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REVOLUTIONIZING ORAL DRUG DELIVERY THROUGH NANOSPONGE ADVANCEMENTS - A COMPREHENSIVE REVIEW

Rakshitha S.*, J. Adlin Jino Nesalin, E. Gopinath, Ganesh N. S. and Vineeth Chandy

Department of Pharmaceutics, T. John College of Pharmacy, Bengaluru, Karnataka, India.

***Corresponding Author: Rakshitha S.**

Department of Pharmaceutics, T. John College of Pharmacy, Bengaluru, Karnataka, India.

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ABSTRACT

Nanosponges are a novel and emerging branch of pharmaceutical nanotechnology that is widely acknowledged for its potential to offer new tools, opportunities, and scope to combine properties that are challenging to achieve by using medicine alone. The development of nanosponges (NSs) has proven to be a crucial step in solving the issues with traditional drug administration. Nanosponges are microscopic sponges that resemble viruses in size and may hold a wide range of drugs within them. These microscopic sponges can move throughout the body until they come into contact with the precise target area, adhere to the surface, and start releasing the drug in a regulated and predictable way. The aqueous solubility of these sponges is another noteworthy feature that makes it possible to use these systems efficiently for drugs with low solubility. Nanosponge delivery systems were originally developed for topical drug delivery, and can now be used for controlled oral drug delivery using water-soluble and biodegradable polymers. This method provides ingredient entrapment, which reduces adverse effects and improves stability, elegance, and formulation flexibility. Moreover, biocatalysts like proteins, enzymes, vaccines, and antibodies can be carried and released via parenteral, topical, aerosol, and oral routes using nanosponges. This review covers a broad overview of nanosponges, their classification, their distinguishing characteristics, their benefits and drawbacks, the chemicals used in their preparation, the preparation processes, the variables influencing their preparation, their mechanism of action, evaluation parameters, and a few instances of their use in oral drug delivery systems.

KEYWORDS: Oral drug delivery, Nanosponges, Biodegradable polymer, Solubility.

INTRODUCTION

In recent years, molecular biology research has revealed the underlying biology of numerous disorders. Innovative ideas and technologies like gene therapy and recombinant DNA have made it possible to develop medications and other treatments intended to target these kinds of illnesses. However, the adoption of these medications outside of the laboratory has progressed very slowly, primarily because there are currently insufficient efficient drug delivery systems. The efficacy of pharmacological therapy can thereby increase by the technological advancements in drug transport and targeting strategies, which positively impact human health.[1]

Oral administration is a commonly utilized and recommended method of drug delivery for both new and old medications. It could be due to its advantages such as non-invasiveness, patient compliance, and convenience of drug administration. To prolong the medication release for several hours, a modified oral-release drug delivery system has been created. Modified release system provides better therapeutic impact, increased bioavailability, dosing frequency reduction, and low incidence of side effects.[2]

The creation and modification of materials at the nanoscale level to produce products with distinctive properties is known as nanotechnology. In 1959, Cal Tech physicist Richard P. Feynman predicted nanomaterials. He said, "There is lots of room at the bottom," implying that the secret to further advancements in nanotechnology was to start at the bottom and work one's way down to the nanoscale. Recently, there has been a lot of interest in nanomaterials. These are the materials with a minimum of one dimension within the vary of 1-100 nanometers.[3]

Nanosponge is a modern category of material that is a type of nanoscopic structure that resembles a mesh that transforms the way many diseases are treated. In comparison to microsponges, a nanosponge's diameter is about between 10 and 25 µm, and its void extent is between 5 and 300 µm which is less than 1 µm in

diameter, giving nanosponges an edge over microsponges. The 3D printing methods will aid in the creation of the nanosponges and in supplying the modifications necessary to meet objectives.[4] Nanosponges are made up of microscopic particles with a few nanometre-wide cavities. These narrow cavities can be filled with various types of substances i.e., these can carry both hydrophilic and lipophilic drug substances and can increase the stability of poorly water-soluble drug substances or molecules. In the beginning, the Nanosponge drug delivery system appeared only as a topical delivery system, but in the 21st century, Nanosponges can be administered by oral as well as intravenous (IV) route.[5]

