BioNanoScience (2022) 12:1018–1031
https://doi.org/10.1007/s12668-022-01000-1

Versatile Applications of Nanosponges in Biomedical Field: A Glimpse on SARS-CoV-2 Management

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Accepted: 8 June 2022 / Published online: 20 June 2022

Abstract
Nanotechnology has a versatile use in the field of disease therapy, targeted drug delivery, biosensing, and environmental protection. The cross-linked nanosponges are one of the types of nanostructures that provide huge application in the biomedical field. They are available up to the fourth generation and can act as a payload for both kinds of hydrophilic and hydrophobic drugs. There are different methods available for the synthesis of these nanosponges as well as loading the drugs inside them. A variety of approved drugs based on nanosponges are already in the market including drugs for cancer. Other applications include the uses of nanosponges as topical agent, in improving solubility, as protein carrier, in chemical sensors, in wastewater remediation, and in agriculture. The present review discusses in detail about different applications of nanosponges and also mentions about the recent SARS-CoV-2 management using nanosponges.

Keywords Nanosponges · Drug encapsulation · Chemical sensors · Cancer drugs · Cyclodextrin

1 Introduction

The last couple of decades have witnessed the significant progress of applied nanotechnology toward the diagnosis and therapy of life-threatening diseases. Nanoparticles have unique properties at their submicron size scale and can be engineered to carry out specific biomedical functions. Nanoparticles can prolong circulation half-life after appropriate surface modifications, and they can be utilized to target-specific diseased cells in vivo. They have also the capacity to carry several types of payloads including therapeutic and imaging agents and can be delivered to the desired diseased cells in a sustained or controlled manner. These are the potential advantages that make them suitable in targeted drug delivery; theranostics [1–9] and numerous nanoformulations are widely used in clinics on a regular basis. Polymeric nanoparticles are used for encapsulating many natural bioactive compounds [10]. On the other hand, there are various green synthesis routes available for the synthesis of nanoparticles using natural products (Fig. 1) [11–14]. Nanosponges (NSs) are an innovative concept for the delivery of drugs. They are nanosized sponge-like structures consisting of numerous cavities that can be filled with payloads.

NSs are polymeric hyper-cross-linked colloidal structure, and their porous external surfaces are ideal for the delivery of payloads. These polymeric sponge-like structures can accommodate both the lipophilic and hydrophilic drugs, and they offer the improved aqueous solubility to poorly soluble drugs with improved bioavailability. Polysaccharides are the good choice to be used as NSs, due to their biodegradable, nontoxic, and hydrophilic nature and cost-effectiveness. The starch derivatives especially cyclodextrin-based NSs are now widely used in pharmaceutical industries because they possess tunable functional groups that make them to interact with biological tissues to promote bioadhesion. Cyclodextrin NSs have unique three-dimensional network where the cross-linked cyclodextrin units are present. The first-generation NSs were synthesized by reacting cyclodextrin with carbonate, ester, ether, and urethane using a potent cross-linking agent. The second-generation NSs were engineered with specific properties like fluorescence or charged terminal group incorporating in the polymeric structures. The third-generation NSs were popularized for their stimuli-responsive nature. These types of NSs have structural transition according to the changes in pH, temperature gradients, or redox condition at the drug delivery

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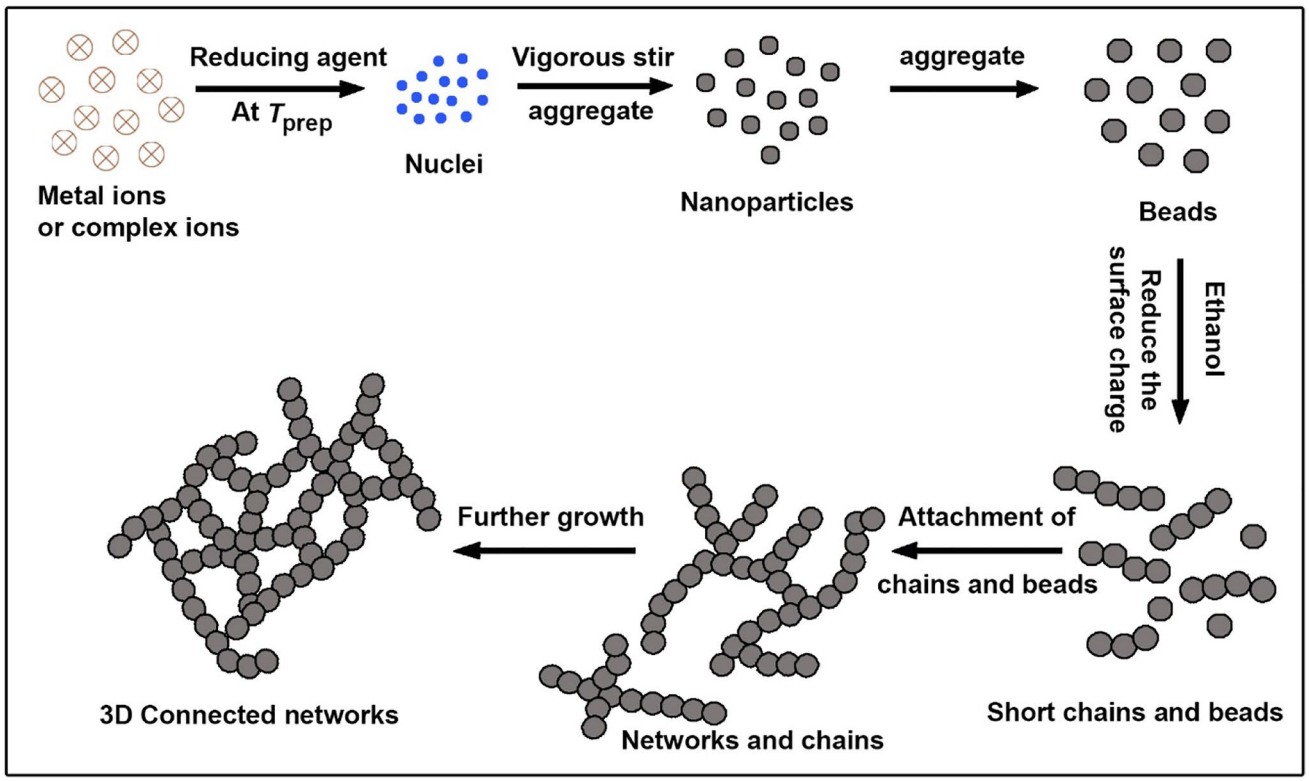

