Nanosponges: Unveiling the Potential of a Promising Drug Delivery System

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Abstract:

This review thoroughly examines the synthesis techniques, structural features, and functional properties of Nanosponges, highlighting their remarkable potential in diverse applications. Specifically, their ability to carry both hydrophilic and hydrophobic medications makes them valuable in overcoming challenges related to drug toxicity and poor bioavailability. Moreover, their porous network enables controlled release of therapeutic chemicals, enhancing their suitability for targeted drug delivery. Beyond medicine, Nanosponges exhibit promise in environmental cleanup, efficiently removing hazardous contaminants from water and air. Additionally, their catalytic characteristics hold potential for facilitating chemical transformations and sustainable energy applications, further underscoring their significance in scientific and technological advancements.

Key words: Nanosponges, Nanocarrier, Targeted drug delivery, Novel drug delivery systems.

Introduction:

Nanosponges (NS) are relatively new nanocarriers for medication administration that has resolved a number of medication delivery issues such as low bioavailability and toxicity. These nanostructures can convey both hydrophilic and hydrophobic medicines with precise targeting for specific drug delivery in conjunction with a stabilized release method.[1] There are many more possibilities for the use of nanosponges in medication administration than just cancer treatment; examples include oxygen carriers, enzyme and biocatalyst carriers, poisons absorbents, enzyme immobilisers and solubility enhancers . In addition, nanosponges can incorporate medications with hydrophilic and hydrophobic characteristics for a variety of disorders. Meanwhile, these

nanostructures are capable of conveying minor drug molecules and can be supplied in a variety of ways. The variety of polymer wrapings and their porosity make nanosponges suitable for holding drug molecules [2] .

Additionally, water solubility and straight chemistry of crosslinking peptides of NS enable engineering. Owing to many pores within the core architecture, the drug component can move freely, which ensures controlled drug release profiles. Owing to their small size, NSs are smoothed into topical hydrogels, or they are can be made into capsules or tablets that evoke oral delivery. NSs are a completely innocent material for both invasive and oral delivery.[3]

Advantages:

Nanosponges present the following advantages when used as drug delivery approach:

- **Biocompatibility and Biodegradability** : As nanosponges are highly biocompatible and biodegradable, it is appropriate for this technology to be used in the biomedical domain.
- **Low Cytotoxicity:** The low cytotoxicity of nanosponge can impact its applicability in the biomedical setting to a great extent.
- **Prevention in Drug Degradation:** As such a technology can prevent drug degradation, it impacts the abilities of pharmaceuticals to remain stable and effective.
- **Increased Drug Solubility and Stability:** This attribute of nanosponges can simplify the delivery of the drug by ensuring that the respective substance is more soluble and stable.
- **Predictable Release Behavior:** Nanosponges offer predictable release behavior, mitigating the burst effect often observed in other systems and ensuring more accurate dosages[4].
- **Versatile:** The duration of action and drug residence time of nanosponges can be adjusted, and they can be used for both hydrophilic and lipophilic drugs [5].
- **Controlled Drug Administration:** Nanosponges can be used for target drug administration with controlled release patterns [5].
- **Environment-Friendly Manufacturing:** Research is being done for the sustainable and green manufacturing process of nanosponges [4].

All these features of nanosponges help to overcome bioavailability and toxicity issues of drugs. This usage of nanosponges makes them a good candidate for cancer therapy and drug delivery in general.

Disadvantages of   Nanosponges for Drug Delivery:

- One drawback of nanosponges is that they can only contain small drugs because larger molecules might fail to fit through the narrow pores upon.
- Large-scale manufacturing of chemicals has historically been complex. In contrast, nanosponges composed solely of polymer and crosslinkers offer a simpler, more scalable solution for commercial production.
- The level of crystallinity in nanosponges affects their drug holding and trapping capabilities.

- As nanosponges are being used across industries, it's important to investigate the toxicity risks when they come into contact with cell membranes, which could lead to harm in different parts of the body.
- To make nanosponges suitable for tumor targeting they must be modified to target tumors.

These challenges highlight the need for further research and development to improve the efficiency and adaptability of NS based drug delivery systems along, with addressing some drawbacks and obstacles associated with them.