Nanosponges are a novel class of tiny sponges that are about the size of a virus, filling them with a drug and connected with unique chemical "linkers" that circulate the body, attach themselves preferentially to a target site, and begin the release of potent drugs in a controllable and predictable manner. The term "Nanosponge" means the nanoparticles having porous structures. Nanosponges resemble a 3D scaffold or network with long polyester strands as the backbone of polyester nanosponges. It is combined in solution with tiny molecules known as cross-linkers, which bind various polymer segments together by functioning as microscopic grappling hooks. Overall, the result is the formation of spherically shaped particles that are packed with cavities that can hold drug molecules. Because polyester is biodegradable, the body breaks it down gradually. By altering the ratio of cross-linkers to polymer, it is also feasible to adjust the size of the nanosponge particles, making them larger or smaller.[6]

As a result of their safety for both oral and invasive administration, they may be used as a medication delivery vehicle in the future. The complexes can be distributed in a matrix of lubricants, diluents, anti-caking agents, and excipients suitable for the manufacturing of capsules or tablets for oral administration. The tiny size of nanosponges also facilitates their topical, pulmonary, and venous administration.[7]

Structure of polymer-based nanosponge[4]

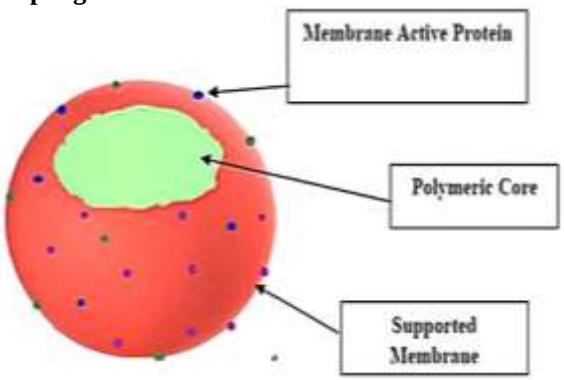

Fig. 1: Nanosponges.

Important characteristics of nanosponges

1. The 3D structure of nanosponges enables the capture, transportation, and selective release of a variety of substances.
2. They form clear and transparent suspensions in water.
3. They form inclusion and non-inclusion complexes with different drugs.
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5. They form inclusion and non-inclusion complexes with different drugs.
6. The 3D structure of nanosponges enables the capture, transportation, and selective release of a variety of substances.
7. These are capable of carrying both lipophilic as well as hydrophilic drugs and are biodegradable in nature.
8. They are non-toxic, porous particles, insoluble in most organic solvents, and stable at high temperatures up to 300^0C.[8]
9. Nanosponges can exhibit magnetic properties when they are prepared in the presence of magnetic substances.
10. Nanosponge with varying polarity and size can be created by adjusting the cross-linker to polymer ratio and the functional group, which is present and has a significant concentration in the crosslinker, influences the nanosponge's porosity and imparts variable polarity.[4]

Advantages of nanosponges

1. This technology offers entrapment of ingredients, increases the solubility of poorly soluble drugs, and reduces side effects.
2. Improved stability, increased elegance, and enhanced formulation flexibility.
3. These formulations are stable over a range of pH 1 to 11.
4. These formulations are compatible with most vehicles and ingredients.
5. These are self-sterilizing as their average pore size is 0.25μm where bacteria cannot penetrate.

6. These formulations are free-flowing and can be cost-effective.
7. These modify the release of drug[9] i.e., a] For oral administration, these may be dispersed in a matrix of excipients, diluents, lubricants, and anticaking agents which is suitable for the preparation of tablets or capsules. b] For parenteral administration, these can be simply mixed with sterile water, saline, or other aqueous solutions. c] For topical administration, they can be effectively incorporated into topical hydrogel.
8. Nanosponges are non-irritating, non-mutagenic, nonallergenic, and non-toxic.[10]
9. Nanosponges improve material processing to change liquid substances into solid form and to cover up offensive flavors and odors.