Fig. 1 The synthesis of metal ion–based nanosponges

site. The fourth-generation NSs are highly selective and specific toward the guest molecules. The potential NSs have the presence of reactive functional groups at their surface where attachment of biomolecules can be done. These biomolecules can target the specific receptors present on the surface of the diseased cells to increase the cellular uptake of the encapsulated drug in the NSs. The fourth-generation NSs are engineered though the interaction of template molecules with the polymers via non-covalent or semi-covalent bonds, and these are grouped as molecularly imprinted polymers (MIPs). This heteropolymer matrix contains particular recognition elements that can recognize the template molecules. The MIP-NSs have many advantages which include fast template extraction from the samples, non-toxicity, and enhanced adsorption efficiency. Moreover, these MIP-NSs are more advantageous compared to the non-molecularly imprinted polymers (NIP NSs) because the template can diffuse easily into the created cavity and have a high surface area. This strategy improves the bioavailability and therapeutic efficacy [15].

NS was formerly evolved for topical delivery of drugs as these ultra-small sponges can encounter the exact targeted site which flow around the body as well as attach to the surface and initiate the drug release in a sequential and orderly mode. Titanium-based nanosponges, silicon nanosponge particles; hyper-cross-linked polystyrene nanosponges, and cyclodextrin-based nanosponges are few popularly recognized nanosponges. Nanosponge (NS) is a system of network or scaffold made up of long extended backbone of a polymer. The cross-linkers present in the solution act as ultrafine grappling hooks that help to fasten diverse parts of the polymer together to form spherical particles whose cavities can store the drug which are either lipophilic or hydrophilic, and this substance helps to improve the soluble nature of poorly water-soluble compounds [16]. In proteomic studies, 3D nanosponges have the potential to fractionalize the peptides. NS have plenty of biomedical applications as they act as carrier for gases like oxygen and carbon dioxide. The nanosponges are encapsulated in various routes of drug administration such as topical, inhalational, parenteral, or oral dosage forms. In oral route, they are consumed as tablets or capsules in which there may be a matrix of lubricants, excipients, diluents, and anticaking agents. In parenteral route, the drugs may be composed of aqueous solutions, saline, and sterile water. In topical administration, the drug can be targeted efficiently by integrating them into topical hydrogel [17]. Some of the NS types are given in Table 1.

2 Synthesis of Nanosponges

2.1 Solvent Method

Solvent method can be used to prepare NSs, by the mixture of polymer and appropriate solvent similar to polar aprotic

Table 1 Types of nanosponges and their application

Types	Description	Application	Reference
Cyclodextrin-based nanosponges	Cyclodextrin-based nanosponges are sponge-like lyophilized structures that have the capability to react by means of small molecules in its matrix. The NSs were developed by cross-linking different categories of cyclodextrin with the cross-linkers like diphenyl carbonate, carbonyldiimidazole dimethyl carbonate, etc. Cyclodextrins are obtained from a certain amount of naturally occurring α-, β-, and γ-cyclodextrin cross-links. They are generally prepared from β-cyclodextrins as they have the highest complexity and stability owing to their suitable cavity size with cross-linkable polymers	Cyclodextrin-based NS is mainly used as drug delivery agent in biomedical application. In addition, it acts as effective agents in removing pollutants from contaminated water, is used in cosmetics, and is used even in agriculture	[18, 19]
Titanium-based nanosponges	Titanium-based nanosponges are the coating of polystyrene microspheres which were prepared from copolymerizing polymerizable surfactants with styrene	Fabrication of TiO_2/ZnO hybrid NSs are used as photoanodes for photoelectrochemical applications. Metallic NS like TiO_2 NS, carbon-coated metallic NS, and silicon NS particles have been reported in a plethora of applications such as recyclable oil absorbents, photocatalytic properties, electrodes, pollutant removal, supercapacitors, antimicrobial application, biosensors, and drug delivery	[20, 21]
Silicon-based nanosponges	Silicon nanosponge particles are prepared from a metallurgical grade silicon powder and nearly 1–4 micron particles were scratched to yield silicon nanosponge particles	The highly porous silicon NS acts a carrier material in the field of sensors, catalysts and drugs, photosensitizers, adsorbents, explosives, and electrode in fuel cells. It is also turned as precursors for ceramic materials which have high surface area like SiNa and SiC	[22]
Hyper-linked polystyrene-based nanosponges	The individual polystyrene coils were suspended in dilute solvents, and rigid intramolecular bridges were introduced in huge amounts resulting in strong contraction of these coils to form spherical NSs. The NS solutions showed high diffusion, low viscosity, and high rates of sedimentation. These NSs exhibited enhanced inner surface area and the swelling was very strong in the presence of linear polystyrene nonsolvent	The hyper-cross-linked NS were used in appropriate separation of inorganic electrolytes by applying the principles of size exclusion chromatography. Hyper-cross-linked polystyrene NS and cyclodextrin-based NS have been used in tissue scaffolds	[23]

solvent such as dimethyl form amide (DMF) and dimethyl sulfoxide (DMSO). The excess quantities of the cross-linker were added with molar ratio of cross-linker and polymer as 1:4, followed by reflux up to 1 to 48 h. Further, the mixture has to be set aside for cooling at room temperature, and excess of distilled water was added to the product. For getting the final product, the solution was filtrated under vacuum, and subsequent purification was also carried out for prolonged Soxhlet extraction with ethanol. It was set to dry under vacuum for completion of the process [24].

2.2 Ultrasound-Assisted Synthesis

In ultrasound-assisted synthesis method, uniform sized NSs are produced in spherical shape. The process of NS synthesis includes sonication using ultrasound water bath during the reaction with polymers and cross-linkers in the absence of solvent. The set was allowed to heat at 90 °C and sonicated for 5 h. Then, the product was allowed to cool followed by crushing the product and washing it for the removal of the non-reacted polymer and was purified by elongated Soxhlet extraction with ethanol. In the final step, the product was dried under vacuum and stored at 25 °C for use in the future [25].

