NANO SPONGES: A NOVEL APPROACH FOR TARGETED DRUG DELIVERY SYSTEMS

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ABSTRACT

To put it another way, targeted drug delivery systems are unusual in that the pharmacologically active experts are only concerned with their site action and not the non-targeted organs, tissues or cells. Nano sponges are powerful pharmaceutical transporters that address difficulties like as harmfulness and inadequate bioavailability, such as the ability to stack hydrophilic and hydrophobic medications together. Nano sponge can stack a variety of pharmaceutical classes for targeted medication delivery. One of the most encouraging methods in the history of science is this approach of delivering drugs precisely where they are needed. Despite their diminutive size and three-dimensional structure, nanosponges have the ability to deform on the nanometer scale. Nanotechnology's most recent creative advance has resulted in the development of a targeted medicine delivery method. The usage of specialised drug delivery systems is required to effectively target a molecule to a specific place using a drug delivery system. Conventional drug delivery technologies have been greatly improved by the development of Nano sponges. Both hydrophilic and hydrophobic medicines can be carried by them. The controlled and predictable release of the medicine to the targeted site is generally provided by nano sponge.
technology. The medicine is released when the Nano sponge particles connect to the target spot and circulate throughout the body. Due to its porosity nature, the Nano sponge formulation can accommodate a wide range of medications. There is a lot of interest in nano sponge technology for the delivery of drugs by oral, topical and parenteral administration. Nano sponges can be utilised to halt the degradation of drugs and proteins. Nano sponges can also boost the solubility of drugs that aren't very water-soluble. A variety of therapeutic formulations and recent studies on Nano sponge were examined for their benefits, composition, preparation process, evaluation, and use in this review.

KEYWORDS: Nano sponges, Targeted drug delivery, Controlled drug delivery, Solubility.

INTRODUCTION

As a new and evolving method of delivering drugs, nanosponge technology employs a tailored drug delivery system that delivers drugs to the targeted spot. When referring to the class of materials known as nano sponges, we mean those having an average diameter less than one micrometre and a microscopic sponge-like structure. A spherical shape with several chambers where the medicine can be stored is formed by cross-linking the segments of polyester into one another. These small spaces can be filled with a variety of different materials. These can contain both hydrophilic and lipophilic medicinal molecules, enhancing the solubility of weakly water soluble therapeutic compounds. In terms of topical drug delivery, this is a cutting-edge method that enables precise control over dosage. Encapsulation of substances with decreased side effects, improved stability, increased elegance, and enhanced formulation flexibility are some of the advantages of this method of delivery.

Nanotechnology indicates the deception of conditions on an atomic, molecular, and super molecular scale, which necessitates the planning, fabrication, evaluation, and implementation of various nano-scale materials in several possible sectors, mostly in the medical profession. Medical domains such as immunology, cardiology, endocrinology, ophthalmology and pulmonology could benefit from nanotechnology. It's employed extensively in targeted locations like as the brain, tumours, and gene delivery. In addition, nanotechnology provides key systems, technologies, and materials that can be used to improve pharmaceuticals.

A new form of material, nano sponge, is composed of extremely small particles with a finite
volume. Many different compounds can be found in these small areas. It is possible to improve the stability of weakly water-soluble compounds by using these tiny particles, which are capable of transporting both hydrophilic and lipophilic molecules.

For many physical, chemical, and biological concerns, the pharmaceutical and health care industries have been supplying and utilising nanoscale data. Nanotechnology has dominated technology since the 1950s.[6]

ADVANTAGES

- Reduction in side effects as well as improved stability,
- Elegance, and formulation flexibility are some of the benefits.
- Stability is maintained up to 130°C for these formulations.
- These formulas can be used with a wide range of vehicles and additives without any problems.
- These are self-sterilizing because bacteria cannot pass through the 0.25m typical pore size.[7]
- It is possible to save money by using these as a free flow.
- These formulations alter the drug’s release.
- They improve the solubility of a medicine that is difficult to dissolve.
- There are a number of ways in which this chemical can be employed.
- Drug bioavailability is enhanced by these formulations.
- They don’t irritate the skin. Allergy-free and non-mutagenic.
- It has a long-lasting effect that lasts for up to 12 hours.
- Scalability for commercial manufacturing is a breeze.
- Biodegradable
- In this technique, the medicine is protected from premature destruction by a protective barrier provided by the substance utilised.

