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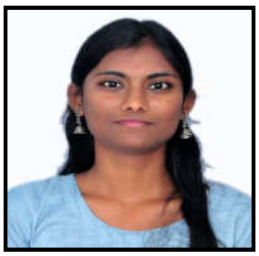

AN OUTLOOK TOWARDS NANOSPONGES: A PROPITIOUS NANOCARRIER FOR NOVEL DRUG DELIVERY

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ABSTRACT

The nanotechnology sector is regarded as a developing technology due to its capacity to improve the already existing items and create new ones for a range of uses. The primary drivers of this expansion are cyclodextrin-based porous nanoparticles or distinctive nanosponges, which have lately been applied in the pharmaceutical, biomedical, and cosmetic industries. This superior technology can circumvent the defects of current techniques through its ability to attack and visualize tumor sites. The organization of this review article is such that we first looked at the distinctive characteristics of these nanosponges and the various synthesizing techniques, then about the drug loading and release principle and applications based on drug delivery, targeting, increasing the solubility of BCS Class II and IV drugs, other applications in biomedicine, and more. The most recent developments on the employment of biomimetic nanosponge as a pandemic tool because of the SARS-CoV-2 virus briefly align. Due to several significant limitations, effective targeted drug delivery systems have long been an aspiration. These issues might be resolved by the creation of new colloidal carriers termed Nanosponges.

KEYWORDS

Nanosponges, Targeted drug delivery, SARS-CoV-2 and Nanotechnology.

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INTRODUCTON

The oral route is one of the main medication delivery methods, particularly for the treatment of numerous chronic disorders. Nonetheless, the high lipophilicity of 50% of the medicines is a significant barrier to oral administration. Class II and IV medications under the biopharmaceutical categorization system provide difficulty to formulators due to their low bioavailability, which is mainly brought about by poor water solubility and limited drug absorption. Several approaches, such as inclusion complexation, drug micronization, prodrug formation and solid dispersions, have been

used to address these issues. Formulators' interest in lipid-based drug delivery systems, such as self-nano emulsifying and self-microemulsifying drug delivery systems (SNEDDS and SMEDDS), has increased due to their capacity to improve solubility and bioavailability[1].

The "Nanosponge" technique delivers the drug payload using a nanoparticle-sized mechanism. “Nanosponges" were regarded as a significant invention in the field, representing versatile activities of cyclodextrin and anodic titanium dioxide (TiO_2) forming their layers to provide a base to deliver both hydrophilic and hydrophobic compounds. Nanosponges had provided excellence in forming the content with reduced side effects providing sufficiency in improving stability and formulation flexibility. Drugs are effectively delivered topically with nanosponges. Nanosponges embrace nanotechnology, which is used in pharmacy as nanomaterials, identifying and concentrating on the proper location in the body, and managing medication release. Nanosponges, which are supported by naturally biodegradable polyester, is about the size of a virus. The cross-linker molecules in the solution that the polyester streams provide the amount of bond in the nanometric form providing various spherical forms with pockets to contain the medicine to promote drug bonding.

Nanosponges is focused on developing solid-state batteries out of polymer or ceramic, with a sustained increase in energy costs and power consumption to provide an alternative energy source such as wind or solar power and their storage to improve the safety of electrolytes. The diameters of nanosponges in nanometric form alter pharmacokinetic parameters and increase drug bioavailability. Nanosponges have an average diameter of less than $1\mu m^2$.

A unique class of colloidal structures based on hyper-cross-linked polymers called nanosponges is made up of solid nanoparticles with colloidal and Nano-sized voids. Some well-known nanosponges include those made of titanium, silicon, cyclodextrin, and hyper-cross-linked polystyrene. By changing the pharmacokinetic properties of the active ingredients, nanosponges improve drug bioavailability by solubilizing weakly water-soluble medicines, enabling prolonged release. Due to their internal hydrophobic chamber and exterior hydrophilic branching, nanosponges are incredibly flexible and can load both hydrophilic and hydrophobic medicinal molecules. Nanospongesare made of a three-dimensional network or Scaffold[3].

