

NANOSPONGES: AS A DYNAMIC DRUG DELIVERY APPROACH FOR TARGETED DELIVERY

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ABSTRACT

Recent advancements in nanotechnology have resulted in improved medicine delivery to the target site. Nanosponges are three-dimensional drug delivery systems that are nanoscale in size and created by cross-linking polymers. The introduction of Nanosponges has been a significant step toward overcoming issues such as drug toxicity, low bioavailability, and predictable medication release. Using a new way of nanotechnology, nanosponges, which are porous with small sponges (below one μm) flowing throughout the body, have demonstrated excellent results in delivering drugs. As a result, they reach the target place, attach to the skin's surface, and slowly release the medicine. Nanosponges can be used to encapsulate a wide range of medicines, including both hydrophilic and lipophilic pharmaceuticals. The medication delivery method using nanosponges is one of the most promising fields in pharmacy. It can be used as a biocatalyst carrier for vaccines, antibodies, enzymes, and proteins to be released. The existing study enlightens on the preparation method, evaluation, and prospective application in a medication delivery system and also focuses on patents filed in the field of nanosponges.

Keywords: Nanosponges, Cross-linkers, Controlled release, Topical application, β -cyclo-dextrin and polymers

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INTRODUCTION

Richard Feynman was the first to coin the term nanotechnology in 1959 [1]. It is described as the subatomic control, detection, and treatment of many human bodily systems using both nano-devices and nanostructures [2]. One of the major recognized areas of logical study, principally for medicinal applications, is nanotechnology [3]. It is one of the newest trends in the pharmacy and biomedical industries for the distribution of drug systems. Drug delivery has a variety of effects on medical innovation, including the development of novel remedies [4]. Medical analysts have long struggled with how to deliver drugs to a target spot in the body whereas limiting the release of medicament to avoid overdosing [5]. Nanosponges (NSs) have been discovered to be a new and complicated chemical with significant effects on the aforementioned issues [6].

As a result, it has only lately been introduced and developed for medication delivery. The NSs drug delivery (NSDD) was previously solely utilized as topical systems; however, there are now oral and intravenous (IV) delivery methods available [7]. NSs, with their tiny size and efficient carrier features, ranging from 100-400 Dalton and a melting point of 250 °C, play an important role in modulating delivery at the target location [8]. NSs are materials made consisting of small particles with large cavities less than one nanometer in diameter, in which a wide range of compounds can be enclosed [9]. By changing the pharmacokinetic properties of medicinal molecules, nanosponges can carry both hydrophilic and lipophilic compounds and their bioavailability [10]. Because of their 3-dimensional scaffold or polyester structure, nanosponges decompose naturally.

In a solution, polyester and cross-linker are combined to generate nanosponges [11].

The medicine contained in the nanosponges releases while the scaffold of the NSs disintegrates [12]. Nanosponges are beneficial for the treatment of a variety of issues, and they are more effective for breast cancer than the traditional way. Instead of being dispersed throughout the body, nanosponges transport the medicine directly to the tumor location [13]. Because a less amount of medicine gets into contact with normal tissues, it is exceedingly adequate for a given dose with fewer side effects [14]. Nanosponges have a diameter of less than one μm and can endure temperatures of around 300 °C [15]. Numerous kind of research has been conducted in the past that unquestionably attest to the numerous therapeutic uses of NSs in a wide range of illnesses. From 1998 to 2022, there have been more than 409 research papers and review articles on nanosponges in the PubMed database, indicating their significant significance. The systemic review inclusion of about 57 studies indicated the therapeutic advantages of NSs in various domains.

Nanosponge's types

There are many different varieties of nanosponges, each of which can be created and constructed differently based on the polymer utilized, its concentration, and the technique used. Beta CD-based nanosponges are the most frequent type of nanosponges that are manufactured and widely used [16]. The formulation of beta-CD nanosponges is a reasonably straightforward process with a wide range of modifications, as shown in fig. 1.

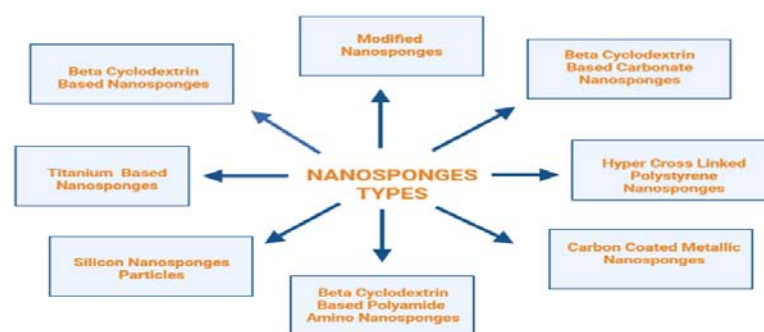


Fig. 1: Type of nanosponges [9]

Cyclodextrin-based nanosponges

Nanosponges made of cyclodextrin resemble sponge-like lyophilized structures and can respond with the help of the small molecules in their matrix. Different types of cyclodextrin were cross-linked using cross-linkers (such as diphenyl carbonate), carbonyldiimidazole dimethyl carbonate, etc. to create the NSs. A certain quantity of α -, β -, and γ -cyclodextrin (naturally occurring) cross-links are used to make cyclodextrin. Since they have the uppermost complexity and stability due to their ideal cavity dimension with cross-linkable polymers, they are typically made from β -cyclodextrin [16, 17].

