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NANO SPONGES - A NOVEL TOOL FOR DRUG DELIVERY SYSTEM

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Abstract:

The progress made in the field of nanotechnology has led to the emergence of targeted drug delivery systems. However, the successful targeting of a molecule to a specific place requires the utilisation of a sophisticated drug delivery system. The identification of nanosponges represents a notable advancement in addressing specific challenges such medication toxicity, limited bioavailability, and controlled drug release, owing to their capacity to accommodate drugs in both hydrophilic and hydrophobic phases. Nanosponges possess an inherent porosity structure that exhibits a distinctive capability to encapsulate drug moieties, hence providing the advantage of controlled release. Nanosponges refer to minuscule sponge-like structures capable of traversing the human body and adhering to the drug's surface, so facilitating a regulated and predictable release. The formulation of these compounds can be achieved through the utilization of cyclo dextrin polymer in combination with crosslinkers. Extensive research has been conducted on the use of nano sponges in various drug delivery methods, including topical, oral, and parental administrations. In addition to their primary applications, nanosponges have demonstrated potential as carriers for various bioactive substances such as enzymes, proteins, vaccines, and antibodies. The present study centres on the preparation, characterization, and possible applications within the realm of drug delivery systems.

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INTRODUCTION:

Targeted drug delivery has emerged as a significant challenge for researchers in contemporary times. The implementation of target-oriented medication administration has been associated with advancements in therapeutic efficacy, decreased occurrence of adverse effects, and the optimisation of dose regimens. The development of efficient targeted drug delivery systems has long been a sought-after goal. However, progress in this field has been hindered by the intricate chemistry associated with the creation of novel systems. The issue of drug delivery targeting has been a longstanding challenge for medical researchers, encompassing the effective transportation of drugs to specific locations inside the body and the regulation of drug release to mitigate the risk of overdosing. The potential resolution of this issue lies in the advancement of a novel and intricate molecular entity known as Nanosponges. Nanosponges are a novel category of diminutive sponge-like structures, comparable in size to viruses. These nanosponges are designed to encapsulate drugs within their structure, while concurrently affixing specialised chemical "linkers" to facilitate attachment. The aforementioned minuscule sponges exhibit a circulating behaviour inside the human body until they come into contact with the surface of a tumour cell or a specific cell of interest. At this point, they adhere to the cell surface and initiate the controlled and predictable release of a highly effective medicine. Nano sponges can be described as delivery systems with a three-dimensional network or scaffold structure. Nanosponges consist of diminutive particles characterized by voids that are only a few nanometers in size, enabling the encapsulation of a diverse array of compounds. These particles possess the capacity to facilitate the transportation of both hydrophilic and lipophilic substances, while also enhancing the solubility of molecules that exhibit limited water solubility. Nanosponges refer to nanoparticles that encapsulate therapeutic compounds within their central core. Nanosponges have distinct characteristics compared to other types of nanoparticles. These include their porous nature, non-toxicity, insolubility in both water and organic solvents, as well as their stability at temperatures of up to 3000 degrees.

Chemicals used in synthesis of Nano Sponges :

polymers	Hyper cross linked Polystyrenes, Cyclodextrins and its derivatives like Methyl β-Cyclodextrin, Alkyloxy-carbonyl Cyclodextrins, 2-Hydroxy Propyl β-Cyclodextrins, ethyl cellulose and **Co polymers** like Poly (valerolactone – allyl valerolactone) & Poly (valerolactone-oxepanedione) and Ethyl cellulose, Poly vinyl alcohol
Cross linkers	,Carbonyl di –imidazoles ,DiphenylCarbonate,Di-aryl carbonates, DiIsocyanates,Dichoro methane, Pyromelliti anhydride,Epichloridrine, Glutraldehyde, Carboxylic acid dianhydrides, 2, 2- bis (acrylamidos), Acetic acid and Pyro mellitic anhydride.