Structure of nanosponges:

A few nanometers, a mini-scale void, and microscopic molecules make up the contemporary material known as a "nanosponge." These nanoparticles can carry both polar and non-polar therapeutic ingredients, which increases the stability of lipophilic pharmacological compounds or molecules. The polyester nanosponges function as a natural degradable 3D scaffold, or backbone, within the matrix. Nanosponges are created by mixing these polyesters with a cross linker because it is typically biodegradable, polyester disintegrates somewhat in the body. A negative release of the drug molecules is caused when the structure of the micro sponges opens[7].
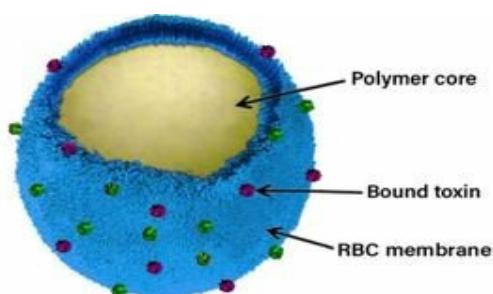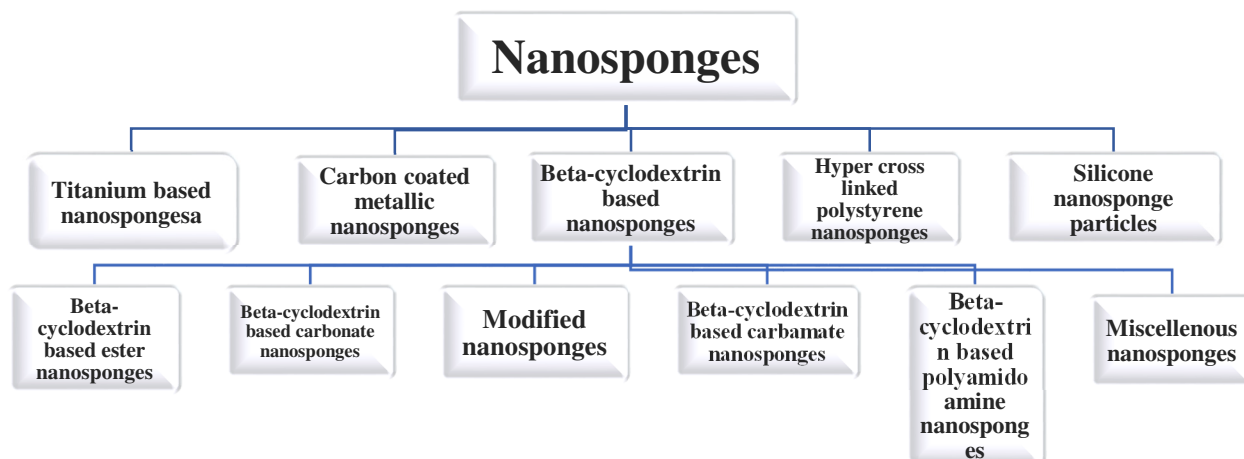

Fig 1: Nanosponge[7]

Types of Nanosponges:
Various types of NS exist. Differences depend on polymer, concentration, and preparation method. The most common are beta CD-based NS. For beta-CD NS, formulation is straightforward with diverse- modifications possible.

Nanosponges

- Titanium based nanospongesa
- Carbon coated metallic nanosponges
- Beta-cyclodextrin based nanosponges
- Hyper cross linked polystyrene nanosponges
- Silicone nanosponge particles

Beta-cyclodextrin based nanosponges:
- Beta-cyclodextrin based ester nanosponges
- Beta-cyclodextrin based carbonate nanosponges
- Modified nanosponges
- Beta-cyclodextrin based carbamate nanosponges
- Beta-cyclodextrin based polyamido amine nanosponges
- Miscellenous nanosponges

Composition of nanosponges:

There are five main parts of nanosponges:

A. Polymer   **B.** A cross-linking facilitator   **C.** Sodium surfactant   **D.** Active pharmaceutical ingredient and Solvent

A. Polymer :The rate at which nanosponges form and release material can be influenced by the type of polymer that is utilized. The polymers are used to encapsulate the active drug moiety or to interact with the medicinal substance. A medication molecule of a particular size should be able to enter the nanosponge's cavity for complexation. The ability of the polymer to cross-link is impacted by the replacement of functional and active groups. To transport medications to the right areas at the right times, the polymer must have the ability to bind to the appropriate ligands. **Ex**: Ethyl cellulose, Eudragit, and Polymethyl methacrylate.[8]

B. Crosslinking agent: Crosslinking agent selection is influenced by the medication of choice as well as the chemical composition of the polymer. Dichloromethane is the most widely used crosslinker for topical treatments. Particle size and drug entrapment in the polymers both increased when internal phase volume grew in an unobservable manner as a result of the internal phase viscosity decreasing. The nanosponges with the best trapping effectiveness were made using 20 milliliters of dichloromethane.
Ex:methanol, ethanol, and dichloromethane. [8]

