

NANOSPONGES: A DRIVEN APPROACH FOR NOVEL DRUG DELIVERY

Abstract

A dynamic and multidisciplinary discipline, nanotechnology encompasses a wide range of generically diverse fields, including nano-electronics, information technology, biotechnology, and cellular and molecular biology. Additionally, it has had a significant impact on the development of biomaterials as well as drug delivery, diagnostics, nutraceuticals, and other aspects of the life sciences. Items that are nanosized and can be modified into many approaches to enhance their qualities to make up pharmaceutical nanotechnology. Targeted drug distribution can be accomplished with the help of nanosponges. Numerous medicines, both hydrophilic and lipophilic, can be employed into nanosponges to deliver drugs to specific areas., improving the drug's solubility and bioavailability in the process. As soon as they come into contact with the particular target site, interact, adhere to the surface, and start to release the medicine in a controlled manner, nanosponge can circulate throughout the entire body. Application of nanosponges, types, preparation techniques, polymers employed, and characterization have all been covered in this review paper.

Keywords: Nanotechnology, Nanosponges, Cyclodextrin

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I. INTRODUCTION

The "Pharmaceutical Nanotechnology" a subfield of medicinal research, provides novel tools, opportunities, as well as research directions that are anticipated to have important consequences for the diagnosis and treatment of disease. Nanotechnology is broadly described as "the manipulation of matter on an atomic, molecular, and supramolecular scale including the design, manufacture, specification, and utilization in a several fields offering advanced technical improvements, primarily in the medical field. Nanotechnology has the potential to have an impact in many areas of medicine, such as immunology, cardiology, endocrinology, ophthalmology, cancer, and pulmonology, among others. Additionally, it is widely used in specialized fields like gene delivery, tumor targeting, and brain targeting.[1]. Nanotechnology had dominated technology since the 1950s. In 1959, Richard P. Feynman, a researcher at Cal Tech, predicted something about nanomaterials. He remarked, "There is plenty of room at the bottom," and offered the idea that scaling down to the nanoscale and beginning at the very bottom became the key to future advancements in nanotechnology. Nanomaterials are defined as substances having minimum one dimension between 1 and 100 nm. Nanoscale materials have been developed and used by the pharmaceutical and healthcare sectors to address a variety of physical, chemical, and biological issues related to the treatment of disease. Nanoparticles have a wide range of uses, including the creation of biocompatible materials, the UV protection of textiles, coatings to prevent microbial growth, the delivery of drugs and DNA, the immobilization of enzymes, etc. Several nanosystems have been developed till date, including micellar systems, dendrimers, solid-lipid nanoparticles, carbon nanotubes, polymeric nanoparticles, nanoemulsions, and nanosponges.[2].

The types of nanoparticles can be categorized based on their interaction with medications.

- **Encapsulating Nanoparticles:** Particulate systems such as Nanosponges and nanocapsules are examples of this class. Alginate nanosponges, sponge-like nanoparticles having many holes for distributing drug components, are examples of nanosponges. Nanoparticles are also enclosed in nanocapsules made of poly (isobutyl cyanoacrylate, or IBCA). They have an aqueous core where drug molecules can be trapped.
- **Complexing Nanoparticles:** These particles attract molecules by electrostatic charges and fall under the category of complexing nanoparticles.
- **Conjugating Nanoparticles:** Covalent linkages connect these conjugating nanoparticles to pharmaceuticals.[3].

Recently, nanosponges have been created and are being considered for drug delivery. Nanosponges have the ability to delay the enhance the bioavailability of medications that aren't easily dissolved in water. Because of their inner hydrophobic chambers and external hydrophilic branches, nanosponges have unrivaled flexibility and is capable of transporting both hydrophilic as well as hydrophobic medicinal molecules. Nanosponges resemble a three-dimensional scaffold or network more so. Figure 1 illustrates a nanosponge, which is a small mesh-like structure that may be utilized to incorporate a variety of ideas of different compounds.[4,5]. Their spherical colloidal nature has been established, and their inclusion as

well as non-inclusion behavior indicate that they have an extremely high rate of solubilization for insoluble medicines.[6]. The polymer's lengthy polyester backbone is combined in solution with smaller molecules which are referred as cross-linkers to serve as a tiny grappling hook for joining the various components of the polymer.[7].

1. Advantages [4,8]

- These compositions maintain their stability between pH 1 and 11.
- These compounds maintain the stability at elevated temperatures.
- These compositions work well with the majority of substances and vehicles.
- Due to their usual 0.25 μ m pore size, they are self-sterilizing and prevent germs from growing.
- These formulations may be inexpensive and flexible.
- This approach gives greater formulation flexibility, increased elegance, higher stability, less negative consequences, and component trapping.
- Nanosponges are neither mutagenic, poisonous, or allergic.
- Activities with extended release that last up to 12 hours are feasible.
- Allows the addition of immiscible liquid; improves material processing by turning liquid into powder.
- Commercial production scaling up is easy.
- The cross-linker to polymer ratio can be varied to alter the size of the nanosponges.
- Depending on the required dose, the medication's release characteristics may be quick, medium, or slow.
- An anticipated release.
- Nanosponges can be renewed by adjusting the pH or ionic strength, light heating, washing with eco-friendly solvents, or stripping with comparatively inert hot gases.
- Less harmful side effects as a result of less frequent drug contact with healthy tissue.

2. Disadvantages [9]

- Nanosponges can only incorporate extremely small molecules.
- Crystalline or paracrystalline nanosponges are also possible.
- The loading ability of nanosponges is mostly determined by the degree of crystallization.
- Paracrystalline nanosponges have various loading capabilities.

3. Characteristic Of Nanosponges [11]

- Nanosponges offer a variety of diameters (1 μ m or less) with adjustable cavity polarity.
- By altering the cross-linker to polymer ratio, nanosponges of a particular size can be created.
- They can appear crystalline or paracrystalline, depending on the conditions of the operation. The crystal structure of nanosponges is crucial in ensuring the complexation of medications with them.
- The drug loading capacity is determined by the degree of crystallization.
- Paracrystalline nanosponges have a variety of drug loading capacities.