Advantages of Nano Sponges

- The water solubility of hydrophobic medicines is enhanced. • Nano sponges offer enhanced elegance, stability, and formulation flexibility.
- One potential strategy for enhancing patient compliance is extending the time between medication doses.
- Nano sponges serve as a protective barrier for pharmaceuticals, shielding them from degradation and so mitigating potential side effects. Additionally, nano sponges has the ability to mask the disagreeable odours associated with certain drugs.
- These properties are attributed to their non-irritating, non-toxic, non-mutagenic, and biodegradable nature. Nanosponges have the capability to systematically release therapeutic molecules in a predictable manner.

- Due to their minuscule pore size of 0.25 µm, bacteria are unable to infiltrate the nanosponges, hence exhibiting a self-sterilizing effect.

Disadvantages of Nano Sponges

- Dose dumping has the potential to occur.One primary drawback of these nano sponges is that their encapsulation capacity is limited to small molecules and not suited for large molecules.
- The nano sponges have the potential to exist in either a paracrystalline or crystalline state.
- The loading capacity of nano sponges is primarily contingent upon the level of crystallisation. Crystalline nanosponges have the ability to exhibit varying loading capacities.

Methods of preparation of Nano Sponges

Solvent Method

Nano sponges are made via the solvent Method by combining the polymer with polar aprotic solvents like dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) as shown in figue 3. and a crosslinker follows added in a 1:4 ratio to this mixture. The aforementioned reaction needs to be carried out at a temperature of 10 °C to reflux the solvent's temperature for a duration of 1 to 48 hours. The solution is cooled to room temperature when the reaction is finished, and the resultant product is then added to bi distilled water.

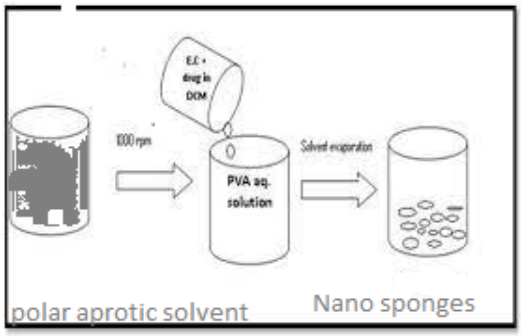

Figure :3 Solvent Evaporation method

Ultra Sound- Assisted Synthesis

In this approach, the synthesis of Nano Sponges is achieved by a solvent-free technique, wherein the reaction between crosslinkers and polymers takes place within a flask. The mixture is subjected to sonication for a duration of 5 hours, during which the flask is immersed in an ultrasonic bath containing heated water at a temperature of 90 °C.Once the combination has reached room temperature, the product is subsequently fragmented into coarse particles. Ultimately, the utilisation of ethanol in the refinement process is employed by the application of the Soxhlet apparatus, resulting in the production of nanosponges subsequent to the elimination of the non-reactive polymer.

