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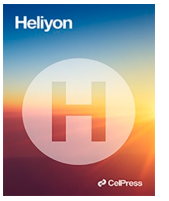

Review article

Nanosponge: A promising and intriguing strategy in medical and pharmaceutical Science

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ABSTRACT

The complicated chemical reactions involved in the production of the newer drug delivery systems have mainly impeded efforts to build successful targeted drug delivery systems for a prolonged duration of time. Nanosponges, a recently created colloidal system, have the potential to overcome issues with medication toxicity, decreased bioavailability, and drug release over a wide area because they can be modified to work with both hydrophilic and hydrophobic types of drugs. Nanosponges are small sized with a three-dimensional network having a porous cavity. They can be prepared easily by crosslinking cyclodextrins with different compounds. Due to Cyclodextrin's outstanding biocompatibility, stability, and safety, a number of Cyclodextrin-based drug delivery systems have been developed promptly. The nanosponge drug delivery system possesses various applications in various ailments such as cancer, autoimmune diseases, theranostic applications, enhanced bioavailability, stability, etc. This review elaborates on benefits and drawbacks, preparation techniques, factors affecting their preparation, characterization techniques, applications, and most current developments in nanosponges.

1. Introduction

Sponges are mesh-like minute structures that can encapsulate a large variety of substances and medication molecules [1,2]. They enhance the solubilization capacity of both water-soluble drugs and lipid soluble drugs and also possess a spherical colloidal nature [3]. They increase the bioavailability of drugs with prolonged drug release [4]. Because of their internal hydrophobic chambers and exterior hydrophilic branching, nanosponges' amphiphile nature enables them to carry therapeutic molecules that are both hydrophilic and hydrophobic [5]. They are like a 3D network having a backbone of long-chain polyesters present in the solution along with crosslinkers that connect different parts of the polymer [6]. It has been revealed that cyclodextrins (cyclic oligosaccharides) can be treated with appropriate crosslinking agents to obtain nanosponges, a unique nanostructured material made of hyper-cross-connected cyclodextrins [7]. According to the agent utilized as a crosslinker, nanosponges can be synthesized as neutral or acidic materials and swell [8]. The result is hollow spheres with voids that can hold medicament molecules [2]. During preparation, the cross-linking-to-cyclodextrin proportion can be changed to enhance drug loading and provide a customized release profile. Their extremely permeable nanomeric nature, in comparison to that of the parent cyclodextrin molecules, makes it possible for drug

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molecules to both arrange themselves in nanosponge inclusion and interact with one another in a mode that does not involve inclusion and offer effective drug loading [2].

Compared to other nanoparticles, they possess some advantages as they are easily reproducible using different treatments such as washing with environmentally friendly solvents, stripping with relatively innocuous hot gases, gentle heating, or changing pH or ionic strength. They are used in different fields [9]. The engineering potential of nanosponges is due to the relatively straightforward chemistry of their crosslinking peptides & polyesters. Being water soluble, they do not break up chemically in water [2]. The nanosponges are made up of several voids in their core structures that provide the free movement of the drug component. The moiety enclosed is able to move freely inside the vehicle, which helps to lower the drug concentration inside the vehicle, creating an unsaturated condition and upsetting the delicate balance. This procedure continues until the body has absorbed all of the drug. As the liquid is prepared, the drug molecule's solubility rises, decreasing the benefit of its progressive release and making the drug moiety behave as though it had been introduced in its free form rather than its trapped form [10]. They combine it with water and then utilize the resulting fluid as a mode of transportation. They are valuable toolls for transforming liquid material into solid forms. The nano-sponges are able to selectively attach themselves to the target due to the chemical linkers [2]. They are shown to be risk-free for both oral and invasive routes, making them a viable medication delivery vehicle [9]. Nanosponges can be delivered through the lungs and veins because of their microscopic size [11]. To make capsules or tablets for oral administration, the complexes may be dispersed in a matrix containing diluents, lubricants, excipients, & anticaking agents. This step is necessary for the manufacturing process. Parenteral administration of the substance may be accomplished by dissolving it in sterile water, saline, or one of many other aqueous solutions. They are capable of being effectively incorporated into topical hydrogels [12].

2. Salient features of nanosponges

The particles of nanosponges are of a specific size, and their polarity can be varied by using different ratios of crosslinking agents and polymers. With variable polarity of voids, nanosponges show diameters in the range of 1 μm or less [13]. They can be para-crystalline or crystalline. The crystalline structure of nanosponges is essential for drug complexation since the level of crystallization dramatically affects the productivity of stacking nanosponges. Para crystalline Nanosponges are proven to have a range of drug-loading capacities, according to the literature [3]. They are found to be stable up to a temperature range of 130 °C and pH in the range of 1–11. They are found to be porous, biodegradable, and non-toxic in nature [14]. Due to their 3-dimensional structure, they can encapsulate, transport, and provide observable release of drugs and other compounds. In water, nanosponges provide a transparent to opalescent colloidal suspension that can be recovered successfully using solvent extraction or thermal desorption by microwaves & ultrasound waves [2]. They show targeted release of various compounds because of their capability to interact with multiple functional groups, which can be improved using synthetic linkers that target the sites. An external magnetic field can be used for targeted discharge by adding magnetic qualities to a configuration of nanosponges during the production process by expanding ferrite and other magnetic materials [2].

Due to their desirable qualities, Nanosponges are chosen as the material of choice, which includes providing sustained release of drug for up to 24 h, can be used to encapsulate immiscible liquids, providing less irritation, increased flexibility, and stability. Nanosponges provide a number of benefits, but they also have certain drawbacks. Mainly, small drug molecules are incorporated in the Nanosponges, but macromolecules and oligonucleotides can also be incorporated [2]. The degree of crosslinking has an impact on the ability to load drugs because it controls the amount of empty space in the nanosponge that is available for loading. The early disintegration of the crosslinker raises the likelihood of dosage dumping [10].

3. Materials used in nanosponge preparation

Numerous substances have produced promising results and can be utilized to produce Nanosponges, depending on the desired type of Nanosponges and the required degree of crosslinking. Due to its impact on the drug release pattern and drug encapsulation, the crosslinking amount is a crucial component of Nanosponges and is dependent on crosslinker concentration. Different components used in the preparation of nanosponges are discussed below [10] (Table 1).

3.1. Polymers and copolymers

The development and performance of nanosponges are affected by the type of polymer utilized for their formulation. In the case of complexation, the cavity of developed nanosponges should be such that it can accommodate a particular drug. The selection of

Table 1
Materials used in Nanosponge formulation.

S. No.	Components used in nanosponge formulation	Examples
1	Polymers	Cyclodextrin and its derivatives, hypercrosslinked polystyrenes, Eudragit RS100, acrylic polymers, etc
2	Copolymers	Polyvinyl alcohol, Poly valerolactone allylvalerolactone, Ethyl Cellulose etc
3	Crosslinkers	Carboxylic acid dianhydrides, Carbonyl diimidazoles, dichloromethane, diphenyl carbonate, Glutaraldehyde, etc.,

polymer also depends on the type of dog to be entrapped and the desired release profile [15]. Some polymers used are Cyclodextrin and its derivatives, hypercrosslinked polystyrenes, Eudragit RS100, acrylic polymers, etc [16].

Amani et al. prepared nanosponges of ferulic acid to enhance its water solubility. The nanosponges were formulated using cyclodextrin as a polymer. Cyclodextrins are an appropriate wall material to entrap both hydrophilic and hydrophobic molecules due to their hydrophobic center chamber and hydrophilic surface. The solubility of ferulic acid enhanced after encapsulation into nanosponges due to the presence of the porous structure of polymer cyclodextrin [17]. Lami et al. developed Temoporfin loaded nanosponges for neck and head cancer. The nanosponges were prepared using hyper cross linked β-cyclodextrin polymer. The use of crosslinked β-cyclodextrin polymer enhances the penetration of the drug [18]. Desai et al. synthesized crosslinked nanosponges of neuropeptide Y using β-cyclodextrin. β-cyclodextrin-crosslinked nanosponges provide improved drug release and stability and are useful for administering medicines [19].