Titanium-based nanosponges

Polystyrene microspheres coated with titanium-based nanosponges were made by copolymerizing styrene and other polymerizable surfactants. To exploit photo anodes for photo-electrochemical applications, TiO₂/ZnO hybrid NSs are manufactured. In a wide range of applications, including photo-catalytic properties, recyclable oil absorbents, electrodes, pollutant removal, biosensors, antimicrobial application, and drug delivery, metallic NS such as TiO₂ NS, carbon-coated metallic NSs, and silicon NSs particles have been reported.

Silicon-based nanosponges

A metallurgical grade silicon powder is used to make silicon nanosponges, which are then produced by scratching nearly 1-4 micron-sized silicon powder particles. The very porous silicon NS serves as a carrier material for fuel cell electrodes, photo-sensitizers, explosives, catalysts, medicines, and adsorbents. Additionally, it is used as a precursor for high surface area ceramic materials such as SiNa and SiC [17].

Hyper-linked polystyrene (HLP)-based nanosponges

Individual polystyrene coils were suspended in weak solvents before being introduced in large amounts to stiff intermolecular bridges, which caused the coils to contract strongly and eventually form spherical NSs. The NS solutions had strong diffusion, low viscosity, and high rates of sedimentation. The linear polystyrene non-solvent considerably exacerbated the swelling of these NSs, which had larger interior surface

areas. The appropriate separation of inorganic electrolytes was achieved by utilizing the hyper-cross-linked NS in size exclusion chromatography. Both cyclodextrin-based NS and hyper-cross-linked polystyrene NS have been used to create tissue scaffolds [18].

Advantages

Poorly water-soluble medications will become more soluble due to nanosponges, which will also help regulate drug molecule release. They are used to remove harmful compounds from the body, prevent side effects, and hence reduce the frequency of dosing. Nanosponges will improve the formulation's stability while simultaneously increasing its flexibility [19]. They're non-irritating, non-toxic, and non-mutagenic, and they're more patient-friendly. Because of their tiny pore sizes, the nanosponges are impermeable to bacteria, which act as a self-sterilizer. Nanosponges administer pharmaceuticals in a controlled manner and deliver drugs specifically [20]. These are used to disguise the bad taste of drugs. Using nanosponges, liquid substances can be turned into solids, and the particles can be designed to be large or tiny by adjusting the cross-linked percentage of the polymer [21]. They also help with the dissolving of medicament in a controlled way.

Disadvantages

Because nanosponges are not appropriate for big molecules, dosage dumping may occur. They are capable of encapsulating smaller molecules [22]. The degree of crystallinity reduces drug loading capacity. Nanosponges can only prepare tiny molecules and are limited by their loading capabilities [23].

Components used in the preparation of nanosponges

Multiple chemicals are effective in the manufacture of nanosponges, and their application is dependent on the type and level of cross-linking required [24]. The level of cross-linking in nanosponges is important and is determined by the concentration of cross-linkers utilized, as it influences the drug release pattern and drug encapsulation [25]. Below is a list of the substances utilized in the technique of preparation is shown in fig. 2.

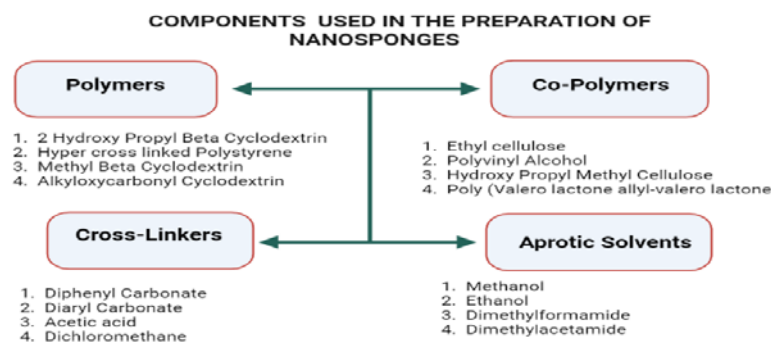


Fig. 2: Different chemicals used for the preparation of nanosponges [25]

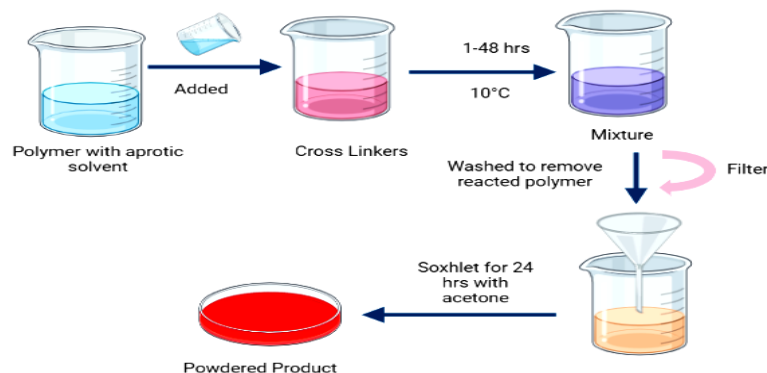


Fig. 3: Preparation of nanosponges by solvent method [30]

Method of preparation

Solvent method

Polymer is mixed with polar aprotic solvents such as dimethylformamide [DMF] and dimethyl sulfoxide [DMSO] to form nanosponges using the solvent method. In a 1:4 ratio, a crosslinker is added to this mixture [26]. Commonly utilized cross-linkers include carbonyl compounds and Carbonyldiimidazole, and the reaction (10 °C) should occur to reflux the solvent temperature for 1 to 48 h [27]. The cooled solution is added to bi-distilled water. The substance is then dried drained and refined using the Soxhlet method with ethanol [28]. The product is vacuum-dried, and then a mechanical mill is used to grind it into a uniform powder as shown in fig. 3.