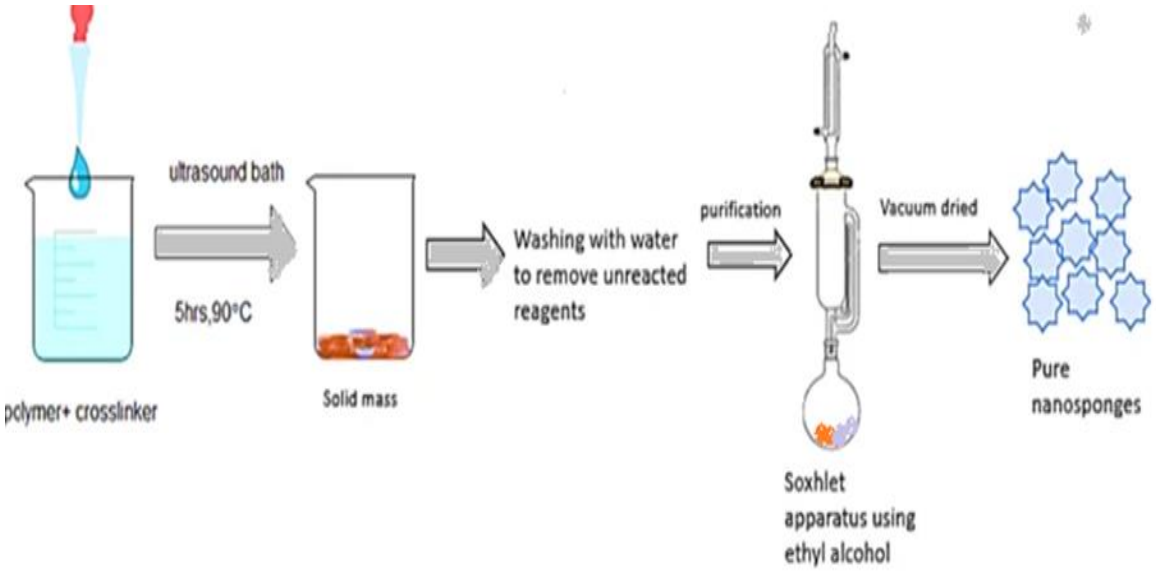

Figure : 4 Ultra Sound- Assisted Synthesis

Emulsion Solvent Diffusion Method

The process of creating nanosponges using the emulsion solvent diffusion method involves the combination of ethyl cellulose and polyvinyl alcohol in different proportions or quantities. This methodology utilises both dispersed and continuous phases. The medication is incorporated with ethyl cellulose to form the dispersion phase, which is subsequently solubilized in a 20 ml solution of dichloromethane. A volume of 150 ml of the continuous phase is subsequently supplemented with a small quantity of polyvinyl alcohol (PVA) in an aqueous form. The combination is thereafter subjected to agitation for approximately two hours, with a rotational speed of 1000 revolutions per minute (rpm). Nanosponges are obtained through the process of filtration. The product undergoes oven drying at a final temperature of 400 °C.

Melt Method

The crosslinker and the polymer are mixed in the melt technique. All the materials were meticulously combined. The acquisition product underwent many washes in an appropriate liquid medium in order to gather nanoparticles (NSs). The product undergoes a cleaning process to eliminate any impurities, including waste polymer and unreacted chemicals. Subsequently, the product is partitioned into nanosheets (NSs). Additional exposure to drug encapsulation was provided to the aforementioned nanoscale structures.

Bubble Electro Spinning Method

The standard and customary electrospinning setup typically comprises a syringe, as described in numerous scholarly works, a syringe pump, a high-voltage power source, and a grounded collector. The quantity of nanofiber production represents a significant constraint on their potential applications.Polyvinyl alcohol may also serve as a polymer in the process of bubble electrospinning. The polymer solution (10% concentration) was prepared by diluting it with distilled water, followed by heating the combination at 80-90 °C for a duration of 2 hours to achieve a homogenous single-phase solution. The polymer solution was thereafter allowed to establish a state of equilibrium at room temperature prior to its utilisation in the synthesis of nanoporous fibrils.

Mechanism of drug release:

Given the absence of a continuous membrane around the nanosponges, the active ingredient is enclosed within the nanosponges and afterwards introduced into the carrier. The encapsulated active ingredient has the ability to move unrestricted inside the vehicle, starting with the particles and continuing until the vehicle reaches saturation and equilibrium. Once the substance is topically administered, the vehicle transporting the active ingredient undergoes unsaturation, hence perturbing the equilibrium. Consequently, once the vehicle undergoes absorption or evaporation, the active chemicals originating from the nanosponge particles commence permeating into it. Despite the fact that the nanosponge particles are present on the stratum corneum of the skin

Factors influencing in the formulation of nanosponges:

Nature of polymer:

The utilisation of polymers in the fabrication of nanosponges can exert a significant influence. Both the formation and pre-formulation stages have an impact. The cavity of a nanosponge should possess sufficient dimensions to effectively accommodate a drug molecule of a particular size for the purpose of complexation.