Hafiz et al. formulated a hydrogel of Carboplatin using nanosponges as a carrier. The nanosponges were formulated using ethyl

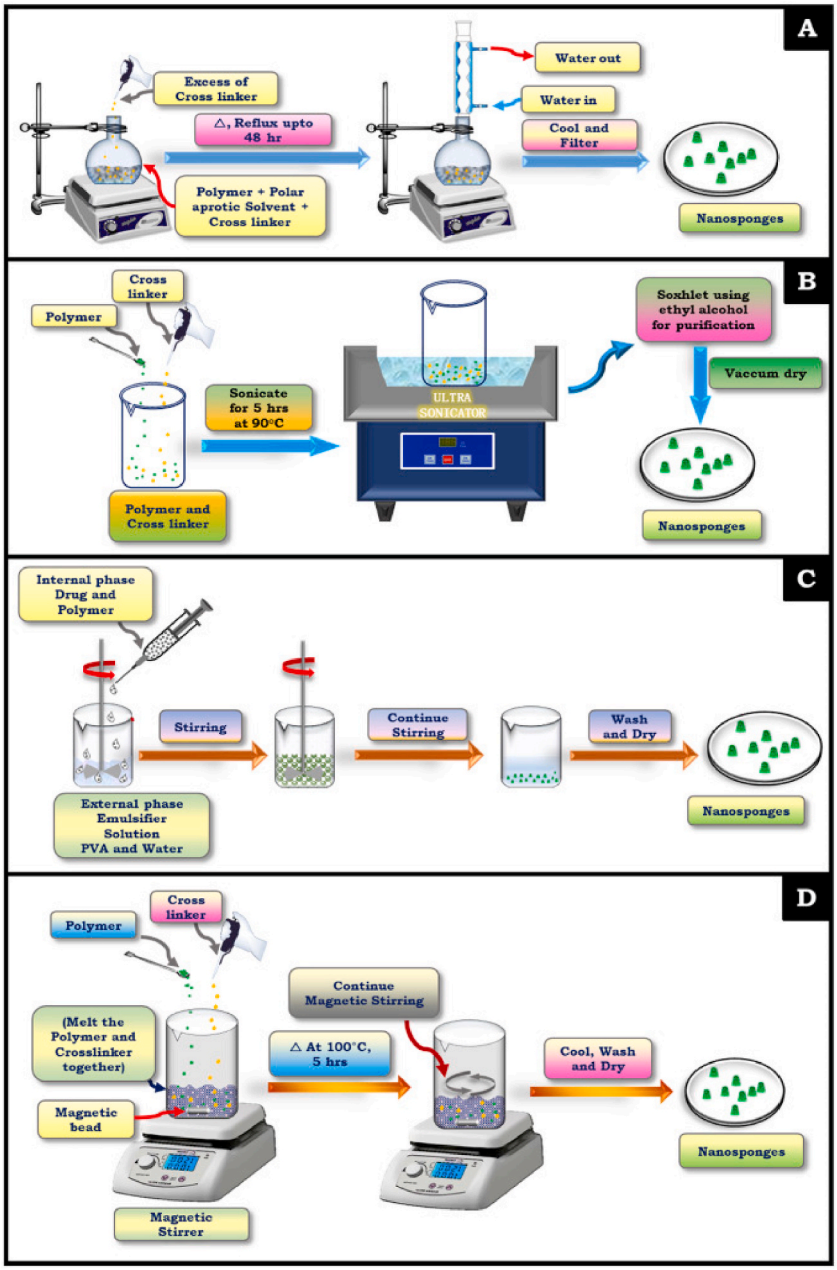

Fig. 1. Formulation methods of Nanosponges (A) Solvent Method (B) Ultra-Assisted synthesis (C) Emulsion solvent diffusion method (D) Melting method Reprinted from Ref. [23] with permission from Elsevier.

cellulose by double emulsion solvent evaporation technique. The formulated hydrogels containing nanosponges showed improved drug efficacy at the target site with prolonged release and bio adhesion [20]. Hao et al. prepared calcium carbonate nanosponges using copolymers Poly lactic-co-glycolic acid and Polyethylene glycol to neutralize tumor acidity by acting as a proton nanosponge [21]. Abemaciclib loaded nanosponges prepared by Anwer et al. using ethyl cellulose and Kolliphor P-188 showed that the amount of ethyl cellulose and Kolliphor P-188 used as copolymers affected the entrapment efficiency of the drug. The results depicted that the presence of a greater amount of ethyl cellulose and a lesser amount of Kolliphor P-188 results in high encapsulation efficiency and prevents drug leakage from nanosponges [22].

3.2. Crosslinking agent

The type of crosslinker to be utilized depends on the structure of the polymer and the drug whose nanosponges are to be formulated [15]. Carboxylic acid dianhydrides, Carbonyl diimidazoles, dichloromethane, diphenyl carbonate, Glutaraldehyde, etc., are some of the crosslinking agents used [16]. Due to its impact on the pattern of drug release and drug encapsulation, the crosslinking amount is a crucial component of Nanosponges and is dependent on crosslinker concentration. (new11) Both hydrophilic and hydrophobic nanosponges can be produced for the delivery of active medicinal molecules by altering the crosslinker's concentration. Depending on the type of crosslinkers used, it is possible to develop water-soluble or insoluble nanosponges structures. Additionally, different crosslinking agents have the power to significantly alter crucial properties, including the polymer's swelling capacity and hydrophilicity or hydrophobicity [23]. Ansari et al. formulated nanosponges of Resveratrol using cyclodextrin as a polymer and carbonyl diimidazole as a crosslinker to enhance the solubility and stability. The use of a crosslinker forms an inclusion complex with a drug, which leads to enhanced solubility of the drug [24]. Taleb et al. prepared Quercitrin loaded nanosponges using β-cyclodextrin and 2-hydroxypropyl- β-cyclodextrin as polymer separately and diphenyl carbonate as crosslinker. The results of particle size depicted that the amount of crosslinker used affects the particle size of nanosponges. For the two types of used Cyclodextrins, it was shown that formulations with greater molar ratios of crosslinker had Particle size that was larger than those with lower molar ratios of crosslinker [25]. To enhance the binding properties of regular Cyclodextrin nanosponges, Massaro et al. proposed the synthesis of cyclodextrin-calixarene copolymers employing triazole as a linker. Quercetin and silibinin, two polyphenolic bioactive chemicals, were employed to produce composites using this combination of cyclodextrin-calixarene Nanosponge materials [26].

3.3. Drug substance

The drug, which is to be formulated as nanosponges, should have a molecular weight between 100 & 400 Da. The solubility should be less than 10 mg/ml in water with a melting point of less than 250 °C. Also, the number of condensed rings in drug molecules should be less than five [15].

4. Methods of formulation of nanosponges

The different methods for the preparation of nanosponges are discussed below (shown in Fig. 1) [23], and the comparison between them is listed in Table 2.

4.1. Quasi-emulsion solvent diffusion

This method utilizes two phases, aqueous and organic phases, in different proportions for the preparation of nanosponges. In the aqueous phase, polyvinyl alcohol is used, and for the organic phase, a solution of the drug and polymer is used. The polymer is selected, and the drug is dissolved in a suitable organic solvent, and slowly, the solution is added to the aqueous phase. The resultant solution is

Table 2
Comparison between different preparation methods of Nanosponges on the basis of different physicochemical properties.

Methods	Parameter					
	Particle size	Shape of Particles	Stability	Zeta potential	Porosity	Ref.
Quasi emulsion solvent diffusion	105–842.2 nm	Spherical shaped nanosponges	Stable.	−1.35 mV	Highly porous with the presence of small size pores.	[27]
Ultrasound-assisted synthesis	97.10–325.90 nm	Sponge like structure favorable for greater drug loading.	Physically stable.	>20 mV	Porous structure.	[25]
Solvent method	316.4–911.6 nm	Spherical structure	Stable at 40 °C for up to 3 months.	−18.5–−11.8	Porous surface.	[28]
Hyper crosslinked method	350–500 nm	Approximately spherical	Stable at 4 °C up to 6 months	Between 31.70 & −35.35	Porous	[3]
Microwave irradiation method	153–400 nm	Spherical shaped	Stable up to 325 °C		Highly porous	[29]
Polymerization	190 ± 20 nm	Sphere like particles	Stable		Porous	[30]

stirred for more than 2hrs at 1000 rpm [Fig. 1 (C)]. The formulated nanosponges are filtered, washed, and dried [31–33].

Anwer et al. developed sustained release nanosponges of Abemaciclib. Ethyl cellulose and Kolliphor P-188 were used as the sustained-release polymer and surfactant, respectively, in the preparation of nanosponges using the emulsion-solvent diffusion method. The formulated nanosponges showed sustained release of the drug for up to 24 h. Aqueous media's slower dispersion inside the hydrophobic polymer matrix is the cause of the prolonged drug release from the Abemaciclib nanosponges [22].

4.2. Ultrasound-assisted synthesis

In this method, the nanosponges are prepared by carrying out a reaction between polymers and crosslinkers without using solvent under sonication. Spherical, uniform-sized nanosponges are prepared by this method. In this procedure, the polymer is combined in the flask at a specific molar ratio with crosslinkers such as di-phenyl carbonate or pyromellic anhydride. After the mixture in the flask had cooled, it was heated to 90 °C in an ultrasonic bath that was water-filled. The mixture is rinsed with water to get rid of the extra non-reacted polymer [Fig. 1 (B)]. Through a protracted Soxhlet extraction process with ethanol, the mixture is purified [33,34].

The ultrasonication method can also be used to create nanosponges since it allows for the simple reaction of polymers and crosslinkers without the need for solvents. Trotta et al. outline the process for creating these kinds of nanosponges. Diphenyl carbonate and anhydrous β-Cyclodextrin were combined in a 250 mL flask, which was then placed in an ultrasound bath with water and heated to 90 °C with sonication for 5 h. The subsequent production crystallization and purification procedures were carried out in a manner that was comparable to the melt/solvent process. Processes with high energy input, like probe sonication, might replace the place of ultrasonication. The benefit of this approach is that no organic solvents are required [35]. In a formulation of quercetin loaded nanosponges prepared by Taleb et al., using ultrasound assisted synthesis showed that the utilized method doesn't involve the use of organic solvents, making it a secured drug delivery system [25].