DISADVANTAGES

- Nano sponges can only be used to describe small particles, not larger atoms.
- Unloading of doses may occur at any time.
- Nano sponges can only hold a small number of atoms.
- In terms of structure, nano sponges can be either transparent or resembling glass.
- The maximum number of nano sponges that can be stacked depends primarily on the
degree of crystallisation.

**COMPOSITION OF NANOSPONGES**

1. **Polymer**
   Selecting the polymer can have a significant impact on the structure and performance of Nano sponges. The size of the cavity must be appropriate for the specific medication molecule to be included.\(^8\) Polymer selection is depending on the amount of release and the medication that is to be contained. The polymer used should be able to bind to specified ligands.

2. **Crosslinking agent**
   It is possible to pick a crosslinking agent depending on the polymer structure and the medication to be manufactured. Diphenyl carbonate, Dichloromethane, Diaryl carbonates, Diisocyanates are only some of the examples.

3. **Drug substance**
   - Molecular weight between 100 and 400 Daltons.
   - Drug molecule consists of less than five condensed rings.
   - Solubility in water is less than 10 mg/ml.
   - Melting point of substance is below 250 °C.

**METHOD OF PREPARATION**

- **Dissolvable technique**
  Mix the polymer with an appropriate dissolving agent, such as Dimethyl formamide or Dimethyl sulfoxide, for example. Cross linker polymer molar proportions between 4 and 16 are optimal for this combination to be added to. At temperatures ranging from 100°C to the dissolvable's reflux temperature, over a period of up to 48 hours, complete the response.\(^9\)

  Carbonyl mixtures are the most often used cross linkers (Dimethyl carbonate and Carbonylic imidazole). Soxhlet refinement can be performed after the response has cooled down at room temperature, and the item is added to a large amount of stilled water to recover it.

- **Nano sponges produced using hyper cross-connected β-cyclodextrins**
  To retain both hydrophilic and lipophilic medicines, the cyclodextrin Nano sponges Because lipophilic medications have a larger number of water-insoluble regions available for drug
complexation, they have a higher drug holding tendency than hydrophilic pharmaceuticals.\textsuperscript{[10]}

To make greater substance sizes, mixing methods such as sonication, which produced Nano sponges, were employed. This appeared to have an effect on the drug retaining propensity.

- **Ultrasound-Assisted Synthesis**
  
  Cross-linkers are not dissolvable or sonicated in this technique, therefore the polymers respond. In this case, use a cup to mix the polymer and cross-linker. For 5 hours, immerse the flagon in an ultrasonic shower filled with water and heat it to 90\degree C. Allow it to cool and then wash it with water to remove the nonreaction polymer. Late Soxhlet extraction with ethanol was used to purify the sample. Vacuum-dry the item and put it away.\textsuperscript{[11]}

- **Emulsion Solvent Diffusion Method**
  
  EC and PVC can be used to make nano sponges, which can be used in a variety of applications (PVA). Dichloromethane breaks down ethyl cellulose. Combine these ingredients in a watery polyvinyl liquor solution. For two hours, whirl the mixture in a pretty stirrer at 1000 revolutions per minute. At this time, transfer the item to a broiler and dry it for 24 hours at 40\degree C.

**Table 1: Materials Used In The Preparation of Nanosponges.**\textsuperscript{[12]}

| Polymer                              | Copolymer                  | Cross linker       |
|--------------------------------------|----------------------------|--------------------|
| Hyper cross linked polystyrene       | Ethyl cellulose,           | Dicarbonate,       |
| Cyclodextrins and its derivatives    | Poly vinyl alcohol [PVA]   | Di- isocyanate     |
| like Methyl β-cyclodextrine, 2hydropropyl β-cyclodextrine |                            |                    |
Flow Chart 1: For the preparation of nanosponges using ultra assisted method.

Flow diagram 2: The preparation of nanosponges using emulsion solvent diffusion method.

FACTORS INFLUENCING NANO SPONGE FORMULATION

- **Type of polymer**

  Polymer selection is critical to both the production and performance of nanosponge. If the nanosponge's pore or cavity size is too small, the medication molecule won't be able to fit.\(^{13-15}\)

- **Type of drug**
  - The molecular weight must be between 100 to 400 Daltons
- The drug molecule structure should contain not more than five condensed rings.
- The solubility in water should be less than 10 mg/ml
- The melting point should be less than 250 °C.