Disadvantages of nanosponges

1. In nanosponge, both crystalline and paracrystalline forms are possible. These paracrystalline nanosponges exhibit varying loading capacities; thus, the loading capacity depends on the degree of crystallization and the degree of cross-linking.
2. A nanosponge is limited to capturing tiny molecules.
3. Due to their small particle size, there is a restricted drug loading capacity.
4. Early crosslinker breakdown may result in dosage dumping.[4]

Types of nanosponges

Cyclodextrin (CDs) Nanosponges[11]

Cyclodextrins are nanometric biomaterials in which supramolecular characteristics and molecular state are closely correlated. The α, β, and γ are the primary native cyclodextrins that consist of six, seven, and eight glucopyranose units, respectively. Their distinct toroidal shape creates a distinct lipophilic chamber in the form of a truncated cone. Compounds whose geometry and polarity match the cavity of cyclodextrins can be included in them.[12]

De Quan Li and Min Ma initially used the word cyclodextrin in 1998, their invention offers a water-insoluble polymeric composition made up of a polyfunctional crosslinker chosen from the group that includes polyisocyanates, dihalohydrocarbons, and dihaloacetylhydrocarbons, and a reaction product of a cyclodextrin monomer. This offers a method for reducing the concentration of the target organic compound in the aqueous composition.[13] Trotta and associates on 2011 worked on the synthesis of novel cyclodextrin nanosponges, which showed off their full potential in a variety of applications, most notably as drug carriers.[14]

Types of CD Nanosponges

1. CD based carbamate NS
2. CD based carbonate NS
3. CD based ester NS
4. CD based polyamido amine NS
5. Modified NS.[1]

Polystyrene-based nanosponges

Hyper-cross-linked polystyrene is a translucent, low-density, microporous material with a high absorption capacity and an apparent interior surface area of 1000 m2/g. For mass transmission to be simple, they are also furnished with opaque transport pores. The comparatively simple chemistry of NS's polyesters and connecting material (peptides) accounts for its engineering capability. Because the polyester is biodegradable, the medication is released according to a predetermined timetable when it breaks down in the body.[11]

V.A. Davankov et al concluded that the intramolecularly hyper-crosslinked polystyrene nanosponges were directly observed for the first time using the scanning AFM technique which is a novel macromolecular species.[15]

Titanium Dioxide (Tio_2) Nanosponges

A porous metal oxide nanoparticle is how titanium dioxide (TiO_2) NS is characterized. Since porous metal oxide nanostructures (NS) exhibit distinct physical and chemical properties, they are favored over their nonporous bulk counterparts. Higher surface area, high mass transfer, and electron mobility are caused by their high porosity.[11]

L. Guo et al described a method for coating functionalized polystyrene spheres with a distinct layer of amorphous titanium dioxide. By calcining the dried particles in a furnace, the core-shell particles can be transformed into TiO_2 nanosponge.[16]

Silicon Nanosponges (Si NS)

A considerable amount of research has been conducted on porous silicon and similar materials to discover potential uses in fields such as optoelectronics, microelectronics, drug delivery devices, chemical and biological sensors, and more recently, energetic material devices. However, thorough material characterization is considered necessary before advancing the development of prospective Si material applications.

Chadwick et al examined the correlation between the porous structure formation due to material composition in detail. Typically, bulk silicon is chemically or electrochemically etched to create porous silicon in solutions based on hydrofluoric acid. This addresses how a chemical etching technique affects silicon powder of metallurgical grade and it is discovered that the Surface-bound impurities present in silicon particles of metallurgical grade cause a reaction with the chemical etchant used to generate a porous structure.[17]

Materials used for preparation

1. Polymers

Hyper cross-linked Polystyrenes, Cyclodextrins, and their derivatives like Alkyloxycarbonyl Cyclodextrins, Methyl β- Cyclodextrin, Hydroxy Propyl β-

Cyclodextrins, Poly valerolactone, Eudragit RS 100, Acrylic polymers.

2. Copolymers

Poly (Valerolactone allylvalerolactone), Poly (Valerolactone-allylvalerolactone oxepanedione), Ethyl Cellulose, Poly vinyl alcohol.

3. Cross linkers

Carbonyl di imidazoles, Carboxylic acid di anhydrides, Di arylcarbonates, Di chloromethane. Di isocyanates, Di phenyl Carbonate, Epichloridine, Gluteraldehyde, Pyromellitic anhydride, 2,2-bis (acrylamido) Acetic acid.[18]

4. Apolar solvents

Ethanol, Dimethylacetamide, Dimethyl formamide.[19]

5. Drug substances

Drug molecules to be formulated as nanosponges should have certain characteristics,

- Molecular weight between 100 and 400 Daltons.
- Drug molecule consists of less than 5 condensed rings.
- Solubility in water is less than 10mg/ml.
- The melting point of the substance is below 250°C.[18]