- They have porous components that are nontoxic, largely insoluble in organic solvents, as well as stable up to 300 °C.
- They can withstand pH levels between 1 and 11.
- In water, they create a clear, opalescent suspension.
- They can be duplicated utilizing straightforward thermal desorption, solvent extraction, microwaves, and ultrasounds.
- Several compounds can be captured, transported, and released under regulated conditions due to their 3D designs.
- Because of their ability to connect with several functional groups, they can be placed at various target places.
- Nanosponges can connect more effectively to the target region thanks to chemical linkers.
- Nanosponges are capable of forming inclusion- as well as non-inclusion-based complexes when they interact with certain medicines.
- Magnetic qualities can also be given to nanosponges by including magnetic particles in the reaction mixture.
- Nanosponges are porous, highly soluble in water particles that are primarily employed to encapsulate poorly soluble medicines.
- These Nanosponges may transport both hydrophilic and lipophilic medications.
- They are able to filter out organic contaminants from water and guard against physicochemical deterioration, which would otherwise destroy the medicine.

II. TYPES OF NANOSPONGES

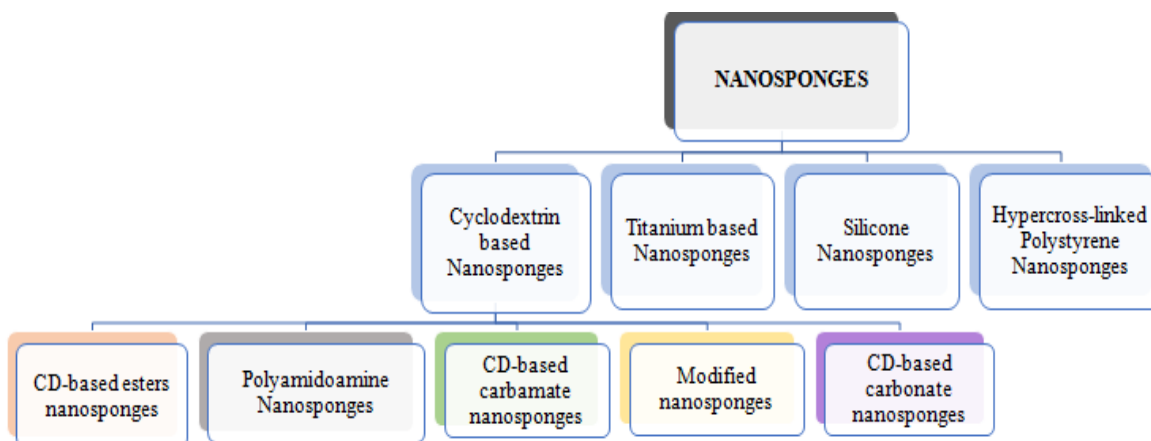


Figure 2: Types of Nanosponges

1. **Cyclodextrin Nanosponges:** The term "cyclodextrin nanosponges" (CDNS) was initially introduced by DeQuan Li and Min Ma in 1998 to describe a cross-linked -cyclodextrin with organic di-isocyanates that results in the creation of a network that is not soluble and indicates a higher inclusion constant with diverse organic contaminants. A new drug delivery system for nanoscales called CDNS is proposed. It consists of a three-dimensional network of cross-linked polymers of cyclodextrin nanostructure. By altering the cross-linker and degree of cross-linking, CD polymer are able to produce spherical, crystalline, or amorphous, porous, insoluble nanoparticles with tunable polarity and size. There are three distinct CD types: Three different kinds of cyclodextrin exist: Alpha-

cyclodextrin (α) Beta-cyclodextrin (β) Gamma-cyclodextrin(γ) Delta-cyclodextrin(δ), the 3 natural CDs, α -, β - and γ - CDs, having different ring size and solubility.[12,13].

A unique nanostructured material made of hyper-cross-linked cyclodextrins has been described which is produced by reaction of cyclodextrins (cyclic oligosaccharides) along with suitable cross-linking reagents. This material is known as nanosponges.[14]. Depending on the agent utilized as a cross-linker, nanosponges can be created as neutral or acidic materials and can swell. The end result leads to the development of spherically shaped particles which has cavities that can hold medicinal molecules.[15].

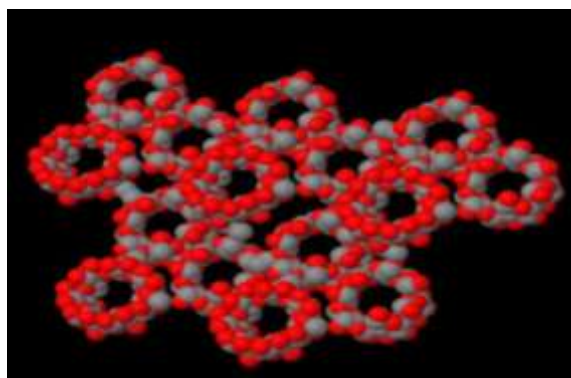


Figure 1: Cyclodextrin carbonates nanosponges' molecular structure.

During preparation, the cross-linking-to-cyclodextrin ratio can be changed to enhance drug loading and create a customized release profile.[15,16]. Compared to the parent cyclodextrin molecules, the extremely porous of nanosponges and the nanomeric nature allows drug molecules to orient themselves in the inclusion of the nanosponge as well as interact in a non-inclusion form.[16]. Comparing nanosponges to ordinary nanoparticles reveals a striking benefit. They are in fact easily regenerable using a variety of processes, including washing with environmentally friendly solvents, stripping with relatively inert hot gases, gentle heating, or altering pH or ionic strength. Nanosponges have previously been used in a variety of applicable domains, including the cosmetic and pharmaceutical industries, due to all these qualities.[7].