Drug:

In order for drug molecules to form complexes with nanosponges, certain properties must be present. The molecule of the medication should possess a molecular weight ranging from 100 to 400 daltons. According to established guidelines, it is recommended that the molecular structure of a drug should not exceed a maximum of five condensed rings. The medicine is expected to have a dissolution rate of 10 mg/ml when dissolved in water. • The drug's melting point should be maintained at 250°C.

Temperature:

The complexation behaviour of drug or nanosponges can vary based on fluctuations in temperature. In a general context, it is observed that an increase in temperature leads to a decrease in the stability constant of the drug or nanosponge complex. This phenomenon can be attributed to a reduction in contact forces, such as hydrophobic forces and Van der Waals forces, as the temperature rises.

Degree of the substitution:

The complexity of nanosponges can be substantially affected by the number, arrangement, and kind of substituents on the parent molecule.

Loading of drug into nano sponges

The manner in which a pharmaceutical compound is encapsulated within a nanosponge can influence the nature of the interaction between the drug and the

nanosponges. The characteristics and composition of the medication and polymer significantly influence the efficacy of a certain approach.

Efficacy, freeze drying has occasionally been known to have an impact on the drug and nanosponge complexation. The procedure is shown in figure.5

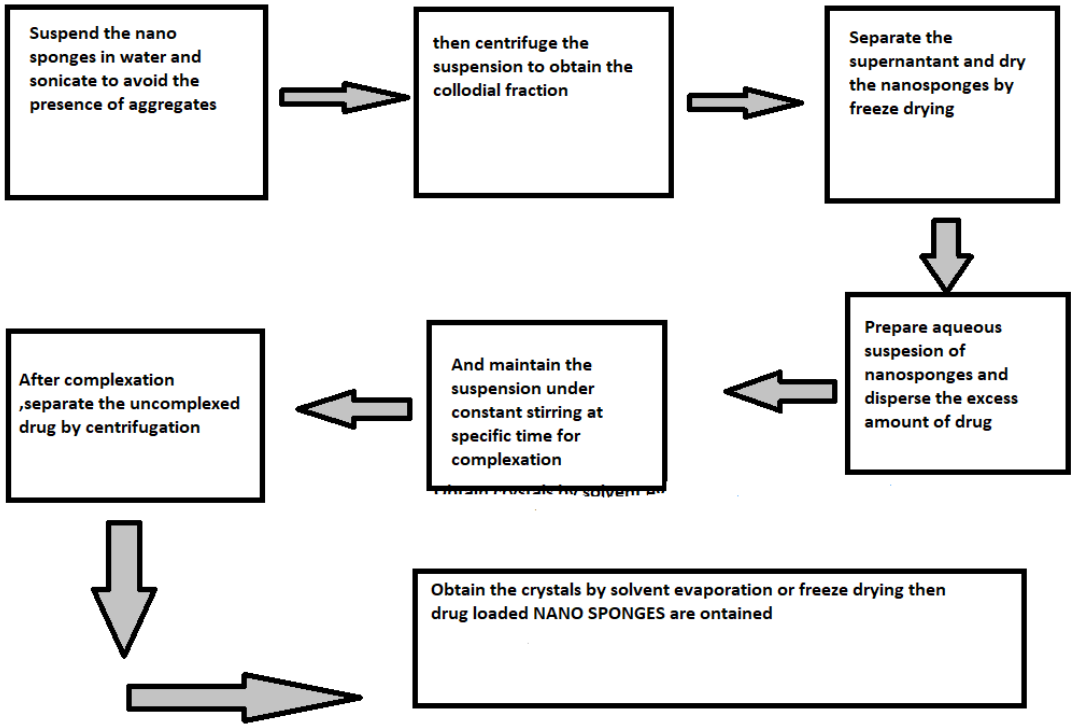

Figure: 5

Characterization and Evalution of nanosponges:

The following is a list of the characterization techniques for the drug/nanosponges complex:

1. Solubility studies:

The assessment of a drug's solubility and bioavailability can be accomplished through the utilisation of inclusion complexes. The method most commonly employed for the analysis of inclusion complexes of nanosponges is the one described above. The phase solubility plot can be employed to ascertain the extent of reaction completion. Research investigations are conducted to examine the solubility of medications, with the aim of elucidating the drug's pH, the mechanisms involved in its solubilization, and the various circumstances that impact its solubility.