Method of preparation

1. Nanosponges prepared from Hyper cross-linked β- (cyclodextrins)

Hyper cross-linking three-dimensional networks made of nanostructured cyclodextrin polymers have a roughly spherical shape, similar in size to a protein, with channels and pores inside. They are produced when cyclodextrin reacts with a cross-linker.[20] Nanosponges can be synthesized in neutral or acid forms.[21] Low cross-linking nanosponges provide rapid drug release.[20]

2. Melt method

Cyclodextrins and the crosslinker are fused. After all the components are well combined, they are put in a 250 ml flask and heated to 100 c. Under a magnetic stirrer, the reaction is conducted for five minutes. After allowing the mixture to cool, the product is broken down. To get rid of byproducts and unreacted ingredients, the final product is cleaned with the appropriate solvents.[22]

3. Emulsion solvent diffusion method

This method makes use of various ratios of polyvinyl alcohol and ethyl cellulose. The drug and ethyl cellulose-containing dispersed phase was dissolved in 20 ml of dichloromethane and then gradually added to 150 ml of the aqueous continuous phase together with a predetermined quantity of polyvinyl alcohol. For two hours, the reaction mixture mentioned above was agitated at 1000 rpm. After that, the NS that had formed was gathered by filtering and dried for 24 hours at 400°C in the oven. To guarantee the elimination of any remaining solvent, the dried NS was kept in vacuum desiccators.

4. Ultrasound- Assisted synthesis

NSs were produced with this process by sonicating and reacting polymers with cross-linkers without the use of a solvent. The NSs produced by this process will have uniform size and spherical shape in the flask, the polymer and cross-linker were combined at a specific molar ratio. The flask was submerged in an ultrasound bath that had been heated to 90°C containing water. For five hours, this mixture was sonicated. After cooling the mixture, the result was roughly broken. After removing the nonreacted polymer with a water wash, the product was further refined using an extended Soxhlet extraction process with ethanol. The final product was vacuum-dried and kept in storage at 25°C until needed again.[20]

5. Solvent method

Dissolve the polymer in a suitable solvent, in particular in a polar aprotic solvent. Next, combine this with an excessive amount of cross-linker. The mixture should be refluxed for 48 hours at 10^{o}C. After that, let this mixture cool to room temperature. Mix this with an excess of bidistilled water, then strain the resulting mixture. Then, using ethanol and a prolonged Soxhlet extraction process, purify. To get a uniform powder, dry the substance and grind it in a mechanical mill.[21,23]

6. Quasi-emulsion solvent diffusion

The polymer was used in varying amounts to prepare the nanosponges. Eudragit RS 100 is used to produce the inner phase, which is then combined with an appropriate solvent. The drug was supplied in a solution, which was dissolved at 35ºC using ultrasonication. As an emulsifying agent, this inner phase is applied to the external phase that contains PVA. The mixture is agitated for three hours at room temperature at 1000–2000 rpm, and then it is dried for twelve hours at 40ºC in an air-heated oven.

7. Polymerization

Aqueous phase, typically comprising surfactant and dispersion to promote suspension, is added to a solution of non-polar drug in the monomer. After suspension with discrete droplets of the appropriate size is established, polymerization is carried out by catalyzing or raising the temperature to activate the monomers. A reservoir-style structure is created as a result of the polymerization process, and it has holes that allow it to open at the surface.[23]

8. Bubble electrospinning

The main components of a traditional and standard electrospinning arrangement are a grounded collector, a high-voltage power source, a syringe, and a syringe pump, as described in numerous literatures. However, a significant constraint limiting their potential uses is the quantity of nanofibers produced. Polyvinyl alcohol can be utilized as a polymer in bubble electrospinning. A

one-phase mixture was obtained by moving the 10% polymer solution at 80–90°C for two hours after adding distilled water to it. After allowing the polymer solution to reach room temperature, it was utilized to create nanoporous fibers.