The reaction, synthesis, and processing conditions largely determine nanosponges' crystalline and para-crystalline forms (200-300nm). The ability of nanosponges to crystallize can help in regulating and manage their ability to load drugs. For the creation of nanosponges, several methods have been developed, including the hot melting process, the interfacial phenomenon, hyper-cross-linked cyclodextrin, microwave (MW)-assisted synthesis, interfacial condensation, chemical synthesis, chain-growth poly-condensation, and emulsion solvent evaporation methods[4].

Nanosponges are tiny mesh-like structures (Figure No.1) in which a large variety of substances can be encapsulated. They have a proven spherical colloidal nature, reported to have a very high solubilization capacity for poorly soluble drugs by their inclusion and non-inclusion behavior (Figure No.2). Nanosponges have already been used in a variety of application domains, including the cosmetic and pharmaceutical industries, due to all these qualities. Nanosponges also have many advantages over other formulations, including predictable, prolonged, and controlled drug release, the potential to administer by many routes (parenteral, oral, inhalational, and topical), specific for targeting to required site, high pH and temperature stability and fewer risks of irritation, allergy, mutagenicity and toxicity. As a result, patient compliance and acceptance are increased. As a result, several researchers have studied Nanosponges and demonstrated the possibility of improving the solubility of the active molecules that are weakly soluble by formulation[5,6].

Advantages of nanosponges

Enhance the drug's low water solubility in an aqueous solution.

The nanosponges function as a self-sterilizer since bacteria cannot pass through their small (0.25m) pore size.

Nanosponges drug delivery systems are non-irritating, non-mutagenic, and non-toxic.

Nanosponges helps to remove toxic and venom substance from the body.
Reduce dosing frequency.
Nanosponges complexes are stable over a wide range of pH (i.e. 1- 11) and a temperature of 130°C.
These formulations are free-flowing and can be cost-effective.
Extended-release action of up to 12 hrs. Can be attained.
Regeneration of nanosponges can be done by washing with eco-compatible solvents, stripping with moderately inert hot gases, mild heating, and changing pH or ionic strength.
Less harmful side effects because the drug has less contact with healthy tissue[7,8].

COMPONENTS EMPLOYED IN THE FORMULATION OF NANOSPONGES

Many substances have produced promising results and can be utilized to create nanosponges, depending on the desired kind of Nanosponges and the required degree of crosslinking. Because of its impact on drug release patterns and drug encapsulation, the crosslinking amount is a crucial component of nanosponges and is dependent on cross-linker concentration. The following is a list of the substances that were employed in the preparation process (Table No.1).

FACTORS CONSIDERATION IN NANOSPONGE FORMATION

Polymer and cross-linkers

The performance of nanosponges as well as their formulation can be impacted by the kind of polymer utilized. A powerful cross-linker changes molecules into a three-dimensional nanoporous structure using nanocavities. Epichlorohydrin is used as a cross-linker to create hydrophilic nanosponges. Hydrophilic nanosponges act as effective drug carriers even in formulations for quick release by altering the pace of drug release and improving drug absorption across biological barriers. Diphenyl carbonate, pyromellitic anhydride, diisocyanates and carbonyl diimidazole can be used as crosslinkers to create hydrophobic nanosponges. They act as sustained-release carriers for peptide and protein pharmaceuticals, among other water-soluble medications.

Type of drug and medium used for interaction

Molecular weight of the drug must be between 100 and 400 Daltons and the drug molecule should consist of less than 5 condensed rings. Drug solubility in water must be less than 10mg/ml and the melting point of the substance should be below 250°C.

Complexation Temperature

Temperature variations affect a complex's stability constant. The relationship between the stability constant and temperature increase is inverse. The apparent stability constant's magnitude decreases with temperature due to weakening the forces that connect drugs and nanosponge molecules. As a result, when making nanosponges, the temperature should be carefully controlled.

