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NANOSPONGES: AN EMERGING APPROACH FOR CONTROLLED AND SUSTAINED DRUG DELIVERY

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Abstract:
Nanosponges are novel nanoporous drug delivery systems designed to improve the therapeutic efficacy, stability, and controlled release of pharmaceutical agents. These tiny sponge-like structures possess nanosized cavities capable of encapsulating both hydrophilic and lipophilic drugs. Nanosponges are generally prepared using biodegradable polymers and cross-linkers, resulting in a three-dimensional porous network that enhances drug solubility, bioavailability, and targeted delivery. They provide prolonged and controlled drug release, reduce dosing frequency, minimize side effects, and protect unstable drugs from degradation. Various preparation methods such as solvent method, ultrasound-assisted synthesis, and drug loading techniques are employed for nanosponge formulation. Characterization of nanosponges includes particle size analysis, zeta potential, microscopy, thermal analysis, solubility studies, and drug loading efficiency. Nanosponges have shown promising applications in oral, topical, parenteral, pulmonary, antiviral, anticancer, and protein delivery systems. They are also useful in enzyme immobilization, oxygen delivery, and SARS-CoV-2 management. Due to their nanoscale porous structure, high stability, biocompatibility, and controlled release properties, nanosponges represent an advanced and versatile approach in modern pharmaceutical drug delivery systems. Their ability to enhance solubility and site-specific delivery makes them highly valuable for future therapeutic applications.

***Keywords**: Nanosponges, Novel drug delivery system, Controlled drug release, Targeted drug delivery, Cyclodextrin nanosponges.*

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INTRODUCTION:

Targeting the shipping of medication has lengthy been a trouble for clinical researchers - a way to get them to the proper vicinity with inside the frame and a way to manipulate the discharge of the drug to save you overdoses. The traits of latest and complicated molecules referred to as Nanosponges have the capability to remedy those problems (Himangshu *et al*., 2018). Nanosponge is a contemporary-day class of cloth and is made of tiny debris with a slender hollow space of few manometers. These slender cavities may be packed with diverse styles of materials. These tiny debris are having a functionality because of which it may bring each hydrophilic and lipophilic drug substance and might boom the steadiness of poorly water-soluble drug substance or molecules. Nanosponges are a brand new elegance of substances and made from microscopic debris with few nanometres extensive cavities, wherein a big kind of materials may be encapsulated. These debris are able to sporting each lipophilic and hydrophilic materials and of enhancing the solubility of poorly water soluble molecules . Nanosponges are tiny mesh-like systems that can revolutionise the remedy of many sicknesses and early trials endorse this era much as 5 instances extra powerful at turning in pills for breast most cancers than traditional methods (Selvamuthukumar *et al*., 2012). The Nanosponges are a three-D scaffold (backbone) or community of polyester which can be able to degrading naturally. These polyesters are combined with a cross linker in a method to form Nanosponges. Here, the polyester is typically biodegradable, so it breaks down with inside the frame moderately.The fundamental trouble with many newly advanced chemical entities is their negative water solubility and pharmacokinetic issues. These poorly water-soluble pills display many issues in formulating them in traditional dosage bureaucracy and the vital trouble related is its very low bioavailability . In recent years Nanosponges have Rece Nanotechnology. These Nanosponges are able to supplying answers for numerous components associated issues (Nagulapati *et al*., 2021).

Nanosponges

Nano sponges are tiny sponges with a length of approximately a virus (250nm-1um), which includes cavities that could be packed with an extensive kind of drugs. The sponge acts as a 3 dimensional community of scaffold, which consist of the returned bone called lengthy period polyester. It is jumbled together answer with cross-linkers to shape the polymer. Targeting the drug shipping has lengthy been a trouble for clinical researchers a way to get them to the proper place withinside the frame and a way to manage the discharge of the drug to save you over dose. The improvement of recent and complicated molecules known as nanosponges has the capacity to clear up those problems. Nanosponge is a unique and rising era which play a essential position in focused on drug shipping in a managed manner (Salman and Thabitha, 2017).