9. Synthesis by the use of microwave radiation

The production of CD NSs by microwave irradiation is a straightforward method that greatly reduces reaction time. The levels of crystallinity in these NSs are higher. When NSs are synthesized using microwave radiation instead of more conventional heating techniques, the reaction time is halved and consistent crystallinity and a homogeneous particle size distribution are created. The advantage of employing microwave irradiation for synthesis is that it provides accurate energy delivery by delivering straight energy to the targeted molecules. Since the energy is not wasted heating the liquid next to the molecules of the reactant or the container walls, the entire effect is seen as the reaction moves closer to completion.[24]

Loading of the drug into nanosponges[25]

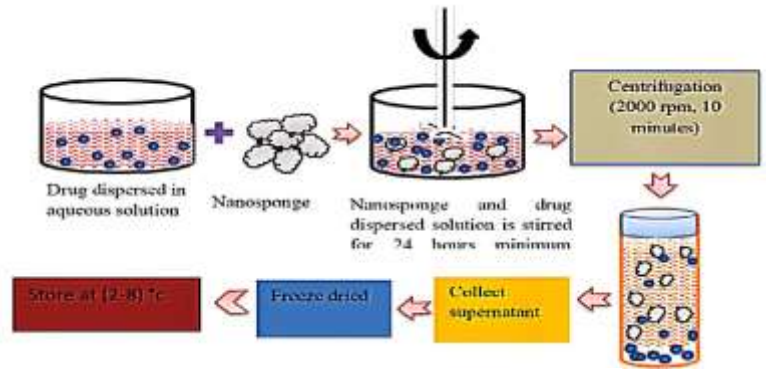

Fig. 2: Loading of drug into nanosponges.

Mechanism of drug release

The active ingredient is given to the vehicle in an encapsulated form since the nanosponges have an open structure, they do not have a continuous membrane enclosing them. The active ingredient that has been encapsulated can freely flow from the particles into the vehicle until the vehicle becomes saturated and equilibrium is reached. The vehicle holding the active ingredient becomes unsaturated as soon as the substance is consumed or applied to the skin, disturbing 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 body or epidermis.[26]

During the preparation procedure, the drug's solubility rises in the liquid, decreasing the benefit of its slow release and allowing the drug to moiety to behave as though it had been added in its unbound state rather than its bound state.[24]

Factors affecting the formation of NSs

1. Drug type

The "Five Rules of Lipinski" describes the characteristics of the medications that influence the development of NSs, in addition to their hydrophilic or hydrophobic nature.

2. Polymer Type and Crosslinkers

A significant factor in the creation of NSs is the type of polymer and the crosslinkers employed. The exact size of NS particles is determined by the molar ratios of the cross-linker and polymer; cross-linker types are crucial in converting NSs into a three-dimensional structure that is appropriate for hydrophilic or hydrophilic drugs.

3. Temperature

Raising the temperature, for instance, may specifically cause the drug and NSs to interact through lessening or decreasing intermolecular hydrophobic forces (such as the Vander Waals force).

4. Method of preparation

Depending on the kind of drug and polymer utilized in the formulation, the efficiency of the approach employed is critical to the synthesis of NS and drug complex as well as the integration of the drug into NS. The freeze-drying method is among the most helpful for the drug/nanosponge combination.

5. Degree of substitution

Depending on the number, position, and structure of the substituent on the parent polymer, different nanosponge complexes may be able to form. For instance, there can be more cross-linking between CD and crosslinker the higher the degree of substitution on the parent polymer.

6. Nanosponge toxicity

To assess the utility of the structure, toxicity tests are vital to determine whether the drug dose employed and the nanocarrier intended for drug delivery are harmful to people and animals.[27]

7. Loading of drug into nanosponge

Compared to paracrystalline nanosponge, crystalline nanosponge has a higher drug loading. Instead of

generating an inclusion complex, drug loading happens as a mechanical mixing in nanosponges with poor crystalline structure.[28]

Characterization of nanosponges

1. Particle size

The Zeta sizer or laser light diffractometry, instruments can be used to determine particle size. Plotting the cumulative percentage of drug release from nanoparticles with varying sizes against time allows one to examine how particle size affects drug release.

2. Polydispersibility index

PDI is a measure of the particle size distribution's variance that can be used to determine spread or width. To calculate PDI, a dynamic light scattering device is utilized. Formula to compute PDI:

PDI=d/d avgΔ

Where d is the width of distribution denoted by SD, and d Avg is the average particle size denoted by MV (nm) in the particle size data sheet.

3. Microscopy studies

The microscopic features of the medication and nanosponge formulation can be studied using Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM). SEM is used to analyze the nanosponges' morphology.