Degree of Substitution

The polymeric molecule's amount, kind, and position of substituents has an impact on the ability of nanosponges to complexes. Because cyclodextrin derivatives come in a variety of forms with varying functional groups on their surface, it is crucial to consider the kind of substitution. Different functional groups produce various sorts of complex materials when they are complexed together with the aid of a crosslinker. The amount of crosslinking and the presence of substitutions are directly correlated; the more substitutions there are, the more likely it is that there will be more crosslinking. Increased crosslinking results in extremely porous nanosponges because more polymers are connected, creating a mesh-like network[8].

METHODS

Emulsion solvent diffusion method

Several ratios of ethyl cellulose and polyvinyl alcohol are used to create nanosponges. The drug and ethyl cellulose dispersion phase was dissolved in 20ml dichloromethane and slowly added to a predetermined quantity of polyvinyl alcohol in 150ml of an aqueous continuous phase. For two hours, the reaction mixture was agitated at a speed of 1000rpm. The generated nanosponges were collected by filtering and dried in an oven at 400^{o}C for 24 hours. To remove all remaining solvents, the dried nanosponges were kept in vacuum desiccators[12].

Quasi-emulsion solvent diffusion

The polymer is distributed in a suitable solvent during this procedure, and this phase is referred to as the inner phase. Drug and solution are combined during ultra-sonication at 35°C. The inner phase is then poured into the water and polyvinyl alcohol-containing outer phase. After that, a magnetic stirrer set at 1000rpm is used to agitate the suspension for 60 minutes. The created Nanosponges are then filtered and dried for two hours at 40^{o}C in a hot air oven[13].

Bubble electrospinning

A high-voltage source, a grounded collector, a syringe, and a syringe pump are the main components of a traditional and typical electrospinning arrangement. The amount of production of nanofibers is one of the main restrictions that restrict their applicability. Polyvinyl alcohol is an additional polymer that can be utilized in bubble electrospinning. It was organized into a polymer solution (10%) by adding distilled water. This solution was then heated to between 80^{o}C and 90°C for two hours to create a one-phase combination. The polymer solution was then allowed to reach room temperature before being employed to develop nonporous fibers[11].

Ultrasound-assisted synthesis

Uniformly sized nanosponges with a spherical shape are created using the ultrasound-assisted synthesis method[14]. Polymer is mixed with cross-linker in the balanced ratio in a flask Then the flask is placed in an ultrasound bath filled with water and the temperature is maintained at 900 ^{0}C.the mixture is sonicated for 5 hours. To remove non-reacted polymer, the product is washed with water and the product is purified with ethanol by soxhlet extraction and Allow the product is to be dried under vacuum at 25^{o}C[15].

Loading of nanosponges

Pretreatment of nanosponges is necessary to achieve a mean particle size of less than 500nm for drug delivery. To avoid the formation of aggregates, sonicate the nanosponges in water, then centrifuge the suspension to separate the colloidal fraction. Freeze-dry the sample after separating the supernatant. Make the nanosponge aqueous suspension, scatter any extra medication, and keep the suspension constantly stirred for the precise length of time needed for complexation. Following complexation, centrifuge the complexed medication to separate it from the uncomplexed (undissolved) drug. Then use solvent evaporation or freeze drying to produce the solid nanosponges crystals[16].

The crystal structure of the nanosponge is crucial for the drug complexation process. According to a study, paracrystalline nanosponges and crystalline nanosponges have distinct loading capabilities. Crystalline nanosponges have a higher drug loading than paracrystalline ones. Instead of an inclusion complex, drug loading happens mechanically in weakly crystalline nanosponges[17].

Characterization of the nanosponges

Polydispersity index and Particle size

The particle size can be estimated using dynamic light scattering, a Malvern Zeta sizer, a laser light diffractometer, or a 90 Plus particle sizer coupled with MAS OPTION particle sizing software. This allows for the calculation of the mean diameter and polydispersity index[16].

Surface topography and Morphology

Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) can be used to study the morphology and surface topography of the drug. The pellets are coated with, gold–palladium orplatinum- palladium in an argon atmosphere and examined under 15kV accelerated voltage. Under an electron microscope, the raw materials and the product's different crystallization states reveal the inclusion complexes' creation[16,18].

