NANOSPONGES: A DRIVEN APPROACH FOR NOVEL DRUG DELIVERY

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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 in a variety of ways to improve their qualities make up pharmaceutical nanotechnology. Targeted drug distribution can be accomplished with the help of nanosponges. Numerous medicines, both hydrophilic and lipophilic, can be loaded into nanosponges for targeted drug delivery, improving the drug's solubility and bioavailability in the process. Until 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

I. INTRODUCTION

The "Pharmaceutical Nanotechnology" a subfield of pharmaceutical sciences, offers new tools, opportunities, and research directions that are anticipated to have important implications 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, production, characterization, and application of various nanoscale materials in a variety of areas providing novel technological advancements, primarily in the field of medicine. 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 has dominated technology since the 1950s. A scientist at CalTech named Richard P. Feynman made a prediction regarding nanomaterials in 1959. 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. Materials with at least one dimension in the 1-100 nm range are referred to as nanomaterials. 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.

1. Encapsulating Nanoparticles: Particulate systems such as Nanosponges and nanocapsules are examples of this class. Alginate nanosponges, sponge-like nanoparticles with numerous pores that transport drug molecules, 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.
2. Complexing Nanoparticles: These particles attract molecules by electrostatic charges and fall under the category of complexing nanoparticles.
3. 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 capacity to delay the release of poorly water soluble medicines and increase their bioavailability. Because of their internal hydrophobic chambers and exterior hydrophilic branches, nanosponges have unrivaled flexibility and can carry both hydrophilic and 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 can be used to encapsulate a wide range of different compounds.[4,5]. Their spherical colloidal nature has been established, and their inclusion and non-inclusion behavior indicate that they have an extremely high solubilization capacity for insoluble medicines.[6]. The polymer's lengthy polyester backbone is combined in solution with tiny molecules known as cross-linkers to serve as a tiny grappling hook for joining the various components of the polymer.[7].

A. ADVANTAGES [4,8]

1. These compositions maintain their stability between pH 1 and 11.
2. These compositions maintain their stability at greater temperatures.
3. These compositions work well with the majority of substances and vehicles.
4. These are self-sterilizing because bacteria cannot pass through their 0.25 m typical pore size.
5. These formulations can be economical and free-flowing.
6. This method offers higher stability, increased elegance, fewer adverse effects, trapping of components, and increased formulation flexibility.
7. Nanosponges are non-toxic, non-allergenic, and non-mutagenic.
8. Extended release activity lasting up to 12 hours is possible.
9. Enables the inclusion of immiscible liquid; enhances the processing of materials by converting liquid to powder.
10. Scaling up for commercial manufacturing is simple.
11. By altering the cross-linker to polymer ratio, the size of the nanosponges can be changed.
12. The medication release characteristics might be fast, medium, or slow depending on the dose requirement.
13. Release that is expected.
14. Modifying pH or ionic strength, light heating, washing with environmentally friendly solvents, or stripping with relatively inert hot gases can all be used to regenerate nanosponges.
15. Less detrimental side effects due to the drug coming into contact with healthy tissue less frequently.

B. DISADVANTAGES [9]

1. Only tiny molecules can be included by nanosponges.
2. Nanosponges may be crystalline or paracrystalline in nature.
3. The degree of crystallization mostly determines the loading capacity of nanosponges.
4. Different loading capacities can be seen in paracrystalline nanosponges.

C. CHARACTERISTIC FEATURES OF NANOSPONGES [11]

1. Nanosponges offer a variety of diameters (1 m or less) with adjustable cavity polarity.
2. By altering the cross-linker to polymer ratio, nanosponges of a particular size can be created.
3. Depending on the circumstances of the process, they can take either paracrystalline or crystalline forms. Nanosponges' crystal structure is essential for the complexation of medicines with them.
4. The degree of crystallization determines the drug loading capacity.