2.3 Emulsion Solvent Diffusion Method

In emulsion solvent diffusion method, the NSs were synthesized with the addition of ethyl cellulose and polyvinyl alcohol in various proportions. The dispersed phase comprising ethyl cellulose and drug was made to mix with 20 ml of dichloromethane, and in the aqueous phase, 150 ml of polyvinyl alcohol was added slowly. This composite was stirred at 1000 rpm for 2 h, and the prepared NS was gathered by filtration followed by oven-drying at 400 °C for 24 h. To ensure the removal of residual solvent, the dried NSs were stored in vacuum [26].

2.4 Hyper-Cross-linking method of β-Cyclodextrin Synthesis

Hyper-cross-linked β-cyclodextrins (β-CD) act as carrier for drug delivery as it is a nonporous material. NSs are synthesized by reacting cyclodextrin and cross-linkers which may be in acidic or neutral form. Usually, nanosponges have a diameter within 1 µm, and they can also be considered if it ranges below 500 nm. Numerous methods were used for loading the drug into NS. In a previous study, the NS were suspended in water followed by sonication to avoid aggregation. Further, the samples were centrifuged, and the supernatant was separated and dried by freeze-drying method to obtain the NS. For drug loading, aqueous suspensions of NS were prepared, and drug was added and was maintained under constant stirring for required time to obtain the complexation. Centrifugation was done to separate the undissolved drug, and solid crystals were obtained by freeze-drying yielding drug-loaded NS [27]. There is also a method called the quasi-emulsion solvent diffusion method where the NSs are also synthesized with different polymer amounts. The inner phase was prepared using Eudragit RS 100 and dissolved with a suitable solvent. Next, the drug was dissolved with the mixture under ultrasonication at 35 °C. This inner phase was added into the external phase containing PVA solution in water, and the mixture was stirred for 60 min. They were filtered to isolate NS and dried using air-heated oven at 40 °C for 12 h to get the final product [28]. In preparation of this type of NSs, there were few cross-linkers used like dimethyl carbonate, diisocyanate, diphenyl carbonate, diaryl carbonate, carbonyldiimidazole, and carboxylic acid dianhydrides which help to deliver the immediate release of a drug [29].

Each of the above synthesis method has both pros and cons. In solvent method, we can isolate the correct phase using the Soxhlet apparatus, but we need a huge volume of solvent for the extraction in this method. In ultrasound-assisted synthesis, although the initial mixture was made by the assistance of ultrasound, for minimizing the aggregation, and we could avoid the Soxhlet solvents, for final purification, Soxhlet was only used. In emulsion solvent diffusion method, it is convenient to incorporate the drugs during the synthesis process to ensure proper loading of the drug, but on the other hand, we need to heat the sample at high temperatures to remove any impurity. The heat-labile drugs, thus loaded, may get disintegrated during this step.

3 Chemistry and Structure of Nanosponges

Cyclodextrin NSs usually have an average diameter within 1 µm, with a very low polydispersity index, showing monodispersed particles. The NSs are very stable with high, usually negative, zeta potential values and possess swelling properties which are dependent on the cross-linker used during synthesis and the ratio between cyclodextrin and the cross-linker. The branching of cross-linker, attachment of basic and acidic groups, also influences the swelling characteristics of the NSs. The amount of cross-linker can influence the surface area and porosity. The NSs made up of cyclodextrin are thermally stable up to 300 °C and show different peaks in FTIR spectroscopy [30].

In another study to find out the β-cyclodextrin NSs applications, minute mesh-like structures composed nanocatalysts of porous three-dimensional structure were synthesized. One-pot condensation reaction with three components

was employed with different aromatic aldehydes that had activated methylene compounds, like thiobarbituric acid, 4-hydroxy-6-methyl-2-pyrone, dimedone, 4-hydroxycoumarin, and nucleophiles that included amines and indole. When the β-cyclodextrin monomer reacted with 1,1′-carbonyldiimidazole, the cross-linked NSs were obtained, and to which the 3-substituted indole moieties were added. The Yonemitsu-type condensation reaction was employed for the 3-substituted indole moieties synthesis with the reaction combination of indole (0.117gr, 1 mmol), 2-chloro benzaldehyde (0.14 gr, 1 mmol), and dimedone (0.14 gr, 1 mmol) as shown in Fig. 2 [31].

4 Loading of Drug into Nanosponges

The main factor for drug delivery into NSs is the size of the particle which should be below 500 nm. The prepared NSs were suspended in the aqueous phase; to prevent from an aggregation of the particles, they were sonicated and centrifuged for the colloidal fraction. After this, the supernatant was detached and then dried by a freeze-dryer. NSs were prepared by separating the aqueous suspension. The additional drug was added, and for some time, they were kept under constant stirring until it forms a complex. Now by centrifugation, the unwanted drug was removed. Finally, the NSs were obtained by solvent evaporation or by freeze-drying the solid crystals. The important role is the complexation with the drug the crystal structure of the NSs. The paracrystalline NSs have greater loading capacities than crystalline NSs. The drug loading occurs as an inclusion complex in crystalline forms while the drug loading occurs as a mechanical mixture in case of poorly crystalline NSs [32].

5 Application of Nanosponges in Healthcare and Environment

5.1 Cancer Therapy

NS productions have a major role in drug delivery particularly in cancer treatment as they are three- to five fold more effective in decreasing the tumor growth when related with direct injection of the drugs. The ultrafine nanosponges are packed in a way such that the drugs are loaded and exposed to targeted site in which the cell surface receptors that are radiated and the peptides gets bonded to the NS for discharging their shipment. An effective antitumor agent, camptothecin, which was extracted from the stem and bark of *Camptotheca acuminata*, is a plant alkaloid known for its anticancer activity. This drug has a low remedial effect due to serious side effects, poor aqueous solubility, and lactone ring instability.