The nanosponges are physically solid in nature.[17]. They are safe for both oral and invasive routes, making them a viable medication delivery vehicle.[18]. Owing to their small size, nanosponges can be delivered through the lungs and veins. The complexes can be dissolved in a mixture of excipients, diluents, lubricants, as well as anti-caking agents that are suitable for making tablets or capsules for oral administration. Saline, sterile water, and other aqueous solutions can all be used to carry the substance and deliver it by parenteral injection. In order to distribute drugs topically, they can be effectively incorporated into topical hydrogel. The medication molecules are contained within the center of encapsulating nanoparticles called nanosponges.[19].

Cyclodextrins have been primarily used in the pharmaceutical industry because,

- They are semi-natural goods made by relatively simple enzymatic conversion from renewable natural starch.

- They are created using environmentally friendly methods at a rate of thousands of tons annually.
- Any hazardous effects they may have are of a minor kind and can be completely avoided by using the proper cyclodextrin type, derivatives, or application method.

2. Additional Classifications of CD-based Nanosponges include

- **CD-based Carbamate Nanosponges:** In the presence of a DMF solution, CDs reacts with appropriate di-isocyanates, like hexamethylene di-isocyanate and toluene-2, 4-diisocyanate, for 16 to 24 hours at 70 °C under a nitrogen environment. By thoroughly washing with acetone, residual DMF is eliminated, and cross-linked polymer powder is produced. These nanosponges are used to purify water because of their capacity for binding to organic compounds. For organic compounds, the loading capacity varies between 20 to 40 mg per cm³. [20,21].
- **CD-based Carbonate Nanosponges:** CD-based carbonate nanosponges are primarily composed of cyclodextrins, which are cyclic oligosaccharides with a hydrophobic inner cavity and a hydrophilic outer surface. They are crosslinked using carbonate-based crosslinking agents, such as carbonyl diimidazole or ethylene carbonate. These crosslinkers connect the cyclodextrin molecules, forming a three-dimensional network. These nanosponges have a porous structure with nanometer-sized cavities. The size and porosity can be tailored by adjusting the type and amount of cyclodextrin and crosslinking agents used during synthesis. CD-based carbonate nanosponges have a high surface area, making them suitable for the encapsulation and controlled release of various substances, including drugs, dyes, and other bioactive compounds. They are known for their excellent stability, biocompatibility, and low toxicity, which are desirable properties for drug delivery systems. [7, 21].
- **CD-based Ester Nanosponges:** CD-based ester nanosponges are primarily composed of cyclodextrins, which are cyclic oligosaccharides with a hydrophobic interior cavity and a hydrophilic exterior. They are crosslinked using ester-based crosslinking agents, such as diacid chlorides or dihydric alcohols. These crosslinkers create covalent bonds between cyclodextrin molecules, resulting in a three-dimensional porous network. The synthesis of CD-based ester nanosponges typically involves the reaction between cyclodextrins and ester-based crosslinking agents in the presence of a suitable solvent and catalyst. The reaction leads to the formation of covalent bonds between cyclodextrin molecules, creating a porous network structure. By modifying their chemical structure, these nanosponges can release encapsulated substances in response to changes in pH, making them suitable for targeted drug delivery. [22].
- **Polyamidoamine Nanosponges:** Polyamidoamine nanosponges are a type of nanosponge material composed primarily of polyamidoamine dendrimers. These dendrimers are highly branched, tree-like polymers that form a three-dimensional, porous network, creating nanoscale spongy structures. Polyamidoamine dendrimers, characterized by their well-defined, highly branched structure, serve as the main building blocks of polyamidoamine nanosponges. Crosslinking agents or methods are often used to connect and stabilize the dendrimers, forming the nanosponge structure. Polyamidoamine nanosponges have a porous and interconnected structure with

nanometer-sized voids and channels. They exhibit a high surface area, making them suitable for various applications, including drug delivery, adsorption, and catalysis. Polyamidoamine nanosponges are used as drug carriers to enhance the solubility, stability, and controlled release of drugs. Their porous structure allows for efficient drug loading and delivery.[23].

- **Modified Nanosponges:** Traditional carbonate-based nanosponges have been modified to better suit the application by changing the reaction conditions. Fluorescein isothiocyanate was combined with carbonate nanosponges in DMSO and heated to 90 °C for a few hours to produce the fluorescent derivative. Fluorescent nanosponges have been employed in biological research, including the treatment of cancer. A cyclic organic anhydride like succinic anhydride or maleic anhydride can be used in a similar way to produce carboxylated nanosponges. Such nanosponges react with proteins, chitosan, or other biologically significant carriers, perhaps resulting in a promising medication targeting action for a particular receptor. These nanosponges are amorphous by nature, according to powder XRD measurements. They are not cytotoxic or hemolytic either. Carboxylated nanosponges seem to offer a viable safe drug delivery system for anti-cancer medications like camptothecin.

III. DRUG RELEASE MECHANISM FROM NANOSPONGES

Up until equilibrium is attained, the sponge atoms are in an open state, permitting the molecules that are active to freely enter and leave the particles as well as the vehicle. In the case of topical distribution, the chemical component that is already present in the vehicle will eventually be absorbed into the target tissue after being administered to it. When a vehicle is depleted, the equilibrium is thrown off because the vehicle will become unsaturated. As a result, an active flow will start from the sponge particle in the vehicle and continue until the vehicle is either dried out or absorbed before moving from the vehicle to the target tissue. The sponge fragments that remained on the tissue's surface would then continue to slowly release the active substance to it, giving the tissue a sustained release over time.[4].