4. Determination of loading efficiency

Loading efficiency can be also calculated by using a quantitative estimation of the drug-loaded into nanosponge by UV spectrophotometer and HPLC method.

$$\text{Loading Efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

5. Solubility studies

Higuchi and Connors described the phase solubility method, which is used to examine inclusion complexation. This approach explains how Nanosponge affects the drug's solubility, a measure of complexation degree.[29]

6. Porosity

A helium pycnometer is used to measure the porosity of nanoparticles since helium gas can pass through both inter- and intraparticular channels in materials. The helium displacement method yields the true volume of the substance. Because they are porous, nanosponges have a larger porosity than the parent polymer that was utilized to create the system.[30]

$$\%\text{Porosity} = \frac{\text{Bulk volume} - \text{True volume}}{\text{Bulk volume}} \times 100$$

7. Drug entrapment efficiency

Drug-loaded NSs are mixed with drug-soluble liquid to test drug snare proficiency. The mixture is then sonicated to break up the complex in the NSs and cause the drug to dissolve in a solvent. The drug concentration in the solvent is then measured using analytical techniques like UV-Vis spectroscopy and HPLC.[24]

$$\%\text{Drug Entrapment Efficiency} = \frac{\text{Drug (encapsulated)}}{\text{Drug (total)}} \times 100$$

8. Swelling and Water uptake

The produced nanosponges can be soaked in an aqueous solvent to measure the water uptake of swellable polymers such as polyamidoamine nanosponges. Equations used to calculate swelling and water uptake:

$$\%\text{Swelling} = \frac{\text{Marking of cylinder at a specified time point}}{\text{Initial marking before soaking}} \times 100$$

$$\%\text{water uptake} = \frac{\text{Mass of hydrogel after 72hrs}}{\text{Initial mass of dry polymer}} \times 100$$

9. Resiliency (Viscoelastic properties)

Sponge resilience can be adjusted to yield beadlets with varying firmness or softness based on the requirements of the finished product. The rate of release is generally slowed down by increased cross-linking. As a result, the study and optimization of the resilience of sponges will consider the release as a function of cross-linking over time.

10. In vitro release studies

A modified basket made of 5 m stainless steel mesh can be used with the dissolution equipment USP XXIII to study the dissolving profile of nanosponge. There is a 150-rpm rotational speed. To guarantee sink conditions, the dissolution medium is chosen while taking the actives' solubility into account. A suitable analytical technique can be used to examine samples from the dissolving medium. investigated using the USP xxiii dissolving apparatus with a modified basket made of 5 m stainless steel mesh. There is a 150-rpm rotational speed. To guarantee sink conditions, the dissolution medium is chosen with the actives' solubility in mind. An appropriate analytical technique can be used to examine samples from the dissolution medium.

11. Permeation studies

To investigate the dissolution release of nanosponge across a cellophane membrane, diffusion studies of the manufactured nanosponge can be conducted in a Franz diffusion cell. A 0.5g nanosponge sample can be placed on a cellophane membrane, and 250 ml of phosphate buffer (pH 7.4) was used as the dissolution medium for the diffusion tests, which were conducted at 37±1°C. Every one to eight hours, 5 ml of each sample can be taken out and replaced with an equivalent volume of brand-new dissolving medium.[30]

12. Thermo-analytical methods

Thermo-analytical techniques are utilized to ascertain if the drug material experiences any modifications before the thermal breakdown of the nanosponge. The changes in the thermogram are produced by DTA and DSC, such

as peaks becoming broader, moving, or disappearing altogether.[31]

13. X-ray diffractometry

One technique to detect inclusion complexation in the solid state is powder X-ray diffractometry. The drug's crystalline structure and diffraction patterns are altered by the complicated synthesis of the drug with nanosponges. A freshly created substance's diffraction pattern is different from an uncomplicated nanosponge's. The complex creation is shown by this discrepancy in the diffraction pattern. Peaks sharpening and the emergence of a few more peaks are visible during the complex's creation.[29]

14. Single crystal X-ray structure analysis

It is used to determine the detailed inclusion structure and mode of interaction. The interaction between the host and guest molecules can be identified and the precise geometrical relationship can be established.