5. Paracrystalline nanosponges can demonstrate various drug loading capabilities.
6. They contain porous particles that are nontoxic, insoluble in the majority of organic solvents, and stable up to 300 °C.
7. They can withstand pH levels between 1 and 11.
8. In water, they create a clear, opalescent suspension.
9. They can be duplicated utilizing straightforward thermal desorption, solvent extraction, microwaves, and ultrasounds.
10. Their three-dimensional design enables the capture, transport, and controlled release of several chemicals.
11. Because of their ability to connect with several functional groups, they can be placed at various target places.
12. Nanosponges can connect more effectively to the target region thanks to chemical linkers.
13. Nanosponges are capable of forming inclusion- and non-inclusion-based complexes when they interact with certain medicines.
14. Magnetic qualities can also be given to nanosponges by including magnetic particles in the reaction mixture.
15. Nanosponges are porous, highly soluble in water particles that are primarily employed to encapsulate poorly soluble medicines.
16. These Nanosponges may transport both hydrophilic and lipophilic medications.
17. 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

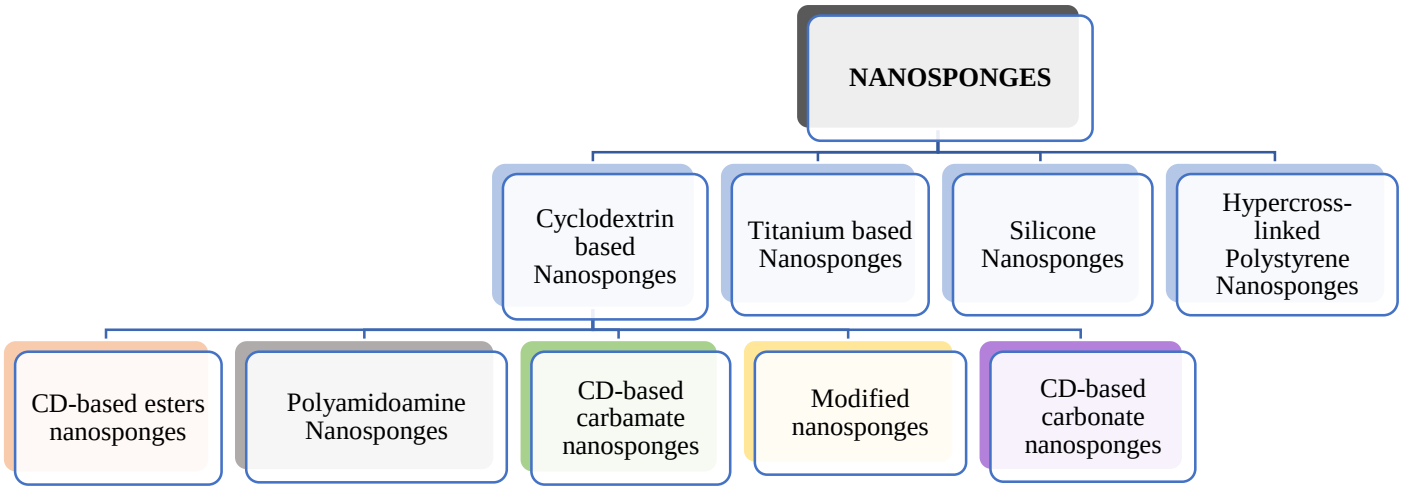

Figure 2: Types of Nanosponges

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 an insoluble network and indicates a high 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 can produce spherical, crystalline, or amorphous, porous, insoluble nanoparticles with tunable polarity and size. There are three distinct CD types: There are three types of cyclodextrin: 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 as being produced by reacting cyclodextrins (cyclic oligosaccharides) 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 is the formation of spherically shaped particles with cavities that can hold medicinal molecules.[15].

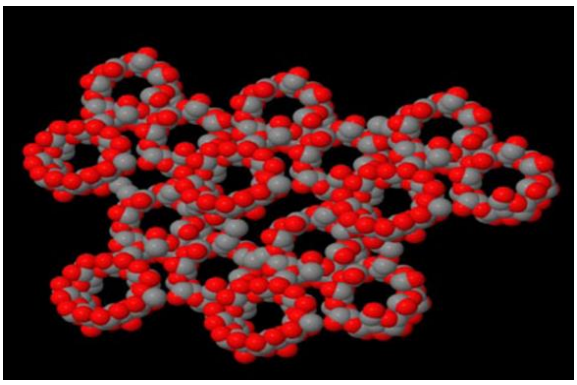

Figure 1. Cyclodextrin carbonates nanosponges' molecular structure.