IV. METHODS OF PREPARATION OF NANOSPONGES

1. **Solvent Method:** This method involves dissolving a polymer (e.g., cyclodextrins, chitosan) and the desired active ingredient (e.g., drugs, proteins) in a suitable organic solvent. The organic solution is then emulsified or dispersed in an aqueous solution containing a stabilizer, such as surfactants. The solvent is evaporated under reduced pressure or at room temperature, leading to the formation of nanosponges as the organic phase solidifies. The resulting nanosponges can be collected, washed, and dried for further.[7].
2. **Ultrasound-Assisted Synthesis:** Using this technique, nanosponges were developed by combining cross-linkers and polymers without the need of a solvent which was being sonicated. Spherical, uniform-sized nanosponges will be created using this method. The cross-linker along with polymer were mixed in a flask at a specific molar ratio. The flask was placed in an ultrasonic bath with water and heated to 90 °C. 5 hours were spent sonicating the mixture. After allowing the mixture to cool, the final product was roughly broken. After being thoroughly cleaned with water to get rid of the non-reacted polymer,

the product underwent a lengthy Soxhlet extraction in ethanol. The finished product was vacuum-dried and kept in storage at 25 °C until needed.[6].

- 3. Emulsion Solvent Diffusion Method:** In this method, a polymer is dissolved in an organic solvent, and the active ingredient is added to create a solution. This solution is then emulsified in an aqueous phase using a surfactant or stabilizer. The organic solvent diffuses into the aqueous phase, leading to the formation of nanosponges in the aqueous medium. The created nanosponges were filtered out, dried in an oven at 40°C for 24 hours, and then packaged. The nanosponges can be separated by centrifugation, filtration, or freeze-drying.[6].
- 4. From Hyper Cross- Linked β -Cyclodextrin:** In this case, cyclodextrin can serve as a medication delivery vehicle. Cyclodextrin and a cross linker can be used to create nanosponges. As a result, 3D networks are created, which might be a somewhat spherical structure with pores and channels inside that is the size of a protein. Sponge size is regulated by porosity and surface charge density for its attachment to various molecules when cyclodextrin reacts with a cross linker such di-isocyanates, diary carbonates, etc. In neutral or acid forms, nanosponges can be created. The typical diameter of a nanosponge is less than 1 μ m, however fractions as small as 500 nm can be chosen. They are used to improve the solubility of weakly water-soluble medicines in aqueous solutions. They are composed of solid components that have been crystallized.[14].
- 5. Polymerization:** The polymerization method for preparing nanosponges involves emulsion polymerization, where monomers and crosslinkers are mixed with water and emulsifiers to create an emulsion. Polymerization is initiated, forming a crosslinked polymer network within nanoscale emulsion droplets, ultimately yielding nanosponges with controlled pore structures. These nanosponges are isolated, purified, and dried for various applications like drug delivery and adsorption.

V. LOADING OF DRUG INTO NANOSPONGES

The goal of pre-treating nanosponges for drug delivery is to achieve a mean particle size of less than 500 nm. Loading drugs into nanosponges is a crucial step in utilizing these nanomaterials for controlled drug delivery. Typically, this process involves immersing the nanosponges in a solution containing the drug of interest. Due to differences in concentration, the drug molecules diffuse into the nanosponge matrix, becoming encapsulated within the porous structure. The loading efficiency can be controlled by adjusting factors like the drug concentration, immersion time, and temperature. Once the drug loading is complete, the drug-loaded nanosponges are separated from the solution, often through filtration or centrifugation, and then dried to remove any residual solvent. This results in drug-loaded nanosponges that can release the drug in a controlled and sustained manner, enhancing its therapeutic efficacy while reducing side effects. This loading method is particularly useful for improving the solubility of poorly water-soluble drugs and ensuring their targeted delivery to specific tissues or cells.[7].

VI. CHARACTERIZATION OF NANOSPONGES

- 1. Particle Size Determination:** An essential consideration in the nanosponge optimization process is the particle size. Both the drug's solubility and release can be impacted by the

drug's particle size. Particle size can be determined using a Zeta sizer or laser light diffractometry.[24]. Plotting the cumulative percentage drug release from nanosponges with different particle sizes against time allows researchers to examine how particle size affects drug release. Particle sizes ranges from 10 and 25 μm may be desirable for topical medication administration, whereas those more than 30 μm may exhibit a gritty sensation.[27].

Babchi oil is encapsulated in herbal formulations using cyclodextrin-based nanosponges. They used five different varieties of babchi oil that were infused with different molar ratios of cyclodextrin nanosponges. The BO nanosponges' particle sizes ranged from 234 to 484 nm (table no 1). The particle sizes of each of the prepared BO nanosponges were in the nano range (1 nm). This shows they are in significant range.[28].

Table 1

Sr.no	Formulation	Particle size (nm \pm SD)
1	BONS1:2	261.6 \pm 14.79
2	BONS1:4	360.9 \pm 11.55
3	BONS1:6	234.3 \pm 15.37
4	BONS1:8	484.2 \pm 19.89
5	BONS1:10	243.3 \pm 12.95

In synthetic the characterization of carboxymethyl chiton nanosponges with cyclodextrin blends were studied to check drug solubility increases or not. The produced nanosponges' average particle sizes (F-0 to F-9) are displayed (table no 2). The particle sizes of all the manufactured nanosponges were in the nano range (1 nm). This shows they are in significant range.[29].

Table 2

Sr.no	Formulation	Particle size (nm)
1	F0	195 \pm 3
2	F1	213 \pm 2
3	F2	238 \pm 5
4	F3	250 \pm 4
5	F4	224 \pm 3
6	F5	209 \pm 4
7	F6	211 \pm 4
8	F7	218 \pm 3
9	F8	205 \pm 4
10	F9	199 \pm 5

- 2. Polydispersibility index (PDI):** The polydispersibility index (PDI) is a measure of the spread or width of the particle size distribution and it reveals variation within it. To calculate PDI, a dynamic light scattering device is employed.[24]. A higher PDI value implies that the sample has a wider particle size distribution and is polydisperse, whereas

a monodisperse sample has a lower PDI. PDI may be computed using the equation below.[27,30].

$$\text{PDI} = \frac{d}{d_{\text{avg}}} \Delta$$

Where,

d is the width of distribution denoted by **SD**, and **d Avg** is the average particle size denoted by MV(nm) in particle size data sheet.