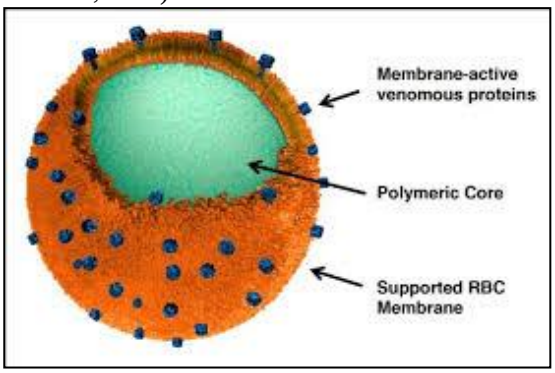

Figure: Structure of Nanosponges

Mechanism of drug release from nanosponges:

The sponge debris have an open shape and the energetic drug moiety movements inside and outside from the sponge debris into the automobile till equilibrium is retained. In case of topical delivery, as soon as the completed dosage shape is carried out directly to the pores and skin, the energetic drug that's already gift withinside the automobile could be absorbed into the pores and skin, depleting the automobile, which turnsinto unsaturated subsequently stressful the equilibrium. This will begin a glide of the energetic drug from the sponge debris into the automobile and from it into the pores and skin till the automobile is both dried or absorbed (Jassal and Jyotsana, 2015).

Method of preparation of nanosponges :

- **Solvent method:**

  The solvent required can be blend with the polymer especially in a polar aprotic solvent for example dimethyl formamide, dimethyl sulfoxide then upload this aggregate to move linker in a exceed quantity, the ratio for move linker/ molar ratio is favoured as four to (Trotta and Cavalli, 2009). The response is continued with a solvent reflux temperature and time starting from 1 to forty-eight hr. The move linkers which might also additionally preferred are dimethyl carbonate and carbonyl diimidazole. In this approach a appropriate solvent is blended with the polymer, particularly in a polar aprotic solvent including dimethylsulfoxide, dimethylformamide. Above aggregate is value-brought to extra amount of crosslinker, preferably in crosslinker/polymer molar quantitative relation of 4 to sixteen. To preserve out the response the temperature have to be starting from ten C to refluxtemperature of the solvent, from time beginning from one to 48 h.

- **Ultrasound-assisted synthesis:**
  Nanosponges are received through reacting the polymer with move linkers without including or without the use of solvent and sonification is maintained. The length received through this method will be round and uniform (Vishwakarma *et al*., 2013).
  Nanosponge is made with the aid of using reacting polymers with cross-linkers withinside the absence of solvent and beneathneath sonication in this process.This method will produce round and uniformly sized nanosponges. At a flask, integrate the polymer and cross-linker in a particular molar ratio. Heat the flask to 900 °c in an ultrasonic tubtub packed with water. For five hours, sonicate the combination. Allow the combination to chill earliepolymer, then purify with ethanol after an extended soxhlet extraction. Dry the finished product beneathneath vacuum and maintain it at 250°C till needed (Shaikh *et al*., 2021).
  In ultrasound-assisted synthesis, polymers blend with cross-linkers in absence of solvent in a flask and location the flask in ultrasound tubtub discipline with water and warmth it for 90oC and sonicate for five hours. Allow aggregate to cool and damage the aggregate roughly. Wash the aggregate with water to eliminate the unreacted polymer. Purify by extended soxhlet extraction with ethanol and dry the product below vacuum and saved at 25oC till similarly use (Trotta and Cavalli, 2009).

- **Loading of the drug into nanosponges:**
  The nanosponges formulated for the drug transport to start with have to be pretreated to reap a median particle length below 500nm. The nanosponges are then suspended in water for a while and subjected to sonication for you to keep away from the formation of aggregates. The acquired product suspension is subjected to centrifugation to reap a colloidal fraction. The acquired product supernantant is separated and pattern is dried via way of means of freeze drying. In different manner a nanosponge aqeous suspension is ready and dispersed it with consistent stirring for a selected period of time (Ravi *et al*., 2019).
  Nanosponges received must be pretreated to hold the suggested particle length below 500nm.Para-crystalline nanosponges found special loading capacities whilst as compared to crystalline nanosponges poorly crystalline nanosponges had act drug loading as a mechanical aggregate as an alternative then inclusion complex.