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 already 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 have been shown to be 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 may be dissolved in a matrix of excipients, diluents, lubricants, and anti-caking agents appropriate for the manufacture of capsules or tablets for oral delivery. The compound can easily be transported in sterile water, saline, or other aqueous solutions for parenteral administration. They can be successfully integrated into topical hydrogel for topical delivery. The medication molecules are contained within the center of encapsulating nanoparticles called nanosponges.[19].

Cyclodextrins have been primarily used in the pharmaceutical industry because,

a. They are semi-natural goods made by relatively simple enzymatic conversion from renewable natural starch.
b. They are created using environmentally friendly methods at a rate of thousands of tons annually.
c. 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.

CD based NS are further Classified into:

A. CD-based carbamate nanosponges:

In the presence of a DMF solution, CDs are reacted 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 cm^3.[20,21].

B. CD-based carbonate nanosponges:

Active carbonyl compounds like CDI, DPC, and tri-fosgene are the primary cross-linkers used to manufacture this sort of nanosponges. Two CD monomers form carbonate bonds in the resultant CD nanosponges. If a solvent is present or absent, the reaction can be conducted at ambient temperature or between 80 and 100°C using either the melt technique or the solvent approach. The polarity and cavity diameters of carbonate-CD based nanosponges can be changed, which is one of their key properties. They can be produced under various conditions to yield various shapes, such as amorphous or semi-crystalline. Numerous medications, including paclitaxel, camptothecin, dexamethasone, flurbiprofen, 5-fluorouracil, cilostazol, progesterone, oxcarbamazepine, nelfinavir mesylate, resveratrol, and tamoxifen, have been encapsulated using carbonate-CD-based nanosponges. Water's surface tension is not considerably impacted by carbonate nanosponges. Due to their non-hygroscopic nature, they maintain their crystal structure both during moisture absorption and desorption. The ability of CD-based carbonate nanosponges to increase solubility depends heavily on their level of crystallinity, which is a distinctive characteristic.[7, 21].

C. CD-based ester nanosponges:

The crosslinking agent employed to create these nanosponges is a suitable dianhydride, such as pyromellitic anhydride. The CD and dianhydride are dissolved in DMSO in the presence of an organic base, such as pyridine or triethylamine (to speed the reaction in a forward direction), to perform the exothermic crosslinking process, which is carried out at room temperature and is very quick (finished in a few minutes). A polar free carboxylic acid group found in these nanosponges allows them to accommodate cations as well as apolar organic molecules concurrently.[22].

D. Polyamidoamine Nanosponges:

These nanosponges are made by performing the reaction in water. After 94 hours at room temperature of prolonged standing, CD polymerizes with acetic acid 2, 20-bis (acrylamide). They have acidic and basic residues, which causes them to swell in water (pH dependant behaviour). When the polymer comes into contact with water, a translucent gel forms immediately. The stability of the gel for up to 72 hours was validated by time-dependent swelling experiments in biorelevant medium. Albumin was used in the studies as a model protein because of its extremely high encapsulation efficiency—roughly 90%. Studies on in vitro drug release demonstrated that the protein release may be controlled for up to 24 hours. The stability of the product was examined using the sodium dodecyl sulfate (SDS) PAGE method. SDS PAGE analysis of the protein's conformational stability revealed that the formulation was stable for up to many months.[23].

E. 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. MECHANISM OF DRUG RELEASE FROM NANOSPONGES

The sponge atoms are set up in an open configuration, allowing the active to freely enter and exit the particles as well as the vehicle until equilibrium is reached. The chemical component that is already within the vehicle will eventually be absorbed into the target tissue in the case of topical distribution after the finished product is applied to it. The balance is upset when a vehicle is depleted because it will become unsaturated. As a result, an active flow will begin from the sponge particle in the vehicle and then from the vehicle to the target tissue, continuing unless the vehicle is either dried out or absorbed. After then, the sponge particles that were left on the tissue's surface would continue to gradually release the active substance to it, giving the tissue a sustained release over time.[4].