Table 3

Polydispersibility Index	Type of Dispersibility
0-0.05	Monodisperse standard
0.05-0.08	Nearly monodisperse
0.08-0.7	Mid-range polydisperse
>0.7	Mid-range polydisperse

After accurately establishing the initial weight of the raw materials and the final weight of the produced nanosponge, the production yield of the nanospunges may be estimated using the equation below.[30].

$$\text{Production yield (PY)} = \frac{\text{Practical mass of NS}}{\text{Theoretical mass (polymer + Drug)}} \times 100$$

As reported cyclodextrin was encapsulated by babchi oil to study the cytotoxicity study and characterization of herbal formulation. They have taken five types of babchi oil which is loaded by Cyclodextrin Nanospunges in Different molar ratio (table no 3). The stability and homogeneity of the nanocolloidal suspensions were demonstrated by reduced PDI values with a constrained range(table). All of the nanoformulations were discovered to be fine, free-flowing powders.[29].

Table 4

Sr.no	Formulation	Polydispersity Index \pm SD
1	BONS1:2	0.312 \pm 0.098
2	BONS1:4	0.311 \pm 0.059
3	BONS1:6	0.188 \pm 0.064
4	BONS1:8	0.509 \pm 0.236
5	BONS1:10	0.361 \pm 0.113

As reported cyclodextrin was encapsulated by babchi oil to study the cytotoxicity study and characterization of herbal formulation. They have taken five types of babchi oil which is loaded by Cyclodextrin Nanospunges in Different molar ratio (table no 3). The stability and homogeneity of the nanocolloidal suspensions were demonstrated by reduced PDI values with a constrained range (table). All of the nanoformulations were discovered to be fine, free-flowing powders.[29].

- 3. Zeta Potential:** By measuring the surface charge of Nano sponges using a tool called a zeta sizer, one may determine the zeta potential. For measuring the Zeta potential and the

magnitude of the electrical surface charge at the double layer is frequently utilized. Zeta potential values greater than 30 mV signify strong formulation stability.[31].

During encapsulation of babchi oil to study physiochemical and characterization with cyclodextrin based nanosponges. They have taken five types of babchi oil which is loaded by Cyclodextrin Nanosponges in Different molar ratio (table no 4). As a gauge of surface charge, the zeta potential of several BO nanoformulations was also examined. The acquired zeta potential data are reported and are in significant range i.e $\pm 30\text{mV}$ a steady nanosponge is indicated by a high zeta potential because of stronger repulsive forces, which reduces their propensity to assemble.[28].

Table 5

Sr.no	Formulation	Zeta Potential (mV \pm SD)
1	BONS1:2	-17.8 ± 2.52
2	BONS1:4	-16.0 ± 1.15
3	BONS1:6	-15.5 ± 1.17
4	BONS1:8	-15.6 ± 2.39
5	BONS1:10	-22.0 ± 2.47

To study synthesis and characterization of nanosponges CDI cross-linked with β -cyclodextrin, F1 and F2 were discovered to have zeta potentials of -14.2 mV and -8.74 mV, respectively.[23].

- 4. Thermodynamical Method:** To determine whether drug molecules or particle modifications occur prior to the heat destruction of Nano sponges, the thermo-chemical technique may be applied. Only a few of the many potential drug particle modifications include melting, evaporation, oxidation, breakdown, and polymeric modifications. Changes in the drug molecules indicate the formation of a potent compound.[31].

In herbal formulation of babchi oil which was encapsuled in cyclodextrin to study characterization, in vitro cytotoxicity and physiochemical. Differential thermal analysis measures the temperature difference between the sample and the reference that led to heat absorption or release.[28]. Carboxymethyl was encapsuled in cyclodextrin blends to improve drug solubility. Overall, the findings of the DSC and TGA investigations demonstrated that bi-polymeric nanosponges were successfully formed, and that thermal stability was improved.[29].

- 5. Microscopy Studies:** Examining the microscopic components of a medication or nanosponge formulation can be done using either scanning electron microscopy (SEM) or transmission electron microscopy (TEM). By using SEM to analyze the morphology of nanosponges, it is possible to determine if inclusion complexes have formed between the raw materials utilized to create a nanosponge and the formulation's ultimate crystallization state.[31].

The loading efficiency (%) of Nanosponge can calculate by using following equation:

$$\text{LE} = \text{Actual drug content in nanosponges} \div \text{Theoretical drug content} \times 100$$

Loading efficiency may also be assessed using an HPLC method and an empirical evaluation of the medication placed in a nanosponge ultraviolet spectrophotometer. This entails counting the number of drug-loaded nanospheres that have been dispersed in appropriate solvent and broken up any complexes using a sonicator for a certain period of time. Following dilution, the sample is analyzed with an HPLC or UV spectrophotometer.[32].

In formulation for herbal babchi oil was encapsulated in cyclodextrin. They have taken five types of babchi oil which is loaded by Cyclodextrin Nanospheres in Different molar ratio. For the babchi oil NS, it was discovered that BONS4 had the maximum encapsulation efficiency up to 93% while BONS10 had the lowest just 61%. A larger amount of oil can be encapsulated in the nanosponge matrix and a cyclodextrin cavity due to optimal crosslinking that involves inclusion and external contacts simultaneously. This may explain why the BO is more fully encapsulated in a 1:4 molar ratio.[28].

Enhancing Drug Solubility using Carboxymethyl Chitosan Nanospheres and Cyclodextrin Blends were being synthesized and characterized. All of the findings, namely those between 85.32 and 87.4% and 89.32 and 91.74%, were deemed to be acceptable. All nanospheres displayed drug loading of at least 70%. The minimal Drug-loaded contents and the effectiveness of drug entrapment were shown by batch no F-8 and F-9, respectively, at 71.40-74.44% and 80.43-83.62%. Due to the product's stickiness, lansoprazole-loaded nanospheres displayed lower DLC% with an increase in polymer concentration. Furthermore, due to the low water solubility of the polymer, the drug entrapment efficiency significantly reduced with increasing polymer concentration.[29].