2. Microscopic study:

Scanning electron microscopes (SEM) and transmission electron microscopes (TEM) are commonly employed for the examination of medicines and nanosponges at the tiny scale. These instruments are utilized for the assessment of both particle size and form. The observed disparity between the crystallization state and the resultant entity discernible using electron microscopy suggests the formation of an inclusion complex.

3. Zeta potential determination:

The zeta potential refers to the difference in electric potential between two layers of fluid that are confined by dispersed particles, namely the dispersion medium and the immobile layer. Zeta potential serves as the principal parameter for assessing the stability of colloidal dispersions. The determination of zeta potential can be achieved by incorporating an additional electrode into the apparatus used for particle size analysis, such as a zeta seizer. The zeta potential value positively correlates with the stability of a colloidal dispersion.

4. Thermodynamical method:

The thermo-chemical technique can be employed to evaluate the occurrence of drug molecule or particle modifications prior to the thermal degradation of nanosponges. Various drug particle alterations can occur, including but not limited to melting, evaporation, oxidation, breakdown, and polymeric modifications. The observed modifications in the drug molecules indicate the formation of a robust complex.

5. Polydispersity and particle size:

Using the 90 Plus particle size determining programme, the dynamic light scattering technique is used to determine the size of the particles. The

definition of dynamic light scattering (DLS) as a method for determining the size distribution profile of nanoparticles. Finally, the poly-dispersity index (PDI) and particle diameter can be calculated.

6. Thin-layer chromatography (TLC):
Thin-layer chromatography (TLC) is a technique utilised for the separation of mixtures that contain components that are non-volatile or have low volatility. If the Rf value of a specific drug molecule falls within the acceptable range in this methodology, it can be employed effectively for the detection of the formation of a complex between the drug and the nanosponges.

7. Infrared spectroscopy:
The application of infrared spectroscopy enables the examination of the interaction between medicine and nanosponges in their solid state. As the formation of complexes progresses, the structural configuration of nanosponge bands may undergo partial modifications. The concealment of the pharmacological spectrum can be effectively achieved by the utilisation of nanosponges, particularly in cases when the number of guest molecules bound in complexes is below 25%. The utilisation of this strategy should not be regarded as a substitute for alternative methods in the identification of the inclusion complex.

8. Loading efficiency:
The loading efficiency of a specific nanosponge particle can be determined by quantifying the drug content using a UV spectrophotometer and high-performance liquid chromatography. The above equation can be employed to ascertain the efficacy of loading nanosponges.
LE = Actual drug content in nanosponges ÷ Theoretical drug content ×100

9. Fourier transform –infrared spectroscopy (FTIR)
A Fourier transform infrared analysis was performed in order to ascertain the potential interaction between a medication and a polymer. The materials were subjected to scanning within the spectral region of 400-4000 cm-1, utilising a carbon black reference. In order to enhance the signal level and mitigate moisture, the detector underwent a meticulous purging process utilising pure, dry helium gas.

10. Swelling and water uptake
These are calculated by using the below formulas :

Percentage of swelling = Marking of cylinder at a specified time point/ Initial marking before soaking x100

Percentage of water uptake = Mass of hydro gel after 72 hrs/ Initial Mass of dry powder x100

Applications of Nano Sponges
Nano Sponges for drug delivery
Nanosponges possess a nanoporous structure that facilitates the efficient transportation of medications that exhibit poor solubility in water, namely those classified as class II pharmaceuticals according to the Biopharmaceutical Classification System. These complexes has the capability to conceal malodorous scents, convert liquid substances into solid forms, and enhance the speed of solubility and stability in medication dissolution. According to sources, it has been reported that nanosponges based on beta-cyclodextrin demonstrate a higher efficiency in transporting medication to the desired location, about three to five times more effectively than direct injection. Nano sponges have been found to be an effective method for administering drugs that have a high solubility requirement for formulation.