IV. CHEMICALS USED FOR THE SYNTHESIS OF NANOSPONGES [4,6]

1) Polymers
   Polymers used for the synthesis of nanosponges are including: hyper-cross linked polystyrenes, cyclodextrins and its derivatives like Methyl β-cyclodextrin (β-CD), alkyloxy carbonyl cyclodextrins, 2-hydroxy propyl β-CDs and copolymers like poly (Valero lactone-allylvalero lactone) and poly (Valero lactone-allyl Valero lactone oxepanedione) and ethyl cellulose and PVA.
2) Cross-linkers
   Crosss-linkers used for the synthesis of nanosponges contain diphenyl carbonate, diarylcarbonates, di-isocyanates, pyromelliticanhydride, carbonyldiimidazoles, epichloridrine, glutarldehyde, carboxylic acid dianhydrides, 2,2-bis(acrylamido) acetic acid and dichloromethane.
3) Co-polymers
   Poly (Valerolactone allylvalerolactone), Poly (Valerolactone-allylvalerolactone oxepanedione), ethyl cellulose, polyvinyl alcohol.
4) Drug substances
   Drug molecule to be formulated as nanosponges should have certain characteristics-
   a) Molecules with a molecular weight of 100 to 400 daltons.
   b) The drug molecule has less than five condensed rings.
   c) Water solubility is less than 10 mg/ml.
   d) The substance's melting point is below 250°C.

V. METHODS OF PREPARATION OF NANOSPONGES

A. Solvent method

The polymer was combined using a suitable solvent in this approach, specifically a polar aprotic solvent like di-methylformamide or di-methylsulfoxide. This combination was added to extra cross-linker, preferably in a 4 to 16 molar ratio between the cross-linker and the polymer. The reaction was run for 1 to 48 hours at temperatures varying from 10 °C to the solvent's reflux temperature. Dimethyl carbonate and carbonyl di-imidazole are preferred cross linkers among carbonyl compounds. After the reaction was finished, the solution was allowed to cool at ambient temperature. Then, the product was added to a significant amount of bidistilled water, which was then filtered under vacuum to recover the product, which was then further purified by prolonged Soxhlet extraction with ethanol. The product was vacuum-dried before being mechanically milled to create a uniform powder.[7].

B. Ultrasound-assisted synthesis

Using this technique, nanosponges were created by combining cross-linkers and polymers without the need of a solvent and while being sonicated. This technique will produce spherical, uniform-sized nanosponges. at a flask, the cross-linker and polymer were combined at a certain molar ratio. The flask was heated to 90 °C by submerging it in a water-filled ultrasonic bath. 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].

C. Emulsion solvent diffusion method

Ethyl cellulose and polyvinyl alcohol can be used in various concentrations to make nanosponges. To enhance drug loading and achieve a customized release, different ratios of medication to polymer are utilized. A specific amount of polyvinyl alcohol in 100 ml of an aqueous external phase was added slowly over the course of three to five hours using a magnetic or mechanical stirrer at a speed of 1000 to 1500 rpm while the dispersion phase, which contained the drug and polymer, was dissolved in 20 ml of dichloromethane. The created nanosponges were filtered out, dried in an oven at 40°C for 24 hours, and then packaged.[6].

D. Quasi-emulsion solvent diffusion

Additionally, the nanosponges can be made utilizing the quasi-emulsion solvent diffusion process at various polymer concentrations. Eudragit RS100 was dissolved in an appropriate solvent to prepare the inner phase. The medicine can then be added to the solution and dissolved using an ultrasonic process at 350 c. The inner phase was added to the water-based PVA solution (the outer phase), and the combination was stirred for one hour before filtering to remove the nanosponges. The nanosponges are dried in an air-heated oven at 40 °C for 12 hours.[16].

E. 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 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].

F. Polymerization

Aqueous phase, typically comprising surfactant and dispersant to enhance suspension, is added to a non-polar drug solution created in the monomer. Once the suspension with the distinct droplets of the correct size is established, polymerization is accomplished by catalyzing or raising the temperature to activate the monomers. A reservoir-like system that opens through holes at the surface is created as a result of the polymerization process.

