

Nanosponges as Emerging Nanocarriers: A Comprehensive Review of Recent Developments and Pharmaceutical Applications

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Abstract

Recent advancements in nanotechnology have revolutionized drug delivery systems by enabling targeted and controlled delivery of therapeutic agents. Despite significant progress, challenges such as poor bioavailability, drug toxicity, limited stability, and uncontrolled drug release continue to hinder the effectiveness of conventional drug delivery approaches. Nanosponges have emerged as a promising nanocarrier system capable of overcoming these limitations due to their unique structural and functional characteristics. Nanosponges are nanosized, three-dimensional porous structures composed primarily of cross-linked cyclodextrins and suitable cross-linking agents. The nanosponge drug delivery system offers numerous advantages, including reduced drug toxicity, prolonged and predictable drug release, enhanced therapeutic efficacy, and site-specific drug targeting. In addition to pharmaceutical applications, nanosponges have demonstrated significant potential in the delivery of proteins, enzymes, vaccines, antibodies, and other biomacromolecules. Their applications extend to various therapeutic areas, including cancer treatment, autoimmune disorders, infectious diseases, and theranostic medicine. This review provides a comprehensive overview of nanosponges, focusing on their preparation methods, factors influencing formulation, physicochemical characterization techniques, advantages and limitations, and diverse pharmaceutical applications. Furthermore, recent developments and future perspectives in nanosponge-based drug delivery systems are discussed. The growing body of evidence suggests that nanosponges represent a versatile and innovative platform with immense potential to enhance the efficacy and safety of modern drug delivery systems.

Keywords: Nanosponges, Targeted Drug Delivery, Cyclodextrins, Controlled Drug Release, Drug Encapsulation, Bioavailability Enhancement, Nanotechnology, Pharmaceutical Applications.

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1. INTRODUCTION

Nanosponges are small mesh-like structures that can contain a wide range of chemicals and pharmaceutical molecules [1, 2]. They increase the solubilization capacity of both water-soluble and lipid-soluble medicines and have a spherical colloidal structure [3]. Targeting medication delivery mechanisms has been a long-term goal in order to get the desired results. Nanosponges (NSs) drug delivery systems were initially only topical, but in the twenty-first century, they can be taken orally as well as intravenously (IV) [4]. Nanosponges are a modern type of material composed of microscopic particles having a narrow cavity of a few nanometres.

These thin spaces can be filled with a variety of materials. These small particles have the ability to transport both hydrophilic and lipophilic therapeutic substances while also increasing the stability of poorly water-soluble pharmacological substances or compounds [5]. Nanosponges with appropriate penetration, absorption, biocompatibility,

bioavailability, and stability have been investigated for targeted and sustained drug administration and cancer therapy [6].

Nanosponges are solid, crosslinked, polymeric, nano-sized, porous structures that are hydrophilic, water-insoluble, and supramolecular three-dimensional (3D) hyper-reticulated nanoporous structures with significant stability over a wide temperature and pH range. They have demonstrated appealing properties, such as good biocompatibility, biodegradability, and low cytotoxicity, making them appropriate for biomedical applications [7]. It has been discovered that incorporating pharmaceuticals into nanosponges improves their solubility and degradability, hence increasing their bioavailability [8].

Nanosponges (200-300 nm) come in both crystalline and para-crystalline forms, depending on the reaction/synthesis and processing circumstances. The property in *Nanomaterials* 2022, 12, 2440 3 of 14 relating to the crystallization of nanosponges can help

manage and govern their drug-loading capability [9]. Carbon nanotubes, silver nanowires, and titanium dioxide (TiO₂) can be used to functionalize/modify the surface of these nanosponges.

TYPE OF NANOSPONGES [29]

There are numerous types of NS available that can be developed and formed according to the polymer utilized, its concentration, and the technique of production used. The most frequent types of NS that are prepared and widely used are beta CD-based NS.

1. Modified Nanosponges
2. Beta Cyclodextrin Based Nanosponges
3. Titanium Based Nanosponges
4. Silicon Nanosponges particles
5. Beta Cyclodextrin Based Polyamide Amino Nanosponges
6. Carbon Coated Metallic Nanosponges
7. Hyper Cross Linked Polystyrene Nanosponges
8. Beta Cyclodextrin Based Carbonate Nanosponges [11].