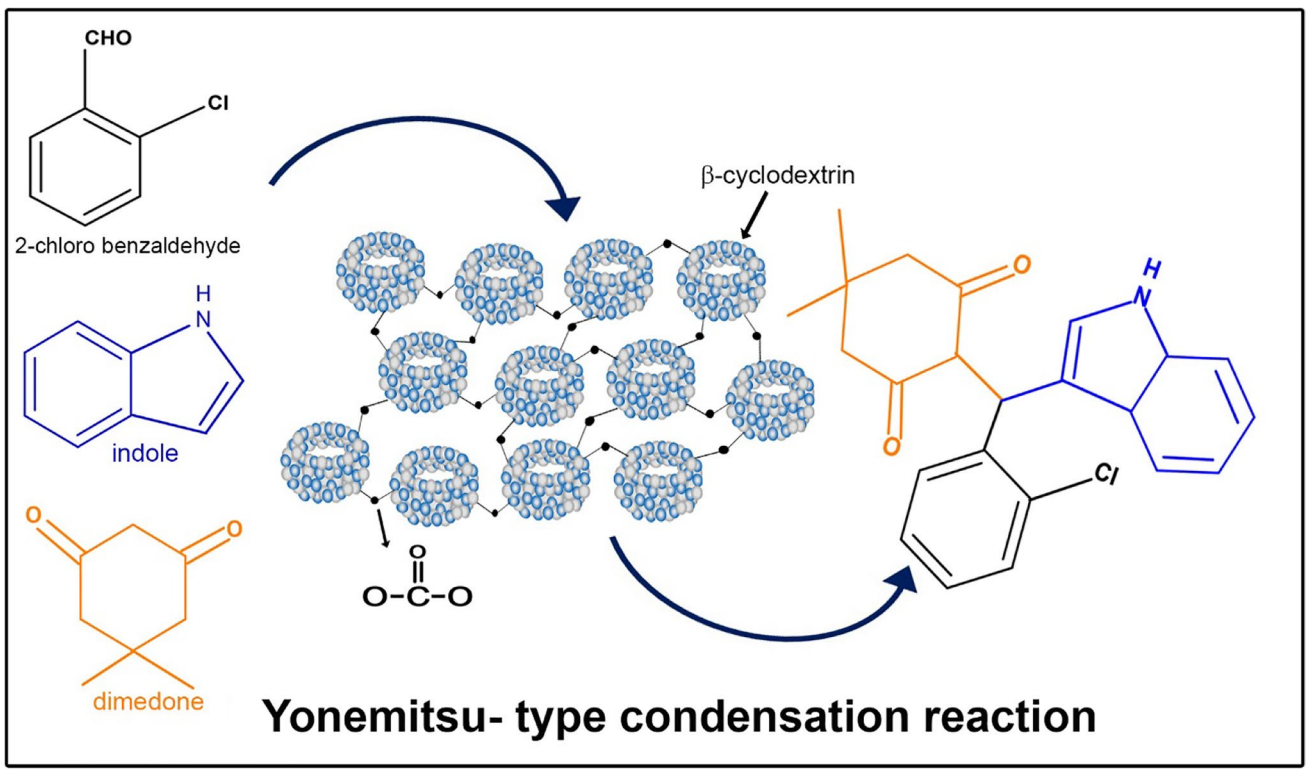

Fig. 2 Scheme representing the cross-linking of β-cyclodextrin–based nanosponges with 3-substituted indole moieties

When the camptothecin was entrapped in cyclodextrin-based NSs, it exhibited a controlled release of drug, could shield the labile groups, and showed improved solubility [15, 33]. Curcumin, a hydrophobic polyphenolic phytochemical is a promising anticancer agent along with other properties, such that they are neuroprotective, potent antioxidant, antiatherosclerotic agent, anti-inflammatory, cardioprotective, and antidiabetic. They modulate the activities of different forms of interleukins, nuclear factor-κB (NF-κB), interferon γ (IFNγ), tumor necrosis factor α (TNF-α), c-Jun N-terminal kinase, mammalian target of rapamycin (m-TOR), cyclooxygenases, mitogen-activated protein kinase (MAPK), protein kinase C (PKC), peroxisome proliferator–activated receptor γ (PPARγ), etc. [34, 35]. Another diterpenoid isolated from the tree bark of *Taxus brevifolia* is paclitaxel (Taxol), and they possess anticancer action against Kaposi's sarcoma, breast, and head and neck, ovarian, pancreatic, and lung cancer [36]. The first NS incorporating Paclitaxel was made by the cross-linker, diphenyl carbonate, and was used for oral delivery to improve the bioavailability. The encapsulation efficiency was more than 99% in paclitaxel-loaded NS, and nearly 1.7% of drug was crystallized after 24 h at 7 ± 2 °C. In Sprague Dawley rats, the paclitaxel NS and standard paclitaxel (Taxol®) was administered both orally and intravenously at 10 mg/kg dose, and the relative bioavailability was compared. The administered NS formulation had 2.56 times higher relative oral bioavailability compared to Taxol® [37]. Tamoxifen is a particular estrogen receptor modulator which plays a role in the treatment of estrogen-positive breast cancer in primary and advanced stages. This drug is insoluble in water with a solubility of (5.9 mg/l) and is known to cause many side effects depending on the dose and its concentration at the organ site, such as liver cancer, endometrial carcinoma, pulmonary emboli, venous thrombosis, and ocular toxicities. Cyclodextrin (CD)–based NS were employed for designing three types of tamoxifen preparations with three different cross-linking densities (F1:2, F1:4, and F1:8). The solubility of tamoxifen increased several times after using F1:4 and F1:8 density of cross-linked NS compared to its "as-is" drug, and there was improvement in drug release also proportional to the cross-linking density of the NSs. In vitro cytotoxicity study using MCF-7 cells showed increased cell killing after treatment with NSs loaded with tamoxifen compared to its "as-is" drug, and the oral bioavailability was also improved as studied in Sprague Dawley rats [18]. In food substances such as pistachios, grapes, blueberries, and peanuts, they produce a non-flavonoid, polyphenolic molecule called resveratrol. It is usually acknowledged as an anticancer agent, a powerful antioxidant, and anti-inflammatory agent, although the oral bioavailability poses a severe problem in executing the anticancer activity of resveratrol. Previous study has been explored in designing carbonyldiimidazole (CDI)–based NS for the improved stability, solubility, and skin permeability upon topical applications of resveratrol using different degrees of CD: CDI cross-linking. There was a 33-fold to 44-fold enhancement in the solubility of resveratrol compared to its "as-is" drug at the cross-linking ratios of F1:2 and F1:4, respectively [38]. NSs have shown five times superior activity than direct injection to cure tumor growth. In drug delivery system, the anticancer drugs were loaded in virus sized sponges where the receptors present on the surface of the tumor cells could chemically linked to these NSs. Then the sponges were injected into the body where they come in contact with the cancer cells, get attached to the cell surface, and are included into the cell, where these sponges unload their drug in a sustainable rate [39]. Thus, the NS-loaded anticancer drugs were showing improved activity against cancer.