15. Drug release kinetics

The release data might be analyzed using models such as Zero order, First order, Higuchi, Peppas, Hixon-Crowell, Kopcha, and Makoid-Banakar to study the mechanism of drug release from nanosponge. The software called Graph Pad Prism can be used to analyze the data. The program calculates the parameters of a non-linear function that fits experimental data and the non-linear function the closest.[26]

Application of nanosponges

1. Nanosponges for drug delivery

The ability of NSs to transport water-insoluble drugs is a result of their tiny porous structure. A drug's permeability, solubility, and rate of dissolution are all significantly increased by the NSs complex. It is possible to successfully administer drugs with solubility issues by infusing them into neural scaffolds. They are manufactured for topical, oral, and parent dosage forms and have a solid composition.[32]

2. Modulating drug release

NSs can alter the pace of drug release, which can be utilized to improve drug absorption via biological barriers and function as a strong drug carrier in formulations intended for instant release. Water soluble medications, such as peptide and protein medications, may be delivered over an extended period by hydrophobic CD NS. Moreover, medications can be transported by nanosponges, which can also shield the drug from stomach acid. i.e., the medicine releases more quickly at a pH of 7.4 than it does at a lower pH of 1.1.[33]

3. Oral delivery of drugs

Oral medication administration employing bio erodible polymers, enhance patient compliance by reducing toxicity and offering site-specific drug delivery systems and extending dosing intervals. The low solubility and limited dissolution rate of BCS class 2 medicines result in reduced bioavailability. But when made using nanosponges, they show improved solubilization effectiveness and the appropriate drug release properties.

4. Targeted site-specific drug delivery

Targeted drug delivery gives more beneficial and effective treatment at the same dose and with fewer side effects. Nanosponges can be used to encapsulate the anticancer medication. Compared to direct injection, the drug delivery method using nanosponges is three to five times more efficient. In this case, the nanosponges are either sucked into or attached to the tumor cells.

By creating a nanocarrier system, several antiviral agents can be given to patients, which helps to deliver more effectiveness than the other formulation. These nanocarriers are intended to target viruses that cause respiratory tract infections (RTIs), including rhinovirus, influenza virus, and respiratory sinurosis.[34]

5. Nanosponges for protein delivery

Proteins can be transported by being encapsulated or adsorbed in cyclodextrin nanosponges. Bovine serum albumin's protein solution is unstable, so it is stored in lyophilized form, which can later convert into a denatured state. Protein stability will be improved by nanosponges, which are also utilized for protein encapsulation, stabilization, enzyme immobilization, and controlled distribution.[32]

6. Topical delivery systems

A novel approach for the regulated release of topical medicines with delayed drug release and skin form retention is the delivery system of nanosponges. The active chemicals in conventional dermatological and personal-care products are usually present in quite high concentrations, and their duration of action is usually brief. As soon as the active substances reach the skin, rashes or more severe adverse effects may happen. This technique minimizes irritation while retaining effectiveness, enabling a consistent and steady rate of release. It is possible to include a wide range of substances in manufactured products including gel, lotion, cream, ointment, and powder.[34]

7. Nanosponges as a carrier for biocatalysts and in the Delivery and Release of enzymes, proteins, Vaccines and Antibodies

Protein molecules may bind to plasma proteins, be quickly removed from the circulation after intravenous injection, and be susceptible to proteolytic enzymes. The issue with oral administration is bioavailability. Proteins, enzymes, antibodies, and macromolecules may all be adsorbed onto cyclodextrin-based nanosponges, making them a very effective carrier. Enzymes in particular can be utilized to preserve their activity, and efficiency, and lengthen their operating range. They can also be employed to conduct continuous flow processes and expand their pH and temperature range of action.

Furthermore, cyclodextrin nanosponges can be used to encapsulate or adsorb proteins and other macromolecules for transportation.[33]

8. Combination therapy

Co-administration of two or more active molecules is known as combination therapy, and it is used to enhance the therapeutic response compared to single medication administration. This tactic is justified by the desire to take advantage of a synergistic effect. One medication can indeed influence the actions of another, leading to a therapeutic advantage. Co-formulations can also increase patient compliance, which lowers the need for repeated drug doses. One classic example of a drug combination is the co-administration of anti-cancer medications to improve the therapeutic index and combat multi-drug resistance in cancer treatment.