Advantages of Nanosponges:

- They cover the unpleasant taste of drugs for oral or buccal administration.
- They encapsulate ingredients used in formulation, reducing side effects.
- Reduced drug administration frequency leads to better patient compliance [12].
- Improve aqueous solubility of weakly water-soluble drugs.
- Nanosponges release medicinal molecules in a predictable manner.
- Nanosponges act as a self-sterilizer due to their tiny pore size of 0.25 μm, preventing bacteria penetration.
- Improve formulation stability and flexibility.

Disadvantages of Nanosponges

- Nanosponges have the capacity of encapsulating small molecules, not suitable for larger molecules.
- Dose dumping may occur at times [13].

Method of preparation of Nanosponges

1) Solvent method

Combine the polymer with an appropriate solvent, preferably a polar aprotic solvent like dimethyl sulfoxide or formamide. Afterwards, add this combination to the surplus cross-linker, ideally in a crosslinker/polymer molar ratio of 4:16. Conduct the reaction for a duration of one to forty-eight hours at a temperature between 10° C and the solvent's reflux temperature. Dimethyl carbonate and carbonyldiimidazole are two preferred carbonyl crosslinkers (5). Once the reaction is finished, let the mixture cool to room temperature. Then, add the product to a significant amount of extra bidistilled water. Recover the product by vacuum filtering, and then purify

it using ethanol-based Soxhlet extraction. To create a uniform powder, dry the product under a vacuum and grind it in a mechanical mill.

2) Ultrasound-assisted method

Using this technique, cross-linkers and polymers can react without a solvent while being sonicated to create nanosponges. This process will yield uniformly sized, spherical nanosponges. In a flask, combine the polymer and cross-linker at a specific molar ratio. Heat the water in an ultrasonic bath to 90°C while the flask is inside. For five hours, sonicate the mixture. After letting the mixture cool, roughly break the product. To remove the nonreacted polymer, wash the product with water. Then, purify it using ethanol and a lengthy Soxhlet extraction process. After obtaining the desired result, vacuum-dry it and store it at 25° C until needed [14].

3) Microwave Irradiation Method

Microwave processes were performed in Cata's scientific microwave system. The temperature of the reaction mixture was measured by inserting a fabric-optic probe into the reaction vessel. Diphenyl carbonate was employed as a crosslinking agent and diphenyl formamide as a solvent to produce cyclodextrin-based nanosponges. In short, a 250 ml flask was filled with a solution of cyclodextrin and diphenyl carbonate in dimethylformamide, and it was microwaved for a predetermined amount of time under particular conditions. The solvent was totally eliminated after some time. After that, the final product was completely cleaned using ethanol and Soxhlet extraction. After that, a white powder was created, which was subsequently dried at 60 °C in an oven to make it usable. In a trial, Singireddy *et al.*, examined the benefits of using a microwave to help with heating instead of more conventional heating techniques for creating nanosponges based on cyclodextrin. The results of the investigation showed that producing NSs with the help of a microwave boosted the model drug's drug-retaining ability by 50%. High-resolution transmission electron microscopy studies showed that the NSs generated by microwave synthesis were more complex and highly crystalline with a narrow size distribution. One benefit of employing microwave irradiation in synthesis is that it provides precise energy delivery to the molecules that are the target of the radiation.

4) Preparation of NSs from hypercrosslinked β-cyclodextrin:-

Another name for it is the melting procedure. A round-bottomed flask was filled with 100 ml of anhydrous Dimethyl Formamide and 17.42 g of anhydrous cyclodextrin. The mixture was slowly stirred until it completely dissolved. This mixture was treated to 9.96 g of carbonyldiimidazole, and the reaction was run for 4 hours at 100°C. After condensation polymerization is complete, Round Bottom Flask produces a hyper-cross-

linked cyclodextrin. To remove any surplus Dimethyl Formamide from the combination above, a large amount of deionized water should be added. Finally, unreacted compounds are removed via Soxhlet extraction, which is ethanol-based. By cross-linking it with polyamidoamine segments produced from 2-methyl piperazine & 2,2-bisacrylamidoacetic acid or 2,2-bisacrylamidoacetic acid, Swaminathan et al. manufactured nanosponges of β -Cyclodextrin. Both of the cyclodextrin-based nanosponges displayed a prolonged release profile of bovine serum albumin and more than 90% protein loading.