- 6. Solubility Studies:** It was explained how Higuchi and Connors created the phase solubility approach to study inclusion complexation. This method was used to explain how the drug's solubility was modified by Nanosponge, which demonstrates the level of complexity.[33].

During study of Itraconazole-Loaded Nanospheres for Topical Drug Delivery for preparation and In-Vitro evaluation. By using the shake flask technique, the solubility of each nanosponge formulation in distilled water and 0.1 N HCl was measured. Itraconazole's solubility increased by around 21 times.[30].

For improving drug solubility via the synthesis and characterization of carboxymethyl chitosan nanospheres with cyclodextrin blends. The outcomes showed that the primary goal of creating nanospheres improving docetaxel's solubility was achieved. Previous research indicated that nanospheres provide the highest solubility improvement for lipophilic medicines. Furthermore, our study showed a much higher drug solubility at pH 6.8 compared to other standard CD nanoparticles. [29].

- 7. FTIR Spectroscopy:** The interaction between drug molecules and drug and nanosponge in the solid state is estimated using IR spectroscopy. When a complex between a drug and a nanosponge forms and a little portion of the drug molecule is allocated to include a portion of other molecule that is designated by bands on the spectra of nanospheres, the IR changes. The use of IR for several medications that include carbonyl or sulfonyl

groups is restricted. Information on functional groups including drugs is provided via IR studies.[27].

While studying physiochemical characterization, photodegradation, and in vitro cytotoxicity studies of babchi oil encapsulated in cyclodextrin-based nanosponges. The distinctive peaks of the BO were widened or shifted in nanoformulations, which implies interactions between oil and nanosponges, according to a comparison of the FTIR spectra of BO, blank NS, and BONS4.[28].

The spectra of loaded formulations showed a decrease in peak height and intensity as well as a complex formation between the drug and the monomer (AMPS) and polymers (CMC and -CD). These changes also showed slight peak shifting, modification, disappearance, and emergence was reported during study of improving drug solubility of carboxymethyl chitosan nanosponges with cyclodextrin blends.[29].

- 8. X-ray Diffractometry:** Using powder X-ray diffractometry, inclusion complexation in the solid state may be identified. The complex manufacturing of the medication using nanosponges changes its diffraction patterns and crystal structure.[27]. A newly created material obviously varies from an uncomplicated nanosponge with regard to its diffraction pattern, nanosponge. The complex creation is shown by this discrepancy in the diffraction pattern. When a complex forms, the peaks get sharper and a few more peaks develop.[32].

For herbal formulation of babchi oil Significant differences between their diffractograms occur, as evidenced by the observed drop in peak intensity. As a result, according to the XRPD experiments, freeze drying (BONS4) produced a fluffy powder with a highly porous structure that had lost its crystallinity. The indicated temperatures correspond to the typical peaks of the blank nanosponges: 10.53°, 12.37°, 15.14°, 16.99°, 18.60°, 19.29°, 20.92°, 22.52°, 24.15°, 25.30°, 26.90°, 28.52°, 31.05°, 34.75°, 36.60°, and 39.83° (2 θ).[28].

During synthetic capsulation the existence of distinctive peaks at 2 θ = 11.52°, 13.10°, 15.80°, 20.31°, 22.11°, 23.10°, 26.55°, and 27.71° demonstrated the crystallinity of AMPS. A PXRD diffractogram of a physical combination of medicine and polymer showed fewer but sharper peaks at 2 θ = 19.21°, 28.11°, and 36.91°, suggesting that the crystalline character largely diminished. The amorphous system of nanosponges, which is more soluble than the crystalline form of DTX, notably covered the strong distinctive peaks in pure drug DTX in an XRD diffractogram of DTX-loaded CD-co-poly (AMPS) and DTX-loaded CD-CMC-co-poly (AMPS) nanosponges. [29].

- 9. In Vitro Release Studies:** It is feasible to analyze the drug release from the enhanced nanosponge formulation using a multi-compartment rotation cell with a membrane for dialysis (cut-off 12,000 Da). The donor phase is composed of the drug-loaded nanosponge complex in distilled water. The receptor phase also contains the same media. The receptor phase is completely withdrawn at specified intervals, diluted adequately with distilled water, and then analyzed using a UV spectrophotometer.[27].

The research of itraconazole-loaded nanosponges for topical drug administration uses information from an in-vitro release trial of a chosen batch and a pure medicine.

After 120 minutes, it was found that 70.62% of the drug had been released from F4 nanosponges.[30].

During synthetic nanosponges study the drug was within five minutes, drug-loaded nanosponges showed initial abrupt drug release characteristics. After reaching equilibrium in twenty minutes, approximately 99% of the medication was released within one hour. As a result, the study's main goal was accomplished, making it a viable drug delivery method to increase DTX's water solubility, which stood out from other nanotechnologies. The overall findings of our dissolving investigations demonstrate that the quantity and type of the basic reactants utilized have a significant impact on altering the release profile of a medication with poor solubility (docetaxel). When compared to pH 1.2 and 4.5, the drug release of synthesized nanosponges was substantially greater at pH 6.8.[29].

- 10. Porosity Study:** A porosity analysis is done to figure out how many nanochannels and nanocavities were created. Since helium gas may move via various inter- and intra-specific channels in materials, a helium pycnometer is used to gauge the porosity of nanosponges. The true volume of the substance is determined using the helium displacement method. Nanosponges have higher porosity than the parent polymer used to form the system because they are porous.[34].