Fourier transmission infrared (FTIR) spectroscopy

The FTIR spectra of pure drug and loaded nanosponges can be carried out by diluting the sample with crystalline potassium bromide and pressing it into a transparent film. The film should be kept on the sample holder and recorded in the spectra[19].

Zeta potential

For zeta potential determination, samples of the nanosponge formulations should be diluted with 0.1M potassium chloride and placed in the electrophoretic cell, where an electric field of about 15V/cm is applied[20].

Loading efficiency and product yield

The equation given below can be utilized to determine the loading efficiency (%) of nanosponges

$$Loading\ efficiency = \frac{actual\ drug\ content\ in\ nanosponge}{theoretical\ drug\ content} * 100$$

After accurately establishing the raw materials' beginning weight and the nanosponge's end weight, the production yield may be estimated using the equation below[16].

$$Product\ yield\ (PY) = \frac{practical\ mass\ of\ nanosponge}{theoretical\ yield\ (\ polymer + drug)} * 100$$

X-ray diffractometry and single-crystal X-ray structure evaluation

Identifying inclusion complexation in the solid state is possible using powder X-ray diffractometry. The complicated drug synthesis in nanosponges modifies the drug's crystalline structure and diffraction patterns. The complicated development causes a few new peaks to arise, some old peaks to get sharper, and some summits to move. The complex creation is shown by this discrepancy in the diffraction pattern. It is necessary to compare the diffractograms of the supposed complex and the mechanical combination of the drug and polymer molecules when the drug compound is a solid entity. The chemical breakdown and complex creation of a combination of substances may be ascertained by looking at the diffraction peaks[21].

Resiliency

Depending on the requirements of the final formulation, the resilience of sponges can be altered to yield beadlets that are either softer or stiffer. The rate of release is typically slowed down by increased cross-linking. To study and improve sponge resilience, it will be necessary to consider how release changes as a function of cross-linking over time[17].

Drug release kinetics

By analyzing release data using models for zero order, first order, Higuchi, Korsemeyer-Peppas, Hixon Crowell, Kopcha, and Makoid-Banakar, as well as Kopcha and Kopcha-Hixon Crowell, it was possible to better understand how drugs are released from Nanosponges. The program determines the non-linear function's parameters based on which experimental results and the non-linear function are most closely matched[17].

***In vitro* Dissolution test**

The dissolving apparatus USP XXIII with a modified basket made of 5 m stainless steel mesh and a rotational speed of 150 rpm can be used to study the dissolution profile of nanosponges. To achieve sink conditions, the dissolving medium is chosen while considering the solubility of the actives. An appropriate analytical method can be used to examine samples from the dissolving media[16].

Application of Nanosponges in Healthcare and environment

Nanosponge for improved dissolution

Poorly soluble drugs can be added to nanosponges to make them more soluble in water by generating inclusion complexes. The entrapped drug is protected against precipitation and agglomeration by the limited solubility of Nanosponges, which prevents supersaturation in the surrounding fluid. The medication is integrated so that its hydrophobic properties occupy the cyclodextrin unit's hydrophobic interior chambers within the Nanosponges, while its hydrophilic groups attach to the hydrophilic external surface that is left exposed to the environment. The drug's crystallinity has decreased, and its thermodynamic energy has increased, according to the XRPD study of drug-loaded nanosponges. Enhancing medication solubility has the knock-on effect of increasing drug bioavailability. Vavia *et al*, successfully enhanced the solubility of Itraconazole by incorporating the drug into nanosponges. To compare the solubilization effectiveness of nanosponges, copolyvidonum, and a combination of the two, they conducted phase solubility studies. Due to an improvement in the drug's amorphous characteristic, Itraconazole's solubility was increased by more than 50 times with a ternary solid dispersion system and by nearly 20 times in nanosponges. Additionally, the success of this procedure has been established with the use of the medications Flurbiprofen, Doxorubicin, Dexamethasone, Tamoxifen, and Paclitaxel[22].