Examples of nano sponges

Drug	**vehicle**	**Indication**	**study**	**In vitro/in vivo mathematical model**
Tamoxifen	Beta-cyclodextrin	Breast cancer	cytotoxicty	MCF7 cell line
Antisense	Sodium alginate	Cancer therapy	Pharmacokinetic studies	Mice
Bovine serum albumin	Cyclo dextrin based poly(amidoamine)	Protine supplement	Drug release and stability studies	In vitro release ,modulation and stability
vorinconazole	Ethyl cellulose ,PVA	Anti fungal	Drug release experiment	rat
Econazole nitate	Ethyl cellulose, PVA	Anti fungal	Irratation study	Rat
resveratol	Beta-cyclodextrin	Inflamtion ,dermatitis, cardio vascular disease, gonorhea ,fever and cyto toxicity	Accumulation of drug in the buccal mucosa of rabbit EX-vivo studypermeation study	HCPC-1 cell line rabbit buccal mucosa pig skin

Nano sponges as Bio Catalysts

The utilisation of nano sponges as bio catalystsNanosponges serve as carriers for the delivery of enzymes, proteins, vaccinations, and antibodies. Chemicals are employed in a multitude of industrial processes to enhance productivity and output. Under certain circumstances, industrial applications necessitate the sustained release of specific enzymes. This objective can be accomplished by the utilisation of nano sponges.

Nano sponges for Cancer Therapy

The utilisation of nano sponges in the field of cancer therapyThe effective administration of anticancer medications is a significant challenge within the pharmaceutical sector due to their limited solubility. According to a scholarly article, the utilisation of nanosponge complexes has demonstrated a threefold increase in efficacy compared to the previous method of direct injection, in terms of inhibiting tumour growth. The nanosponge complex encapsulates a therapeutic agent and presents a targeting peptide that strongly binds to the surface of radiation-induced cancer cells.Upon encountering a cancer cell, nanosponges exhibit adhesion to its surface and initiate the release of therapeutic chemicals. The advantage of targeted medicine delivery is the potential to achieve enhanced therapeutic efficacy using reduced dosages, hence minimising the occurrence of adverse effects.

Several examples of nano sponges utilised in cancer therapy include Camtothecin, Paclitaxel, and Antisense.

Solubility Enchancement

The utilisation of nano sponges as adsorbents for the treatment of blood poisoning has been investigated.Nanosponges possess the capability to effectively eliminate toxic substances from the bloodstream through their capacity to absorb those toxins. The administration of nanosponges into the bloodstream offers the potential to substitute conventional antidotes with this innovative technology.Assimilate the toxins. The nanosponge exhibits biomimetic properties resembling those of a red blood cell within the circulatory system, effectively luring poisons to engage with it prior to their subsequent absorption. The absorption capacity of each nanosponge varies depending on the specific poison.

CONCLUSION:

Nanosponges can serve as a medication delivery mechanism by forming a complex to encapsulate or accumulate both hydrophilic and lipophilic substances. The administration of medication can be effectively achieved by a controlled delivery system, ensuring targeted delivery to the specified site. Nanosponges can be incorporated into topical preparations such as lotions, creams, and ointments. Comparable in both liquid and powder states. One advantage of this technology lies in its capacity to target the medicine to a specific location, hence minimising adverse effects and enhancing stability, formulation adaptability, and patient adherence. Nanosponges find potential applications in various areas such as agrochemistry, biomedicine, cosmetics, bioremediation, and catalysis.

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