VI. 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. To avoid the presence of aggregates, the nanosponges were left suspended in water and sonicated. The solution was then centrifuged to get the colloidal fraction. The material was dried by freeze drying after the supernatant was separated. The surplus medication was disseminated into the aqueous suspension of nanosponges, and the solution was kept under constant stirring for the allotted amount of time needed for complexation. Following complexation, the complexed drug has been separated from the uncomplexed (undissolved) medication using centrifugation. The solid nanosponges crystals were then produced through solvent evaporation or freeze drying. The nanosponge's crystal structure is crucial for the complexation of drugs. According to a study, paracrystalline nanosponges and crystalline nanosponges have distinct loading capabilities. Crystalline nanosponges have a higher drug loading than paracrystalline ones. Drug loading takes place as a mechanical mixing rather than an inclusion complex in weakly crystalline nanosponges.[7].

VII. CHARACTERIZATION OF NANOSPONGES

A. 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. Laser light diffractometry or a Zeta sizer can be used to measure particle size.[24]. To investigate the impact of particle size on drug release, cumulative percentage drug release from nanosponges of various particle sizes can be plotted versus time. Particle sizes between 10 and 25 µm may be desirable for topical medication administration, whereas those more than 30 µm may exhibit a gritty sensation.[27].

In herbal formulation for encapsulation of babchi oil in cyclodextrin based nanosponges. They have taken five types of babchi oil which is loaded by Cyclodextrin Nanosponges in Different molar ratio. The particle size of the BO nanosponges ranged from 234 to 484 nm (table no 1). All the prepared BO nanosponges depicted particle size in the nano range (<1 µm). This shows they are in significant range.[28].

Table no. 1

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

In synthetic the characterization of carboxymethyl chiton nanosponges with cyclodexin blends were studied to check drug solubility increases or not. The average particle sizes of the developed nanosponges (F-0 to F-9) are presented (table no 2). All the prepared nanosponges depicted particle size in the nano range (<1 µm). This shows they are in significant range.[29].

Table no 2

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

B. 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].

PDI = d/d avg Δ

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 no 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

The production yield of the nanosponges can be calculated by following equation after determining accurate initial weight of the raw materials and final weight of the nanosponge obtained.[30].

Production yield (PY) = Practical mass of NS ÷ Theoretical mass (polymer + Drug) × 100

As reported cyclodextrin was encapsuled 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 Nanosponges 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 no 4

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

As reported for synthetic nanosponges during characterization of carboxymethyl chitosan nanosponges encapsuled with cyclodextrin blends to check solubility is improves or not. The value of the polydispersity index (PDI) was discovered to be 0.279. The poor affinity of produced nanosponges to form aggregates was shown by the low PDI value. Created nanocrystals to improve the solubility of nifedipine, and they found that a smaller particle size led to a faster release of the medication.[29].

C. 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 size of the electrical surface charge at the double layer, zeta potential 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 ±30mV High zeta potential indicates that the nanosponge would remain stable because of stronger repulsive forces, which reduces their propensity to assemble.[28].

Table no 5

Sr.no	Formulation	Zeta Potential (mV ± 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].

D. Thermodynamical method:

The thermo-chemical approach may be used to assess if drug molecules or particle alterations take place before the thermal destruction of Nano sponges. Melting, evaporation, oxidation, breakdown, and polymeric modifications are only a few of the possible drug particle alterations. The drug molecules' alterations show that a strong complex has formed.[31].

In herbal formulation of babchi oil which was encapsuled in cyclodextrin to study characterization, in vitro cytotoxicity and physiochemical. The temperature difference between the sample and the reference that caused heat absorption or release is measured by differential thermal analysis. [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].

E. Microscopy studies:

Both transmission electron microscopy (TEM) and scanning electron microscopy (SEM) can be used to examine the microscopic components of a drug or nanosponge formulation. SEM is used to examine the morphology of nanosponges, and the difference between the raw materials used to make a nanosponge and the final formulation's crystallization state indicates the formation of inclusion complexes. [31].

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

LE = Actual drug content in nanosponges ÷ Theoretical drug content x 100

Utilizing an HPLC approach and a quantitative evaluation of the drug put into a nanosponge UV spectrophotometer, loading efficiency can also be evaluated. This involves measuring the quantity of drug-loaded nanosponges that are distributed in an appropriate solvent and sonicated for a certain amount of time to break up any complexes. After dilution, the sample is then examined using a UV spectrophotometer or HPLC technique.[32].

