.

Drug molecule

A drug molecule needs certain characteristics, such as a molecular weight between 100 and 400, in order to form a compound with a polymer. Its melting temperature must be below 250° C, its water solubility must be less than 10 mg/ml, and it must have less than five condensed rings.

Temperature

The apparent stability constants of the drug and polymer combination decrease in magnitude with increasing temperature. It could lessen the forces that interact between the medication and the polymer.

Method of preparation

The drug, polymer, and cross-linker that are employed determine how efficient the various formulation techniques are; generally, in freeze-drying has been shown to be safer than vacuum-drying for drug and polymer complexes.

Degree of substitution

The quantity, kind, and location of substituents on the main medication and polymer chain determine the nanosponges ability to complex.

Table 1: Components used in preparation of nanosponges

Polymer	Copolymer	Cross linkers	Polar solvents
Methyl β-Cyclodextrin	Ethyl cellulose	Di-aryl-carbonates	Dimethylformamide
Hyper Crosslinked Polystyrene Cyclodextrin (alkoxy carbonyl cyclodextrins)	Poly (Valero lactone allyl Valero lactone)	Carbonyl diimidazole	Ethanol
Hydroxy propyl β-cyclodextrin	Polyvinyl alcohol	Dichloromethane	----------
Eudragit RS100	----------	Glutaraldehyde	----------

Types of Nanosponges:

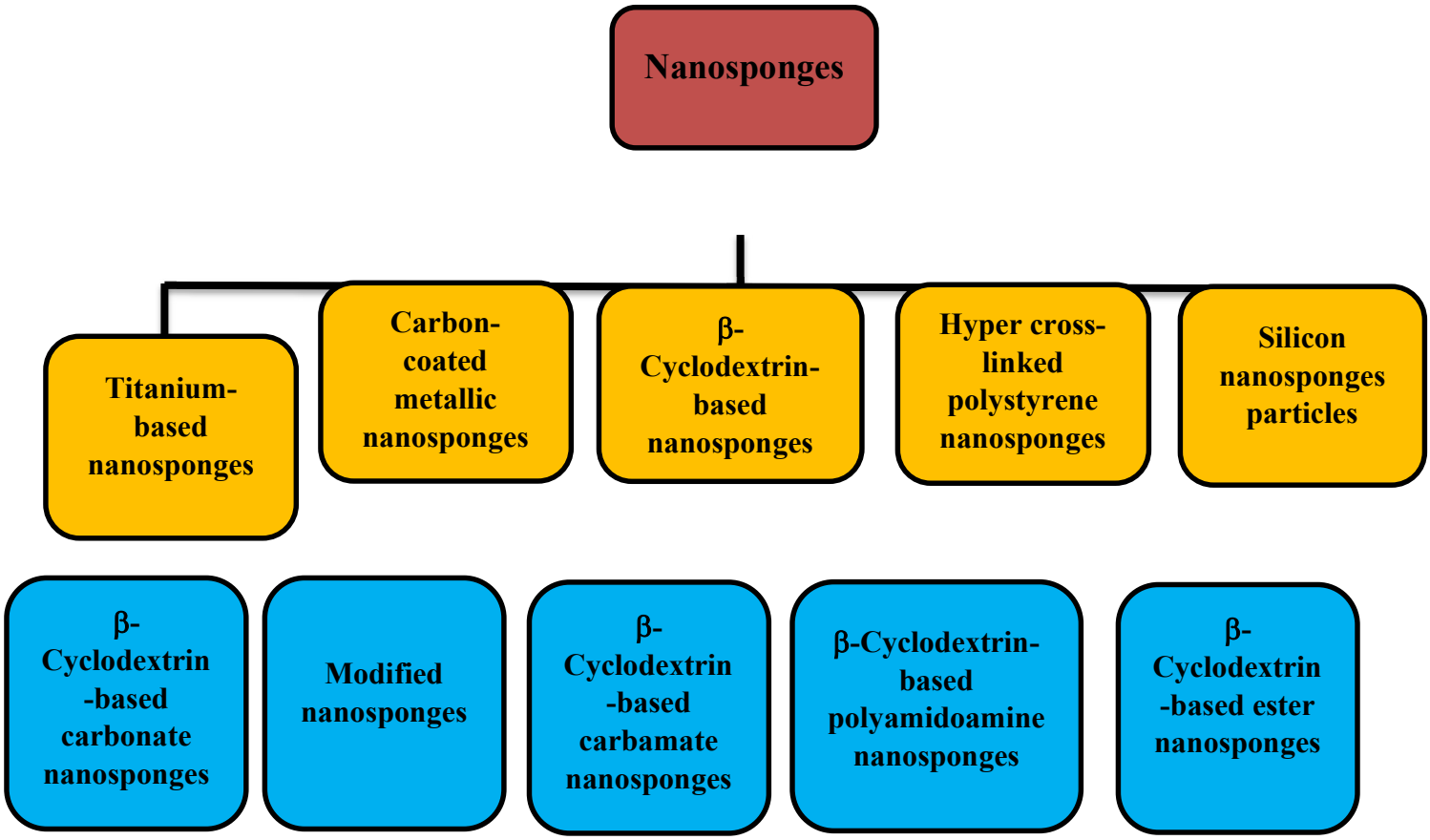


Figure 3: Types of Nanosponges

Composition of Nanosponges:

1. Polymer and copolymers

The creation and functionality of nanosponges may be impacted by the polymer selection. The size of the cavity has to be suitable for inserting the particular drug molecule. The medication to be encapsulated and the required release dictate which polymer is used. The polymer of choice must be able to bind to the designated ligands.

Example: Nanosponges are made from a variety of polymers, including methyl cyclodextrin, ethyl cellulose, and PVA.[8]

2. Cross linking agents

The polymer's structure and the medication that will be manufactured might be taken into consideration while choosing the cross-linking agent. One may produce water soluble or insoluble nanosponge structures depending on the sort of cross linkers that are employed.

Examples include epichloridrine, glutaraldehyde, diphenyl carbonate, di-methyl carbonates, isocyanates, pyromellic anhydride, carbonyl-di imidazoles, 2,2-bis(acrylamido) acetic acid, and dichloromethane.[2]

Method of Preparation:

There are various methods of preparation of Nanosponges:

1. Emulsion solvent diffusion method.
2. Solvent method.
3. Ultra-sound assisted synthesis.
4. Hyper crosslinked β-cyclodextrin.

1. Emulsion solvent diffusion method:

This technique uses two phases, the organic phase and the aqueous phase in varying ratios. Polyvinyl alcohol (PVA) is present in the aqueous phase, whereas the medicine and polymer are present in the organic phase. The aqueous phase is gradually filled with a mixture of the drug and polymer dissolved in an organic solvent. After that, the combination is thoroughly agitated for two hrs at 1000 rpm. The resulting nanosponges were gathered using filtering and then dried for 24 hrs at 40°C in an oven. Ultimately, in order to guarantee that all remaining solvents were eliminated, the dried out nanosponges were kept in a vacuum desiccator.[1, 2]

2. Solvent method:

Using this method, nanosponges are prepared by mixing suitable polar aprotic solvents like Dimethyl sulfoxide (DMSO), Dimethylformamide (DMF) with the polymer. Then, a crosslinker is then added to this mixture in the ratio of 1:4. The above reaction is carried out at a temperature of 10°C to reflux the solvent temperature for a period of 1 to 48 hours. Once the reaction has completed, the solution is cooled down at room temperature and then obtained a product is added to bi-distilled water. The product is recovered by filtering the product under vacuum and refining by Soxhlet extraction with ethanol followed by drying.[2, 5]