Ultra-sound-assisted synthesis

The uniform, spherical nanosponges are made with the aid of ultrasonic synthesis. Except for the solvent, the polymers and cross-linkers react in a flask before being put into an ultrasonic bath with

water that has been heated to 90 °C. The mixture is broken up into rough bits [29] after being ultrasonically processed for five hrs and cooled to room temperature. Using the Soxhlet apparatus and washing, the non-reacting polymer is eliminated, resulting in nanosponges. The cross-linkers utilized in this approach are diphenyl carbonate or pyromellitic anhydride as shown in fig. 4 [30].

Emulsion-solvent diffusion method (ESDM)

Various quantities of ethyl cellulose (EC) and polyvinyl alcohol (PVA) are employed to manufacture nanosponges using the emulsion solvent diffusion process. The two phases used in this procedure are continuous and dispersed [31]. The dispersion phase is made up of drug and ethyl cellulose, which is then progressively introduced to the aqueous phase, which is made up of PVA. After swirling for 2-4 h at 2000 rpm, the crosslinker is applied and filtered before drying in an oven at 40 °C (24 h) [30, 32]. Dried nanosponges are maintained in vacuum desiccators to eliminate any leftover solvent as shown in fig. 5.

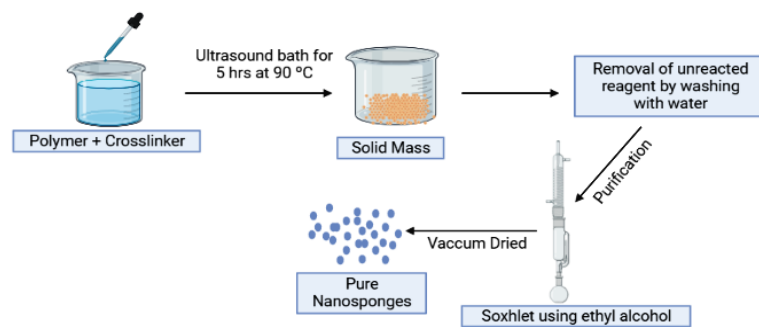


Fig. 4: Nanosponges by ultra-sound assisted synthesis [30]

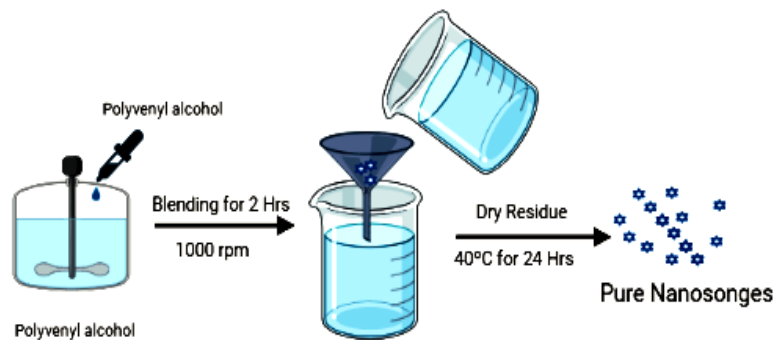


Fig. 5: Nanosponges by ESDM [35]

Melt method

During the melting process, the crosslinker and the polymer are combined. Nanosponges were collected by periodically washing

them with a suitable liquid [30, 33]. Nanosponges are obtained after product cleaning, removing the waste polymer and unreacted chemicals [34]. These blank Nanosponges were then exposed to narcotic encapsulation, as revealed in fig. 6.

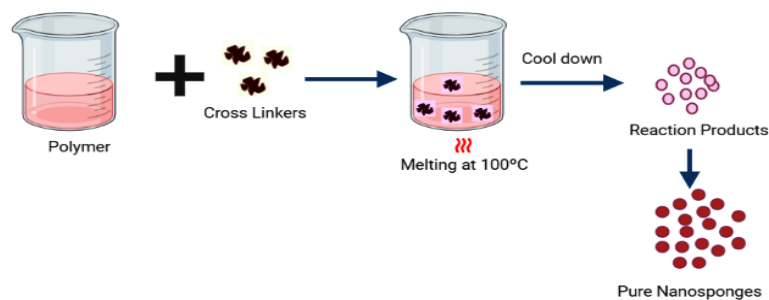


Fig. 6: Nanosponges by melt method [30]

Bubble electrospinning

A syringe, syringe pump, grounded collector, and high-voltage power are the key components of a standard electro-spinning setup,

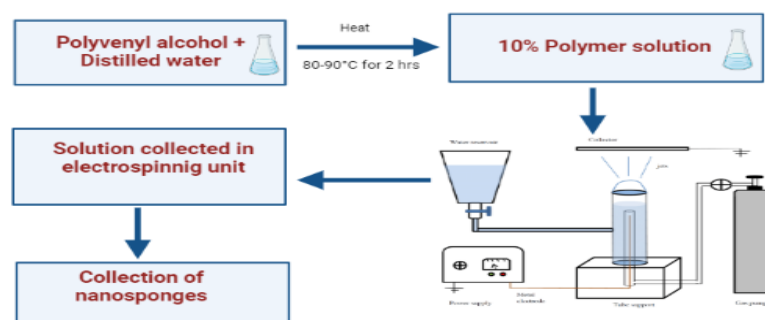


Fig. 7: Nanosponges by bubble-electro method [35]

The solution of polymer (10%) was organized by adding distilled water and further moved at 80–90 °C for 2 H to form a one-phase mixture [36]. The solution (polymer) was then left to reach room temperature before being used to manufacture nano-porous fibers (fig. 7).