5) Emulsion solvent diffusion method

This approach involves manufacturing nanosponges using varying proportions or amounts of polyvinyl alcohol and ethyl cellulose. This approach uses two phases: continuous and dispersed. The drug and ethyl cellulose make up the dispersed phase. The drug is dissolved in 20 milliliters of dichloromethane, and 150 milliliters of the continuous phase (aqueous) are mixed with a little quantity of polyvinyl alcohol (PVA). After that, the mixture is agitated for roughly two hours at a speed of 1000 rpm. The product, or nanosponges, is gathered through filtration. At 400°C, the product is lastly dried in an incubator.

6) Quasi emulsion solvent method

This process makes use of two phases—the organic and aqueous phases—in varying ratios to create nanosponges. Polyvinyl alcohol is employed in the aqueous phase, whereas a medication and polymer solution is used in the organic phase. After choosing the polymer and dissolving the medication in an appropriate organic solvent, the mixture is gradually introduced to the aqueous phase. The final mixture is agitated at 1000 rpm for over two hours. After formulation, the nanosponges are dried, cleaned, and filtered. Abemaciclib sustained release nanosponges were created by Anwer *et al.*, Using the emulsion-solvent diffusion approach, ethyl cellulose and Kolliphor P-188 were employed as the sustained-release polymer and surfactant, respectively, in the creation of nanosponges. The medication was released continuously from the prepared nanosponges for up to 24 hours. The extended release of medication from the Abemaciclib Nanosponges is due to the slower dispersion of aqueous media within the hydrophobic polymer matrix.

7) Polymerization

After dissolving a non-polar drug in the monomer, an aqueous phase—usually consisting of surfactants and dispersants to facilitate suspension—is added. Catalyzing the monomers or increasing the temperature is how polymerization is done once the suspension containing the separate droplets of the required size is produced. The polymerization process produces a system that resembles a reservoir and opens at the surface through pores. Glutathione pH dual-

bioresponsive degradable Nanosponges, 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, were used by Dai *et al.*, to deliver doxorubicin. It offered improved doxorubicin loading within a three-dimensional network of nanosponges [15].

Mechanism of drug release from nanosponges

The active ingredient is given to the vehicle in an encapsulated form since the nanosponges have an open structure, meaning that there is no continuous barrier around them. The active ingredient that has been encapsulated can freely flow from the particles into the vehicle until the vehicle is saturated and equilibrium is reached. The vehicle holding the active ingredient becomes unsaturated as soon as the product is applied to the skin, upsetting the equilibrium. As a result, until the vehicle is either absorbed or dried, the flow of active chemicals from nanosponge particles into vehicles begins at the epidermis. The release of active substance into the skin lasts for a considerable amount of time even after the nanosponge particles are retained on the stratum corneum, the skin's outermost layer [13].

Factor Affecting Formulation of Nanosponges

1. Nature of Polymer and crosslinkers

Both the pre-formulation and the development of the nanosponges might be impacted by the polymer utilized in their manufacture. A nanosponges' hollow should be large enough to hold a drug molecule of a specific size within for complexation [16]. The type of polymer employed in the formulation of nanosponges has an impact on their performance. Three-dimensional (3D) structures are created from nanoporous molecular structures by efficient crosslinkers. By adjusting the degree of crosslinking, hydrophilic or hydrophobic portions can be created that entangle target molecules. Water soluble or insoluble nanosponges are created based on the crosslinkers' properties [17]. Hydrophilic nanosponges can be created by using epichlorohydrin as a crosslinker. These can be used as efficient drug carriers and improve medication absorption across biological membranes [18]. Hydrophobic nanosponges were created by employing crosslinkers such as diphenyl carbonate [19], pyromellitic anhydride, and diisocyanates [20]. These nanosponges might be used to transport hydrophilic drugs like proteins and peptides over a prolonged amount of time [21].