In formulation for herbal babchi oil was encapsuled in cyclodextrin**.** They have taken five types of babchi oil which is loaded by Cyclodextrin Nanosponges 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].

When Carboxymethyl Chitosan Nanosponges with Cyclodextrin Blends for Drug Solubility Improvement 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 nanosponges displayed drug loading of at least 70%. The minimal drug entrapment efficiency and drug-loaded contents were shown by Formulations F-8 and F-9, respectively, at 71.40-74.44% and 80.43-83.62%. Due to the product's stickiness, lansoprazole-loaded nanosponges 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].

F. **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 Nanosponges 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 nanosponges with cyclodextrin blends. The outcomes showed that the primary goal of creating nanosponges improving docetaxel's solubility was achieved. Previous research indicated that nanosponges 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].

G. **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 another molecule that is designated by bands on the spectrum of nanosponges, 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].

H. X-ray diffractometry:

Inclusion complexation in the solid state may be detected using powder X-ray diffractometry. The diffraction patterns and crystalline structure of the drug are altered by the intricate synthesis of the drug with nanosponges.[27]. A newly created material obviously varies from an uncomplicated nanosponge in terms of its diffraction pattern. 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 forumation of babchi oil Significant differences between their diffract grams 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° (2Θ).[28].

During synthetic capsulation the existence of distinctive peaks at 2Θ= 11.52º, 13.10º, 15.80º, 20.31º, 22.11º, 23.10º, 26.55º, and 27.71º demonstrated the crystallinity of AMPS. A PXRD diffractogram of a physical combination of medicine and polymer showed fewer but sharper peaks at 2Θ = 19.21º, 28.11º, and 36.91º, 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].

I. In Vitro release studies:

Using a multi-compartment rotating cell with a dialysis membrane (cut-off 12,000 Da), it is possible to analyse the drug release from the improved nanosponge formulation. The drugloaded nanosponge complex in distilled water makes up the donor phase. The same medium is present in the receptor phase as well. After predetermined time intervals, the receptor phase is entirely removed, appropriately diluted with distilled water, and then examined using a UV spectrophotometer.[27].

For topical drug delivery the study of itraconazole loaded nanosponges data from an in-vitro release trial of a pure medication and a chosen batch. It was discovered that 70.62% of the medication had been released from F4 nanosponges after 120 minutes.[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). The drug release of fabricated nanosponges was significantly higher at pH 6.8 as compared to pH 1.2 and 4.5. [29].

10. Porosity study:

To determine the amount of produced nanochannels and nanocavities, a porosity analysis is conducted. A helium pycnometer is used to measure the porosity of nanosponges since helium gas may pass via both inter- and intra-specific channels in materials. The helium displacement technique is used to calculate the material's real volume. Because they are porous, nanosponges have more porosity than the parent polymer that was utilized to create the system.[34].

Percent Porosity equation: % Porosity (E)= Bulk volume – True volume ÷ Bulk volume × 100

VIII. APPLICATIONS OF NANOSPONGES

A. **Solubility enhancement**: Nanosponges can enhance the solubility and wetting of molecules having very low water solubility. The dissolution process can be skipped if the medications are molecularly disseminated inside the nanosponge structure and subsequently released as molecules. As a result, the drug's perceived solubility can be improved. By increasing a substance's solubility and rate of dissolution, various formulation and bioavailability issues can be resolved, and nanosponges can significantly increase a drug's solubility.

B. **Nanosponges for drug delivery**: The nanosponges can be made into dosage forms for oral, parenteral, topical, or inhalation use. They are solid by nature. The complexes may be disseminated in a matrix of excipients, diluents, lubricants, and anticaking agents appropriate for the manufacture of capsules or tablets for oral delivery. The compound can easily be transported in sterile water, saline, or other aqueous solutions for parenteral administration. They can be successfully integrated into topical hydrogel for topical delivery.[5].

C. **Topical agents**: 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. Drugs that are easily manufactured as topical nanosponges include local anesthetics, antifungals, and antibiotics. When active substances enter the skin, rashes or more severe adverse effects may develop. In contrast, this technique enables a steady and prolonged rate of release, minimizing discomfort while preserving effectiveness. A designed product can have a wide range of ingredients, including liquid, gel, cream, lotion, ointment, and powder.[16].