4.3. Solvent method

This method involves adding a solution of polymer to an excess of the crosslinker, maintaining a temperature of 10 °C for 48 h. Further, the mixture is cooled, and excess water is added to it, which results in the formation of nanosponges. The prepared nanosponges were filtered under a vacuum and collected [Fig. 1 (A)]. Through a long-term Soxhlet extraction process with ethanol, the mixture is purified [33,36].

Naproxen sodium Nanosponges were developed by Ilyas et al. utilizing the solvent diffusion method, and it was discovered that formulations had a diffusion rate equal to 89 % and a drug loading efficiency near 98 %. Additionally, they investigated stability studies, zeta potential, viscosity, and particle size. The Fourier Transform Infrared Spectroscopy results did not show any evidence of a drug-excipient interaction. The findings also demonstrated outstanding drug release characteristics and higher drug loading efficacy [10].

4.4. Hyper crosslinked method

It can also be called as Melting method. 100 ml of anhydrous Dimethyl Formamide and 17.42 g of anhydrous-cyclodextrin were added to a flask with a round bottom, and the mixture was gently stirred until fully dissolved. 9.96 g of carbonyl diimidazole was added to this combination, and the reaction was carried out at 100 °C for 4 h. Round Bottom Flask develops a hyper-cross-linked cyclodextrin when condensation polymerization is finished [Fig. 1 (D)]. Deionized water should be added in excess to the mixture above to eliminate any excess Dimethyl Formamide. Finally, ethanol-based Soxhlet extraction is used to eliminate unreacted chemicals [33,35].

Swaminathan et al. synthesized nanosponges of β-Cyclodextrin by cross-linking it with either polyamidoamine segments derived from 2-methyl piperazine & 2,2-bisacrylamidoacetic acid or 2,2-bisacrylamidoacetic acid. Both the cyclodextrin based nanosponges showed more than 90 % protein loading with a prolonged release profile of bovine serum albumin [37].

4.5. Microwave irradiation method

In the scientific microwave system of Cata, microwave reactions were conducted. A fabric-optic probe was put into the reaction vessel to measure the temperature of the reaction mixture. In order to create cyclodextrin-based nanosponges, diphenyl carbonate was used as a crosslinking agent, and diphenyl formamide served as a solvent. Briefly, a mixture of cyclodextrin and diphenyl carbonate in dimethylformamide was added to a 250 ml flask and microwaved under specific conditions for a specified time. After some time, the solvent was removed entirely. The resulting product was then thoroughly cleaned by Soxhlet extraction with ethanol. A white powder was then produced, which was dried in an oven at 60 °C until it was ready for use [2,29].

In an experiment, Singireddy et al. investigated the advantages of microwave-assisted heating over traditional heating methods during the synthesis of Cyclodextrin-based Nanosponges. According to the study's findings, the model drug's drug-retaining capacity was increased by half when NSs were produced using microwave assistance. The results of high-resolution transmission electron microscopy demonstrated that the NSs produced by microwave synthesis were highly crystalline and had a limited size distribution in addition to a higher degree of complexity. 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 an accurate form [10].

4.6. Polymerization

A non-polar medication is dissolved in the monomer, and then an aqueous phase is added, typically comprising surfactants and dispersants to aid in suspension. Once the suspension with the distinct droplets of the necessary size is established, polymerization is carried out by catalyzing the monomers or raising the temperature. A reservoir-like system that opens at the surface through pores is created by the polymerization process [15].

Dai et al. delivered Doxorubicin using Glutathione pH dual-bio responsive degradable Nanosponges that were developed based on β-Cyclodextrin-appended hyper-cross-linked polymer by one-pot polymerization of acryloyl-6- ethylenediamine-6-deoxy-Cyclodextrin, acrylic acid & N, N-bis(acryloyl)-cystamine as a crosslinking agent. It provided enhanced loading of Doxorubicin in a 3D network of nanosponges [30].

5. Factors affecting the formation of nanosponges

Nanosponges, being 3D network-like structures, are used to encapsulate both hydrophilic and hydrophobic compounds. The formulation of nanosponges by various methods is affected by different parameters discussed below.

5.1. Type of polymer & crosslinkers

The performance of nanosponges is affected by the kind of polymer used for their formulation. Effective crosslinkers transform nanoporous molecular structures into three-dimensional (3D) structures. To entangle target chemicals, hydrophilic or hydrophobic sections can be produced by varying the degree of crosslinking. On the basis of the nature of crosslinkers, water soluble or insoluble nanosponges are developed [38]. Using epichlorohydrin as a crosslinker, hydrophilic nanosponges can be invented, which will provide better absorption of drugs across biological membranes & can be utilized as effective drug carrier [39]. By using crosslinkers such as diphenylcarbonate [40], pyromellitic anhydride, and diisocyanates [41], it is possible to generate hydrophobic nanosponges that may be utilized for delivering hydrophilic pharmaceuticals such as proteins and peptides for an extended period [2].

5.2. Type of drug & medium used for interaction

The type of drug that needs to be loaded and the solvents can have an impact on the production of Nanosponges, in addition to the type and nature of the crosslinker and polymer used. To be adequately entrapped in nanocavities, drug molecules must have specific properties. Molecules having a molecular mass from 100 to 400 Da, less than 250 °C melting point, with fewer than five condensed rings, and less than 10 mg/ml solubility in water are able to be effectively trapped inside a nanocavity [42]. Compounds with a higher melting point tend to lose stability after being loaded into Nanosponges, making it impossible for them to form stable complexes between medicines and Nanosponges. Temperature variations affect a complex's stability constant. The relationship between the stability constant and temperature increase is inverse. As temperature rises, drug or nanosponge contact forces weaken, causing the apparent stability constant's magnitude to drop. Therefore, when making nanosponges, strict temperature control should be kept [35].

The drug loading is significantly influenced by the greater melting point of the drug. Additionally, due to the stiffness of the compound's structural makeup, the melting of compounds at higher temperatures results in decreased drug loading [2]. In the presence of a hydrophilic medium, organic guest molecules will be compelled to enter hydrophobic cavities, while an organic solvent tends to release the organic molecules trapped in Nanosponges. The medium has a significant impact on how targeted compounds interact with Nanosponge's cavity [2].

5.3. Degree of substitution

The ability of complexation of nanosponges is affected by the kind of substituent, number & position of the polymeric molecule [43]. The type of substitution is necessary because the functional groups present on the surface of Cyclodextrin derivatives allow for extensive accessibility of the Cyclodextrin derivatives in various structures. Different varieties of complexed material, such as Cyclodextrin Nanosponges, Cyclodextrin -carbonate Nanosponges, etc., can be produced by different functional groups when they are complexed together by crosslinker [2]. There is a legitimate relationship between the number of substitutions and the degree of crosslinking. This suggests that adding more substituents could increase the likelihood of higher levels of crosslinking, which could produce highly porous nanosponges due to increased linkages between polymers and the construction of a mesh-like network [2].

As the functional group on the parent compound may occupy a different location due to a change in the production method, new materials with different physicochemical properties may be formed. For instance, if produced under different production conditions, samples of hydroxypropyl-cyclodextrin with the same degree of substitution may not have the same physicochemical characteristics. This could be explained by the possible fact that the hydroxypropyl groups on the parent Cyclodextrin molecule reside in different locations. As a result, the degree of polymer substitution is high and has a significant impact on the final quality of Nanosponges, which is demonstrated by the production process and material purity [2].

5.4. Temperature

The complexation of nanosponges is affected by variations in temperature. The stability constant of a drug or nanosponges complex

typically decreases with temperature, which may be due to reduced contact forces, such as hydrophobic forces and van der Waals forces [31,43].

6. Characterization of nanosponges

The Nanosponges are subjected to numerous tests that assess their strength, degree of crosslinking, and rate of drug delivery, among many other factors, all of which help determine whether the formulation has appropriate characteristics [10].

6.1. Microscopic study

Transmission and scanning Microscopical research on medicines and nanosponges is possible using electron microscopes [5]. The production of the inclusion complexes is shown by the difference in crystallization state between the starting materials and the final result, as seen by electron microscopy [43,44].

6.2. Solubility study

The phase solubility method is used to study inclusion complexation. The degree of complexity is shown using solubility diagrams [43]. In this procedure, a flask containing an aqueous solution of varying percentages of nanosponges was taken, and the drug was added to each. At room temperature, the flask was shaken using a mechanical shaker. After the suspension had reached a stable state, it was subjected to centrifugation and then filtered through a 3000 Da molecular filter. The resultant solution was analyzed using high-performance liquid chromatography to figure out the drug content. Research on medication solubility is conducted to know the drug's pH, the solubilization process, and the variables impacting drug solubility [44].

6.3. Thermodynamic study

The thermo-chemical approach can be used to identify any modifications that drug molecules or particles go through before the annihilation of nanosponges due to heat. Melting, oxidation, and polymeric modifications are just a few of the ways that drug particles might alter [31]. The thermogram that is generated by differential scanning calorimetry and differential thermal analysis may be used to analyze widening, shifting, and the introduction of new peaks and the elimination of particular peaks. Additional information for the formation of inclusion complexes can be provided by variations in weight loss [44,45].

6.4. Thin layer chromatography

In thin layer chromatography, the Rf values of a drug molecule are evaluated, which makes it easier to recognize the complex formation that occurs between the drug and nanosponges [44,45].