2. Drug and medium used for interaction

The following features of drug molecules are necessary for them to form a compound with nanosponges:

- ❖ The medication molecule's molecular weight should fall between 100 and 400 daltons.
- ❖ A drug molecule's structure should include no more than five condensed rings.
- ❖ The medication should dissolve in water at a rate of

less than 10 mg/ml.

❖ The medication's melting point needs to be below 250 °C.

The kind and nature of the crosslinker and polymer utilized, along with the kind of medication that must be loaded, might all affect the creation of nanosponges. Drug molecules need certain characteristics in order to be effectively entrapped in nanocavities. A nanocavity can successfully trap molecules with molecular masses between 100 and 400 Da, a melting point of less than 250 °C, less than five condensed rings, and a solubility of less than 10 mg/ml in water [22]. It is impossible for compounds with a high melting point to create stable complexes between medications and nanosponges because these compounds tend to lose stability after being loaded into Nanosponges. The stability constant of a complex is influenced by temperature changes. The connection between the stability. Furthermore, melting compounds at high temperatures lead to less drug loading because of the structural rigidity of the compound. While organic solvents prefer to liberate the organic molecules imprisoned in Nanosponges, hydrophilic media will force organic guest molecules to enter hydrophobic cavities. The interaction between targeted molecules and the cavity of Nanosponge is significantly influenced by the medium [21].

3. Temperature

Temperature variations can have an impact on how medication or nanosponge complexes. Raising the temperature often reduces the strength of the drug's or the nanosponge complex's stability constant. This may be because the drug and nanosponges' hydrophobic and Van der Waals forces weaken as the temperature rises [23].

Temperature changes have an impact on the complexation of nanosponges. It is common for a drug or nanosponges complex's stability constant to decrease with temperature. This could be because of a reduction in contact forces such hydrophobic and van der Waals forces [24, 25].

4. Degree of substitution

The quantity, orientation, and kind of the parent molecule's substituents can have a bigger impact on the nanosponges' capacity to complex [26]. The type of substituent, quantity, and location of the polymeric molecule all influence the capacity of nanosponges to complex [25]. The kind of substitution is required because the surface functional groups of cyclodextrin derivatives provide wide accessibility to the derivatives in different configurations. When distinct functional groups are complexed together by a crosslinker, several types of complexed material, such as Cyclodextrin Nanosponges, Cyclodextrin -carbonate Nanosponges, etc., can be produced [22]. The quantity of substitutions and the degree of crosslinking have a valid relationship. This implies that increasing the number of substituents

may raise the possibility of higher crosslinking levels, which may result in very porous nanosponges because of the creation of a mesh-like network and enhanced links between polymers. When the production process is altered, the functional group on the parent compound could occupy a different site, resulting in the formation of new materials with distinct physicochemical features. For example, samples of hydroxypropyl-cyclodextrin with the same degree of substitution may not have the same physicochemical properties if synthesized under different manufacturing conditions. This could be explained by the possibility that the parent Cyclodextrin molecule's hydroxypropyl groups are located in various places. As a result, the production process and material purity show that the degree of polymer substitution is considerable and has a substantial impact on the final quality of Nanosponges [22].

5. Method of preparation

The way that the drug is loaded into the nanosponges may alter how the drug and the nanosponges complex. While the type or properties of the medication and polymer have a major role in a method's efficacy, freeze drying has occasionally been found to have an impact on the drug and nanosponge complexation.

Characterization of Nanosponges

The following is a list of the characterisation techniques for the complexed drug/nanosponges:

Solubility studies

One method for figuring out the drug's solubility and bioavailability is inclusion complexes. The most used method for analyzing the inclusion complexes of nanosponges is this one. The phase solubility plot can be used to determine the degree of completion. medication solubility is investigated through solubility studies in order to determine the medication's pH, the solubilization profile, and the factors influencing drug solubility [27].