5.2 Topical Agents

NS in drug delivery method is an irreplaceable technology for the controlled and extended release of the skin retaining drugs. Conventional dermatological and personal-care products characteristically deliver active constituents in reasonably high concentrations; on the other hand, they take very short action time. These occur in a repeated way such as a short-term overmedication followed by a long-term undermedication. When the active ingredients penetrate the skin, they may cause rashes and supplementary side effects. In contrast with this technology, the NS-based drug delivery system allows a uniform and continuous rate of drug release, reducing the irritation despite the fact that they maintain efficiency. An extensive range of substances can be incorporated into an articulated product such as cream, liquid, gel, ointment, powder, or lotion [16]. An antifungal agent econazole nitrate is available in ointment, solution, cream, and lotion forms and is used topically to revive the indications of dermatophytosis, skin and vesicular infections, and superficial candidiasis. In econazole, high concentration of active agents is required to incorporate into skin for effective therapy as its adsorption is insignificant. By emulsion solvent diffusion method, the econazole nitrate NSs were fabricated and composed of hydrogel as a local depot for continuous drug release [26, 40]. The prepared hydrogel NSs were integrated with the lipophilic and low aqueous solubility celecoxib for tropical application. During pharmacokinetics studies on the mouse, the developed formulations of NS-4 are non-irritating in mouse skin. So, the formulation can meet the requirements for human exposure, and it can be utilized for topical drug release for the use of celecoxib [41].

5.3 Nanosponge as Carrier for Biocatalyst and Protein Delivery

In drug delivery system, NS is the vector to deliver proteins, enzymes, antibodies, and vaccines for diagnosis resolution. Cyclodextrin-based NSs are the predominant carrier to

adsorb enzymes, macromolecules, enzymes, and proteins. In vivo, these carriers may aid to safeguard the protein and modify their pharmacokinetics, improve their stability, and prevent from breakdown. In certain enzymes it is possible to extend their operation, pH, temperature series of reactions, conserve their activity, tolerates the behavior of continuous flow methods and efficiency. In cyclodextrin NS, proteins and other macromolecules were encapsulated such as the industrially beneficial enzymes trypsin, alpha amylase, cellulase, and pectinase [42]. At the time of protein production, they undergo the issues regarding long-term storage and its native structure maintenance. This may be rectified by encapsulating the protein in cyclodextrin-based polyamidoamine NS which enables the stability of the proteins [43]. Moreover, some NSs can selectively trap a few families of protein molecules from the blood and hence can be used in safeguarding those proteins from undergoing enzymatic degradation [44].

5.4 Nanosponge as Chemical Sensors

NSs composed of metal oxides were utilized as chemical sensors for the detection of hydrogen (H_2) gas. The study has demonstrated a 3D interconnected nanoscale walls and wires made from nanosponge TiO_2 (NST), which showed ultrasensitive detection of H_2 gas. There were 4.7 orders increase in the magnitude of current when these NST were exposed to H_2 gas at 4000 ppm in synthetic air. The sensitivity for H_2 gas of the synthesized NST was intermediate between the individual structures like nanotubes and nanoparticle agglomerates [45]. In a recent study, a fluorimetric detection of environmental pollutant, volatile organic compounds (VOCs) like xylene, was investigated using nanoparticle-based NS. The turn-on fluorescent sensor could detect as low as 7 ppm of xylene by the NS sensor made from polythiophene and nanoparticles. The poly(3-octylthiophene)–loaded poly(maleic anhydride-alt-1-octadecene) nanostructures PMAO(POT) NSs were used for this study which showed a linear increase in fluorescence with increasing concentration of xylene [46]. As a carrier for delivery of gases for therapy and diagnosis, NS have shown some promising applications. Hypoxia is the deficiency of oxygen supply which gives rise to numerous diseases from simple inflammation to risky cancer. In clinical practices, the delivery of oxygen gas in apt dosage is a difficult process. In the oxygen delivery system, the formulation of NSs has gained the advantage of storing and slow release of oxygen at a considerable period of time [47]. Lee et al. prepared graphite nanofiber-supported porous Pt–Ag NSs and mesoporous platinum NSs as electrocatalysts for the oxygen reduction reaction. The challenging aspect is that the accurate control of photochirogenesis, which is supramolecular, offers the exciting state chirality transmission from chiral host to a prochiral substrate [48, 49]. As there are 3 cyclodextrin-based NSs occurring naturally, all the three α-, β-, or γ-CD can entrap the efficiency of oxygen for a longer duration. These NSs can release oxygen with or without ultrasound. This type of NSs has evolved with the noticeable potential in controlled oxygenation [50].

5.5 Nanosponges for Solubility Enhancement

The solubility in water is an important factor which is necessary for the formulation of drugs as it is a major problem which affects the performance of the drug formulations. This can be rectified by means of NS as a carrier system which aids to entrap the drug into a particular pore and raises the bioavailability and solubility of drug formulations in controlled release profile. Moreover, conformation and molecular dimensions are vital aspects altering complexation progression and also may not be appropriate to all molecules. The drug cefpodoxime proxetil NS showed improved dissolution rate compared to regular cefpodoxime proxetil. Three-armed biodegradable star polymers were constructed using polystyrene (polySt) and poly (polyethylene glycol) acrylate (polyPEG-A) through a "core first" method where a trifunctional RAFT agent was used. The RAFT agents were created by attaching them through R-groups to the core, and the engineered three-armed polymeric structures were used to prepare the NS. By aminolysis and additional reaction with dithiodipyridine (DTDP), the synthesized three-armed polymers were capable to be tailored with sulfhydryl and pyridyldisulfide (PDS) end functionalities. They were available for reacting with any kind of free-sulfhydryl group that contain precursors to make disulfide linkages and the intradisulfide linkages existing between the arms, and the core could lead to the biodegradability of the star architectures. Furthermore, cholesterol was attached to the arm-termini through disulfide linkages, and this cholesterol terminated arms could form complex with beta-cyclodextrin (beta-CD) to yield a star architecture NS [51, 52]. Addition of compound β-cyclodextrin NS has gained greater attention as it helps to enhance the bioavailability and solubility of drugs. Cyclodextrin-based NSs have the capacity to improve the permeability of hydrophobic drugs via increasing the dissolution rate and drug solubility. This makes the NS available on the surface of the biological barrier so that they can be introduced into the membrane without distracting the lipid layers of the barrier. Additionally, β-cyclodextrin NSs have gained greater attention as it helps to enhance the bioavailability and solubility of drugs like naproxen and ketoprofen [53]. The solubility of the drug resveratrol was also increased by entrapment into cyclodextrin based NS [38]. Rilpivirine, a drug used for HIV, was also entrapped in cyclodextrin-based NS to improve the solubility. The cross-linking agents used with beta-cyclodextrin were carbonyldiimidazole and pyromellitic dianhydride for the preparation of NS. The drug was loaded in the manufactured NS using solvent evaporation method, and the results showed a threefold enhancement in dissolution with