Nanosponges for stability enhancement of drug

Drug molecules can degrade in many ways when exposed to oxygen in the air, water, radiation, or heat. The molecule can be kept inside the nanosponges to avoid this degradation, which stops the reactants from diffusing into the cavity and reacting with the protected guest. Poor water solubility and a chemically brittle lactone ring characterize the anti-cancer drug Camptothecin (CAM). The cytotoxicity of CAM-NS was characterized, stabilized, and researched by Swaminathan *et al*, They discovered that the nanosponges structure's high inclusion abilities prevented the lactone ring from opening, increasing the drug's stability as well as delaying the release and boosting its cytotoxic potential[20]. Nolan et al. discovered that adding the anti-asthmatic and anti-allergic drug sodium cromoglicate to nanoporous nanoparticles/microparticles with sponge-like structures increased its stability[23].

Controlled and sustained release of the drug

There is a growing interest in creating controlled medication delivery systems to keep drugs. Levels below acceptable limits while still maintaining therapeutic efficacy. Controlling drug release predictably has never been easy. Due to less frequent administration, using such systems ensures optimal drug usage and patient compliance. The careful loading of active pharmaceutical ingredients into nanosponges guarantees controlled drug release. Cross-linking nanosponges create nano-cavities that could be loaded with drugs for slow, steady release. An anti-cancer drug called Doxorubicin's nanosponges have also been prepared, and a time-dependent drug delivery profile was obtained[24]. After 24 hours, CAM-loaded nanosponges made by Swaminathan *et al*, released 20% to about 25% of the drug, demonstrating a potent drug-nanosponges interaction. The drug was likely present as a non-inclusion complex in the exterior cavities, which caused the initial burst effect. After that, the drug release was virtually linear and persistent release profiles were subsequently noticed[23]. Nanosponges are promising drug delivery systems that offer controlled, sustained drug release.

Nanosponges as a carrier for biocatalysts and in the delivery and release of enzymes, proteins, vaccines, and antibodies

Numerous mechanisms for the transportation of enzymes and proteins including hydrogels, micro-, nanoparticles, and liposomes. Carriage in a certain system prevents the protein from degrading, alters the pharmacokinetics and increases *In vivo* studies. It has been found that cyclodextrin-based nanosponges are a very potent carrier for the adsorption of proteins, enzymes, antibodies, and macromolecules. It is feasible to sustain enzyme activity and efficiency, prolong operation, expand the pH and temperature range of action, and carry out continuous flow operations, especially when enzymes are utilized. Furthermore, proteins and other macromolecules can be carried by cyclodextrin nanosponges by adsorbing to or encasing them in them[24].

Absorbent in blood poisoning treatment

By integrating ovine erythrocyte vesicle and poly (d, l-lactic-co-glycolic acid) (PLGA) cores, researchers have created a Nanosponge. The lysis of streptolysin O was particularly susceptible to ovine erythrocytes. Streptolysin O, a recognized cholesterol-binding toxin at human body temperature, was adsorbed by ovine nanosponges, particularly in situations that resemble human sepsis[25].

Nanosponge that absorbs pore-forming toxins

A biomimetic poison nanosponge that serves as a toxin decoy in vivo was demonstrated by researchers. The red blood cell membranes that surround a polymeric nanoparticle core in the nanosponge absorb toxins that damage the membranes and direct them away from their intended cellular destinations[26].

Nanosponges as a Photo Degradation Protection Agent

According to Sapino *et al*, sunscreen is commonly used for gamma-oryzanol (a ferulic acid ester combination), an antioxidant often used to preserve food and pharmaceutical raw materials. Because of its high instability and photodegradation, its uses are limited. Gamma-oryzanol is used to create nanosponges, which exhibit good photodegradation resistance. A gel and an O/W emulsion were created using the gamma-oryzanol-loaded nanosponges[27].