The inclusion complexation process is studied using the phase solubility approach. Diagrams of solubility are used to display the degree of complexity [25]. The medication was added to each flask that held an aqueous solution of different percentages of nanosponges in this technique. A mechanical shaker was used to shake the flask while it was at room temperature. Following centrifugation, the suspension was filtered through a 3000 Da molecular filter once it had stabilized. To determine the drug content of the final solution, high-performance liquid chromatography was used for analysis. The pH of the medicine, the solubilization process, and the factors influencing drug solubility are all studied in relation to medication solubility [28].

Microscopic study

Scanning electron microscopes and

transmission electron microscopes can be used for microscopic investigations of drugs and nanosponges. The disparity between the product observed under an electron microscope and the crystallization state indicates the production of inclusion complexes.

Sending and receiving Electron microscopes can be used for microscopical study on drugs and nanosponges [29]. The difference in crystallization state between the final product and the starting materials, as shown by electron microscopy, indicates the creation of the inclusion complexes [25, 28].

Zeta potential determination

The potential difference between two layers of fluid bound up with dispersed particles—the dispersion medium and the immobile layer—is known as the zeta potential. The primary critical indicator of the colloidal dispersion's stability is the zeta potential. The zeta potential can be determined by adding an additional electrode to particle size equipment or a zeta separator. The stability of a colloidal dispersion increases with increasing zeta potential value.

Zeta potential is used to assess surface charge [29]. To find the zeta potential of the nanosponges, samples were diluted with 0.1 mol/L KCl. The mean hydrodynamic diameter and polydispersity index of the particles were recalculated by averaging all measurements [30, 28].

X-ray diffractometry

Powder X-ray diffractometry can be used to detect inclusion complexation in the solid state. Diffraction peaks can be used to determine the intricate growth and chemical breakdown of a mixture of substances. The drug's crystalline structure and diffraction patterns are altered during the formation of the drug-nanosponge combination. A few new peaks emerge, some old peaks become sharper, and some peaks move as a result of the complicated formation [28, 31].

Thermodynamical method

The thermo-chemical approach can be used to assess whether any changes in drug molecules or particles experience alterations prior to the thermal destruction of nanosponges. Drug particles may undergo polymeric modifications, melting, evaporation, oxidation, and breakdown. The medication molecules' alterations show that a good combination is forming.

Any changes that drug molecules or particles undergo prior to the heat-induced annihilation of nanosponges can be found using the thermo-chemical method. Medication particle modifications can occur by melting, oxidation, and polymeric changes, to name a few [25]. Differential scanning calorimetry and differential thermal analysis provide a thermogram that can be used to examine changes in peak width, shifting, addition of new peaks, and removal of specific peaks.

Variations in weight loss can provide additional information for the establishment of inclusion complexes [28, 32]. Particle size and polydispersity

Using 90Plus particle size determining software, dynamic light scattering is used to determine the size of the particle.

A 90Plus particle size sensor can be used to measure the particle size via dynamic light scattering. This makes it possible to estimate the mean diameter and polydispersity index [15]. The measurements were made at the same 90-degree angle for every sample. The samples were suitably diluted with Milli Q water for every assessment [30, 28]. Finally, the polydispersity index (PDI) and particle ultimate diameter can be determined.

Thin layer chromatography (TLC)

One definition of TLC is a method for separating evaporative or non-volatile mixtures. This method helps identify the development of a complex between a drug and nanosponges if the R_f value of a specific drug molecule is within an acceptable range.

The evaluation of a drug molecule's R_f values in thin layer chromatography facilitates the identification of the complex formation between the drug and Nanosponges [29, 33].

Infrared spectroscopy

Infrared spectroscopy can be used to determine how the medicine interacts with nanosponges in the solid state. The development of complexes can cause modest changes in the nanosponge bands. With less than 25% of guest molecules bound to the complexes, the drug spectrum can be readily obscured by the nanosponges' spectrum. Compared to previous methods, the strategy is inappropriate for identifying the inclusion complex [34].