Advantages of nanosponges:

- Increase the aqueous solubility of the lipophilic drugs.
- Protects degradable drugs.
- Reduce dosing frequency.
- They are non-irritating, non-mutagenic and non-toxic.
- Efficient entrapment of components and decreased aspect effects (Nagulapati *et al*., 2021).
- Improved stability, elevated beauty and superior system flexibility.
- These formulations are strong as much as a temperature of 130°c.
- These formulations are well matched with maximum automobiles and components (Ravi *et al*., 2019).

Disadvantages of nanosponges:

- Nanosponges have the capability of encapsulating small molecules, now no longer appropriate for large molecules.
- Dose dumping may also arise at times.
- Nanosponges consist of the most effective small molecules.
- Depend most effective upon loading capacities.
- Nanosponges may be paracrystalline or crystalline in nature (Ajay *et al*., 2013).

Characterization of Nanosponges:

Thermoanalytical methods:

It displays the adjustments arise in drug substance earlier than present process thermal degradation of nanosponges. DTA and DSC determined for broadening, moving and look of new peaks. If adjustments in weight reduction happens can offer proof for formation of inclusion complexes. The thermogram received by DTA and DSC may be located for broadening, transferring and look of latest peaks or disappearance of sure peak (Lala *et al*., 2011).

Microscopy research:

The morphology and floor topography of the drug, nanosponges and the product (drug/nanosponge complicated) may be studied through Scanning electron microscopy and transmission electron microscopy. The distinction in crystallization kingdom of the uncooked substances and the product determined below electron microscope suggests the complicated formation. The distinction in crystallization nation of the uncooked substances and the product visible below electron microscope shows the formation of the inclusion complexes (Trotta *et al*., 2007).

Solubility research: It isthe maximum broadly used method to look at inclusion complicated and specifically defined through Higuchi and Connor's equation for section solubility and enables in study the impact on solubility of drug through Nanosponge. The maximum extensively used

method to look at inclusion complexation is the segment solubility method defined via way of means of Higuchi and Connors, which examines the impact of a nanosponge, at the solubility of drug. Phase solubility diagrams suggest the diploma of complexation (Ajay *et al*., 2013).

IR spectroscopy:

It is used to estimate interplay among nanosponges and drug molecule in stable Kingdom. It regularly adjustments upon complicated formation and if small fraction of molecule is encapsulated in complicated much less then 25 percentage band and assigned to consist of a part of different molecule that are marked through bands of spectrum of nanosponges. It is used to estimate the interplay between nanosponges and the drug molecules withinside the solid state. Nanosponge bands frequently alternate simplest slightly upon complicated formation and if the fraction of the visitor molecules encapsulated withinside the complicated is much less than 25%, bands which may be assigned to the covered a part of the visitor molecules are easily masked through the bands of the spectrum of nanosponges. The method isn't always usually appropriate to locate the inclusion complexes and is much less clarifying than other methods (Sailaja *et al*., 2021).

X-ray diffractometry:

Powder x-ray diffractometry used to locate inclusion complicated in stable kingdom. If we remember liquid, then it has no diffraction sample in their personal and definitely differs from incomplexed Nanosponge. If drug is a stable substance evaluation ought to be made among diffractogram of assumed complicated and mechanical aggregate of dry and it alters diffraction patterns. A diffraction sample of a bodily aggregate outcomes from mixture of two components. But complexes having diffraction sample specifically differs from the constituent they comprise and deliver upward push to "new" stable section having exclusive diffractogram. They deliver upward push to exclusive peaks for an aggregate and beneficial in figuring out chemical decomposition and complicated formation. -Single crystal X-ray shape analysis. The complicated formation of drug with nanosponges alters the diffraction styles and additionally adjustments the crystalline nature of the drug. The complicated formation ends in the sprucing of the present peaks, look of some new peaks and moving of certain peaks.

Loading performance:

It describes the performance or decided through quantitative estimation of drug loaded into nanosponges through UV spectrophotometer & HPLC methods.

Zeta potential:

Its degree floor price and through including a electrode it could be measured in particle length equipment. Zeta capacity of any gadget beneathneath research is a degree of the floor price. Surface price is the parameter that influences frame distribution and interplay with the organic environment.