Nanosponges against the SARS-CoV-2 virus

According to Rao *et al*, a potent two-step neutralization strategy against COVID-19 based on a decoy nanoparticle includes neutralizing SARS-CoV-2 first, then neutralizing cytokines. By fighting with host cells for virus binding, these nanosponges effectively shield them from SARS-CoV-2 infection. With the addition of these nanosponges, interactions between the SARS-CoV-2 S protein complex and human ACE2 were reduced, and viral receptors on the nanosponges showed a high affinity for binding to ACE2[28]. Zhang Q *et al*, reported that the cellular nanosponges were a powerful medicinal defense against the SARS-CoV-2 virus. Plasma membranes from human macrophages or type II lung epithelial cells were used to create two forms of cellular nanosponges. These nanosponges exhibited the identical protein receptors both known and unknown needed by SARS-CoV-2 to enter cells. It is demonstrated that SARS-CoV-2 is neutralized and unable to infect cells after being incubated with the nanosponges[29].

The nanosponge platform is crucially insensitive to viral alterations and prospective viral species. The nanosponges will be able to kill the virus as long as the identified host cell of the virus's target[29]. To identify IgG and IgM antibodies in cases of SARS-CoV-2 with the shortest possible diagnostic time, i.e., less than 10 min, gold nanoparticles (AuNPs) were produced. Nevertheless, this resulted in sample deterioration[14].

Nanosponges for topical applications

A novel method for the controlled release of topical agents of prolonged drug release and retention of drug form on the skin is the nanosponge delivery system. Traditional dermatological and personal-care treatments frequently offer active substances in relatively high concentrations but with a limited period of action. This could result in a vicious cycle of short-term overmedication and long-term under medication. When active substances enter the skin, rashes or more severe adverse effects may develop. This technique, in contrast, enables a consistent and prolonged rate of release, minimizing discomfort while preserving effectiveness. An array of ingredients, including gel, lotion, cream, ointment, liquid, and powder, can be included in a manufactured product[30].

Other Applications of Nanosponges

It is possible to attribute the capacity to entrap organic molecules to the pores created by the polymerization step, the cyclodextrin (CD) cavities, and the swelling characteristic of water absorption. The fractionalization of peptides for proteomic applications requires the use of three-dimensional nanosponges. Several biomedical applications might benefit from the usage of nanosponges, which can transport gases like oxygen and carbon dioxide. Further to conveying fluorescent dyes and other substances, nanosponges may be utilized to selectively absorb biomarkers for the diagnosis of various illness states[31]. Salazar S *et al*, found that Magnetic nanosponges ultimately may become an improved technology for the removal of neonicotinoids from aquatic environments because they are efficient, economic, non-toxic, and reusable materials[32].

Table No.1: Various polymers used in nanosponge formulation[9-11]

S.No	Polymer	Copolymers	Crosslinkers
1	Hyper cross-linked styrenes. Cyclodextrins derivatives like Methyl β-Cyclodextrin, Hydroxy Propyl, β-Cyclodextrins Alkyloxy carbonyl Cyclodextrins Eudragit RS100 Acrylic Polymer Poly-Valerolactone	Poly (valerolactone allylvalerolactone), Poly (valerolactone-allylvalerolactone oxepanedione), Ethyl Cellulose, Polyvinyl alcohol	Carbonyl diimidazoles, Carboxylic acid, Dianhydrides, Diarylcarbonates, Dichloromethane, Diisocyanates, Glutaraldehyde, Diarylcarbonates Diisocyanates Pyromellitic anhydride Carbonyldiimidazole Diphenhydramine Pyrometallic anhydride Diphenyl carbonate