Infrared spectroscopy is utilized to ascertain how pharmacological molecules interact with nanosponges in the solid state. Bands on nanosponges shift somewhat when a compound forms. The bands of the nanosponges' spectrum easily mask the bands that may be attributed to the included fraction of the guest molecules if less than 25% of the guest molecules are encapsulated inside the complex [32]. The use of infrared spectroscopy is limited to drugs that have identifiable bands, like sulfonyl or carbonyl groups [29].

Loading efficiency

By measuring the amount of drug loaded into the nanosponge using a UV spectrophotometer and a high-performance liquid chromatography method specifically designed for nanosponges, one can ascertain the loading efficiency of a nanosponge particle.

By using a UV spectrophotometer to provide a quantitative estimate of the amount of medicine loaded

into the nanosponges, one can ascertain the loading efficiency of the nanosponges [34]. The following formula can be used to determine how much medication is added to nanosponges [35, 29]:

The following formula can be used to determine how well nanosponges load.

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

Applications of Nanosponges

Nanosponges' biocompatibility and adaptability make them useful in a variety of therapeutic applications. Nanosponges can be utilized as an excipient in the pharmaceutical sector for formulating tablets, capsules, granules, pellets, suspensions, solid dispersions, and topical dosage forms. Lipophilic and hydrophilic drug molecules—that is, those that fall under the biopharmaceutical classification system (BCS-class II)—as well as poorly water-soluble drugs—can both be accommodated by nanosponges [36].

Nanosponges for drug delivery

The water-insoluble medication can be transported via nanosponges due to their minuscule porosity structure. The solubility and permeability of drug nanosponges complexes are important factors in increasing the rate of dissolution. β -cyclodextrine-based nanosponges are reportedly three to five times more effective in getting the medication to where it's needed. Typically solid in nature, nanosponges can be manufactured for topical, oral, parental, or inhalation dose forms. A suitable excipient, such as lubricants, diluents, or anti-cracking agents, is used to dissolve the nanosponges complexes in order to prepare tablets and capsules for oral administration.

Nanosponges for cancer therapy

The administration of anticancer drugs is one of the most difficult tasks in the pharmaceutical industry these days due to their low solubility. According to one report, direct injection is three times less effective than nanosponge complex at slowing down tumor growth. The drug-loaded nanosponge combination exposes a targeting peptide that firmly bonds with the tumor receptor's radiation-induced cell top layer. Upon encountering a tumor cell, nanosponges adhere to its surface and initiate the release of medication molecules. Targeting drug delivery has the benefit of maximizing therapeutic impact at the same dose while minimizing side effects [37].

Nanosponges for delivery of protein

Using bovine serum albumin (BSA) as a model protein, the encapsulating capacity of β -cyclodextrin-based nanosponges was investigated. Because the protein solution containing bovine serum albumin (BSA) is unstable, it is kept in lyophilized form. When proteins are lyophilized from their original structure, they might

become denatured. The primary challenge in the formulation and development of proteins is preserving their natural structure for extended periods of time both during and after processing. When proteins like bovine serum albumin (BSA) are delivered using cyclodextrine-based nanosponges, the proteins' stability is increased. Additionally, enzyme immobilization, protein encapsulation, controlled administration, and stabilization have all been accomplished with nanosponges [38].

Role of nanosponges for treatment of fungal infections

One of the most serious illnesses in the world is fungus-induced skin infections [39]. Due to its many benefits, including the ability to target the exact site of infection and lessens systemic side effects, topical therapy is a popular option for treating cutaneous infections. A topical antifungal or pharmaceutical fungicide called econazole nitrate (imidazole) is used to treat vaginal thrush, ringworm, athlete's foot, jock itch, and tinea pityriasis versicolor. Econazole nitrate is accessible as cream, ointment, lotion, and solution across the market. When applied topically, econazole nitrate does not significantly adsorb; instead, successful therapy requires a combination of highly concentrated active drugs. Because of this, econazole nitrate nanosponges were created using the emulsion solvent approach and then put into a hydrogel for topical distribution of the medication that would release over time [40, 41].

Another antifungal medication, itraconazole, belongs to class II of the biopharmaceutical classification system and has a low bioavailability and restricted dissolving rate. Therefore, the goal of this work was to make itraconazole more soluble in order to address the issue of bioavailability. Itraconazole's solubility can be enhanced in these nanosponges by loading it with itraconazole and using β -cyclodextrine that has been cross-linked with carbonate bonds.