ternary complexes. The oral bioavailability increased two-fold using this NS-loaded rilpivirine in the study using rats [54]. Ferulic acid (FA) is an anticancer agent which is poorly soluble with antioxidant properties, and its solubility was increased using cyclodextrin-based NS. The encapsulation of FA (ratio, 1:4 (FA:NS)) was done in the beta-cyclodextrin NSs where diphenyl carbonate was used as a cross-linker. The NS encapsulation improved the solubility of FA up to 15-fold [55]. Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) that can reduce the pain causing hormone levels. The activity was compromised due to its poor solubility, and in a study, cyclodextrin-based NSs were developed to encapsulate meloxicam. The anti-inflammatory activity was studied using carrageenan-induced rat paw edema model, acetic acid–induced writhing was used for studying the analgesic activity, and the NS encapsulated drug improved the analgesic and anti-inflammatory activity [56]. Cavalli et al. tested the capacity of carbonate CDNSs to load drugs both hydrophilic-like doxorubicin and lipophilic-like dexamethasone or flurbiprofen drugs, and a sustained release of the drugs was achieved. This carbonate CD NSs were capable of increasing the solubility of the antifungal drug itraconazole and advanced its bioavailability. This could be enhanced by consuming additives such as copolyvidonum [57].

5.6 Removal of Organic Pollutants from Water

The β-cyclodextrin NSs are insoluble in water; therefore, they have the ability to encapsulate the organic pollutants from water. Some NS impregnation of ceramic porous filters resulting in hybrid organic/inorganic filter modules might confirm the purification of water in a variety of water pollutants. This enhances the removal of polycyclic aromatic hydrocarbons (PAHs) competently about 95%. Characterization of the pollutant group of pesticides (simazine), monoaromatic hydrocarbons (BTX), and trihalogen methanes (THMs) can also be removed [58]. For typical removal of contaminants in water, a popularly known NS was used, namely nanoporous cyclodextrin (CD) polyurethanes. The CD polymer forms inclusion complexes of the guest–host type which has the capacity to attract a series of organic compounds where the absorption of organic molecules is hooked on the cavities of the CDs to acquire a guest–host complex and the adsorption gets altered wherever molecules are devoted to the surfaces of constituents [59]. On the new creation of organic nanoporous polymers with the help of cyclodextrin as building blocks, there were about 0.7–1.2-nm-sized nanomaterial synthesized which exhibited greater adsorption of organic molecules present in polluted water. The cavity in cyclodextrin offered a hydrophobic environment so it can enrich the strong affinity to organic molecules at water solid interfaces [60]. For the removal of organic pollutants, the cyclodextrin-based NSs have gained a lot of attention; rather it has gained an additional advantage of trapping the heavy metals. This has enriched the field of pharmaceutical and also in the environmental sector. Few common heavy metals include copper, mercury, arsenic, chromium, nickel, cadmium, and lead. The contaminated water has these heavy metals which upon intake may accumulate in tissues and cause severe damage to human health. The remediation of polluted water from these heavy metals could be achieved using these NSs [61]. Moura and Lago worked on the oil spill remediation utilizing floatable hydrophobic NSs produced from catalytic growth of carbon nanotubes and nanofibers on vermiculite [62].

5.7 Nanosponges in Agriculture

The appearance of the growing plant is not only due to the climate, but also the technology applied for its growth plays the major role. The invention of functionalized nanosponges (FNS) in agriculture has added the advantage of plant growth and advances their appearance by nourishing them with the ideal amount of active ingredients and micro-nutrients which is essential for their healthy growth. Additionally, these NSs have notable benefits in the reduction of herbicide and fertilizer usages. It helps to improve productivity by its quality levels both in cultivation and environmental safety. By performing synthesis method, the nutritive ingredients like iron and zinc are encapsulated into the nanosponge's cavity and in a very specific way, these are added to the soil dropwise, and the plants proceed toward photosynthesis. The production rate is higher and the cultivation is similar to organic products as there is a reduction in the usage of fertilizers. This furnishes to give healthier food with low production cost, and on the other hand, FNSs with iron formulation have resolved several problems faced by plants, such as iron chlorosis (yellowing of leaves), followed by efficient photosynthesis and higher growth of the plants. The foremost fact of this innovation is the creation of ad hoc formulations for diverse applications [63].

5.8 Absorbent in Blood Poison Treatment

NSs have a typical style being used as nanocarriers for the detoxification of blood. As an alternative of antidote, NSs were injected into the blood which could sop up the toxins. The NSs look similar to RBCs and can trick the toxins for attacking it, a sop to shot away their path from the cellular target. Researchers have constructed a NS by combining poly (d, l-lactic-co-glycolic acid) (PLGA) cores with ovine erythrocyte vesicle. Ovine erythrocytes were most vulnerable to streptolysin O lysis. Ovine NSs adsorbed streptolysin O which is a known cholesterol binding toxin at 37 °C and 40 °C [64, 65]. Another compound, RBC-NPs, was prepared which were derived from human RBCs onto PLGA polymeric cores through a sonication process. This

has gained therapeutic applications such as anti-virulence treatment for local bacterial infections [66]. NSs are capable of absorbing toxin particles depending upon toxins. For example, β-cyclodextrin complexed polyurethane polymer NS was employed to eliminate the ochratoxin A levels from red wine and aqueous solutions. About 0.22-mg ochratoxin A per mg of polymer was absorbed by NSs [67].