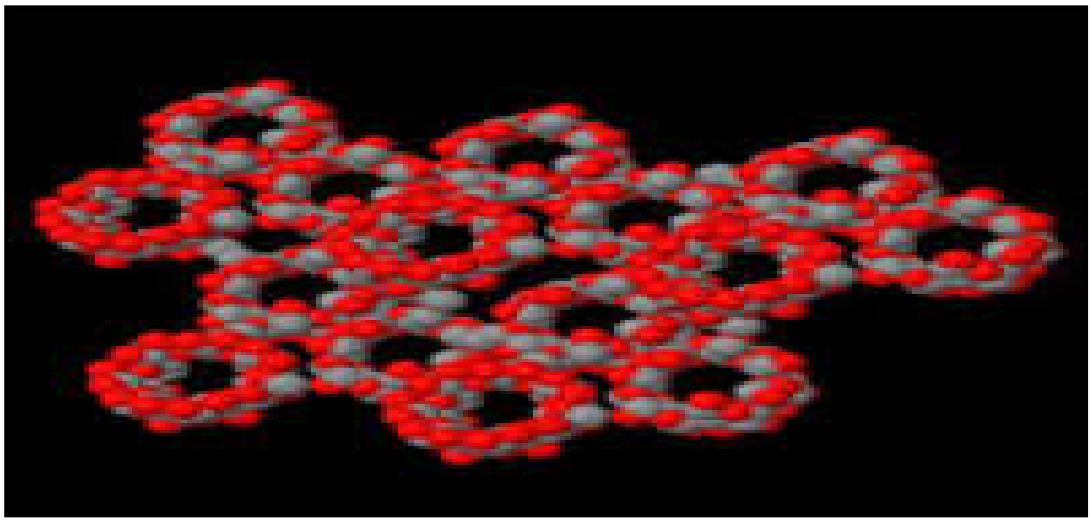

Figure No.1: Molecular structure of cyclodextrin carbonates nanosponges

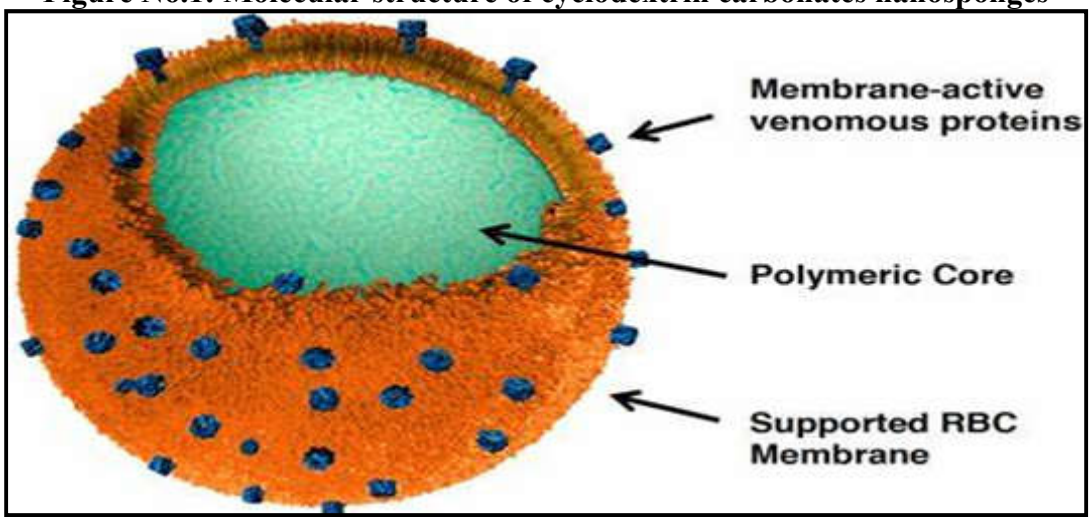

Figure No.2: Structure of nanosponge

CONCLUSION

By producing inclusion and non-inclusion complexes, nanosponges are a unique family of biocompatible, multifunctional drug delivery systems that can transport hydrophilic and hydrophobic medicines. They use a variety of ways to administer the medications, including parenteral, topical, and oral. Nanosponges boost the drug's bioavailability by releasing the medication to the target location in a regulated and predictable way. Apart from the field of drug delivery, prospective uses include those in the fields of cosmetics, biomedicine, bioremediation techniques, agro chemistry, catalysis, etc. Clinical investigations that show the drugs delivered by nanosponges have the potential to be used in humans will be very beneficial to pharmaceutical businesses[2,7]. Several different nanosponges-based medication types are already on the market and many more are undergoing clinical testing. Moreover, nanosponges are employed in bio-sensing to efficiently detect a variety of illness indicators. Using nanosponges, SARS Cov-2 management was. As a result, nanosponges play a significant part in the positive effects on human health and the environment.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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