C. Surfactants: Polyvinyl alcohol is generally employed as a surfactant in the manufacturing process to create nanosponges with lower particle sizes. Research revealed that the particle size increased in tandem with the surfactant content. Aggregates are produced as a result of foaming brought on by higher surfactant concentrations. The efficacy of drug entrapment declined as surfactant concentration rise. This may be the result of insufficient concentrations of the drug's particular polymer for particle encapsulation.[9] **Ex:** Dichloromethane, ethanol, and polyvinyl alcohol

D.Active Pharmaceutical ingredient: The following qualities of drug molecules need be present in order for them to be manufactured into nanosponges: Molecular weight in the range of 100–400 Daltons. There should be no more than five condensed rings in a drug molecule. Molecules should only dissolve in water at a rate of 10 mg/ml. The active moiety's melting point needs to be lower than 250°C. [8]

E. Solvent: The only solvent utilized in the production of nanosponges is water. The temperature and volume of the solvent used in the final stage of nanosponge synthesis are critical factors that affect both the production yield and the pore diameter on the surface of the nanosponges. [8]
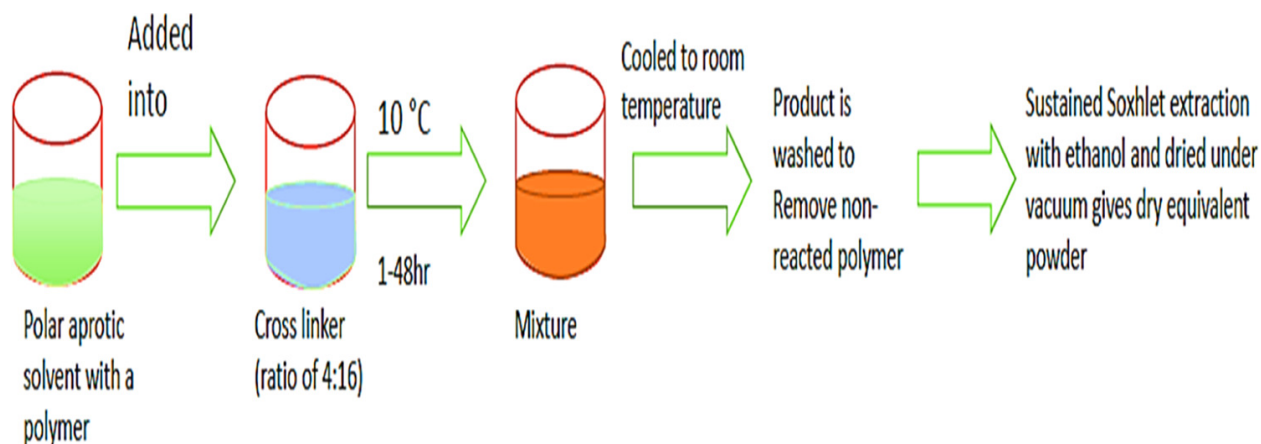
Method of preparation :

There are several ways to prepare nanosponges:

1.Solvent technique, 2.Melting method, 3. Emulsion solvent diffusion, 4. Quasi Emulsion solvent evaporation, and Ultrasound-assisted method.

These strategies are less labor-intensive, cost less and can be assessed with advanced tools for regular analysis. Cross-linkers such as cyclodextrins, eudragit RL 30 D, poloxamer 188, and ethyl cellulose are used in the manufacture of nanosponges. Methods such as freeze-drying are used to load the medication into the nanosponges. Through techniques like freeze-drying, the medication is incorporated into the nanosponges. To guarantee the quality of the nanosponges, their particle size, zeta potential, and drug entrapment effectiveness are assessed. For oral use, the nanosponges can be further processed into tablets. Drug loading, polymer selection, and cross-linking techniques are combined during the nanosponges' production to achieve controlled and improved release of the drug.