Quasi-emulsion solvent method

The polymer was used to assemble the nanosponges in various quantities. The inner stage is produced and added to a reasonable dissolvable stage using Eudragit RS 100. Under ultrasonication, the medication employed elicited a response and broke down at 35 °C [37]. This internal procedure utilized in the exterior phase containing PVA goes around as an emulsifying operator [38]. The mix is blended for 3 h at room temperature at 1000-2000 rpm, then dried (12 h) in an oven (40 °C).

Microwave radiation synthesis of nanosponges

This straightforward method of microwave irradiation synthesis of cyclodextrin nanosponges greatly reduces reaction time and produces these nanosponges with higher levels of crystallinity and homogeneity than conventional heating techniques. To compare the advantages of microwave-assisted heating to traditional heating during the synthesis of CD-based NSs, Singi Reddy *et al.* experimented. The study's findings revealed that the holding drug capacity had been quadrupled by nanosponges produced with microwave-assisted technique. The nanosponges produced by microwave synthesis were extremely crystalline, demonstrated higher levels of complexity, and had a limited size distribution, according to the findings. Under microwave-assisted heating conditions, the reaction products improved and the reaction time for all reactions was significantly reduced. The advantage of using microwave irradiation for synthesis is that it delivers direct energy to the targeted molecules, allowing for the provision of energy in precise form [30].

Nanosponges loading

Particle size should be determined through pre-treatment of the nanosponges (500 nm). The colloidal fraction was obtained by centrifuging the nanosponges [39]. The sample was dried using the freeze-drying method after the supernatant was separated. An excessive drug amount was dispersed; nanosponges suspension was made, and continuously stirred during the complexation process [40]. Using the solvent evaporation approach, nanosponges were made into solid crystals [41]. Drug complexation with nanosponges depends on their crystal structure. Crystalline nanosponges have a higher drug-loading capacity than paracrystalline nanosponges [42].

Nanosponge's mechanism for drug release

Due to the nanosponge structure, active chemicals are delivered to the vehicle in an encapsulated state that can easily move from the particle into the vehicle. Further, the vehicle reaches equilibrium and becomes saturated [43]. While the drug is administered to the skin, the vehicle containing active medicinal components is not

as defined in several kinds of literature. The amount of production of nano-fibers, however, is one of the major restrictions that limit their applicability [30, 35]. Polyvinyl alcohol (PVA) can also be utilized as a polymer in bubble electro-spinning.

saturated, resulting in a disturbance in the balance. When active ingredients from nanosponge particles move into vehicles, the vehicle may get dried or absorbed [44]. Even after the preservation of nanoparticles on the skin surface, the active substance remains on the skin for a long time [45].

Factors influencing the formation of nanosponge

Depending on the cross-linker and polymer properties

Cross-linkers help Nanosponges form a three-dimensional structure. The amount of cross-linker utilized affects organ targeting as well as determining drug entrapment [46]. The type of crosslinker utilized influences whether the NS is water or solvent-soluble. Epichlorohydrin will be used as a crosslinker to create hydrophilic nanosponges [47]. The usage of hydrophilic NSs in drug delivery has the advantage of improving drug absorption through biological membranes and serving as a helpful transporter for medicines with quick-release formulations. DPC, pyromellitic anhydride, diisocyanates, and carbonyl imidazoles are used as cross-linkers in the water-hating nanosponges [48].

The medium used to demonstrate medication interaction and properties

A chemical that is suitable for incorporation into nanosponges must have specific features that make it ideal for medicament encapsulation. The drug mass should be between 100-400 Da with a melting point and solubility of 250 °C less than 10 mg/ml, respectively. After entrapment in nanosponges, high melting point compounds have a lesser stability constant value, resulting in unequal complexes between the drug and nanosponges [49]. Furthermore, medicines having a high melting point will be low entrapped, reducing drug loading capacity. Because it helps create contact between the nanosponges cavities and the targeted chemical, the medium in which the drug loading is done is also crucial in finding the drug release rate. In the case of the hydrophilic medium, the organic drug molecules become trapped in the hydrophobic cavities of the nanosponges, whereas if the media is an organic solvent, the organic molecules are released from the nanosponges [50]. Physical and chemical attractions influence the attraction between the guest molecules and the host [51].

Cross-linking substitute degree

The cross-linking degree and the substituent have a direct relationship; with the larger the number of substituents, the higher the cross-linking degree, resulting in highly porous nanosponges with mesh-type networking in the interior structure [52]. Because the functional group occupies multiple positions on the parent molecule, a change in the production process may result in varying physicochemical qualities in the substance that forms [53]. The importance of the polymer degree of substitution is determined by the nanosponge's ultimate value, which is determined by product processing and material purity.

Nature's complexity

The drug and the nanosponge complexation are affected by temperature changes. With increasing temperature, the drug consistency constant and the nanosponge composite lowers the lowering contact forces such as Vander Waal and water-hating forces [54].

Nanosponges characterization

Solubility studies

The phase solubility method is a widely used approach for studying inclusion complexes, in which the efficiency of nanosponges on the solubility of pharmaceuticals, which displays the complexation degree, is explained and the drug's bioavailability is measured. In this procedure, an Erlenmeyer flask containing an aqueous solution containing varying percentages of nanosponges was filled with the medication. At room temperature, the Erlenmeyer flask was shaken using a mechanical shaker. After reaching a steady state, the suspension was centrifuged and filtered using a 3 000 Dalton molecular filter (MICRON YN 30, Millipore Corporation U. S. A). High-performance liquid chromatography was used to examine the resulting solution to determine the drug concentration [55].