**Temperature**

The drug complexation can be affected by changes in temperature. The apparent stability of the nanosponge complex reduces as the temperature rises, possibly due to a decrease in the drug nanosponge interaction forces, van der waals force, and hydrophobic forces.\[16\]

**Method of preparation**

If the nanosponge formulation is loaded with drugs, the complexation could be affected. Complexation can be affected by the nature of the medicine and the polymer used to make it. It was observed that in many circumstances, freeze drying was a more efficient technique of combining drugs.\[17,18\]

**Degree of substitution**

The parent molecule's substituent type, number, and location can have a significant impact on the nanosponge formulation.

**LOADING OF DRUG INTO NANOSPONGE**

Pretreatment of the nanosponges is necessary to ensure that they have a particle size of less than 500nm. Sonication is then applied to the nanosponges for a period of time to prevent them from aggregating. A centrifuge is used to separate the colloidal fraction from the product suspension. Afterwards, a freeze-dried sample of the product supernantant is obtained.\[19\]

To make a nanosponge aqueous suspension, a certain amount of time is spent agitating the mixture to scatter the nanosponge particles. When the solvent is evaporated or freeze-dried, the nanosponge crystals are formed. An essential role in drug complexation is played by the crystal structure of the nanosponge nanoparticles. The crystalline nanosponge has a higher drug loading than the paracrystalline version. Mechanical mixing rather than inclusion complexes are used to load drugs into nanosponges with weak crystal structure.\[20\]
EVALUATION OF NANOSPONGES

- **Microscopic studies**
  Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) can be used to examine the tiny features of a medicine, Nano sponge, or the product (TEM). Inclusion complexes can be seen in the crystallisation differences.[21]

- **Loading efficiency**
  Quantitative measurement of drug loading into nanosponge can be done using UV spectrophotometer or HPLC methods. This can be used to calculate the loading efficiency.[22]

- **Solubility studies**
  Higuchi and Connors' phase solubility method is the most commonly employed to investigate the impact of nanosponge on medication solubility. " This information was provided by the phase solubility diagram.

- **X ray diffraction studies**
  Powder X-ray diffractiometry can be used to determine the complexation of inclusions in the solid state. Diffraction patterns of newly created substances obviously differ from those of uncomplicated nanosponge when the drug molecule is liquid. The fact that the diffraction pattern is different shows that something complicated has formed. When the drug compound is a solid substance, the diffractogram of the complex and the mechanical combination of the drug and polymer molecules must be compared. Mixtures of physical components are commonly found to have identical diffractograms, whereas complexes appear to have distinct diffractogram patterns and can rise to a new solid phase with distinct diffractograms. The chemical decomposition and complex creation can be determined from diffraction peaks for a mixture of chemicals. Nanosponge-based drug complexes modify the diffraction pattern and the crystal structure of the drug. The complicated development causes existing peaks to be sharpened and certain peaks to be shifted.[23-25]

- **Single crystal x ray structure analysis**
  Single crystal X-ray structural analysis is utilised to determine the precise inclusion structure and the mechanism of interaction between the individual atoms and molecules. It is possible to determine the host-guest interaction and build an exact geometrical relationship.
• **Infra red spectroscopy**

In the solid state, this spectroscopic approach is utilised to determine how the nanosponge and the drug molecule interacted. There are a number of bands that shift frequently in the spectrum of nanosponges as they form complexes, and these bands tend to obscure the bands that may be assigned to the guest molecules that are enclosed by nanosponges if they are less than 25%. Infra-red spectroscopy can only be used for medications with a carbonyl or sulfonyl group in their structure. Infra-red spectroscopy can reveal the presence of hydrogen in a variety of different functional groups.\[26-27\]

• **Thin layer chromatography**

TLC can be used to identify drug-nanosponge complexes because Rf values of drug molecules decrease significantly in thin layer chromatography (TLC).

• **Particle size and polydispersity**

It is possible to determine the particle size of a nanosponge formulation using dynamic light scattering and the MAS OPTION particle sizer. The mean diameter and the polydispersity index can be calculated from the data obtained.