1.Technique of solvent :
In the procedure, appropriate solvents such as polar aprotic solvents like dimethylformamide and dimethyl sulfoxide were utilized. This was mixed well after the addition of polymer. For best results, the aforementioned mixture should be applied to a crosslinker/polymer ratio of 8:2. Following the aforementioned mixing, the mixture was allowed to react for 48 hours at temperatures between 10 °C and the solvent's reflux temperature. Upon reaching room temperature, the solution underwent cooling to complete the reaction[10]. The product was recovered using vacuum filtering after an excessive amount of bi-distilled water was added to the above-cooled solution to extract it.
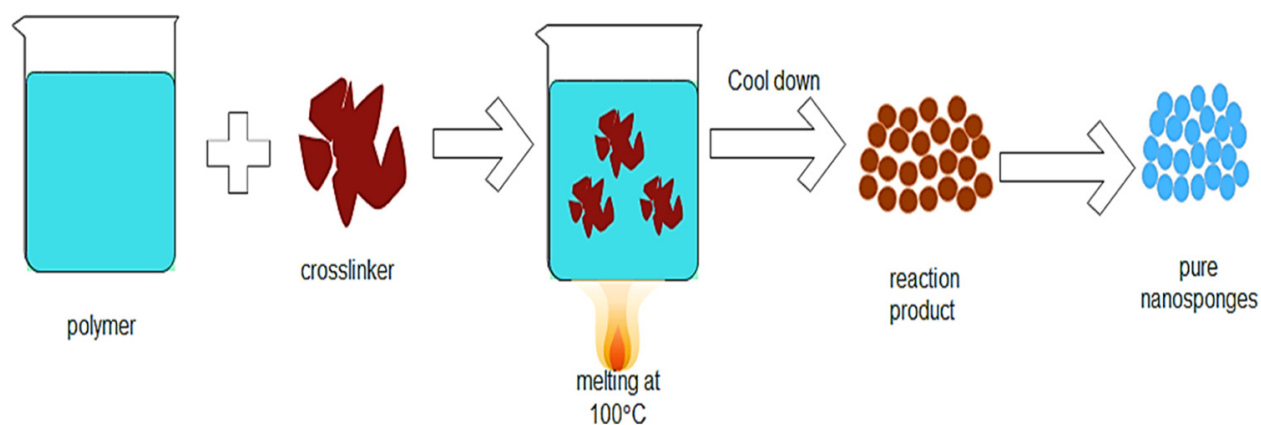
Fig 02 : Solvent method[16]

2.Melt method

The crosslinker and the polymer are melted together in the melting process. All the ingredients were finely homogenized. NSs were collected by washing the acquired product repeatedly with a suitable liquid. Cleaning the product, extracts the waste polymer and reagents which are unreacted and divides the product into the form of NSs [12]. Such blank NSs were further exposed to the encapsulating of narcotics


Fig 03 : Melt method[16]

3.Emulsion – Solvent diffusion method:

The diffusion emulsion solvent method alters aqueous levels (such as polyvinyl alcohol and ethyl cellulose). First, ethyl cellulose and dispersants are dissolved in 20 ml of dichloromethane. Second, 150 ml of polyvinyl alcohol is gradually added, and the mixture is blended thoroughly for 2 hours at 1000 rpm. Filtering captures desired nanosponges. Oven-drying at 40°C for 24 hours follows. Dried nanosponges stored in desiccators, ensuring solvent removal[13].
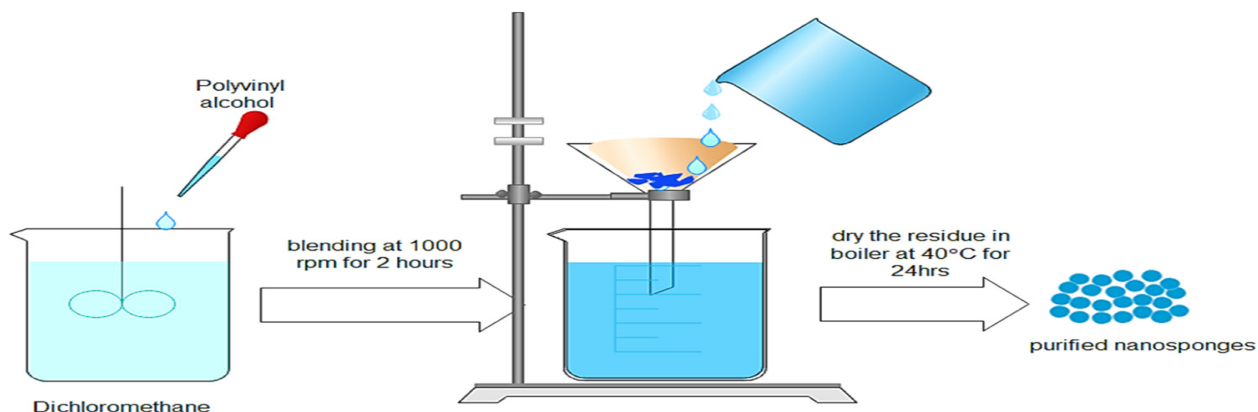
Fig 04: Emulsion-Solvent diffusion method[16]