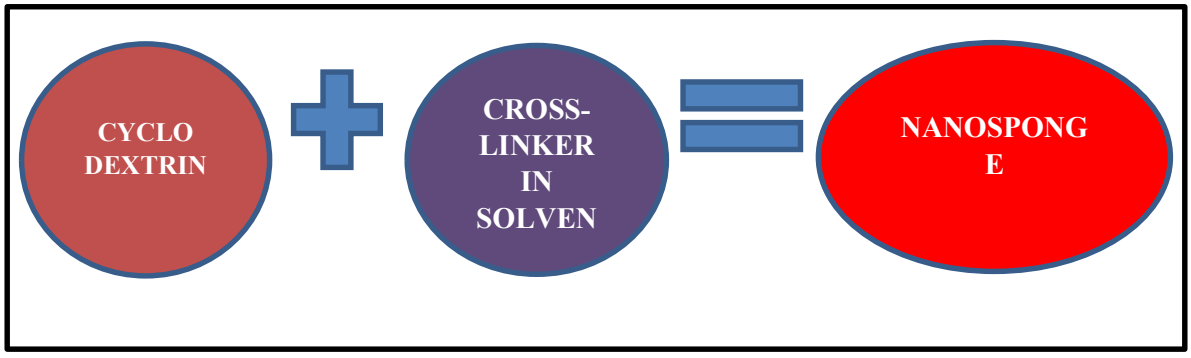
3. Ultra-sound assisted synthesis:

In this method, nanosponges can be obtained by reacting polymers with cross-linking agents in the absence of solvent and sonication. The obtained nanosponges will be spherical in shape, uniform in size and less than 5 microns in diameter. In this method di-phenyl carbonate (or) pyromellitic anhydride is used as cross-linking agent. Here, mix the polymer and cross-linker in a flask. Place the flask in an ultrasound bath filled with water and heat it to 90° C and sonicate the mixture for 5 hours. The solids are then ground in a mortar and the Soxhlet is extracted with ethanol to remove impurities (or) unreacted polymers. After purification, the nanosponges were stored at 25° C. [1]

4. **Hyper crosslinked β-cyclodextrin:**

Nanosponges are obtained by reacting cyclodextrin with a cross-linking agent such as di-isocyanates, di-aryl-carbonates, dimethyl carbonate, diphenyl carbonate, and carbonyl di-imidazole, carboxylic acid dianhydrides and 2, 2-Bis (acrylamido) acetic acid. The surface charge density, porosity and pore size of sponges can be controlled to attach different molecules. Nano sponge with low cross-linking agents gives a fast drug release. They are used to improve the aqueous solubility of poorly-water soluble drugs, mainly BCS class II drugs.

β-cyclodextrin nanosponges are prepared by placing 100 ml of dimethyl formamide (DMF) in a round bottom flask and adding 17.42 g of anhydrous β-CD to achieve complete dissolution. Then, this solution is added to 9.96g of carbonyl di-imidazole (61.42 m mol) and allowed to react for 4 hours at 100°C. After condensation polymerization was completed, the transparent block of hyper cross linked cyclodextrin was roughly ground and an excess of deionised water added to remove DMF. Finally, the remaining by-products or unreacted reagents were completely removed by Soxhlet extraction with ethanol. The resulting white powder thus obtained was dried overnight in an oven at 60°C and ground in a mortar. Water is used to disperse the fine powder that had been obtained. The colloidal part of the solution that remained suspended in water is extracted and lyophilized. The resulting obtained nanosponges are sub-micron in size with a spherical in shape.[1, 2]



Characterization of Nanosponges:

The drug and the nanosponge can be characterized by using the following methods.