D. **Nanosponges as a carrier for biocatalysts and in the delivery and release of enzymes, proteins, vaccines and antibodies**: Many systems, including nano and microparticles, liposomes, and hydrogels, have been designed to transport proteins and enzymes. Proteins can be stabilized in vivo, have their pharmacokinetics changed by carriage in a specific system, and be protected from deterioration. The ability to adsorb proteins, enzymes, antibodies, and macromolecules is now known to be particularly well suited for cyclodextrin-based nanosponges. When enzymes are utilized, in particular, it is possible to preserve their activity, efficiency, prolong their operation, and expand the pH and temperature range of their activity, which enables the conduct of continuous flow operations. Furthermore, by adsorbing or encasing them in cyclodextrin nanosponges, proteins and other macromolecules can be transported.[36].

E. Nanosponges as a carrier for delivery of gases: Gases are used in medicine for both diagnostic and therapeutic purposes. Hypoxia, or a lack of sufficient oxygen supply, is linked to a number of diseases, including cancer and inflammatory diseases. In clinical practice, it can be challenging to administer oxygen in the right form and amount. As topical oxygen delivery systems, Cavalli et al. created formulations for nanosponges that have the capacity to store and release oxygen gradually over time.[35].

F. Nanosponges as protective agent from light or degradation: A ferulic acid ester combination known as gamma-oryzanol has recently gained a lot of attention due to its potential as a natural antioxidant. It is typically used to preserve food and pharmaceutical raw materials as well as a sunscreen in the cosmetics sector. Due to its high level of instability and photodegradation, its use is restricted. Nanosponges were used to encapsulate gamma-oryzanol, which demonstrated good photodegradation. The nanosponges that were loaded with gamma-oryzanol were used to create a gel and an O/W emulsion.[36].

Table 6: A list of drugs complexed by using nanosponge

Sr. No.	Drug	Therapeutic Activity	Vehicles used in Nanosponges	Attributes	Route of Administration	References
1.	Curcumin	Anti-neoplastic	β-CD, di-methylcarbonate	Enhanced activity, Solubilization	Parenteral	[35]
2.	Acetylsalicylic acid	Anti-inflammatory	β-CD, pyromellitic dianhydride	Prolonged drug release	Oral	[6]
3.	Resveratrol	Anti-oxidant	β-CD, carbonyldiimidazole	Enhanced stability, permeation, cytotoxicity, controlled drug release	Oral, Topical	[6]
4.	Tamoxifen	Anti-estrogen	β-CD, carbonyldiimidazole	Enhanced bioavailability, solubility	Oral	[10]
5.	5-Fluorouracile	Antineoplastic	β-CD	Enhanced drug stability	Parenteral, Topical	[32]
6.	Gamma-oryizanol	Antioxidant	β-CD, diphenylcarbonate	Enhanced stability, solubility, permeation	Topical	[32]
7.	Nelfinavir mesylate	Antiviral	β-CD, dimethylcarbonate	Enhanced drug solubilization	Oral	[6]
8.	Doxorubicin	Antineoplastic	β-CD, diphenylcarbonate	Sustained drug release	Parenteral	[12]
9.	Dexamethasone	Anti-inflammatory	β-CD, diphenylcarbonate	Enhanced drug solubility	Oral, Parenteral	[12]
10.	Itraconazole	Antifungal	β-CD, copolyvidonum	Enhanced drug solubility	Oral, Topical	[10]