6.5. Drug loading efficiency

It is possible to determine the loading efficiency of nanosponges by utilizing a UV spectrophotometer to get a quantitative estimate of the quantity of drug loaded into the nanosponges [34]. The quantity of medicine that is put into nanosponges may be calculated with the help of the following equation [4,44]:

$$\%\text{Drug Loading} = (\text{drug loaded in nanosponge} / \text{Total amount of drug and polymer added}) \times 100$$

6.6. Infrared spectroscopy

To determine the interaction between nanosponges and drug molecules in the solid state, infrared spectroscopy is used. When a complex is formed, nanosponges bands undergo minor changes. If fewer than 25 % of the guest molecules are encapsulated inside the complex, the bands that may be assigned to the included fraction of the guest molecules are readily obscured by the bands of the spectrum of the nanosponges [46]. Infrared spectroscopy is restricted to medications with recognizable bands, such as carbonyl or sulfonyl groups [44].

6.7. Particle size determination

Dynamic light scattering can be used to determine the particle size utilizing a 90Plus particle size sensor. This allows for the estimation of the polydispersity index and means diameter [5]. For all samples, the measurements were taken at a constant 90-degree angle. For each evaluation, the samples were appropriately diluted with Milli Q water [1,44].

6.8. Zeta potential

Surface charge is measured by zeta potential [5]. Samples of the nanosponges were diluted with 0.1 mol/L KCl in order to determine their zeta potential. Using an average of all measurements, the mean hydrodynamic diameter and polydispersity index of the particles were determined [1,44].

6.9. X-ray diffractometry

It is possible to identify inclusion complexation in the solid state using powder X-ray diffractometry. The complex development and chemical decomposition of a combination of substances can be ascertained by investigating diffraction peaks. The drug-nanosponge complex development modifies the diffraction patterns and the drug's crystalline structure. The complex formation causes a few new peaks to appear, some old peaks to get sharper, and some peaks to shift [44,46].

7. Applications

Due to biocompatibility and adaptability, Nanosponges offer a wide range of potential uses in the realm of nanotechnology. There are numerous applications of Nanosponges, some of which are discussed here [23]. Table 3 lists several more recent Nanosponge applications with their relative importance.

Table 3
Various drug containing nanosponge formulations.

S. No.	Drug	Carrier	Inference	Reference
1	Ferulic acid	Cyclodextrin nanosponges	Enhanced the antibacterial activity and stability of Ferulic acid during storage.	[17]
2	Carboplatin	Hydrogel of Ethylcellulose based nanosponges	The Nanosponge based hydrogel provided a sustained release.	[20]
3	Oxyresveratrol	Cyclodextrin based nanosponges	The activity of oxyresveratrol against colon and prostate cancer cell lines increased.	[47]
4	Doxorubicin	Carbon quantum dots based nanosponges containing hydrazine and polyethylene glycol.	The nanosponges showed very little drug leakage and complex disintegrated in the tumor microenvironment for theranostic effect.	[48]
5	Temoporfin	Hyper crosslinked β-cyclodextrin	It showed similar photodynamic therapy as a free drug and enhanced penetration and uniform distribution of temoporfin in spheroids.	[18]
6	Celecoxib	β-cyclodextrin & NN-methylene bisacrylamide nanosponge based hydrogel	It enhanced the solubility and bioavailability of celecoxib up to 30 to 65-fold.	[49]
7	Dithranol	Diphenyl carbonate & β-cyclodextrin	The formulated Nanosponge loaded hydrogel showed better anti-psoriatic activity with significant epidermal thickness.	[50]
8	Neuropeptide Y	β-cyclodextrin crosslinked nanosponges	The synthetic Neuropeptide Y-loaded nanosponges demonstrated significant antiepileptic effects comparable to those of the standard drug.	[19]
9	Nisin	Crosslinked cyclodextrin nanosponges	It acts as an efficacious anticancer drug by enhancing cytotoxicity and apoptosis against melanoma cancer cell lines.	[51]
10	Linagliptin & Empagliflozin	Multilayer nanosponges	The multilayer nanosponge loaded buccal films showed a better permeation of empagliflozin with controlled efflux of linagliptin.	[52]
11	Calcium carbonate	Polylactic-co-glycolic acid (PLGA) and PLGA polyethylene glycol.	The nanosponges can aid in reviving both worn-out $CD8^+$ T cells and innate antitumor immunity. In order to prevent $CD8^+$ T cell exhaustion and activate innate antitumor immunity, nanosponges injection may enhance the therapeutic efficacies of three Immune checkpoint blockade treatments against both CT26 and B16F10 tumor xenografts.	[21]
12	Doxorubicin	Glutathione nanosponges using β-cyclodextrin	The prepared nanosponges showed high antitumor activity with glutathione pH-based drug release. It also provided targeted controlled release in tumor treatment.	[30]
13	Quercitrin	cyclodextrin nanosponges	Quercitrin was released more effectively from cyclodextrin nanosponges formulations in vitro. Researchers investigated the biological effects of free Quercitrin and Quercitrin loaded cyclodextrin nanosponges on the SARS-CoV-2 virus and the lung cancer cell line A549. The findings showed that free Quercitrin had higher IC50 values against the SARS-CoV-2 and lung cancer cell line A549 than did Quercitrin loaded cyclodextrin nanosponges.	[25]
14	Econazole nitrate	β-cyclodextrin, N, N-Carbonyl diimidazole	The formulated hydrogel of econazole nitrate-loaded nanosponges better release and improved efficacy against fungal infection.	[53]
15	Norfloxacin	β-cyclodextrin nanosponges	Animals treated with formulations compared to free drugs showed fewer colony-forming units per milliliter in their kidneys. The norfloxacin was shielded against uptake transporter depletion by an enhanced permeability.	[54]

7.1. Covid

Numerous antiviral medications, immunological modulators, and possible inhibitors—organic or inorganic substances—have been suggested against SARS-CoV-2 [55,56]. Numerous research domains, particularly medicine, have undergone revolutionary change as a result of recent advancements in nanoscience and nanotechnology [57]. Researchers are moving towards nanocarriers with distinctive properties, optimal effectiveness, specificity, and fewer adverse effects due to limitations in drug efficacy and delivery [58,59].

Nanosponges have a number of advantages: they improve the bioavailability, stability, and solubility of therapeutic agents or drugs to provide the desired pharmacokinetic effects [60–62]. Nanosponges can also form a variety of complexes with hydrophilic or lipophilic molecules, improving their transferring and shielding them from harmful substances [63,64]. For instance, β-cyclodextrin nanosponge-based delivery systems were developed for drugs that are lipophilic, providing a different method for increasing their solubility and facilitating their oral administration [61]. In addition to their potential for personalized therapies and targeted or controlled distribution, nanosponges can be effective solutions for enhancing immunization [65–67].

Acyclovir has been delivered using cyclodextrin-based nanosponges that contain carboxylic groups within their structural makeup. These nanosponges have a high loading capacity for this antiviral medication and exhibit prolonged-release performance; however, additional in vivo testing is necessary to fully evaluate the efficacy and biodistribution of these nanosponges. Particularly, cytotoxicity and biosafety criteria are essential for future clinical and biological applications of nanosponge-based technology [68].

According to Rao et al., a potent two-step neutralization strategy against COVID-19 based on a decoy nanoparticle includes neutralizing SARS-CoV-2 first and then neutralizing cytokines. By fighting with host cells for virus binding, these nanosponges effectively shield them from SARS-CoV-2 infection [69]. With the addition of these nanosponges, interactions between the SARS-CoV-2, S-protein complex, and human ACE2 were reduced, and viral receptors on the nanosponges showed a high affinity for binding to ACE2 [70]. In order to capture and neutralize SARS-CoV-2 through natural cellular receptors, cellular nanosponges resemble host cells, offering a multifaceted antiviral strategy. The inhibitory effects of heparin against the virus were increased by increasing the density of heparin on the cellular nanosponge surface [59].

The bioengineered 3D models offer a more realistic platform than straightforward 2D monolayer cell cultures. 3D in vitro models have been widely used in viral and antiviral studies, with encouraging results. In order to replicate the SARS-CoV-2 virus infection and replication for the ultimate development of new treatments or vaccines to treat COVID-19, they can also accurately and sufficiently recapitulate the physiological environment of the tissue and organs of the body [71]. Potential platforms for the early identification of symptoms connected to multiorgan infection include organoid models loaded with several cell lineages and nanosponges or microfluidics-on-a-chip [72]. SARS CoV-2 can quickly infect and spread to several human organs, which is very pertinent [59].

7.2. In drug delivery

Because of their spherical shape and nanometric size, nanosponges can be manufactured in a variety of dosage forms, including topical, parenteral, aerosol, tablet, and capsule [34]. In order to alleviate the symptoms of superficial candidiasis, dermatophytosis, and skin infections, the antifungal medication econazole nitrate, which is available in cream, lotion, ointment, and solution forms, is administered topically to the affected area of the skin. When econazole nitrate is applied to the skin, limited absorption occurs, which limits its therapeutic success. The emulsion solvent diffusion process was used to formulate econazole nitrate nanosponges, which were then loaded in hydrogel to serve as a local depot for sustained drug release [12].