1. **Thermo-analytical methods:**

Thermo-analytical analysis evaluates whether the drug or substance changes before the nanosponge is thermally degraded. Melting, evaporation, decomposition, oxidation and polymorphic conversion are examples of transformation of drugs into substances. The presence of a change in the drug substance means the formation of a complex. The expansion, displacement of water and the appearance of new peaks or the elimination of some peaks can be

detected in the thermogram obtained by DTA and DSC. Changes in weight loss can also be used as evidence for the formation of inclusion complexes. [9]

2. Microscopy studies:

The microscopic characteristics of medications, nanosponges, and other products (nanosponge/drug complexes) may be studied using, Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM). Even if the raw material's crystallization state seems to vary, differences between the raw materials' and the product's states as seen under an electron microscope suggest the creation of inclusion complexes. Using the co-precipitation process, raw materials and products were obtained.[10,11]

3. Particle size determination:

One crucial factor during the nanosponge optimization procedure is the size of the nanoparticles. Both the release and solubility of a medication may be impacted by its particle size. Particle size may be measured using a Zeta sizer or a laser light diffractometer. Plotting the total percentage of drug release from nanosponges with varying particle sizes over time may be used to study how particle size affects drug release. For topical medication delivery, nanoparticles between 10 and 25 m are better appropriate since bigger particles might feel grainy.[4]

4. Thin Layer Chromatography:

In Thin Layer Chromatography (TLC), the Rf value of the drug molecule reduced dramatically, which helped detect the complex formation between the drug and the nanosponge. There is a reversible mechanism involved in the inclusion and complexation of host and guest molecules. Hence, only spots of the guest and host molecules are observed on the TLC plate, indicating that the complex may completely separate into guest and host molecules during chromatography.[2, 3]

5. Zeta potential determination:

The difference in potential between the fluid's immobilized layer and dispersion medium layer, which are both surrounded by scattered particles, is known as the zeta potential. The primary metric used to assess the stability of colloidal dispersion is the zeta potential. The zeta potential may be determined by incorporating an extra electrode into the particle size apparatus or zeta seizer. The higher the zeta potential value of a colloidal dispersion, the higher its stability.[5,12]

6. Infrared (IR) spectroscopy:

The interaction between drug molecules in the solid state and nanosponges is estimated using infrared spectroscopy. It often varies when a form is complex and if a little amount of the molecule is included in a complex with a bond strength of less than 25% that is designated to incorporate a part of another molecule that is identified by spectral bands on nanospheres. The

use of IR is restricted to certain medications that include bands or characteristics like sulfonyl or carbonyl groups. Information regarding hydrogen in different functional groups is included in infrared investigations. As a result, the absorption band intensifies and shifts to lower frequencies. The stretching vibrations of the group involved in the creation of hydrogen bonds cause the bands to widen.[6,11]

7. **X-ray diffractometry and single crystal X-ray structure analysis:**

- Complexes in the solid state are found via X-ray powder diffractometry measurements. When we think of a liquid, it is quite different from a simple nanosponge and lacks its own diffraction pattern. In the event that the drug is a solid, the diffraction pattern should be compared between the mechanical combination of the dry material and the hypothetical complex, which modifies the diffraction pattern. A physical mixture's diffraction pattern is the outcome of the interaction of two elements. However, the complexes form a "new" solid phase with a distinct diffraction arrangement, and their diffraction pattern is fundamentally different from that of the element they contain. They result in different mixture peaks and are helpful in figuring out complicated formation and chemical breakdown.
- **Analyzing an individual crystal X-ray spectrum:**
  It can also be used to identify the inclusion structure and how it interacts. The interactions between the host and foreign molecules can be precisely determined and the exact relationship can be established.[6, 11]

8. **Solubility studies:**
   The phase dissolution method is the most widely used technique to analyse inclusion and complexation because it looks at how nanosponges affect medication solubility. The phase dissolution diagram indicates the degree of complexity.[2,13]

9. **Loading efficiency:**
   The effectiveness of loading of nanosponge complex should be dissolved in a suitable solvent, sonicated to disrupt the complex, diluted appropriately and then analysed by UV spectroscopy and HPLC.[6,9,11]

Applications of Nanosponges:

Nanosponges for drug delivery

Because nanosponges are nonporous, they may be used to administer medications that are insoluble in water. Drugs may dissolve more quickly using nanosponge, which may also improve their solubility and stability, mask unpleasant odors, and change liquids into solids. It has been observed that cyclodextrin-based nanosponges deliver drugs to the intended location more effectively than direct injection. Because nanosponge is solid, it may be created in dosage forms for oral, parenteral, topical, or inhalation. They may be combined to create tablets or capsules for oral administration by mixing them with lubricants, diluents, excipients, and anti-caking agents.