Percent Porosity equation: % Porosity (E) = $\frac{\text{Bulk volume} - \text{True volume}}{\text{Bulk volume}} \times 100$

VII. NANOSPONGE APPLICATIONS

- 1. Solubility Enhancement:** Nanosponges can help molecules with very limited water solubility become more soluble and moist. If the drugs are molecularly distributed within the nanosponge structure and then released as molecules, the dissolving process can be avoided. The drug's apparent solubility can be enhanced as a result. Numerous formulation and bioavailability concerns can be overcome by improving a substance's solubility as well as rate of dissolution, and nanosponges can dramatically improve a drug's solubility.
- 2. Nanosponges for Drug Delivery:** Nanosponges can be used as drug carriers to encapsulate various drugs, including poorly water-soluble compounds. They can improve the solubility, stability, and bioavailability of these drugs, making them more effective. Nanosponges can release drugs in a controlled and sustained manner. This controlled release profile helps maintain therapeutic drug levels in the body over an extended period, reducing the frequency of dosing and minimizing side effects[5].
- 3. Topical Drug Delivery:** Nanosponges can be incorporated into topical formulations like creams and gels. They help in maintaining a sustained release of drugs on the skin or mucous membranes, improving the efficacy of dermatological and topical medications. A novel method for the controlled release of topical medications of prolong drug release and retention of drug forms on skin is the nanosponge delivery system. This technique enables a steady and prolonged rate of release, minimizing discomfort while preserving effectiveness. A designed product includes a wide range of ingredients, including liquid, gel, cream, lotion, ointment, and powder.[16].

4. **Using Nanosponges to Carry and Release Enzymes, Proteins, Vaccines, and Antibodies:** Nanosponges can encapsulate enzymes to protect them from harsh environments, such as acidic stomach conditions or high temperatures. This protection ensures that the enzymes remain active until they reach their target site in the body. Therapeutic proteins, such as insulin or growth factors, can be encapsulated within nanosponges to extend their release and improve their stability. This approach allows for controlled and sustained protein delivery. Nanosponges can serve as carriers for vaccines, protecting antigens from degradation and enhancing their immunogenicity. They can also provide controlled release of antigens, potentially reducing the number of required vaccine doses. Monoclonal antibodies or therapeutic antibodies can be loaded into nanosponges for targeted delivery. This approach can improve the distribution of antibodies in the body and enhance their effectiveness.[36].

5. **Carrier for Delivery of Gases:** For both medicinal and diagnostic purposes, gases are utilized in medicine. Numerous disorders, including cancer and inflammatory conditions, are associated with hypoxia, or an inadequate oxygen supply. It might be difficult to give oxygen in the proper form and dosage in clinical settings..[35].

6. **Nanosponges as a Barrier Against Light or Deterioration:** Gamma-oryzanol, an ester combination of ferulic acid, has recently attracted a lot of interest because of its potential to serve as a natural antioxidant. In the cosmetics industry, it is frequently used as sunscreen and for preserving food as well as pharmaceutical raw materials. Its application is constrained due to a high degree of instability and photodegradation. Gamma-oryzanol was enclosed in nanosponges, which showed good photodegradation. A gel and an O/W emulsion were produced using the gamma-oryzanol-loaded nanosponges..[36].

Table 6: A List of Drugs Complexed by Using Nanosponge

Sr. No	Drug	Therapeutic Activity	Vehicles used in Nanosponges	Route of Administration	References
1	Curcumin	Anti-neoplastic	β -CD, di-methylcarbonate	Parenteral	[35]
2	Acetylsalicylic acid	Anti-inflammatory	β -CD, pyromellitic dianhydride	Oral	[6]
3	Resveratrol	Anti-oxidant	β -CD, carbonyldiimidazole	Oral, Topical	[6]
4	Tamoxifen	Anti-estrogen	β -CD, carbonyldiimidazole	Oral	[10]
5	5-Fluorouracile	Antineoplastic	β -CD	Parenteral, Topical	[32]
6	Gamma-oryzanol	Antioxidant	β -CD, diphenylcarbonate	Topical	[32]
7	Nelfinavir mesylate	Antiviral	β -CD, dimethylcarbonate	Oral	[6]
8	Doxorubicin	Antineoplastic	β -CD, diphenylcarbonate	Parenteral	[12]

9	Dexamethasone	Anti-inflammatory	β -CD, diphenylcarbonate	Oral, Parenteral	[12]
10	Itraconazole	Antifungal	β -CD, copolyvidonum	Oral, Topical	[10]

VIII. PATENTED NANOSPONGES

Table 7: List of Patented Nanosponges

Sr. No	Title of Patent	Inventors	Year	Patent No.
1.	Nanosponges as vehicle for antimicrobial medications	Francesco Trotta, Vander Tumiatti, Roberta Cavalli, Carlo Maria Roggero, Barbaramognetti, Giovanni Nicolao Berta	2008	CA2692493A1 Canada
2.	Nanosponges of silicon..	Declan Farrell, Santosh Limaye Shanthi Subramanian	2009	WO2006121870A3 WIPO (PCT)
3.	Nanosponges are used in the transport and release of enzymes, proteins, vaccines, and antibodies, as well as as a biocatalyst carrier.	Gianfranco Gilardi Francesco Trotta, Roberta Cavalli, Paolo Ferruti, Elisabetta Ranucci, Giovanna Di Nardo, Carlo Maria Roggero, Vander Tumiatti	2009	WO2009149883A1 WIPO (PCT)
4.	Metal, nanosponge, and a method involving them that are template- and polymer-free	Eswaramoorthymuthusamy, Sai Krishna Katla	2009	US8404280B2 United States
5.	Making dextrin nanosponges: the method.	Francesco Trotta, Pravin Shende, Miriam Biasizzo	2012	WO2012147069A1 WIPO (PCT)
6.	An example of a composite sound-absorbing board made with nanosponges.	Li Ligen, Wang Xiaocun	2017	CN107498936A China
7.	Application of the nanosponge in the field of air purification as well as a technique and tool for processing finely ground particles with negative ion air.	Wang Xiaocun, Wang Zilong	2017	CN105180312B China
8.	Nanoparticles, nanosponges, synthesis processes,	<u>Kun Lian</u>	2017	US20170152439A1 United States