4. Quasi emulsion solvent method :

The polymer was used to arrange NSs in different amounts. An inner phase was made with Eudragit RS 100 and added to a soluble phase. The drug had an effect at 35°C under ultrasonication[15]. This inner process acted as an emulsifying agent in the- outer polyvinyl alcohol phase. The mixture stirred at 1000-2000 rpm for 3 hours at room temp. It then dried for 12 hours at 40°C in an air oven.
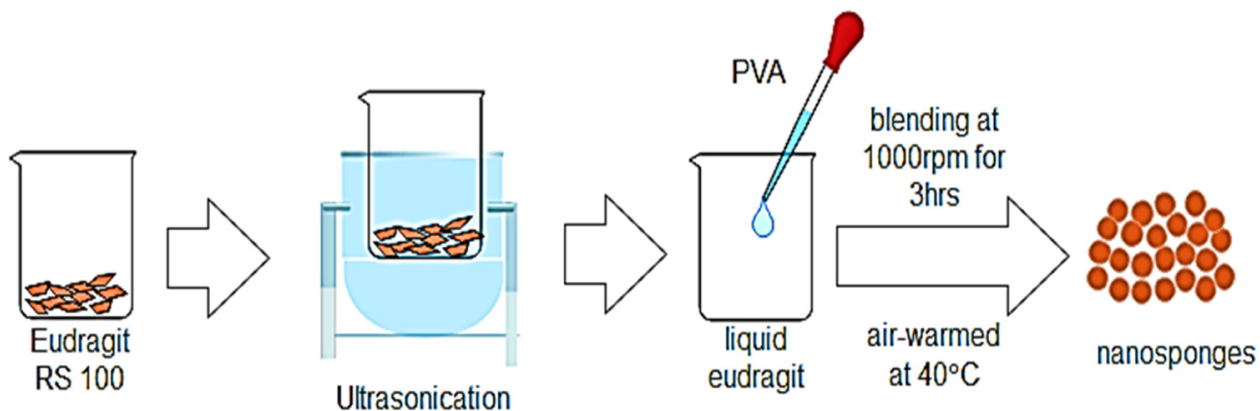
Fig 05 : Quasi emulsion solvent method[16]

Ultrasound-assisted method:

The synthesis process that uses ultrasound assistance makes use of polymer ultrasonics connection. Ultrasonic waves cause polymer crosslinking, which can be obtained without the use of a solvent. A suitable molar ratio was established between the polymer and crosslinker in a flask. The flask was placed in an ultrasonication bath for five hours at a temperature of ninety-three degrees Celsius. After sonication, the temperature of the gathered mixture was lowered,