Tamoxifen and quercetin have been co-encapsulated using polyester nanosponges that have been synthesized. By adding the two-molecule solution to a pre-made nanosponge suspension, co-loading was achieved. On the 4T1 cell line, a synergistic anti-cancer impact was seen in vitro, with the combined drug's anti-cancer activity being higher than that of the drug alone.[35]

9. SARS-CoV-2 inhibition

Biocompatible nanomaterials are allowed to be used by the NS for the treatment and prevention of several serious illnesses, including the Zika virus, COVID-19, and SARS. The spike glycoprotein, a "S" protein (SARS-CoV-2) virus that promotes cellular contact and entry, is the cause of severe acute respiratory syndrome. It interacts with human angiotensin-converting enzyme two receptors as well as glycosaminoglycans like heparin. Polymeric cores wrapped in plasma membranes derived from human lung epithelial type II cells or macrophages were used to create ACE2-containing NS. Via native cellular receptors, cell membrane-coated nanoparticles (cellular NS) ensnare and neutralize SARS-CoV-2 by imitating host cells. This leads to an all-encompassing antiviral strategy.[36]

Other applications

1. Delivery system for oxygen.
2. To boost EVA combustion properties, by use of novel flame retardants containing cyclodextrin nanosponges and phosphorus compounds.
3. Use of nanosponges as a diagnostic tool.[24]
4. Nanosponges as a carrier for the delivery of gases.
5. Nanosponges as a protective agent against photodegradation.
6. Removal of organic pollutants from water.
7. Biomedical Applications
8. For Hydrogen Storage
9. In Agriculture, floriculture, and in food Industry
10. As Chemical Sensors.[26]
11. As absorbent in treating poison in blood.[32]

Nanosponges formulated as drugs for oral administration

Table 1: Nanosponges formulated as drugs for oral administration.

Sr. No.	Title of Work	Drug	Nanosponge Vehicle	Category	Dosage Form	Ref
1.	Formulation and Evaluation of Indomethacin Loaded Nanosponges for Oral Delivery.	Indomethacin	Ethyl cellulose and PVA	NSAID	Sustained release tablet	[37]
2.	Formulation and Evaluation of Lansoprazole Loaded Nanosponges	Lansoprazole	Ethyl cellulose and PVA	Proton pump inhibitor	Enteric-coated tablet	[38]
3.	Formulation and Evaluation of Cyclodextrin-based nanosponges of Griseofulvin as Pediatric Oral Liquid Dosage form for Enhancing Bioavailability and Masking bitter taste.	Griseofulvin	B-CD and diphenyl carbonate	Antifungal agent	Dry suspension (oral liquid dosage form)	[39]
4.	Formulation and Evaluation of Lamotrigine	Lamotrigine	Ethyl cellulose and PVA	Anti-epileptic drug	Immediate release tablet	[40]

	Loaded Nanosponges					
5.	Preparation and Characterization of a Novel Mucoadhesive Carvedilol Nanosponge: A Promising Platform for Buccal Anti-Hypertensive Delivery	Carvedilol	Bilosomes	3rd generation beta blocker, antihypertensive agent	Mucoadhesive buccal formulation	[41]

Marketed preparation[36]

Table 2*: *Marketed preparation.

Sr. No.	Drug	Composition	Trade Name	Dosage Form
1.	Piroxicam	Piroxicam and β-CD	Brexin	Capsule
2.	Dexamethasone	Dexamethasone and β CD	Glymesason	Tablet
3.	Iodine	Iodine and β CD	Mena-gargle	Solution
4.	Alprostadil	Prostaglandin E1 and α CD	Provastatin	Injection

CONCLUSION

The oral delivery system is considered to be the most promising administration route with numerous advantages and meets the need for self-administered drugs but solubility, targeted, sustained release, and increased bioavailability present the areas of difficulty in meeting the emerging value proposition. To address this, technologies such as nanosponges have been recognized as a delivery system to accumulate both hydrophilic and lipophilic drugs to deliver the drug in a controlled manner at a target site by forming a complex. Apart from improving the pharmacokinetic and pharmacodynamic properties of drug nanosponges also solves formulation-related problems such as improving solubility and stability. Nanosponge technology not only gained popularity due to its applications in the fields of medicine, agriculture, biomedical sciences, and engineering technology but also due to its rationale and simplicity of approach. As one of the NDDS nanosponge techniques is considered economical, reproducible, eco-friendly, and applicable for scale-up in a short time.

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