	and application techniques.			
9.	Licoflavone nanosponges and its preparation process	Li Xiaofang, Sun Qiang	2018	CN108703944A China
10.	Method and preparation of composite of Cu ₂ O And Cu nanosponges.	Liao Jiakuan, Wu Mengqiang, Xu Ziqiang, Gong Feng, Song Yaochen, Ma Yunfei, Li Shi	2018	CN109712817A China
11.	A kind of bianry alloy PtCu nanosponges	Yuan Qiang, Hu Yanna, Liu Sun	2018	CN108372315A China
12.	Materials Based on Cross-Linked Nanoporous Saccharides and Their Fabrication	Wing Nien Wylie O, Tin Lok Li, Zhijian Lin, Dan Cheng, Jifan Li	2019	US20210122875A1 United States
13.	Method of making cross linked nanoporous carbohydrate	Ke Yingnian, Li Tianle, Lin Zhijian, Cheng Dan, Li Jifan	2019	CN112469775A China
14.	A method for making a nanosponge.	Francesco Trotta, Alberto Rubin Pedrazzo	2020	WO2021053039A1 WIPO (PCT)
15.	An etoricoxib loaded nanosponge hydrogel for arthritis & process to prepare thereof	Dr. Ashishyashwantrao Pawar, Dr. Deepak Devidas Sonawane, Dr. Rajendra, Sudhakar Bhambar, Dr. Khanderao Rajaram Jadhav, Kisan Tukaram Pawara, Sejal Rajesh Jadha	2021	IN202121042889
16.	Apomorphine formulation : a controlled and extended release	Francesco Trotta, Alessandro, Mauro, Roberta Cavalli, Lorenzo Priano, Stefania Cattaldo	2022	WO2022223522A1 WIPO (PCT)
17.	A method for creating a topical gel with nanosponges to treat psoriasis more effectively	Sherbudeen Shakila, Dr. Tiruchirappalli, Ismail, Abdulrahim Mohamed, Prof. Dr., Tiruchirappalli, Mehta, Farhad, Monisha, Janarthanan	2023	DE202023101573U 1 Germany

The preparation of dextrin nanosponges which includes the steps of preparation of dextrin solution by dissolving it in a basic solution have a $\text{pH} \geq 10$. Thus, preparing a cross-linking agent solution by dissolving a polyfunctional cross-linking agent in a water-impermeable organic solvent, and bringing the cross-linking agent solution and dextrin solution are been summarized in the above patent. Also, the above-mentioned patent provides the data one of the kinds of nanosponges that composites of sound-absorbing board and its

application, belonging to sound-absorbing material field. The invention mentioned in the application of nanosponge in air purification states that an exhaust gas purification system for a tunnel, which is distinguished by having sequentially placed negative ion purification devices on two sides of the tunnel, sequentially placed air purification devices at the top of the tunnel, and sequentially placed exhaust purification devices on the ground of a tunnel exhaust outlet. The invention relating about application of nanospunges as a vehicle of pharmaceutical formulation comprising of the cyclodextrin nanospunges which acts a vehicle for antitumoral drugs which are insoluble in water. The silicon nanospunges are prepared from a metallurgical grade silicon powder having an initial particle (10) size ranging from about 1 micron to about 4 microns. The invention mentioned for metallic coated nanoparticles states that novel metallic nanoparticles are coated with a thin protective carbon shell, and three-dimensional nano-metallic sponge and its uses which includes wood preservation, strengthening of polymer and fiber/polymer building materials, and catalysis. The cyclodextrin nanospunges which acts as a carrier the invention is all about the use of nanospunges as carriers for enzymes, antibodies, proteins, vaccines and macromolecules. The invention about the formulation for controlled and extended release containing at least one apomorphine-loaded nanosponge made of: apomorphine or its pharmaceutically acceptable salt; and a cross-linked polymer made of either dextrin or amaltodextrin. The methods used to process licoflavone nanospunges are likewise included in the invention also inventions of licoflavone nanospunges have a high rate of licoflavone dissolution and bioavailability, which enhance patient compliance and guarantee clinical efficacy. The invention related to the technical disciplines of electrode materials, specifically a type of nanospunges carbon composite Cu_2O and Cu flexible electrode. requisites and planning. Reconstitutable hydrogel powder of dapsone nanospunges for the treatment of acne are the subject of the current invention. Consisting of preservatives, raw donkey milk, porous nanospunges creating pharmaceutically acceptable polymers, and dapsone. The invention about the synthesis of a gel for the treatment of psoriasis and the technique for creating a topical gel that is laden with nanospunges for improved psoriasis treatment is the focus of patent relating to nanosponge related to topical gel. The etoricoxib nanospunges loaded hydrogel primarily consists of etoricoxib loaded nanospunges made using the emulsion solvent diffusion method. The creation of cross linked nanoporous Nanosponge material will be possible through the reaction of saccharides with cross-linkers in a single pot at various saccharides to cross-linker ratios. The employment of suitable cross-linkers and surface grafting agents allows for the introduction of new functional groups onto this material. The crosslinking nano-porous carbohydrate material that uses carbohydrates as its structural building blocks material also the presence of nano-pores or nano-cavities, the nano-porous nano-sponge material has a larger inner surface area and can be widely applied to the aspects of heat insulation, water retention, hydrophobic finishing, deodorization, metal ion exchange or absorption from water or soil, and similar processes. The template polymer free nanospunges invention is successful in offering a straightforward, single-step procedure producing porous, low density, high surface area metal nanospunges which have strong anti-bacterial action and were discovered to be effective self-supported substrates for surface-enhanced Raman spectroscopy (SERS).

IX. CONCLUSION

The original purpose of nanosponge was to deliver medications topically. They are the latest discoveries of colloidal carriers and recommended for administering drugs while their application may solubilize poorly water soluble medications and give delayed release as well as enhancing drugs bioavailability and in certain cases also changes its pharmacokinetics

parameters. As potential substitutes for targeted drug delivery, nanosponge-based systems with exceptional porosity, straightforward functionalization procedures, distinctive topologies, and cost as well as eco-effectiveness have been investigated. The pharmaceutical industry will benefit considerably when clinical trials are able to demonstrate that medications delivered by nanospunges are safe for use in humans. Future research should focus on effectively functionalizing nanospunges to reduce potential toxicity, improve their biosafety, and increase their specificity and selectivity.

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