For parenteral administration, they may be carried in sterile water, saline, or other aqueous solutions. For topical administration, they might be mixed to create a topical hydrogel.[14]

Nanosponges for cancer therapy

Distribution of anticancer medications is one of the most difficult tasks in the pharmaceutical industry today due to their low solubility. One study found that the combination of nanosponge and injection is three times more effective in preventing the growth of tumors than straight injection. After a complex process of loading the nanosponge with a medication, a particular peptide is firmly attached to a top layer of radiation-induced cells on the cancer receptor. The nanosponges adhere to the surface of cancer cells upon contact and start to release therapeutic chemicals. One advantage of targeting medicine delivery is that it may have a greater beneficial pharmacological action at identical dose with minimum side effects.[15]

Nanosponges for delivery of protein

Using bovine serum albumin as a model protein, the encapsulating capacity of β-cyclodextrin-based nanosponges was assessed. Because the protein solution containing bovine serum albumin is unstable, it is stored in lyophilized form. When proteins are lyophilized from their native structures, they may change into denatured forms. The primary drawback for protein formation and research is the need to preserve its natural structure throughout long-term storage both before and after processing. Nanosponges may improve the stability of proteins such as bovine serum albumin (BSA) when they are distributed using cyclodextrin-based technology. Additionally, enzyme immobilization, protein encapsulation, controlled delivery, and stabilization have all been accomplished using nanosponges.[16]

The role of nanosponges in fungal infection treatment

Fungal diseases of the skin are among the world's most serious ailments. Because topical therapy offers so many advantages over systemic side effects, including the ability to customize medicines to reach the sickness site directly, it is a promising therapeutic alternative for skin illnesses. Class II biopharmaceuticals, such as itraconazole, are antifungal medications with limited bioavailability and a delayed breakdown rate. It has been discovered that itraconazole nanosponges ameliorate the bioavailability issue and increase its solubility. When itraconazole is put into these nanosponges with cyclodextrin acting as a carbon cross, the solubility of the itraconazole may be improved.[16]

As absorbent in treating poison in blood

Through toxin absorption, nanosponges may eliminate harmful substances from our blood. If we introduce nanosponges into the bloodstream, we can use them to absorb poisons instead of employing antidotes. The nanosponge imitates a red blood cell in the circulation, deceives poisons into attacking it, and then absorbs them. The poison determines how many molecules of the toxin each nanosponge can absorb.[17]

To enhance the low solubility of drugs

Poor solubility is the most crucial problems to deal with the design and development of materials. Problems with the solubility of medications may compromise a formulation's effectiveness. Molecules are carried by nanosponge, which encapsulates them in its core and works to increase the formulation's solubility. Currently, a cyclodextrin nanosponge is used to increase solubility.[18,19]

Table 2: Marketed preparations of Nanosponges:

S. No.	Drug	Method of preparation
1	Miconazole nitrate	Solvent evaporation technique
2	Cephalexin	Emulsion Solvent diffusion method
3	Isoniazid	Emulsion Solvent diffusion method
4	Tazarotene	Emulsion Solvent diffusion method

Conclusion:

This review has been shown that hydrophilic and lipophilic drugs may be encapsulated or accumulated using nanosponges as a drug delivery device by generating a complex. They are able to efficiently and under control administer the medication at the intended location. Topical preparations like lotions, creams, ointments, gel etc. may include nanosponges in liquid or powder form. This technology's benefit is that it targets the medicine to a particular spot, which lowers side effects, improves stability, increases formulation flexibility, and improves patient compliance. Moreover, nanosponges have applications in agrochemistry, biomedicine, cosmetics, bioremediation, and catalysis, among other fields.

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