The BCS Class II medication Telmisartan (TEL) has a dissolution rate-restricted bioavailability. By crosslinking β-cyclodextrin with carbonate bonds, -CD based nanosponges were developed. The nanosponges contained TEL in them. Comparing the -CD complex of TEL to plain TEL and nanosponge complexes of TEL, researchers looked at the compounds' saturation solubility and in vitro dissolution. By introducing NaHCO3 in the drug-nanosponges complex rather than TEL, it was discovered that the solubility of TEL was enhanced by 8.53-fold in distilled water, 3.35-fold in 1 mol HCl, and 4.66-fold in phosphate buffer pH 6.8. The inclusion complex made from nanosponges and NaHCO3 showed maximum solubility and in vitro drug release [44,73].

By loading drugs into the nanosponges, it is possible to successfully administer medications whose solubility is very important for formulation. Drugs' solubility, stability, and rate of dissolution can all be improved with the help of nanosponges, which can also be employed to mask unpleasant flavors and turn liquids into solids [74]. The nanosponge 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 [34]. Itraconazole in Nanosponges was examined by Swaminathan et al. Itraconazole, a BCS Class II drug, has a low bioavailability and a slow rate of dissolution. The drug's solubility was enhanced more than 27-fold by nanosponges. This increased to 55-fold when copolyvidonum was included in the formulation of the Nanosponge as a support material. The hydrophobic groups of itraconazole may be concealed by nanosponges, which may also increase the drug's wetting and/or reduce its crystallinity [13,44].

7.3. Enzyme immobilization

For lipases, in particular, the issue of enzyme immobilization is important since it increases their stability and controls factors like enantioselectivity and reaction speeds [75]. The need for new solid supports that are appropriate for this family of enzymes is consequently increasing [44]. According to Boscolo et al., Pseudomonas fluorescent lipase exhibits strong catalytic activity on a novel class of cyclodextrin-based nanosponges [33,76]. When enzymes are utilized, it is possible to preserve their activity efficiency, prolong their operation, and expand the pH and temperature range where they are active by using β-Cyclodextrin nanosponges as the carrier.

This also enables the conduct of continuous flow processes [34].

7.4. Delivery of protein and peptides

Because of its large molecular size, hydrophilic nature, degree of ionization, high surface charge, chemical and enzymatic instability, and low permeability through mucous membranes, the majority of protein medicines are poorly absorbed through biological membranes. Protein molecules may be quickly removed from the blood after intravenous delivery, bind to plasma proteins, and be vulnerable to proteolytic enzymes. The issue with oral administration is bioavailability [34]. The long-term stability of proteins is crucial to their development [77]. However, upon lyophilization, proteins can reversibly denature and, after that, acquire conformations that are very different from their natural ones. Therefore, maintaining the natural protein structure both throughout the formulation process and after long-term preservation is a significant challenge in the development of protein formulations [44,78].

Nanosponges have the ability to regulate distribution, immobilize and stabilize enzymes & encapsulate proteins in addition to increasing protein stability [32,33]. According to Swaminathan et al., by crosslinking β-Cyclodextrin with either 2,2-bis-acrylamidoacetic acid or a short Polyamidoamine chain derived from 2,2-bis-acrylamidoacetic acid and 2-methyl piperazine, respectively, new swellable cyclodextrin-based polyamidoamine nanosponges named nanosponges 10 and nanosponges 11 were produced. It was discovered that the polyamidoamine-based β-Cyclodextrin nanosponges were stable at 300 °C and possessed a high capacity for protein complexation [3]. It has been discovered that cyclodextrin-based nanosponges are an extremely effective carrier for protein adsorption. Additionally, by adsorbing or encapsulating proteins and other macromolecules in cyclodextrin nanosponges, they can be transported [34].

7.5. Delivery of gases

Gases are used in medicine for both diagnostic and therapeutic purposes. Hypoxia 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 (Nanosponge). As topical oxygen delivery systems, Cavalli et al. designed formulations of nanosponges that have the capacity to store and release oxygen gradually over time [44,79].

7.6. Cancer

Mesoporous and nanoporous drug delivery structures, such as inorganic or organic nanosponges, have been developed as a result of recent research. In vivo, tests on inorganic systems based on metal revealed toxicity and no biodegradability. As a result, organic nanosystems became the subject of further research [80]. Cyclodextrin-based nanosponges are building blocks of novel drug delivery systems, which are hyper-cross-linked polymers forming nanoporous system [1,11]. The extremely low water solubility of many anticancer medications is one of their biggest drawbacks. The wetting and solubility of molecules with extremely poor water solubility can be improved by nanosponges [13,81].

Cyclodextrin nanosponges were used as a solubilizing agent to produce a novel paclitaxel formulation free of the chromophore. In a nutshell, paclitaxel was well-complexed and soluble in carbonate nanosponges of around 450 nm. About 2 mg of paclitaxel could be solubilized in 1 mL of a 1.5 % w/w nanosponge aqueous suspension, generating a homogenous dispersion that was devoid of paclitaxel crystals. Paclitaxel-loaded nanosponges kept in an aqueous solution have good physical stability for 6 months, according to studies on short-term stability [82]. Without producing paclitaxel crystals, the paclitaxel-loaded nanosponges held at 4 °C as an aqueous nanosuspension generated a stable colloidal system [81]. Paclitaxel administration by nanosponges is allowed to remove the harmful substance Chremophor EL from the drug formulation as well as an increase in the amount of paclitaxel that entered cancer cells and a decrease in the drug's 50 % inhibitory concentration (IC50), which improved its pharmacological action [81,82]. One of the significant medications developed as nanosponges was paclitaxel. The two main tumor types studied by the researchers were fast-acting mouse glioma and slow-growing human breast cancer in animals. In both instances, they discovered that drug delivery using nanosponges boosted the mortality of cancer cells and inhibited tumor growth [33].

The effectiveness of nanosponges in increasing the solubility of tamoxifen, another anticancer medication with limited solubility, was subsequently demonstrated. Tamoxifen was successfully enclosed in nanosponges. Tamoxifen in nanosponges significantly inhibited cell proliferation more than free tamoxifen, as seen in cytotoxicity experiments on MCF7 cells [81,83].

A pH-controlled release nanosponge system for targeted codelivery of Doxorubicin and capsaicin to colorectal cancer cells was developed by Asakiya et al. The two drug combinations loaded onto the DNA nanosponges together reduced mitochondrial membrane potential, generated intracellular Reactive oxygen species burst, and hindered SW480 cell proliferation. These findings demonstrated the potential of this innovative delivery mechanism in biomedical applications [84].

As a precursor for the fluorescent traceable prodrug, Carbon dots-based hybrid nanosponges were created with the appropriate diameter, and Doxorubicin was conjugated using acid-labile bonds by Li et al. The drug showed strong pH-triggered drug release. The proposed fluorescent traceable hybrid prodrug nanosponges are promising nanotheranostics for the treatment of tumors in the future since the fluorescence of the Carbon dots was recovered during the drug release in the simulated tumor intracellular surroundings [85].

MS et al. formulated a multidrug containing one nanosponge to deliver Paclitaxel, Doxorubicin, & Tetrandrine simultaneously. The formulated all in one Nanosponge showed pH dependent and controlled release. On P-gp-overexpressing colorectal cancer cells and solid tumor mouse xenografts, all in one nanosponges demonstrated more potent anticancer effects without significantly increasing toxicity. A notable difference between all-in-one nanosponges made of pluronic shell and Tetrandrine was the induction of in vitro P-gp

inhibition, suggesting a synergistic anticancer action [86].

Anwer et al. formulated nanosponges of Abemaciclib to enhance its bioavailability and decrease dosing frequency so as to increase patient compliance for the treatment of breast cancer. The results showed sustained release of the drug. Further, Abemaciclib nanosponges were identified by the MTT assay as a possible cytotoxic nanocarrier against the human breast cancer cells MCF-7 and MDA-MB-231. It demonstrated that the produced Nanosponges would serve as a reliable carrier to maintain the release of Abemaciclib and increase breast cancer-fighting effectiveness [22].

7.7. Protective effect against light or other chemicals

Additionally, nanosponges can transport molecules and shield them from light, chemicals, and enzymes that might otherwise cause them to break down. 5-fluorouracil was utilized as a light-sensitive model medication to assess protective potential. Up to 30 % of 5-fluorouracil was able to be incorporated into ϒ-Cyclodextrin nanosponges. Despite the drug's hydrophilic qualities, the in vitro release of 5-fluorouracil at pH 7.4 was around 60 % of the encapsulated amount after 2 h, demonstrating an interaction between the drug and nanosponge structure. Additionally, 5-fluorouracil was enclosed in nanosponges for 6 months, preserving its protection and cytotoxicity against MCF-7 cells. This research proved that hydrophilic molecules can be captured by nanosponges and released slowly [11,81].

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 stabilize food and pharmaceutical raw materials, as well as sunscreen in the cosmetics industry. Due to its high instability and photodegradation, its use is restricted. Nanosponges were used to encapsulate gamma-oryzanol, which demonstrated good photoprotection. The nanosponges that were loaded with gamma-oryzanol were used to create a gel and an Oil-in-water emulsion [44,87].