Microscopy studies

The nanosponges, drug, and (complex of drug/nanosponges) are seen using transmission electron microscopy (TEM) and scanning electron microscopy (SEM). Inclusion complexes occur under an electron microscope, indicating a difference in crystallization state between the product and the raw material. Using the scanning electron microscope (JEOL JSM-5610LV) for 30 kV transmissions, the NS surface morphology was examined. The sample was created by the JEOL JFC-1600 auto fine coater, which aids in coating the product with a gold-palladium alloy. In a different analysis, the TEM JEOL 1400 was employed with transmissions of 60 kV and about 10 L of NS sample were diluted to 100 L with Milli-Q water. 5 L of the watery mixture was used to create the sample, which was then held on a network and placed on a glass plate to be examined under a microscope [56].

Polydispersity index (PDI), size, and zeta potential (ZP)

The size of the drug's particles can affect its solubility and release. The technique of dynamic light scattering (DLS) is utilized to determine particle size distribution, and software called 90plus is used to do PDI and the mean particle diameter. The charge of nanosponges can be examined by assessing the zeta potential with a zeta sizer. If the ZP is more than 30mV, the formulation is considered to be stable. Samples of the nanosponges were diluted with 0.1 mol/l KCl before being placed in the electrophoretic cell, which had an applied electric field of roughly 15 V/cm, to determine their zeta potential. Following the averaging of all measurements, the mean hydrodynamic diameter and polydispersity index of the particles were computed using the cumulated analysis [57, 58].

Thin layer chromatography (TLC)

The retention factor (Rf) value of a medicinal component decreases to a significant range in TLC, which aids in evaluating the development of complexes among nanosponges and the drug [59].

Drug loading efficiency

It can be measured using HPLC and an ultraviolet spectrophotometer to quantify the drug injected into the nanosponges. The drug amount in the nanosponge is diffused in a suitable solvent before being sonicated for a specific period, diluted, and quantified using a UV spectrophotometer or HPLC procedure [60]. The equation can be used to estimate the percentage of nanosponges loading.

$$\text{Loading efficiency} = \frac{\text{Drug content (Actual)}}{\text{Drug content (Theoretical)}} \times 100$$

Infra-red (IR) spectroscopy

Employ spectroscopy to investigate the interaction between the medication and the nanosponges (solid-state). The nanosponges bands are somewhat altered when the complexes are created.

Because little guest molecules (25%) are linked to nanosponges complexes, the drug's spectrum can simply conceal by the nanosponges spectrum [61]. This approach is ineffective for locating inclusion complexes. The use of IR spectroscopy is partial to medications with certain distinctive bands, such as the carbonyl or sulfonyl groups [62].

In vitro release study

The rotating cell (multi-compartment) was used to measure the release pattern of the nanosponges. In the donor compartment, drug complexes with aqueous nanosponges dispersion and phosphate buffer in the receptor compartment for investigations. Between the two compartments, a membrane (hydrophilic dialysis) acts as a divider. The receptor buffer is fully functional. The buffer (receptor) was drawn out and replaced with buffer (unsaturated) regularly. The analytical method is used to fig. out how much medicine is left and when it will be released [63].

Fourier transform IR-spectroscopy (FTIR)

The FTIR analysis of the material reveals structural details, particularly the presence of the functional group. For medicines, polymers, drug-polymer complexes, blank nanosponges, drug-loaded nanosponges, and potential interactions, the detection range is 4000 to 650 cm⁻¹. The results of the FTIR analysis aid in the identification of hydrophilic and hydrophobic sites in nanosponges. In the event that the functional group is hidden, it means the complexation of the functional group. After complicated formation, nanosponges bands alter slightly. Infrared spectrum analyses reveal the existence of hydrogen in several functional groups [64, 65].

Powder X-ray diffraction experiment

Chemical breakdown and encapsulation can be defined using powder X-ray deflection. When a drug is complexed with a CD or NS, the diffraction pattern changes, as does the crystallinity of the drug. A scattering angle function is used to find the diffraction pattern of a trial model. Peak sharpening, peak disappearance or appearance, and peak shifting are all visible in the resulting complex. The detection is possible when the solid state reveals Inclusion complexation. There is no diffraction pattern while the inclusion complex is liquid; hence a significant diffraction pattern helps distinguish between complexes nanosponges and newly formed substances.

Thermal analysis

The melting point (Tm), temperature for crystallization (Tc), crystallinity degree (Xc), and pure medication are all determined via thermal analysis. Differential thermal analysis and scanning calorimetry studies look for widening, altering, new peaks appearing or peaks disappearing. Shallow or disappearing peaks indicate a molecular combination of polymer and drug complex inclusion complexes are confirmed using weight variation experiments [65].

Raman spectroscopy

When CD NSs go from a dry to a swelled condition, Raman spectroscopy is a useful method for analyzing their behavior. For conformational changes, the Raman peaks are sensitive to molecules and the strength, quantity, and distance of intermolecular interactions. It can also be applied to the investigation of molecular structure. Additionally, it provides information on the water's condition between the nano-porous structure and the dissolved solution. The vibration modes of dissociated OH and CH groups in the setting of bulk water can be used to analyze the dynamics of hydration.