and the product underwent a rigorous splitting process to remove unreacted polymer and reagents using an excessive amount of water[11]. Soxhlet extraction was used to purify the cleaned solid using ethyl alcohol. Prior to additional drug loading, the filtered NSs were carefully processed, vacuum dried, and stored.
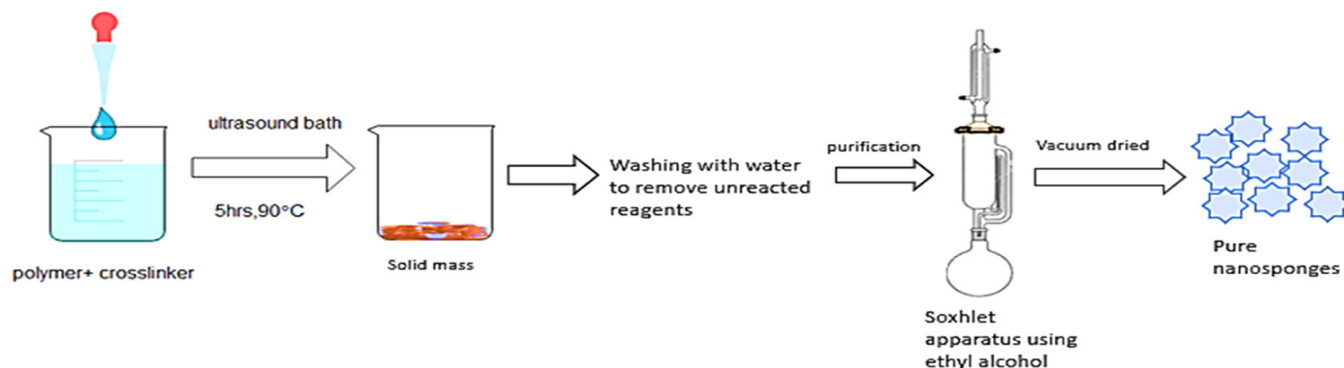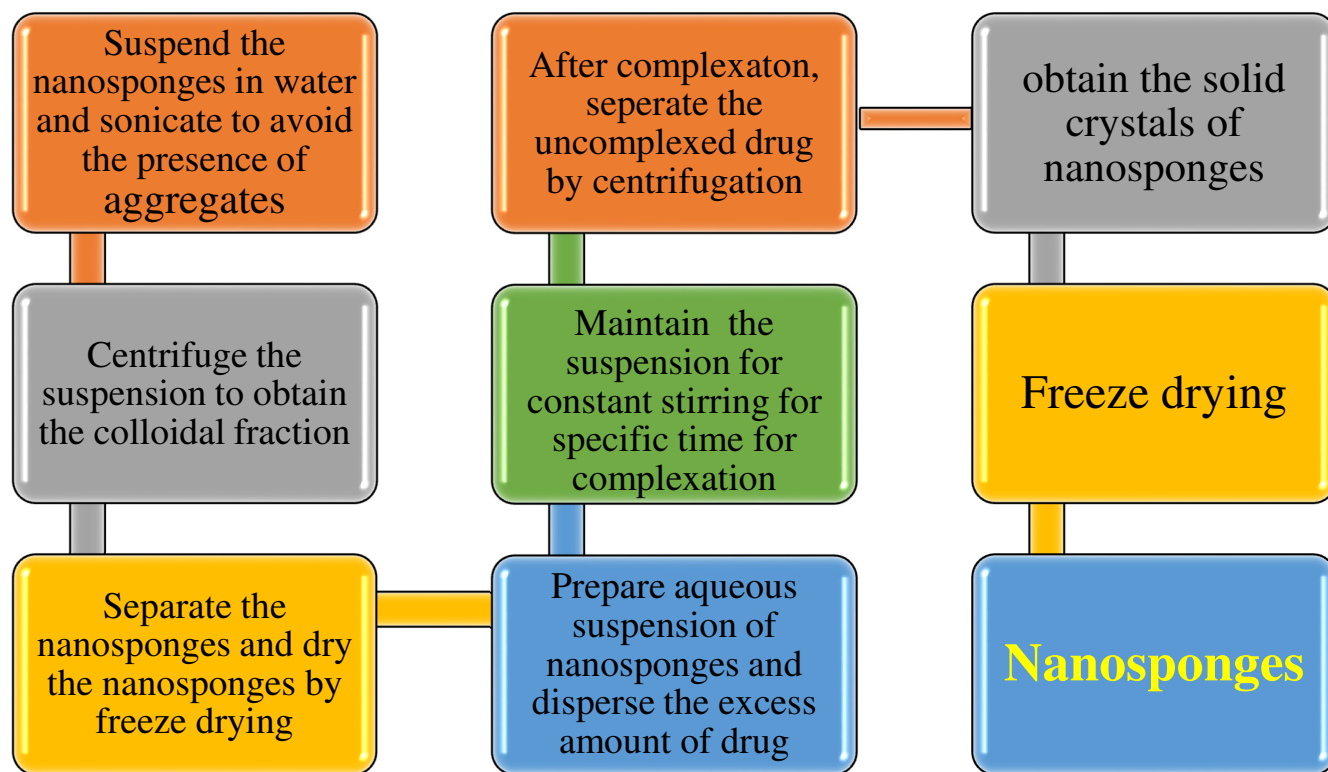

Fig 06: Ultrasound-assisted method[16]

(Tiwari, K., Bhattacharya, S. The ascension of nanosponges as a drug delivery carrier: preparation, characterization, and applications. *J Mater Sci: Mater Med* **33**, 28 (2022). https://doi.org/10.1007/s10856-022-06652-9)

Loading of drug into nanosponges:

Suspend the nanosponges in water and sonicate to avoid the presence of aggregates	After complexaton, seperate the uncomplexed drug by centrifugation	obtain the solid crystals of nanosponges
Centrifuge the suspension to obtain the colloidal fraction	Maintain the suspension for constant stirring for specific time for complexation	Freeze drying
Separate the nanosponges and dry the nanosponges by freeze drying	Prepare aqueous suspension of nanosponges and disperse the excess amount of drug	Nanosponges

Evaluation of nanosponges:

A distinctive family of nanomaterials called nanosponges might have many uses in the field of medicine delivery, environmental remediation, and neutralisation of toxins. The testing of the nanosponges is usually made with an eye to their chemical and physical properties in addition to their functionality when it comes to certain applications. Here are some typical tests being used to assess the nanosponges:

- **Morphological characterization**: In this, size, shape, and surface topography are characterized by measuring and imaging the nanosponges through scanning electron microscopy (SEM) and transmission electron microscopy (TEM) techniques. It might reveal both the integrity and homogeneity of the nanosponge structure.
- **Particle size and size distribution** : Laser diffraction techniques or dynamic light scattering (DLS) measures the size distribution of nanosponge particles in a solution in order to understand the stability and potential for uses, such as medication distribution.
- **Surface area and porosity:** The specific surface area and porosity will be determined from gas adsorption techniques or the BET analysis of Brunauer-Emmett-Teller.
- **Adsorption/Encapsulation Capacity**: In order to examine the nanosponges' adherence to or the trapping of the target molecules (eg, pharmaceuticals, toxic evidences or pollutants), a set of methods including UV-visible spectroscopy, fluorescence spectroscopy or chromatography are frequently employed.

- **Kinetics of release:** in vitro release studies are performed on the nanosponges to understand their kinetics for the release of drug, over time, in order to characterise their controlled release behaviour.
- **Biocompatibility and Toxicity:** Cell viability assays (eg, MTT assay or live/dead staining) and in vivo studies in animal models may be used to test biocompatibility of nanosponges and systemic toxicity and biodistribution.
- **Functional Performance:** Once the actual application is decided upon (for toxin-neutralising nanosponges, for instance), the appropriate functional test can be run (in this case, a toxin-neutralisation assay).

Applications of nanosponges:

- ❖ **Nanosponges as chemical sensors**: Nanosponges, a subclass of "metal oxides," function as chemical sensors and are employed in the highly sensitive detection of hydrogen through the use of titania nanosponges. Because there is initially no point of contact in the nanosponge structure, electron transport is less hampered and the resulting greater 3D interconnect nanosponges titania, which is sensitive to H2 gas, is produced.
- ❖ **Oxygen delivery system** :The oxygen delivery system is characterized by the use of α, β, and ϒ cyclodextrins, which are suspended in water and then saturated with it. With the use of a hydrogel/nanosponge system, silicone membranes can also be employed to allow oxygen to pass through. They can also apply it to hypoxic tissues brought on by different kinds of illnesses.
- ❖ **Uses in biomedicine** :You can use a nanosponge to clean up contaminated water. Organic contaminants in water have been eliminated with the help of nanosponge technology.
- ❖ **Using nanosponges as a vehicle for biocatalysts and releasing proteins, enzymes, antibodies, and vaccines:** It covers industrial processes that are related to operational conditions.Non-specific reactions result in low yields and need high temperatures and pressures, which use a lot of energy and cold water in the downstream process. The disadvantages can be overcome by employing nanosponges with enzymes as biocatalysts since they function well in moderate conditions and at high reaction speeds.
- ❖ **Solubility enhancement:** Itraconazole nanosponges based on β-cyclodextrin have improved the solubility of the poorly soluble medication. 50 times more solubility was achieved than with a ternarym dispersion system.
  For example: copolyvidonum.
- ❖ **Topical agents:** The nanosponges delivery system is a novel technology that enables the regulated release of topical medicines with extended drug release and skin form retention.
- ❖ **Antiviral administration:** Nasal and pulmonary routes with nanosponges. It offers selectivity in targeting viruses like the influenza and rhinoviruses that can cause respiratory tract infections (RTIs) by delivering antiviral drugs on RNA to the lungs or nasal passage via nanocarriers.
  Ex: saquinavir and zidovudine.

CURRENT CHALLENGES AND FUTURE PROSPECTIVES:

Challenges with Nanosponges: Nanosponges still go up against a few impediments in show disdain toward of their potential:

Scalability and cost-effectiveness: Fabricating critical sums of nanosponges for common utilize can be exorbitant and include complicated methods. In an exertion to diminish costs, analysts are optimizing generation techniques.

Targeted Conveyance: Whereas it is conceivable to make nanosponges with accuracy focusing on to specific organs or tissues, this is still a challenging task.

Long-Term Security: Inquire about is as of now underway to decide the long-term results of nanosponges on the body. To ensure their security for delayed utilization, more ponder is required.