IX. PATENTED NANOSPONGES

Table 7: List of patented nanosponges

Sr. No	Title of patent	Inventors	Year	Patent No.
1.	Cyclodextrin-based nanosponges as a vehicle for antitumoral drugs.	Francesco Trotta, Vander Tumiatti, Roberta Cavalli, Carlo Maria Roggero, Barbaramognetti, Giovanni Nicolao Berta	2008	CA2692493A1 Canada
2.	Silicon nanosponge particles.	Declan Farrell, Santosh Limaye Shanthi Subramanian	2009	WO2006121870A3 WIPO (PCT)
3.	Cyclodextrin nanosponges as a carrier for biocatalysts, and in the delivery and release of enzymes, proteins, vaccines and antibodies.	Gianfranco Gilardi Francesco Trotta,Roberta Cavalli, Paolo Ferruti, Elisabetta Ranucci, Giovanna Di Nardo, Carlo Maria Roggero, Vander Tumiatti	2009	WO2009149883A1 WIPO (PCT)
4.	Template free and polymer free metal, nanosponge and a process thereof	Eswaramoorthymuthusamy, Sai Krishna Katla	2009	US8404280B2 United States
5.	Method for preparing dextrin nanosponges.	Francesco Trotta, Pravin Shende, Miriam Biasizzo	2012	WO2012147069A1 WIPO (PCT)
6.	A kind of nanosponges composite sound-absorbing board and its application.	Li Ligen, Wang Xiaocun	2017	CN107498936A China
7.	Application of the nanosponge in air purification field and the method and apparatus with negative aerion combined purifying processing finely ground particles.	Wang Xiaocun, Wang Zilong	2017	CN105180312B China
8.	Nanoparticles, Nanosponges, Methods of Synthesis, and Methods of Use.	Kun Lian	2017	US20170152439A1 United States
9.	Licoflavone nanosponges and its preparation process	Li Xiaofang, Sun Qiang	2018	CN108703944A China
10.	A kind of nanosponges carbon composite Cu2O and Cu flexible electrode material and preparation method thereof	Liao Jiaxuan, 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.	Cross-linked Nanoporous Saccharide-based Material and Methods for Fabrication Thereof	Wing Nien Wylie O, Tin Lok Li, Zhijian Lin, Dan Cheng, Jifan Li	2019	US20210122875A1 United States
13.	Cross-linked nanoporous carbohydrate-based materials and methods of making the same	Ke Yingnian, Li Tianle, Lin Zhijian, Cheng Dan, Li Jifan	2019	CN112469775A China
14.	Process for preparing 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.	Extended and controlled release formulation of apomorphine.	Francesco Trotta, Alessandro, Mauro, Roberta Cavalli, Lorenzo Priano, Stefania Cattaldo	2022	WO2022223522A1 WIPO (PCT)
17.	A system to develop a nanosponge-loaded topical gel for enhanced treatment of psoriasis	Sherbudeen Shakila, Dr. Tiruchirappalli, Ismail, Abdulrahim Mohamed, Prof. Dr., Tiruchirappalli, Mehta, Farhad,Monisha, Janarthanan,	2023	DE202023101573U1 Germany

The preparation of dextrin nanosponges which includes the steps of preparation of dextrin solution by dissolving it in a basic solution have a pH≥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 nanosponges as a vehicle of pharmaceutical formulation comprising of the cyclodextrin nanosponges which acts a vehicle for antitumoral drugs which are insoluble in water. The silicon nanosponges 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 nanosponges which acts as a carrier the invention is all about the use of nanosponges 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 nanosponges are likewise included in the invention also inventions of licoflavone nanosponges 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 nanosponges carbon composite Cu_2O and Cu flexible electrode. requisites and planning. Reconstitutable hydrogel powder of dapsone nanosponges for the treatment of acne are the subject of the current invention. Consisting of preservatives, raw donkey milk, porous nanosponges 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 nanosponges for improved psoriasis treatment is the focus of patent relating to nanosponge related to topical gel. The etoricoxib nanosponges loaded hydrogel primarily consists of etoricoxib loaded nanosponges 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 nanosponges invention is successful in offering a straightforward, single-step procedure producing porous, low density, high surface area metal nanosponges which have strong anti-bacterial action and were discovered to be effective self-supported substrates for surface-enhanced Raman spectroscopy (SERS).

CONCLUSION

The original purpose of nanosponge was to deliver medications topically. They are colloidal carriers that have recently been discovered and proposed for drug administration while their application may solubilize poorly water soluble medications and give delayed release as well as enhancing drugs bioavailability and in certain cases changing 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. If clinical trials can demonstrate the possibility for human usage of drugs delivered via nanosponges, the pharmaceutical businesses will gain significantly. Future research should focus on effectively functionalizing nanosponges to reduce potential toxicity, improve their biosafety, and increase their specificity and selectivity.

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