Stability study

The nanosponges have been tested for stability under accelerated circumstances and photo-degradation experiments. The formulation is evaluated every three months for three months. The features of the medicine are evaluated in terms of changes in physical attributes, appearance, and size. The photodegradation analysis is carried out in the dark for 1 h under the UV lamp. Ten centimetres separate the nanosponges from the lamp are best suited. The sample is extracted and tested using HPLC [66].

Recent advancements in nanosponges

Over the years, the nanosponges medication delivery system has experienced a number of upgrades and innovations. The list of

pharmaceuticals that have been placed into them, as well as the process of production, has grown. The entrapment efficiency has also risen, as have the types of polymers utilized as components. Table 1 lists the most recent improvements in nanosponges.

Table 1: Recent advancements in nanosponges

Project's name	Findings of note	Conclusions	Year	Reference
Cyclodextrin nanosponges for the L-DOPA controlled release	No L-Dopa degradation was seen during storage when L-Dopa was integrated with MIP-NSs, which exhibit slower, longer release profiles.	A viable approach for L-DOPA storage and distribution management is MIP-NSs.	2016	[63]
Glipizide nanosponges' formulation.	The drug release is shown by the regression line from the Higuchi plot, further supporting the diffusion mechanism.	The improved formulation's release kinetics demonstrated zero-order (fickialdiffusion) with Higuchi model.	2017	[67]
Erlotinib glutathione nanosponges for lung cancer.	Tumor volume dramatically decreased; modest dosages of medication are more efficient over longer times, are more targeted to the goal, and therefore limit adverse effects.	High-efficiency anti-cancer medications can be encapsulated in nanosponges, which have a lengthier release, a stronger anti-proliferative outcome than free pharmaceuticals.	2018	[68]
Nonviolent Self-Catabolic DNA zyme nanosponge for smart anticancer drug delivery	The multivalent tandem aptamer used in DNAzyme nanosponges helps deliver cancer cells with efficiency, as well as.	The present DNAzyme nanosponges could have applications in bioengineering and biomedicine.	2019	[69]
A gel-loaded nanosponge with a curcumin and caffeine mixture was utilised to treat psoriasis.	When compared to Curcumin alone, which takes roughly 20 d, curcumin plus caffeine gel loaded nanosponges showed anti-psoriatic effectiveness for up to 10 d.	According to the results of the experiments, nanogel would be an essential drug delivery mechanism for anti-psoriatic therapy.	2020	[70]
Cyclodextrin nanosponges for organic hazardous compound removal: preparation and characterization.	Oral cyclodextrin nanosponges do not tend to collect and damage gastrointestinal tissues, according to animal studies, and are ejected from the GI system with low absorption.	This research demonstrates CD-NS preparation is both safe and effective when it comes to eliminating harmful compounds from the body.	2020	[71]
SARS-CoV 2 Infectivity is Inhibited by Cellular Nanosponges.	SARS-CoV-2 is neutralized and unable to infect cells using the nanosponges. Importantly, the nanosponge platform is immune to viral alterations as well as viral species.	The nanosponges will be able to neutralize the virus as long as the virus's target remains the recognized host cell.	2020	[72]
Nanosponges topical gel of cinnamon oil.	The results revealed the strong antibacterial efficacy of a nanosponge carrier of cinnamon oil against <i>Staphylococcus aureus</i> , with no skin irritation.	Essential oils may be more therapeutically effective when carried in nanosponges carriers.	2020	[73]
Cyclodextrin-nanosponges	<i>In vitro</i> and <i>ex-vivo</i> , investigational models reveal that Dox-GSH-NSs have a fair safety profile, with their hepatotoxicity being comparable to that of free Dox.	The hepatic accumulation of Dox loaded in the NS is comparable to the free drug, according to studies.	2020	[74]
Nanosponges-based gel with butenafine for fungal skin infection: formulation and <i>in vitro</i> evaluation	In the (1 percent, w/w or w/v) carbopol gel, optimized NS (BNS3) was mixed with an identical amount of (1 percent, w/w or w/v) BTF. Because the nano-carrier may infiltrate the medicine deeper into the skin layer than conventional topical semisolid preparations, the nano-based gel formulation is appropriate for the successful treatment of fungal infections.	Nanocarriers boost therapeutic efficacy by channeling drugs deeper into the epidermal layers, allowing fungal infections to be eliminated.	2021	[75]
Olmesartan medoxomil-loaded nanosponges	In comparison to pure OLM, the optimized formulation showed greater cytotoxicity (against A549). Finally, compared to control and pure OLM medication, this system (ONS4) considerably (p 0.01) lowered the systolic blood pressure (SBP).	This study offers a solid scientific foundation for future investigations into the efficacy of NSs as potential drug carriers to circumvent pharmacokinetic restrictions.	2021	[76]

Application of nanosponges

Nanosponges in management of sars cov-2

The SARS-CoV-2 virus can be captured by NSs made from human macrophages or lung type II epithelial cells and eliminated after infection. As a result, it was utilized in the creation of SARS-CoV-2 preventative measures. The researchers have created two different forms of cellular NSs based on the existing structure of SARS-CoV-2, namely human lung type II epithelial cell nanosponge (epithelial-NS) and human macrophage nanosponge (M-NS). It was hypothesized that after interacting with these NSs, coronavirus would not be able to enter the cell because the NSs had the same receptors that the viruses rely on for their entry. When SARS-CoV-2 is incubated with NSs, it gets neutralized and loses its ability to infect cells. NSs can make viral mutations and viral species unclear. Additionally, it can

recognize the host cell that the virus continues to use as a target and take action to neutralize the infection. It was shown that SARS-CoV-2 may be neutralized by both epithelial-NS and M-NS in a concentration-dependent manner. Further barriers against SARS-CoV-2 are helped by the greater surface heparin density of cellular NSs, which can bind firmly with the viral S proteins [17, 94].