Zeta capacity size includes attention of the electric powered capacity, i.e., diffusion coefficient and electrophoretic mobility. It may be measured via way of means of using extra electrode withinside the particle length equipment (Trotta *et al*., 2007).

Application of nanosponges:

Long-term delivery system:

One of the most often utilised antiviral medications for the treatment of herpes simplex virus infection is acyclovir. Its digestion by the gastrointestinal tract occurs slowly, insufficiently, and with great variability. The acyclovir in vitro release profile from several nano sponge types demonstrated prolonged drug release. After 3 h of treatment, carb-nanosponges and nanosponges released acyclovir in amounts of around 22 % and 70 %, respectively. Since there was no first burst effect seen, the medication was not adsorbed on the surface of the nanosponges (Ansari *et al*., 2011; Lembo *et al*., 2013).

Solubility enhancement:

Itraconazole is a Biopharmaceutics Classification System (BCS) class II medication with low bioavailability and a dissolving rate restriction. Thus, the use of nanosponges increased the drug's solubility by a factor of over 27. When copolyvidonum was introduced as a supporting component, the solubility was shown to be 55 times greater. Nanosponges increase the medication's solubility by either disguising the hydrophobic groups of itraconazole, enhancing the drug's wetting ability, or reducing the crystallinity of the drug (Mognetti *et al*., 2012).

Drug delivery:

Nanosponges are excellent for carrying medications that are not soluble in water due to their nanoporous nature (BCS class-II drugs). These complexes can be used to hide disagreeable odours, turn liquid substances into solids, and enhance the pace, solubility, and stability of medication dissolution. Compared to direct injection, cyclodextrin-based nanosponges are said to transport the medication to the target spot three to five times more efficiently (David, 2010). By loading into the nanosponges, medications that are particularly important for formulation in terms of their solubility may be properly supplied.

The nanosponges can be made into dosage forms for oral, parenteral, topical, or inhalation use. They are solid by nature. The complexes may be disseminated in a matrix of excipients, diluents, lubricants and anticaking agents appropriate for the manufacture of capsules or tablets for oral delivery (Alongi *et al*., 2011). The compound can easily be transported in sterile water, saline, or other aqueous

solutions for parenteral administration. They can be successfully integrated into topical hydrogel for topical delivery (Sharma and Pathak, 2011).

Enzyme immobilization:

The enzyme has frequently been stabilised using nanosponges. When compared to cyclodextrin, Cyclodextrin Nanosponge (CD-NS) exhibits substantially higher inclusion constants and is an appropriate support for enzyme immobilisation. They aid in maintaining the stability and catalytic efficiency of the immobilised enzymes. Enzyme immobilisation is crucial for enzyme recycling and makes it easier to separate and recover the generated products. It also increases the biocatalysts' thermal and operational stability. The high catalytic activity of various lipases from *Pseudomonas flurescens* adsorbed on cyclodextrin-based nanosponge was also examined by Boscolo *et al*.. Numerous industrial applications include the hydrolysis of triacylglucerols and trans esterification processes, both of which are catalysed by lipases (Boscolo *et al.*, 2010).

Protein delivery:

The preservation of the original protein structure during the formulation process and during longterm storage represents a significant hurdle in the creation of protein formulations. Swaminathan *et al*. explored novel swellable poly nanosponges based on cyclodextrin. They discovered very strong swelling capacity that remained steady for 72 h through research on water intake. As a model protein, bovine serum albumin was employed and it was integrated into the finished nanosponge. Protein stability was raised and its enhanced swelling property was seen. The lactone ring opens up and transforms into an inactive carboxylate form at physiological pH. Camptothecin is fused in nanosponges, resulting in a longer release profile in an active state that prevents the hydrolysis of the lactone form and leads to increased stability (Swaminathan *et al*., 2010).

Protective agent from light or degradation:

It is possible to encapsulate gamma-oryzanol in the form of a nanosponge, which exhibits good photo-degradation protection. Gamma oryzanol is a naturally occurring antioxidant and ferulic acid combination that is primarily utilised to stabilise food and pharmaceutical raw materials. Due to its high instability and photogegradation, its applicability is restricted (Minelli *et al*., 2012).