7.8. Autoimmune diseases

In autoimmune disease, the body's own defense system attacks itself due to over-activation of immunity. Recently, there has been a lot of interest in the development of biomimetic nanoparticles in the field of nanomedicine, which derives inspiration from nature and improves the interaction of synthetic materials with biological systems [88–91]. Nanosponges bind toxic molecules and neutralize them, protecting healthy cells from damage. The nanosponge platform sets itself apart from conventional nanomaterial-based techniques that function via complimentary structures by using a function-based approach to achieve broad-spectrum neutralization [92]. This idea has been shown for a variety of pore-forming toxins, including melittin from bee venom, streptolysin O from group A streptococcus, and α-toxin from methicillin-resistant *Staphylococcus aureus* [92–94]. Each of these toxins could be totally neutralized by being incubated with red blood cell membrane-coated nanosponges, which also reduced cytotoxicity and lysis in a dose-dependent way [95].

The nanosponge approach has more recently been extended for usage against autoimmune antibodies in place of neutralizing exogenous poisons. This innovative method may make it possible to treat many types of type II immunological hypersensitivity specifically, especially when it's unclear which specific antigen triggers autoimmunity. The antibody nanosponge utilizes the natural connections between the pathogenic antibodies and their biological targets, much like their toxin-neutralizing counterparts [95]. For the treatment of autoimmune hemolytic anemia, a nanosponge formulation based on red blood cells was created. Red blood cell antibody nanosponges, which were produced by covering the red blood cell membrane around a polymeric core, had the same affinity as native red blood cell ghosts for anti-red blood cell antibodies. In both pre-incubation and competitive settings, the nanosponges were successful in preventing the binding of anti-red blood cell autoantibodies to healthy red blood cells in vitro. These antibody nanosponge formulations have shown great promise for treating antibody-mediated type II hypersensitivities in a way that differs from any existing therapy [96]. An important benefit of this strategy is that it can produce a suitable formulation capable of binding poly specific antibodies just by knowing the cellular target, without the requirement to discover specific self-antigens [95,97].

7.9. Treatment of blood poison

For the purpose of detoxifying the blood, Nanosponges offer a unique method. Instead of using an antidote, Nanosponges can absorb the toxins by injecting them into their bloodstream. These Nanosponges imitate Red Blood Cells to deceive poisons into attacking them, sop them up, and divert their path from the target cell [93]. By joining poly (d,l-lactic-co-glycolic acid) cores and ovine erythrocyte vesicles, Chhabria et al. formulated Nanosponges. The erythrocytes from ovine animals were more vulnerable to streptolysin-O lysis. At 37 and 40 °C, ovine nanosponges absorbed the cholesterol binding toxin streptolysin-O [23,98].

7.10. Photothermal therapy

Conventional phototherapy was found to be ineffective as it was harming other cells along with cancer cells. As the light-activated heating nanocarrier can be directed at the tumor location, nanocarrier-based Photothermal therapy seems promising. This reduces the killing of healthy, normal tissues or cells by limiting the thermal ablation to the tumor site [99].

Deoxy ribozyme Nanosponges were developed by Jin et al. utilizing the FDA-approved Photothermal therapy dye indocyanine green. The temperature increased much more in the Nanosponges indocyanine green group than in the indocyanine green group. Antitumor results demonstrated that Photothermal therapy could stop tumor growth after Nanosponge-indocyanine green injection

without causing any negative side effects, indicating that this strategy is promising for gene silencing by Photothermal therapy [23, 100].

7.11. Fungal infections

Kumar et al. formulated nanosponges loaded hydrogel of Clobetasol propionate β-cyclodextrin & diphenyl carbonate to increase its solubility, stability and provide controlled release. The in vitro cell viability test was done using THP1 cells. The results showed that Clobetasol propionate nanosponges had an excellent payload and controlled-release capability. Additionally, in vitro testing demonstrated its effectiveness against THP1 cells, demonstrating anti-inflammatory and immune-modulatory effects. Figure showed comparison of histopathological study of control [Fig. 2 (a)], Clobetasol Propionate 0.05 % w/v gel [Fig. 2 (b)], and Clobetasol Propionate -Cyclodextrin based Nanosponges [Fig. 2 (c)]. By regulating antioxidant enzymes and oxidative stress, Clobetasol propionate nanosponge based hydrogel treatment reduced the severity of Clobetasol propionate's side effects in Swiss mice and increased its therapeutic effectiveness [101].

Kumar et al. formulated Dithranol nanosponges loaded hydrogel for the management of psoriasis using Carbopol. On application of dithranol, cyclodextrin Nanosponge based hydrogel, the production of reactive oxygen species was reduced, which leads to decreased oxidative stress with beneficial effects on psoriatic skin, as shown in Fig. 3 [50].

Ahmed et al. formulated a Nanosponge based gel of Butenafine for the treatment of fungal infections. By delivering drugs to the target site deeper into the epidermal layers, nanocarriers enhance therapeutic effectiveness and completely cure fungal infections. The newly created Butenafine loaded Nanosponge impregnated carbopol polymeric gel may be an effective drug delivery system of an antifungal agent for the successful treatment of fungal infections by prolonging the drug release [102].

7.12. Improve solubility, stability, and bioavailability

Salehi et al. formulated β-cyclodextrin nanosponges of D limonene to overcome the problem of high volatility and poor solubility. The results suggested that β-cyclodextrin nanosponges are a suitable carrier for hydrophobic and sensitive compounds, and Limonene nanosponges can be used as a food additive. Encapsulated Limonene showed higher antibacterial activity compared to free Limonene, and the minimum inhibitory concentration of free Limonene was decreased significantly after encapsulation in β-cyclodextrin nanosponges. The findings suggested that Limonene nanosponges can be a promising preservative with increased antibacterial activity in food applications [103].

Sesamol has several advantages in pharmaceuticals, but its poor stability hinders its utility. Gupta et al. formulated a cyclodextrin nanosponge of Sesamol to protect it from degradation. The findings showed that Sesamol was successfully encapsulated in cyclodextrin nanosponge, which had a nanoscale size & high encapsulation efficiency. The study of photostability's results revealed that cyclodextrin nanosponge might shield Sesamol against photodegradation. Additionally, it was discovered that Sesamol's oxygen radical absorbance capacity was still intact, particularly when it was enclosed in cyclodextrin nanosponge [104].

Prabhu et al. formulated nanosponges of Lapatinib to increase its bioavailability & solubility. Studies on saturation solubility and in vitro dissolution showed that the aqueous solubility and dissolution rate of Lapatinib in the form of Nanosponges increased when compared to the pure form of Lapatinib. The AUC and Cmax showed a significant improvement in the form of nanosponges. As a result, it has been demonstrated that Lapatinib-loaded Nanosponges have a high bioavailability and offer the possibility of lowering the oral dose of Lapatinib [105].

The applications of essential oils are restricted by their high volatility, limited solubility, and sensitivity to environmental factors.

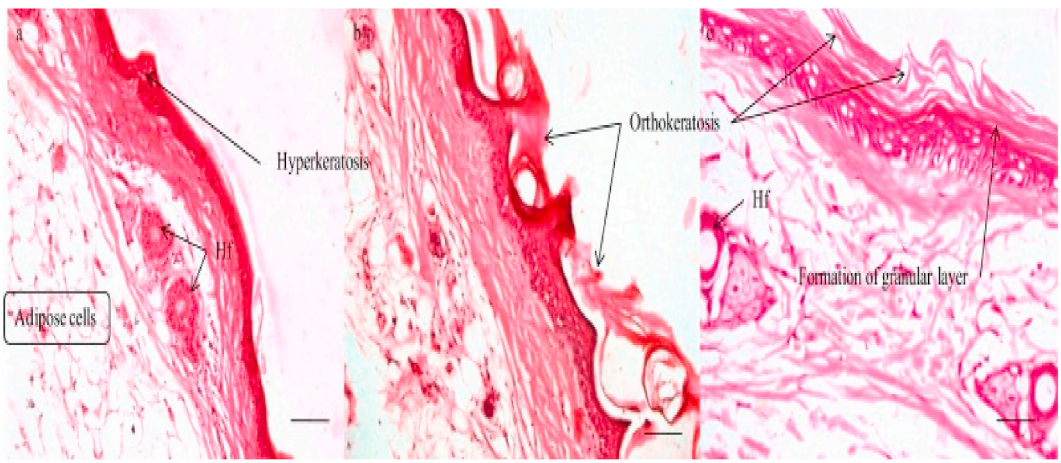

Fig. 2. Histopathological evaluation of tail of mice after different treatments (a) Control, (b) Clobetasol Propionate 0.05 % w/v gel, and (c) Clobetasol Propionate -Cyclodextrin based Nanosponges14 (equivalent to CP 0.05 % w/v gel) Reprinted from Ref. [101] with permission from Elsevier.