6 Other Applications

The other applications of NSs are described by Pawar et al. and Pandey et al. [17, 68]. Pawar et al. have described in detail about the mesh-like structures of NSs made from solid nanoparticles that have cavities where they can encapsulate many substances such as proteins and peptides, genetic materials, antineoplastic agents, and volatile oils. The surface functionalization has made these NSs to be used for protein delivery, detection of explosives, water purification, chemical sensors, agriculture, etc. Many NS-based drug formulations are also available in the market, and many are undergoing clinical trials like brexin, mena-gargle, prostavastin, and glymesason. The patents on NSs from 2006 to 2018 and the versatile cyclodextrin-based NS applications in cancer therapy, vaccine delivery, water purification, and fire engineering were described by Pawar et al. [68]. Pandey et al. also described the properties of NSs that they can carry both hydrophilic and lipophilic drugs. The different characteristics, advantages, patents, preparation methods, and characterization along with methods of preparation were also discussed [17]. Drug molecules are susceptible to various processes of degradation by water, heat exposure, and oxygen. NSs can encapsulate the drug molecules in such a manner that it does not diffuse into the cavity and react with protected guests to avoid such degradation [69]. NSs act as preventive agent from degradation of gamma-oryzanol which is a ferulic acid ester mixture and a natural antioxidant that is generally used to stabilize food and therapeutically raw materials and even sunscreens in cosmetics industry. A good defense from photodegradation is showed when the gamma-oryzanol was encapsulated in the NS. When the NSs were loaded in gamma-oryzanol and oil in water emulsion, a gel was yielded which was used further for a long-term use as food stabilizer [70]. The nanocarriers can deliver the antiviral drug to the lungs or nasal route which was used to encounter the virus that causes infection to the respiratory tract, such as rhinovirus and influenza virus. The NS was used as an antiviral agent to target the drug in nasal and pulmonary tract, and some of the drugs manufactured using the NSs are zidovudine and saquinavir [27]. Another compound, quercetin, was encapsulated in five different types of NSs composed of five different concentrations of β-cyclodextrin and diphenyl carbonate, with size ranging from 40 to 100 nm. The solubility as well as antioxidant capacity of the NS-loaded quercetin was found to be improved in comparison to only quercetin. The NS encapsulated quercetin was also much more stable in the simulated GI fluid compared to free quercetin. The NS encapsulated quercetin also exhibited higher photostability than free quercetin [71]. NSs were also found to be beneficial as a carrier to pulmonary, head, and nasal diagnosis. In infections like rhinovirus, respiratory syncytial virus (RSV), HBV, HSV, influenza virus, and HIV, the nanocarriers aid to supply antiviral drugs or small interfering RNA to the nasal epithelia as well as lungs. Some of the drugs used as nanocarrier are acyclovir (Eudragit-based), zidovudine, interferon-α, and saquinavir [72]. Omar et al. developed griseofulvin (GRI)–loaded β-cyclodextrin (β-CD)–based NSs for improving the dissolution rate, bitter taste masking, and enhanced oral bioavailability. The study was carried out by performing ultrasonication method where the fabrication of the plain NSs (NS1, NS2, and NS3) were achieved with β-CD and the cross-linker diphenyl carbonate at different molar ratios (1:2, 1:4, and 1:6), respectively. This resulted in 1:4 (NS2) as the most appropriate ratio of β-CD to the cross-linker diphenyl carbonate that could be used for GRI loading [73].

7 Current Development in SARS-CoV-2 Management

NSs which are developed from human macrophages or pulmonary type II epithelial cells have suitable attractant of SARS-CoV-2 virus, and after capturing, they can be removed. So, it was used in the development of protective measures of SARS-CoV-2 [74]. Depending on the current structure of SARS-CoV-2, the researchers have developed two types of cellular NSs, namely, human lung epithelial type II cell nanosponge (epithelial-NS) and human macrophage nanosponge (MΦ-NS). The NSs contained the same receptors on which the viruses depend for their entry, and it was speculated that after binding with these NSs, coronavirus will not be able to infect the cell. Incubating with NSs, SARS-CoV-2 will be neutralized and will in turn lose its potential to infect the cells. NSs can create confusion for viral mutations and viral species. Also, it can identify host cell which remains as the target for the virus and acts against the virus to neutralize it. But the rapid rate of mutation will create several challenges for therapeutics and prevention development. Both epithelial-NS and MΦ-NS demonstrated its potential to neutralize SARS-CoV-2 in a concentration-dependent manner [75]. Cellular NSs have higher surface heparin density that has the capacity to bind strongly with the viral S proteins, which helps further restrictions against SARS-CoV-2 [76]. Cellular NSs act as versatile tools for biological neutralization in comparison to the traditional neutralization strategies. They mimic susceptible host cells rather than accommodating the structures of the causative agents for the design of therapeutics

[77]. The coating of NSs with PLGA core in the membrane of cellular targets in virus showed a good result. When tested with Vero E6 cells, they could effectively enter into the cell and block the SARS-CoV-2 infection. When the cellular NSs were administered into the lungs of mice, surprisingly there was no such toxicity found in them. NSs are agnostic to many species of viruses and viral mutations, and that is why they can protect the current and upcoming emerging coronaviruses [78]. Nanoparticles covered in human lung and immune cell membranes act as decoys to neutralize SARS-CoV-2 in cell culture and help to avoid the host cell to cause infection. At 5 mg/ml, the lung and macrophage membrane cloaked sponges restrict 93% and 88% of SARS-CoV-2, respectively. Cloaking NSs with the cell membranes of macrophages conferred the extra advantage of soaking up circulating inflammatory cytokine proteins attached in the immune response along with the infection. Yet additional studies are required to measure the NSs' efficacy in animal disease models, along with long-term biocompatibility [79].

Numerous nanomaterial-based detection methods have evolved during COVID-19. At the stage of the infection, the entry of host is performed with higher affinity from SARS-CoV-2 surface spike protein to its receptor human angiotensin-converting enzyme 2 (ACE2). To overcome this, nanotraps were developed which efficiently blocked this binding by abrogation of SARS-CoV-2 entry and also led to subsequent phagocytosis. The engineered nanotraps were composed of a polymeric core, a liposome shell, a phosphatidylserine ligand, surface ACE2/neutralizing antibodies, and Food and Drug Administration (FDA)–approved polylactic acid (PLA). This material was advantageous because of its small size and it is ready for mass production, effective, convenient to use, biocompatible, and safe. NSs were also developed, but it was an option for viable treatment as it was important to collect the sample from each patient to make personalized NSs which are similar to chimeric antigen receptor T (CAR-T) cell therapy. In contrast, nanotraps obstructed both, the entry of the cell and activate virus's phagocytic clearance [78].