Carrier for biocatalyst:

The biological and therapeutic fields can also make use of proteins, peptides, enzymes and their derivatives. While DNA and oligonucleotides are utilised in gene therapy, proteolytic enzymes can be employed to treat cancer or type I mucopolysaccharidosis. These molecules' administration comes with a number of drawbacks and issues. Because of their large molecular size, hydrophilic nature, degree of ionisation, high surface charge, chemical and enzymatic instability and limited permeability across mucous membranes, the majority of protein medicines are poorly absorbed through biological membranes. Protein molecules may be quickly removed from the blood after IV delivery, bind to plasma proteins and be vulnerable to proteolytic enzymes. The issue with oral administration is bioavailability. There are other methods for therapeutic usage, such raising the dosage or utilising absorption boosters, which may result in toxicity issues. There are several mechanisms for transporting enzymes and proteins, including hydrogels, nano and microparticles, and liposomes. Carriage in a certain system can alter the pharmacokinetics of proteins, prevent them from degrading, and increase their *in vivo* stability. Cyclodextrinbased nanosponges have now been discovered to be a very effective carrier for the adsorption of proteins, enzymes, antibodies and macromolecules. It is possible to maintain enzyme activity and efficiency, prolong operation, increase the pH and temperature range of activity, and perform continuous flow operations, in particular when enzymes are utilised. Additionally, by adsorbing or encapsulating proteins and other macromolecules in CD-NS, they can be transported (Selvamuthukumar *et al*., 2012).

Gas delivery system:

Hypoxia, the lack of a sufficient oxygen supply, is linked to a number of diseases, including cancer and inflammatory diseases. A nanosponge formulation for topical oxygen delivery was created by Cavalli *et al.* In vero cells, the safety of nanosponge was investigated. Using a CD-NS hydrogel combination technology, oxygen penetration across a silicone membrane was investigated. For the encapsulation of 1-methylcyclopropene, oxygen, and carbon dioxide, Scientist described the preparation of CDNS utilising carbonildiimidazole cross-linker (Lee *et al*., 2011).

Cancer therapy:

The distribution of anticancer drugs is now one of the most difficult tasks in the pharmaceutical industry because of their poor solubility. According to one report, direct injection is three times less efficient than nanosponge's complex at slowing tumour development. The complex of the nanosponge loads a medication and exposes a targeting peptide that adheres firmly to the tumour receptor's top layer of radiation-induced cells. When nanosponges come into contact with a tumour cell, they adhere to its surface and begin to release medication molecules. Targeting medication delivery has the benefit of achieving a more potent therapeutic impact at a lower dose and with fewer adverse effects (Bhowmik *et al*., 2018).

Oral delivery:

For oral delivery as capsules or tablets, the complex can be disseminated in a matrix comprising diluents, excipients, lubricants and anti-caking agents. Nanosponges can increase the wetting and solubility of molecules that have low water solubility. The medications may be molecularly disseminated inside the nanosponge structure and subsequently released as molecules, eliminating the need for disintegration. As a result, the drug's perceived solubility can be boosted. Many formulation and bioavailability issues may be overcome by increasing a substance's solubility and dissolving rate, and nanosponges can significantly increase medication solubility. BCS class II medicines have relatively poor solubility and are thus great candidates for nanosponges (Ghurghure *et al*., 2018). To produce nanosponges for use in an oral medication administration system, acetyl salicylic acid, a Nonsteroidal Anti-Inflammatory Drug (NSAID) classed as a BCS class II agent, was utilised. When taken orally, it creates a nanosponge system with holes that speed up the solubilization of medications with low water solubility by trapping them in the pores (Vyas and Saraf, 2008).

Topical delivery:

Topically, nanosponge components can be administered in the form of a gel or cream. Resveratrol-loaded nanosponges were thought to improve drug penetration on pig skin *in vitro*. The capacity of nanosponges to boost solubility at the skin's surface may also be linked to their ability to improve guest molecule absorption by the skin (Shah *et al*., 2021).

Chemical sensors:

Titanium nanosponges, a particular kind of "metal oxides," are utilised in the very sensitive detection of hydrogen as chemical sensors. Since there is initially no point of contact, there is less resistance to electron transport, which leads to a greater level of 3D interconnect and more sensitive nanosponge materials to H_2 gas (Kfoury *et al*., 2018).