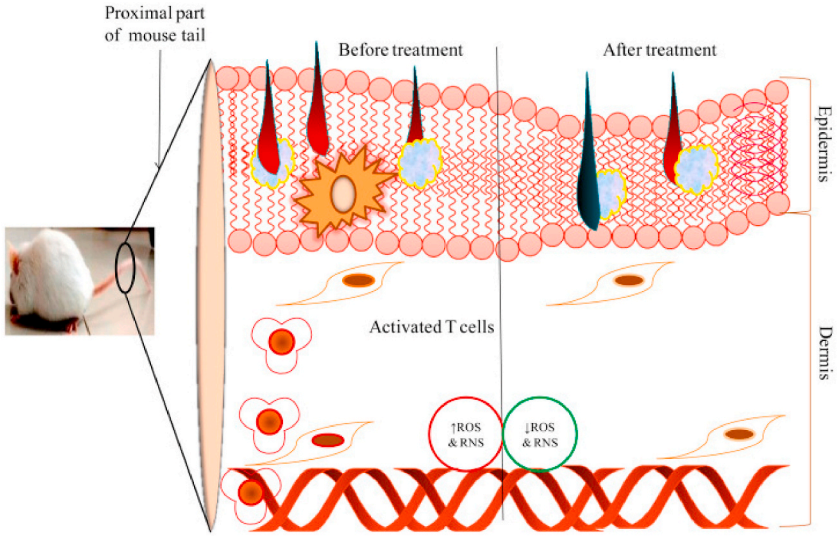

Fig. 3. Role of oxidative stress indicators in the mouse tail before and after the application of a dithranol nanosponge loaded hydrogel. (ROS- Reactive oxygen species, RNS- Reactive nitrogen species, T cell- T lymphocyte) Reprinted from Ref. [50] with permission from Elsevier.

Rezaei et al. incorporated Thyme essential oil in β-cyclodextrin nanosponges using diphenyl carbonate as a crosslinker. The Thyme essential oil nanosponges improved the antibacterial activity of Thyme essential oil. Thyme essential oil aqueous solubility was 15 times greater after being enclosed inside nanosponges, and their minimum inhibitory concentration was lowered by up to 29.4 folds. The findings imply that -cyclodextrin nanosponges have the potential to be utilized as a delivery mechanism for hydrophobic and sensitive substances to boost their utilization in the food and pharmaceutical sectors [106].

Numerous nutraceuticals have issues of poor water solubility & stability, which prevents the development of the desired bioactivity. Monfared et al. developed nanosponges of Kynurenic acid, a nutraceutical using different complexes such as β-cyclodextrin carbonyl diimidazole and Hydroxypropylated β-cyclodextrin. The bioavailability was found to be highest when Kynurenic acid was complexed with β-cyclodextrin carbonyl diimidazole. The optimum formulation was Nanosponges of carbonyl diimidazole because the formulation of Kynurenic acid lessened the temporal oxidative stress damage in the kidney and liver. These findings indicate a significant future use of cyclodextrin-based nanosponges for the stabilization and oral delivery of nutraceuticals [107].

The nanosponges of Risedronate sodium were developed for enhancing bioavailability and were optimized using factorial design. The results of the in vitro release investigation revealed burst release for the first 2 h, accompanied by slow and sustained release for the next 24 h, which followed the Higuchi model's diffusion-controlled release mechanism. A study using scanning electron microscopy revealed spherically evenly discrete, porous particles without any aggregation. The study's findings suggest that the nanosponges of the Risedronate sodium could be an outstanding drug delivery method for improved osteoporosis therapy [108].

7.13. Other applications

Titanium dioxide is the most used semiconductor as a photocatalyst. Due to its high electron carrier movement, chemical stability, lack of toxicity, relative affordability, and strong photocatalytic activity, Titanium dioxide performs well in photoelectrochemical applications. Titanium dioxide's broadband gap value, which restricts the photoelectrochemical applications it may be used for, is the fundamental disadvantage of employing it as a photocatalyst. Different substances, such as ions and noble metals, have frequently been added to TiO2 nanostructures to help solve this problem. In a study by Gazquez et al., zinc oxide and titanium dioxide hybrid nanostructures were developed. The best samples were zinc oxide and titanium dioxide hybrid nanostructures electrodeposited with 30 mM Zn (NO3)2 because they were resistant to photo corrosion, had a 204 % higher photoelectrochemical activity than Titanium oxide nanosponges, had less charge transfer resistance with a higher donor density. Due to a maximization of the zinc oxide and titanium dioxide interaction and the avoidance of the production of non-interacting Zinc oxide structures, the most effective samples overall showed an intermediate Zn-loading [109].

Huang et al. synthesized nanosponges of silver (Ag) using amino acid and solvent, which can be employed as surface enhanced Raman Scattering substrates for detecting minute amounts of hazardous antibiotics & chemical dyes. The performance of surface-enhanced Raman scattering was examined using rhodamine 6G (R6G) as a probe & revealed that the uniform Ag nanosponges had an intense and enhanced Raman scattering. These homogeneous nanosponges served as surface-enhanced Raman scattering substrates and made it simple to detect pazufloxacin mesylate (PM). For the rationally regulated production of additional metal nanomaterials, the current study may provide some direction. The results of the current study may provide some direction for the rationally regulated production of additional metal nanomaterials [110].

Rodrigues et al. formulated, optimized & evaluated Hesperetin nanosponges based gel for long lasting anti-inflammatory effects.

Small, porous, and spherical Hesperetin significantly delayed drug release for up to 8 h compared to pure drug & physical mixture. It showed no skin irritation. Additionally, Hesperetin-treated rats exhibited 33.16 % inflammation inhibition compared to the control group. Nanosponges slowed topical distribution and potentially overcame Hesperetin bioavailability problems [27].

Utzeri et al. investigated the sequestrating activity of Imidacloprid by formulating its Cyclodextrin based nanosponges. Two different linkers were used for the synthesis of nanosponges: Hexane-1,6-diamine (am_6) & Dodecane-1,12–diamine (am_{12}). The Dodecane-1,12–diamine (am_{12}) showed a more prominent sensitivity to pH change because of the more compact structure that resulted in fewer accessible amine groups. A superior sorbent action for Imidacloprid was provided by the Nanosponge that contained Hexane-1,6-diamine (am_6) [111].

Nazerdylami et al. prepared β-cyclodextrin based Nanosponge using pyromellitic anhydride as a crosslinker for the fluorescent detection of diclofenac. According to fluorescence experiments, the probe shows a remarkable affinity for diclofenac and can distinguish it from Amphetamine, Morphine, Codeine, and Ibuprofen at an emission wavelength of roughly 423 nm. The probe can be used as an efficient method for determining the amount of diclofenac in tablets [112].

Sadjadi et al. developed a composite using chitosan beads and cyclodextrin nanosponge and analyzed its activity as a metal-free catalyst. The composite's performance outperformed that of its constituent parts. Incorporating cyclodextrin nanosponge, having a high capacity for inclusion complex formation, into the composite's structure enabled the catalyst to function as a molecular nanoreactor & promote reaction effectively in aqueous media [113].

For the treatment of Hemophagocytic Lymphohistiocytosis, Wang et al. formulated Lipopolysaccharide stimulated macrophage membrane coated nanoparticles to exhibit substantial Interferon-ϒ and Interleukin-6 sponge capacity, as well as to inhibit the JAK/STAT signaling pathway both in vitro and in vivo to limit macrophage overactivation. It showed that biocompatible Lipopolysaccharide stimulated macrophage membrane coated nanoparticles had a high potential for clinical transformation in dampening Hemophagocytic Lymphohistiocytosis. This finding also offered new treatment options for other cytokines storm-mediated pathologic conditions, like cytokine releasing syndrome during CAR-T therapy, COVID-19 infection, etc. It also removed symptoms related to Hemophagocytic Lymphohistiocytosis, such as hepatorenal dysfunction and cytopenia [114].

It is extremely desirable yet still difficult to develop multifunctional, effective, and long-lasting membranes for treating complicated oily wastewater because of the severe membrane fouling. A nanosponge membrane for oil-water treatment & antifouling capabilities was created by Ma et al. using an azide-alkyne click reaction with a 3D-macrocycle cyclodextrin as the molecular cage. Compared to a pure Ethylene vinyl alcohol membrane, the molecular cage-grafted membrane demonstrated greater antifouling performance, with a smaller water flux decline and a higher water flux recovery. The membrane displayed a desired level of stability. The development of hydrophilic membrane surfaces by the suggested 3D membrane method based on molecular cages holds tremendous promise for possible uses, including the separation of oil-in-water emulsions [115].

The cell membrane coated nanoparticles, also known as cellular nanosponges, are being used due to their broad-spectrum mitigation capability, which is difficult to be obtained in conventional countermeasure technology. Cellular nanosponges' applications become even more adaptable and distinct when combined with different synthetic substrates. The development of broad-spectrum medical countermeasures is required for effectively neutralizing and inhibiting diversified & ubiquitous biological signaling in complicated disorders. These cellular nanosponges are created by covering the cores of synthetic nanoparticles with natural cell membranes. Surface receptors that are inherited from the donor cells enable cellular nanosponges to perform like actual cells. Researchers have begun to utilize them for biological neutralization. According to this theory, all poisons must interact with host cells in order to be bioactive, regardless of their molecular makeup or modes of action. As a result, cellular nanosponges serve as cell dummy agents that capture and inhibit the bioactivities of these harmful substances [116].

Red blood cell (RBC) membrane–coated poly (lactic–co–glycolic acid) nanoparticles, also referred to as "RBC-NPs," were the first formulation to illustrate this concept. By disguising as real RBCs, they served to counteract bacterially produced pore-forming toxins. Later, promising results were achieved when RBC-NPs were used to neutralize various toxic agents, including pathogenic antibodies and small-molecule toxicants. After the development of RBC-NPs, several cellular nanosponges containing membranes from other cell types, such as platelets, white blood cells, neuron cells, and bacteria, have also been developed. The variety of targets that cellular nanosponges can neutralize has increased as a result of this diversity. Lipid insertion, metabolic engineering, genetic manipulation, and membrane hybridization are a few techniques that have been employed to functionalize cell membrane coatings. Through these techniques, multitasking cellular nanosponges with improved neutralization ability and versatility can be created [116].