Nanosponges in cancer treatment

The development of nanomedicine, or medical devices in the nanometre order of magnitude, as a delivery mechanism of anticancer medicines, has drawn a great deal of attention in recent years due to its potential to raise the therapeutic index of numerous substances. Complex molecules called nanosponges can be utilized to deliver anti-cancer medications to specific locations in the body. The extremely low water solubility of many anticancer medications

is one of their biggest drawbacks. When complexes with nanosponges, molecules with very poor aqueous solubility can be made more soluble. Drugs can also be molecularly disseminated inside the nanosponge structure to prevent crystallization. Although the technology is still under development, studies have shown that it can deliver breast cancer medications up to five times more effectively than current approaches. Instead of the medicine dispersing broadly throughout the body; nanosponges release it at the site of the tumor. So, because less of the drug comes into contact with healthy tissue, it is more effective for a given dosage and also has fewer negative side effects. In contrast to many other nanoparticle delivery methods, which release the majority of their medicine in quickly and unpredictably when they reach their target, they release the drug in a predictable manner [73]. It is challenging to estimate optimal dosage levels because of this phenomenon, known as the burst effect. For better anti-tumor action, glutathione-responsive cyclodextrin nanosponges have been developed for the targeted delivery of doxorubicin. The primary component of Paclitaxel is Taxol, a powerful drug that is effective in the treatment of cancer and was created in an NS formulation. The creation of self-catabolic, bioinspired DNAzyme nanosponges with adjustable drug delivery behaviours and effective gene silencing capabilities has been described, providing a new avenue for creating intelligent nanosystems with gene therapy and individualized biomedical commitments. For targeted delivery into malignant cells, the created DNAzyme nanosponges could be encoded with multivalent tandem aptamer configurations [30, 74].

Nanosponges as a carrier for protein and biocatalysts

NS serves as the vector in drug delivery systems to transport proteins, enzymes, antibodies, and vaccinations for the treatment of diagnoses. The most common carrier to adsorb enzymes, macromolecules, enzymes, and proteins is an NS made of cyclodextrin. These carriers may help to protect the protein *in vivo* by altering its pharmacokinetics, enhancing its stability, and preventing protein degradation. Proteins can be transported by adsorbing or encapsulating them in cyclodextrin nanosponges. Because the protein solution of bovine serum albumin is unstable, it is stored in lyophilized form, and lyophilization can cause it to denature [76]. The primary drawback in protein synthesis and development is preserving its native structure and storing it for lengthy periods of time during and after processing. Nanosponges will be used to improve protein stability and will be utilized for enzyme immobilization and stabilization [77].

Nanosponges as chemical sensors

As chemical sensors, metal oxide-based NSs were used to identify hydrogen (H_2) gas. In the study, nanoscale walls and wires built of nanosponge TiO_2 (NST) were shown to be 3D interconnected and capable of extremely sensitive H_2 gas detection. In recent work, the use of NS based on nanoparticles was examined for the fluorimetric detection of environmental pollutants, such as volatile organic compounds (VOCs) like xylene. The NS sensor consisting of polythiophene and nanoparticles could detect xylene at concentrations as low as 7 ppm using the turn-on fluorescence sensor. NS has demonstrated several intriguing applications as a carrier for the transfer of gases for treatment and diagnosis. Hypoxia, which results from a lack of oxygen, can cause anything from mild inflammation to dangerous cancer. The creation of NSs in the oxygen delivery system has the benefit of storing and releasing oxygen slowly over a long period of time [17, 75].

Nanosponges for delivery of medicament

Nanosponges can carry water-insoluble medications due to their microscopic porosity structure. The nanosponge complex is important for increasing a drug's dissolving rate, permeability, and solubility. Nanosponges (β -cyclodextrin-based) deliver the medicine 3 to 5 folds more to the target site than direct injection. Drugs with solubility issues could be successfully given by injecting them into nanosponges. They're solid by characteristic and can be used in topical, oral, or parental dose forms. The complex forms are dispersed in a diluents matrix, anti-caking agent's excipients, and

lubricants for delivery (orally) when making tablets or capsules [75].

Blood poison treatments

Nanosponges are utilized to absorb harmful compounds from the blood and eliminate them from the body. When supplied through injection, nanosponges can absorb poisons and are more effective than antidotes [78]. Nanosponges, which resemble red blood cells in the bloodstream, fool toxins into targeting and absorbing them. Depending on the poison, nanosponges can absorb the chemicals. For example, ochratoxina levels in red wine and aqueous solutions are removed using α -Cyclodextrin complexes polyurethane polymer nanosponge. The nanosponges may absorb 0.22 mg of ochratoxin A per milligram of the polymer [79].

Antiviral application

In addition to targeting viruses that affect the respiratory tracts the nanosponges are a good vehicle for delivering small antiviral medicament and interfering RNA to nasal epithelial (HSV) and lungs. E. g. capacity of the drug Acyclovir in carboxylated nanosponges was discovered to be 60% w/w [80]. Furthermore, when compared to pure medicines, the drug release was sustained in an *in vitro* profile, indicating better antiviral efficacy against HSV. Saquinavir, zidovudine, and acyclovir are among the drugs utilized [81].