Antiviral application:

Nanosponges are administered via the nasal and pulmonary routes. It offers selectivity to target viruses that may cause respiratory tract infection, such as influenzavirus and rhinovirus and deliver antiviral drugs on Ribonucleic Acid (RNA) to the lungs or nasal pathway using nanocarriers. Zidovudine and Saquinavir are two medications utilised as nanocarriers (D'Emanuele and Dinarvand, 1995).

Oxygen delivery system:

Oxygen delivery system characterised using cyclodextrins of the molecular weights alpha, beta, and gamma that are suspended in water and become saturated with water. With the aid of a nanosponge/ hydrogel combination, a silicone membrane may likewise be employed to let oxygen through (Alfred *et al*., 1983).

SARS-CoV-2 Management:

Nanosponges made from human macrophages or lung type II epithelial cells are a sufficient attractant for the SARS-CoV-2 virus and may be eliminated after capture. As a result, it was employed to create SARS-CoV-2 preventive strategies. The researchers created two types of cellular nanosponges based on the existing structure of SARS-CoV-2; human lung epithelial type II cell Nanosponge (epithelial-NS) and human Macrophage Nanosponge (M-NS). Nanosponges carried the same receptors on which viruses rely for entrance and it was hypothesised that after interacting with these nanosponges, the viruses would be unable to enter the cell (Tharayil *et al*., 2021).

Factors Affeting Formulation of Nanosponge

Degree of substitution:

The complexation ability of the nanosponge may be strongly influenced by the kind, quantity, and location of the substituent on the parent molecule (Challa *et al*., 2005).

Method of preparation:

The complexation may be impacted by the drug's loading into the nanosponge formulation. The complexation may be impacted by the type of the medication and polymer. Freeze drying has proven to be a more productive approach for pharmacological complexation in many instances (Sinha *et al*., 2005).

Temperature:

Drug complexation may be impacted by temperature changes. Due to a potential reduction in drug nanosponge contact forces, van der waals forces, and hydrophobic forces with rising temperature, the apparent stability of the nanosponge complex diminishes with temperature.

Type of drug:

The following qualities for drug compounds that will be complexed with nanosponges should be present. Water solubility should be less than 10 mg/ml. No more than five condensed rings should be present in the medication molecule structure. Less than 250° should be the melting point. 100 to 400 Da is the required molecular weight range (Vyas *et al*., 2008).

Type of polymer and crosslinkers:

The choice of an appropriate polymer affects both the production and performance of nanosponge. The nanosponge's cavity or pore size should be able to fit a medication molecule of the appropriate size (Sherje *et al*., 2017). Crosslinkers aid in the formation of a 3D structure of nanosponges. The amount of crosslinker utilized affects drug entrapment as well as organ targetin (Tiwari and Bhattacharya, 2022). The crosslinker utilised determines whether the nanosponge is soluble in

water or any other solvent. Epichlorohydrin will be used as a crosslinker to create hydrophilic nanosponges. The benefit of utilising hydrophilic nanosponges in drug delivery is that it enhances drug absorption across biological membranes and is a valuable transporter for pharmaceuticals in order to produce quick release formulations (Shivani and Poladi, 2015; Shringirishi *et al*., 2014).

CONCLUSION:

Novel drug delivery systems are being researched extensively, with nanosponges being one of the most successful, as they may carry either lipophilic or hydrophilic drugs and release them at the target location in a controlled and predictable manner. The particle size and release rate may be controlled by adjusting the polymer-to-crosslinker ratio. Nanosponges facilitate the release of insoluble medicines while protecting the active moieties from physicochemical degradation. They are built on Nano, polymer-based spheres that may suspend or entrap a wide range of chemicals before being mixed into a prepared product such as a gel, lotions, cream, ointments, liquid, or powder. This method allows for the trapping of substances, resulting in fewer adverse effects, higher stability, increased elegance, and increased formulation flexibility. Nanosponges can be effectively incorporated into topical drug delivery systems for dosage form retention on skin, as well as used for oral drug delivery using bio erodible polymers, particularly for colon specific delivery and controlled release drug delivery systems, thus improving patient compliance by providing site specific drug delivery systems and prolonging dosage intervals.

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