The removal of harmful compounds from the body is thought to be safe and biocompatible with the use of cyclodextrin-based nanosponges. Novel cyclodextrin polymers were created to create nanosponges that can remove indole before it may cause the body to produce poisonous indoxyl sulfate. Additionally, in vivo research was done. With an in vitro indole adsorption capability of over 90 %, nanosponges made from cyclodextrin crossed-linked with toluene diisocyanate were discovered to be the most efficient nanosponges. Oral cyclodextrin-based nanosponges did not generally tend to accumulate. According to this study, cyclodextrin-based nanosponge formulations can safely and effectively remove harmful compounds from the body. Their prospective application in veterinary and human medicine may lessen the need for dialysis while preventing damage to the heart and liver and the development of indoles [117].

8. Clinical findings

Over the past few years, the nanosponges as a delivery system have undergone numerous enhancements and innovations. Various kinds of research have been performed on different animal models, which are discussed below:

Rao et al. examined the nanodecoys in vivo after verifying their in vitro capacity to neutralize cytokines. Initially, mice were given

fluorescently labeled nanodecoys via inhalation, and the nanodecoys' in vivo biodistribution was examined. Even after 72 h, a single dosage of nanodecoys demonstrated good retention in the lungs, suggesting the possibility of using nanodecoys delivered via downstream inhalation for in vivo cytokine neutralization. They also utilized an acute lung inflammation animal model to evaluate the in vivo efficacy of nanodecoys. The lung bronchoalveolar lavage fluid's levels of IL-6, GM-CSF, and total protein were all significantly reduced by the nanodecoys, indicating the promising effects of nanodecoys on the wide-spectrum suppression of inflammatory cytokines. In a dose-dependent way, lung injury was greatly decreased by the nanodecoys, indicating the promise of nanodecoys in the prevention of lung injury and COVID-19-associated immunological disease [69].

In order to test the antiepileptic activity of the crosslinked nanocarriers of neuropeptide-Y nanosponges powder, various doses were given intravenously via a metered-dose inhaler in an animal model by Desai et al. At higher doses, the synthetic NPY-loaded nanosponges demonstrated strong antiepileptic effects comparable to the standard medication taken orally in maximum electroshock & chemically-induced seizures. This was due to an increase in NPY in the brain that was directly correlated with increased GABAergic signaling, which attenuated convulsions [19].

Monteil et al. demonstrated that SARS-CoV-2 survival from Vero cells was lowered by a factor of 1000–5000 when using therapeutic grade human recombinant soluble Angiotensin converting enzyme-2 (hrsACE-2). An equivalent rsACE2 mouse had no response. Additionally, we demonstrate that hrsACE2 can block the direct infection of designed human kidney and blood vascular organoids by SARS-CoV-2. After completing phase 1 & phase 2 clinical trials, hrsACE-2 is being investigated as a potential COVID-19 therapy [71].

The nanosponges of Telmisartan formulated by Rao et al. were evaluated for in-vivo activity in rats. In vivo experiments were conducted on the ternary complexes of Telmisartan with β-CD and nanosponges, specifically IC6 and IC8. When ternary Telmisartan complexes with NS and b-CD are compared to the pure drug, the pharmacokinetic data indicates enhanced bioavailability. The ternary NS complex showed a 54.4 % rise in AUC, whereas the β-CD ternary complex showed a 79.65 % increase in AUC. The drug molecule is more easily entrapped and can be released under regulated circumstances when it is inside the nanosponge structure due to the nanocavities present in it [73].

Kumar et al. evaluated the anti-psoriatic potential of formulated nanosponge loaded hydrogel of Clobetasol propionate. Compared to plain and Clobetasol propionate hydrogels, the results showed that Clobetasol propionate nanosponge-loaded hydrogels had a substantially greater anti-psoriatic effect. Because Clobetasol propionate is encapsulated in cyclodextrin nanocarriers, its dose is reduced in comparison to pure medication, which may account for the hydrogel's potential anti-psoriatic effect. It is possible that the increased activity of Clobetasol propionate nanogel arises from the penetration of Clobetasol propionate loaded nanosponges & their targeting to the layers of epidermal skin [101].

The formulated hydrogel of Dithranol nanosponges by Kumar et al. was evaluated for in vivo anti-psoriatic activity using a mouse tail model. Studies revealed a notable increase in drug activity in the Dithranol nanosponge-loaded hydrogel-treated group when compared to the control group. The evaluation of oxidative stress indicators determined the formulation's efficacious role in managing psoriasis by regulating oxidative stress in keratinocytes [50].

The formulated nanosponge of Lapatinib by Prabhu et al. showed that the initial mean plasma concentration profile of Lapatinib was slow, with a Tmax of 4.33 h, but the Tmax of lapatinib nanosponges was reached at 3.16 h with quicker absorption. The nano size of nanosponges contributed to this increase in AUC and Cmax. Comparing the group receiving lapatinib nanosponges to those receiving pure medication, there was a statistically significant increase in plasma concentration. When comparing the Cmax of lapatinib nanosponges to the pure drug group, the results revealed a three-fold rise [105].

The nanosponges of Hesperetin by Rodrigues et al. showed promising in vivo results. The therapeutic efficacy of four formulations— Hesperetin nanosponge based gel, blank gel (control), hesperetin gel & standard Diclofenac 5 % gel—was evaluated for a period of 10 h after application to shaved rat skin. In comparison to the control group, the topical treatment of Hesperetin nanosponge-based gel demonstrated a significant ($p < 0.05$–0.01) percent decrease in paw edema at two, four, six- and 8 h following carrageenan injection [27].

According to in vivo experiments of celecoxib nanosponge-based gel, the prepared topical nanosponge formulation had a much higher bioavailability than the plain gel, indicating that the generated formulation was more therapeutically effective than the plain gel [49].

In another study, Nisin encapsulation in cyclodextrin nanosponges increases cytotoxicity, cellular absorption, and assays for apoptosis in melanoma cancer cell lines. Moreover, researchers found that Nisin in pyromellitic dianhydride nanosponges was significantly better than free Nisin at suppressing the development of melanoma cells in an in vivo mouse model [51].

The broad range of applications for nanosponges has created significant opportunities for drug release, diagnosis, and treatment. Hence, the formulation is and can satisfy the standards for human exposure.

9. Conclusion

It has been investigated that nanosponge-based systems, which feature tremendous porosity, straightforward functionalization procedures, distinctive topologies, eco-friendliness, and cost-effectiveness, are attractive substitutes for targeted drug delivery. Cyclodextrin nanosponges stand out among the others due to their distinctive qualities, excellent biocompatibility, low toxicity, and simplicity of surface modification, making them the most often tested nanosponges in nanomedicine. The appropriate size can be obtained by adjusting the polymer or other material concentration and crosslinker ratio. This also aids in improving the solubility of various drugs that are poorly soluble and safeguards them against degradation. The nanosponges offer applications in a variety of areas, including targeting, improving stability and solubility, preventing photodegradation of the medication, improving formulation flexibility, gas administration, blood purification, etc., which is not achievable with other nanocarriers.

It is important to note that while nanosponges show promising results in various areas like drug delivery, cancer, and COVID-19, further research and development are necessary to define their properties, optimize their performance, and ensure their safety. Ethical considerations, regulatory approvals, and scalability will also play a role in determining the practical applications and widespread adoption of nanosponges in future. Despite the applications discussed above, nanosponges have various other applications like environmental clean-up (absorption of pollutants and other contaminants) and industrial applications (absorb and recover valuable materials from waste during the manufacturing process).

10. Future perspectives

Nanosponges have been found as the prominent drug delivery system in the field of Pharmaceutics. Future research should be focused on the effective functionalization of nanosponges to reduce toxicity, increase their specificity, and biosafety betterment. Innovative nanosponges with various characteristics and multifunctionality can be produced. In order to develop multifunctional systems with cancer theranostic applications, further research is required to concentrate on the specific surface functionalization of nanosponges utilizing different materials, such as fluorescent chemicals, Magnetite nanoparticles, etc [16]. The use of 3D printing techniques can help in the easy and faster production of nanosponges [23].

The application of nanosponges in the oral delivery of proteins and peptides still needs to be investigated. A case study was done on insulin in which nanosponges were developed using β-cyclodextrin and crosslinking it with Pyromellitic dianhydride. The nanosponges were investigated for in vitro, in vivo, and other physicochemical properties. The in vitro study showed pH-dependent drug release of insulin from nanosponges with enhanced permeability in Caco-2 cells. On treatment, the in vivo study showed the presence of insulin in the plasma of rats with a hypoglycaemic effect. These early findings are encouraging for further research into this -cyclodextrin nanosponge technology for the oral administration of insulin and the potential application of this method to other pharmaceutically relevant proteins. In upcoming years, nanosponges, being an effective and reliable drug delivery system, can be an innovative nanotechnological method for oral delivery of proteins [118]. Continued research and development efforts are crucial to fully unlock the potential of nanosponges and translate them into practical applications in the future.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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