Nanosponges in fungal infections

Fungal infection is one of the most feared diseases globally. Topical therapy is an excellent way to treat these coetaneous infections since it has several advantages, such as directing medications to the specific location of infection and reducing side effects [82]. Conazole nitrate is a topical antifungal or fungicide that is used to treat ringworm, vaginal thrush, jock itch, tinea pityriasis Versicolor, and athlete's foot. Nanosponges containing conazole nitrate were manufactured as hydrogel to release the medicine in a sustained way as a topical treatment using the emulsion solvent approach [83].

Topical delivery systems

Nanosponges delivery is a unique method for the controlled release of topical medicines. They keep their effectiveness by lowering skin irritation. Antibiotics, antifungals, and local anesthetics (LA) are some of the medications that are made into topical nanosponges [84]. These encapsulate nanosponges and suspend a wide range of compounds before being transformed into creams, capsules, liquids, and tablets. Miconazole nitrate, itraconazole nitrate, ketoconazole, and voriconazole are examples of antifungal nanosponges [85].

Diagnostic application of nanosponges

β -CD is commonly employed in the production of a variety of diagnostic items. CD-nanosponges are ideal for usage as a diagnostic agent because of their good biocompatibility, prolonged blood circulation, permeability, and ease to the target [86].

Cosmetics with nanosponges

In the cosmetics sector, nanosponges have a variety of applications. Cosmetic compounds that are susceptible to photodegradation benefit from nanosponges. It has the ability to catch up with and delay volatile oils release [87]. Sweating produces a foul odor that can be absorbed. It can gently release volatile compounds, giving oral cosmetics an enduring freshness, and furthermore, it can also be utilized to give a long-lasting effect to products like rouge and lipsticks [88].

Patents

New patents in the field of nanosponges have recently been filed and accepted, and they have been used [89]. Patents have been submitted for their utility as toxin absorption agents, preservation agents for growth, release agents for an enzyme, and biocatalyst research. They've also shown promise as cancer-fighting agents. As noted below, the authority has also granted further patents that will help shift demand toward nanosponges as a revolutionary pharmaceutical delivery technique, as shown in table 2.

Table 2: List of patents on nanosponges

S. No.	Patent title	Patent number	Inventor	Grant date	Country patent
1.	Anti-fungal preparation with curcumin and luliconazole nanosponges and	202121024881	Jayadeep R. Yadav,	06.08.2021	India
2.	A method for producing stable lithium silicate nanosponges for capturing CO ₂	202021008717	Vivek Polshettiwarand Rajesh Belgamwar	31.07.2020	India
3.	Reconstituable hydrogel powder of dapsonenanosponges useful in the treatment of acne	201821029366	Dhamane suchita prabhakar and Sonar Sagar Suresh	24.08.2018	India
4.	Synthesis of Nanoparticles and nanosponges	US09574136 B2	Kun Lian	21.02.2017	US
5.	Polycarbonate-containing compounds and methods related thereto	US 09580548B2	Eva M. Harth and David M. Stevens	28.02.2017	US
6.	Starch nanosponges	2071/MUM/2014	Vavia Pradeep Ratila and Jadhav Nitin Vitthalrao	29.01.2016	India
7.	Metal nanosponges	US08404280B2	Muthusamy eswaramoorthy and Katla Sai Krishna	26.03.2013	US
8.	Polycarbonate-containing compounds and methods related thereto	WO2013169938	Harth, Eva, M. Stevens and David, M.	08.05.2013	International patent
9.	Ultrasound-assisted nanosponges synthesis	US20080213384 A1	Trotta Francesco	04.09.2008	US

Toxicity studies and acute toxicological study

Toxicity testing is necessary for determining drug safety profiles and determining the most effective doses for use in both animals and humans [90]. After 28 d of oral treatment of nanosponges at doses ranging between 300 to 2000 mg/kg, negative mortality was seen in male Wistar rats. In addition, there were no variations in appearance [91]. The animals treated showed no signs of diarrhea, tremors, convulsions, or other symptoms as compared to the control groups. As a result, when given orally at a dose of >2000 mg/kg body weight, β -cyclodextrin nanosponge is exceedingly safe and non-toxic [92, 93].

Future trend

The introduction of nanosponges, which have been reduced down to the nanoscale, has ushered in a medical, scientific revolution. A revolution has begun in the world of medical science, as technology has been exploited to reach the nanoscale. Drug toxicity is decreased when a targeted and regulated drug release mechanism is used since better therapeutic results can be attained. The importance of nanosponges in medicines and nanotechnology development cannot be overstated. Nanosponges could be utilized as a basic water purifier in the future. The key challenge is to reduce production costs, which will entail the development of novel polymers and cross-linkers as well as new manufacturing methods. They play a crucial role in downstream production due to their unique character, needing extensive investigation.

CONCLUSION

Nanosponges with a porous characteristic and nano-size allow them to easily permeate the skin. These particles can carry therapeutic compounds that are hydrophilic and lipophilic and they can administer the drug material in a regulated manner at a specified location. As a result, nanosponges have benefits such as better safety, increased stability, decreased adverse effects, increased bioavailability, and improved patient compliance. Because of its tiny size and efficient qualities, it can deliver medications to the target site via multiple modes of administration, including oral, topical, and parenteral. In addition to their usefulness in medication delivery, agro chemistry, bioremediation processes, cosmetics, biomedicine, and catalysis all have some intriguing uses. Drugs supplied via nanosponges have been shown to be safer and more effective, and the pharmaceutical industry will benefit greatly.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

All authors declare no conflict of interest

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