Gold nanoparticles (AuNPs) are also developed for identification of IgG and IgM antibodies in case of SARS-CoV-2 with minimal diagnostic time, i.e., less than 10 min, but this led to degradation of the sample. In nanotechnology, the sample collection kit was prepared which contained an RNA stabilization fluid which safeguarded the sample in transportation [74]. AuNPs were made to interact with polyclonal antibodies which targeted the envelope protein, membrane protein, and spike protein of SARS-CoV-2 that resulted in 98% specificity and 96% sensitivity. Similar to this, AuNPs were coupled with an N-acetylneuraminic acid, a glycan moiety which binds to SARS-CoV-2 S protein (glycan-AuNPs). For detection, the sample was loaded in lateral flow immunoassay strip (LFIA) that resulted in the gathering of AuNPs at the test line by the interaction of the S protein and the glycan in virus-like nanoparticles (VLPs). Colorimetric signal was generated for visual detection, and moreover, this device detected SARS-CoV-2 VLPs with spike protein concentration of 5 μg/ml.

Selenium nanoparticles (SeNPs) were incorporated with SARS-CoV-2 nucleoprotein to notice virus-specific IgG and IgM in LFIA. This showed enhanced sensitivity of about 800 times higher than the AuNP-based LFIA. Another nanoparticle poly(lactic-co-glycolic) (PLGA) was functionalized with 3,3′,5,5′-tetramethylbenzidine denoted as TMB-PLGA NPs and that is couples' antibodies against the SARS-CoV-2 S protein. This strategy analyzed SARS-CoV-2 RNA in 10 min, and concentration was in femtogram/ml range and simple to operate. Another material, fluorescent europium-chelate nanoparticles (FNPs), was conjugated with S9.6 antibodies that effectively bound RNA–DNA hybrid strands. While comparing with rtPCR tests, it resulted with 99% specificity and 100% sensitivity [80].

Lung spheroid cells (LSCs) are the combination of lung epithelial and mesenchymal cells. Hence fabrication of LSC membrane nanovesicles as ACE2 nanodecoys was done by resident lung cells as they expressed ACE2. This LSC-nanodecoys (act as cell mimics) bind to SARS-CoV-2 spike (S) protein and activates a phagocytosis for viral eradication. Inhalation of the LSC-nanodecoys enhances the clearance of SARS-CoV-2 mimics of the lungs and did not elicit any toxicity. Additionally, nanodecoy technology was extremely translatable because presently parental cells were in primary clinical trial stage so it was a potential therapy for pulmonary fibrosis [81].

During COVID-19 infections, Novochizol (chitosan nanoparticles) helped for easy encapsulation of drug moieties into the lungs. They were more beneficial as it had low toxicity, biodegradation ability, good applicability, and good mucoadhesive properties. It was observed that even after the recovery from SARS CoV-2 infection, the patient had gastrointestinal infection. To overcome this, chitosan nanoparticles showed controlled release of the drug which benefited at the pulmonary and intestinal level. The combination of carbon quantum dots (CQDs) and boric acid exhibited inhibitory effect on human CoV-2. In this study, the communication between them with receptor and S protein led to the blockage of virus binding to the cells. This helped to control the spread of SARS-CoV-2 infection at different levels [82].

Nanotechnology-based vaccine manufacturing has also emerged in SARS-CoV-2 period. VLPs and lipid nanoparticles (LNPs) are the foremost nanoparticle used for synthesis of vaccines. LNP-based mRNA vaccines are one of the leading, safe, and rapidly manufactured vaccine against COVID-19. The mRNA is encapsulated into LNPs comprising SM-102 (a synthetic amino lipid), cholesterol, PEG 2000-dimyristoyl glycerol, and 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC). This directed to effective anti-SARS-CoV-2 vaccination. In case of VLP-mediated vaccines, they do not require any boost immunization, and they are made up with a popular protein named

ferritin. The development of vaccine against SARS-CoV-2 is because nanoparticles can gain good stability to the antigens, present antigens multivalently, and co-deliver adjuvants with the antigens [80].

8 Conclusion

The versatile application of NS has opened a great avenue in the field of diagnosis, treatment, and environmental benefits. Cyclodextrin-based NSs are widely used to improve the solubility and bioavailability of drugs for different kinds of diseases including cancer. In the market, many types of NS-based drugs are already available, and many are in clinical trials. NSs are also used in biosensing, for the effective detection of many disease biomarkers. The field of wastewater remediation and oil spillage are also dependent on the different functionalized NSs, thereby contributing in environmental protection. In agriculture also, the use of NSs in trapping the essential nutrients and deliver them in a sustained manner to the plants has improved the crop production as well as made the cultivation environment-friendly by decreasing the use of fertilizers. SARS Cov-2 management was also executed using NSs.Thus, in many aspects, we could understand that NSs have a huge role in the beneficial effect of the health and environment.

Author Contribution Atchaya J has written the first draft of the paper. Agnishwar Girigoswami and Koyeli Girigoswami have given the concept and prepared the final manuscript.

Funding The study was funded by Council of Scientific and Industrial Research (CSIR), INDIA, Scheme No. 01(2868)/17/EMR-II.

Data Availability All the authors declare that all data and materials support their published claims and comply with field standards.

Code Availability Not Applicable.

Declarations

Ethics Approval

The manuscript has not been submitted to more than one journal for simultaneous consideration.
The submitted work is original and should not have been published elsewhere in any form or language (partially or in full).
A single study is not split up into several parts to increase the quantity of submissions and submitted to various journals or to one journal over time (i.e., "salami-slicing/publishing").
Results are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation (including image-based manipulation). The authors have adhered to discipline-specific rules for acquiring, selecting, and processing data.
No data, text, or theories by others are presented as if they were the author's own ("plagiarism"). Proper acknowledgements to other works have been given.

Informed Consent Not applicable.

Consent for Publication Yes.

Conflict of Interest The authors declare no competing interests.

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