Future Prospects:

The science of medicine has undergone a radical change since the discovery of NSs, or nanoscale substances. Medical science is undergoing a revolution thanks to technological developments at the nanoscale. When a targeted and regulated drug release mechanism is employed, drug toxicity is decreased because better therapeutic outcomes can be obtained.

NSs play a crucial role in the development of nanotechnology in the realm of therapeutics. NS might be applied as a conventional water filter in the future. Reducing manufacturing costs is the primary issue, which calls for the development of new production techniques as well as the

They require a great deal of research because of their special qualities, which are crucial to downstream production. There is a lot of potential in the way that crosslinking strength, porosity, synthesis, crystallinity, and particle size affect drug release. Thus far, the most often documented methods of preparation have been the conventional method and ultrasound-assisted synthesis; however, innovative techniques including solvent evaporation and bubble electrospinning are also being updated and created. Increasing yields, cost-effectiveness, and repeatability is currently in style since they will all enable quick mass production. The current methods for producing NS are simple, but a major flaw in the chemical process is that the final product may contain leftover liquids or reaction residues that could have harmful consequences.

Patents:

Recently, new patents in the field of nanotechnology have been submitted and approved. These patents describe the use of nanoparticles to improve the preparation procedure, hence improving process efficiency. The patents have been filed for applications including growth preservation, enzyme release, biocatalyst investigations, and toxin-absorbing agents. As antitumoral drugs, they have also had encouraging outcomes. Additionally, the authority grants new patents that have been regarded as helping to shift demand towards nanoscale drug delivery systems, or NSs.[2]

S.NO	Patent/App. No.	Applicant	Title
1.	US8828485B2	Kun Lian, Qinglin Wu	Carbon-encased metal nanoparticles and sponges as wood/plant preservatives or strengthening fillers
2.	WO2007095454A2	Kun Lian, Qinglin Wu	Carbon-encased metal nanoparticles and sponges, methods of synthesis, and methods of use
3.	WO2012147069A1	Francesco Trotta, Pravin SHENDE, Miriam BIASIZZO	Method for preparing dextrin nanosponges
4.	WO2009138998A3	Eswaramoorthy Muthusamy, Saikrishana Katla	A template free and polymer free metal nanosponge and a process thereof
5.	US9574136B2	Kun Lian	Nanoparticles, nanosponges, methods of synthesis, and methods of use
6.	US20170152439A1	Kun Lian	Nanoparticles, nanosponges, methods of synthesis, and methods of use
7	ITMI20071321A1	Giovanni Nicolao Berta, Roberta Cavalli, Barbara Mognetti, Carlo Maria Roggero, Francesco Trotta, Vander Tumiatti	Nanosponges based on cyclodextrins as a vehicle for anticancer drugs
8.	W02009149883A1	Gianfranco Gilardi, Francesco Trotta, Roberto Cavalli, Paolo Ferruti, Elisabetta Ranucci, Giovanna Di Nardo, Carlo Mario Roggero, Vander Tumiatti	Cyclodextrin nanosponges as a carrier for biocatalysts, and in the delivery and release of enzymes, proteins, vaccines and antibodies.
9.	W02006002814A1	Francesco Trotta,Wander Tumiatti, Orfeo Zerbinati, Carlo Roggero,Roberto Vallero	Ultrasound-assisted synthesis of cyclodextrin-based nanosponges
10.	W02012147069A1	Universita DegliStudi Di Torino, Sea Marconi, Technologies Di	Method of preparing dextrin nanosponges
11.	CA2692493A1	Sea Marconi, Technologies Di Vander Tumiatti, S.A.S, Francessco Trotta, Vander Tumiatti, Roberta Cavalli, Carlo Mario Roggero, Barbar Mognetti, Giovanni, Nicolao Berta	Cyclodextrin-based nanosponges as a vehicle for antitumoral drugs
12.	ITTO20110873A1	Vecchi Marco DeCarlo Stefano DiShubhen KapilaCarlo Maria RoggeroValentina ScariotMichela Tumiatti	Use of nanosponge functionalized for growth, preservation, protection and disinfection of plant organisms

Marketed formulations:

DRUG	TRADE NAME	ADMINISTRATUIN ROUTE	DOSAGE FORM
Iodine	Mena- gargle	Topical	Kyushin pharmaceutical Co., Ltd. (Tokyo, Japan
Piroxicam	Brexin	Oral	Chiesi Pharmaceuticals (Parma, Italy)
Dexamethasone	Glymesason	Dermal	Fujinaga Pharmaceutical Co., Ltd. (Tokyo, Japan)

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