As absorbent in treating poison in blood

By absorbing the toxin, nanosponges can remove harmful substances from our blood. By injecting nanosponges into the bloodstream, we can absorb toxins instead of employing antidotes. The nanosponge imitates a red blood cell in the bloodstream, deceiving toxins into attacking it before absorbing them. Each type of nanosponge has a limited capacity to absorb different numbers of poison molecules [42].

Covid

Many antiviral drugs, immunomodulators, and potential inhibitors (either organic or inorganic) have been proposed to combat SARS-CoV-2 [43, 44]. Recent developments in nanoscience and nanotechnology have brought about dramatic change in many study fields, most notably medicine [45]. Due to restrictions on medication efficacy and delivery, researchers are shifting

their focus to nanocarriers with unique qualities, maximum effectiveness, specificity, and fewer side effects [46,47]. In order to achieve the intended

pharmacokinetic effects, therapeutic agents or medications are more bioavailable, stable, and soluble when applied on nanosponges [48, 49].

Additionally, hydrophilic or lipophilic compounds can form a variety of complexes with nanosponges, enhancing their transport and protecting them from hazardous substances [50, 51]. For lipophilic medicines, for example, delivery methods based on β -cyclodextrin nanosponges were created to increase the solubility of the medication and make oral administration easier [52]. Nanosponges can be useful tools for improving immunization in addition to having the ability to be targeted or regulated in their distribution and used for tailored therapies [53, 54].

Cyclodextrin-based nanosponges, which have carboxylic groups in their structural composition, have been used to transport acyclovir. These nanosponges work well for sustained release and have a high loading capacity for the antiviral drug; nevertheless, more *in vivo* research is required to properly assess the effectiveness and biodistribution of these nanosponges. For clinical and biological applications of nanosponge-based technology in the future, in particular, cytotoxicity and biosafety requirements are crucial [56, 57].

Future Perspectives

The most common medication delivery method in the world of pharmaceuticals has been determined to be nanosponges. The efficient functionalization of nanosponges to lower toxicity, improve selectivity, and enhance biosafety should be the main emphasis of future study. It is possible to create novel nanosponges with a range of properties and multifunctionality. More study is needed to focus on the precise surface functionalization of nanosponges using various materials, such as fluorescent compounds, magnetic nanoparticles, etc., in order to build multifunctional systems with cancer theranostic applications [58]. Nanosponges can be produced more quickly and easily with the use of 3D printing techniques [59]. Further research is required to determine the effectiveness of nanosponges in the oral transport of proteins and peptides. A case study on insulin was conducted, wherein β -cyclodextrin was used to create nanosponges. Other physicochemical parameters as well as *in vitro* and *in vivo* investigations were conducted on the nanosponges. The *in vitro* investigation demonstrated that insulin was released from nanosponges with increased permeability in Caco-2 cells in a pH-dependent manner. Following therapy, the *in vivo* investigation revealed that rats' plasma contained insulin, which had a hypoglycemic impact. These preliminary results support the need for more investigation into the cyclodextrin nanosponge technology for insulin delivery by mouth as well as

possible extensions of this technique to other pharmaceutically significant proteins. In the years to come, nanosponges—a dependable and efficient drug delivery system—may represent a cutting-edge protein delivery technique through nanotechnology [60]. In order to fully realize the potential of nanosponges and turn them into useful applications in the future, research and development activities must continue.

CONCLUSION

It has been established that hydrophilic and lipophilic drugs can be encapsulated or accumulated using nanosponges as a drug delivery device by creating a complex. They are able to precisely and safely administer the medication at the intended location. Topical preparations in liquid or powder form, such as lotions, creams, ointments, etc., can comprise nanosponges. This technology's benefit is that it targets the medication to a specific spot, which lowers side effects, improves stability, increases formulation flexibility, and improves patient compliance. Moreover, nanosponges have applications in agrochemistry, biomedicine, cosmetics, bioremediation, and catalysis, among other fields.

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