• **Zeta potential**

The surface charge is determined by measuring the zeta potential. Additional electrodes can be added to particle size equipment to measure it.

**PHARMACEUTICAL APPLICATIONS OF NANO SPONGES DRUG DELIVERY**

Nanosponges can be used in a variety of pharmaceutical applications because of their biocompatibility and adaptability. To prepare tablets, capsules, powder, granules, suspensions, solid dispersions, or topical dosage forms, nanosponges can be employed as excipients.\[28-30\]

**Nanosponges as a sustained delivery system**

Herpes simplex virus infection can be treated with acyclovir, one of the most commonly used antiviral medications. A sluggish and partial and very variable absorption in the GIT. Different varieties of Nano sponges were shown to provide a continuous release of acyclovir in vitro. After 3 hours of treatment, carb-nanosponges and nanosponges released around 22% and 70% of acyclovir, respectively. Since no first burst effect was seen, the medication was not adsorbed onto the nanosponge surface.
Nanosponges in solubility enhancement

BCS class II Itraconazole has a poor bioavailability due to a low dissolution rate. The drug's solubility was increased by more than 27-fold as a result of the use of nanosponges. When copolyvidonum was used as a supporting component, the solubility was found to be increased 55-fold. Nanosponges can improve the solubility of itraconazole by masking the hydrophobic groups, increasing the wetting of the medication, or decreasing the crystallinity of the drug.

Nanosponges in drug delivery

It is possible to create nanosponges in a variety of dose forms, including topical, parenteral and aerosol. Telmisartan (TEL) is a class II medication that has a limited bioavailability because of its slow dissolving rate. The nanosponge formulation included TEL. TEL's -CD complex was tested in vitro and in comparison with plain TEL and the nanosponge complexex to see which had the best saturation solubility and vitro dissolution. Inclusion complexes of nanosponge and NaHCO₃ were found to have the maximum solubility and in vitro drug release. Paclitaxel is a water-insoluble anticancer medication. In contrast to traditional cremophor formulations, -CD based nanosponges are an excellent option since cremophor decreases the tissue penetration of paclitaxel. Paclitaxel's biological activity in vitro is greatly increased by the use of nanosponge-based formulations.[31] For the treatment of skin infections and dermatophytis, you can use the antifungal drug econazole nitrate. When econazole is administered to the skin, adsorption is insignificant. In this way, econazole nitrate hydrogel nanosponges are created using the solvent diffusion approach.

Nanosponges in enzyme immobilization

The enzyme can be stabilised by using nanosponges. If you are looking for a substrate for enzyme immobilisation, CD-NS should be your first choice. They aid in the preservation of the enzymes' catalytic efficiency and stability. Immobilizing enzymes is critical to enzyme recycling, as it improves the separation and recovery of the product and increases the biocatalysts' thermal and operational stability. Lipases from pseudomonas flurescens were shown to be highly active when attached to cyclodextrin nanosponge. Triacylglycerol hydrolysis and trans esterification reactions, which are used in a variety of industrial processes, can be facilitated by lipases.

Nanosponges for protein delivery

The formulation process and long-term preservation of proteins pose a substantial challenge to the development of protein formulations. Poly nanosponges based on swellable
cycloextrins were investigated by Swaminathan et al. They were able to observe a constant 72-hour swelling capacity using water uptake trials. An example protein, bovine serum albumin, was used in the creation of the nanosponge. Swelling and protein stability were both improved in this study. The lactone ring opens up and becomes inactive carboxylate form at a pH of 7.0 or higher. Nanospomes containing camptothecin resulted in a sustained release of the active form, which prevented the hydrolysis of lactone and resulted in a more stable product.

**Nanosponges as protective agent from light or degradation**
It is possible to encapsulate Gamma–oryzanol in nanosponge form to protect it from photodegradation. In food and pharmaceutical manufacturing, gamma oryzanol is primarily used to stabilise raw ingredients such as ferulic acid, which acts as a natural antioxidant. Because of its instability and photodegradation, its use is restricted.

**Nanosponges as a carrier for biocatalyst**
Delivery of enzymes, vaccines, proteins and antibodies for diagnostic purposes is made possible by nanosponges. The cyclodextrin nanosponge is used to adsorb and encapsulate proteins and other macromolecules.

**Nanosponges as gas delivery system**
Hypoxia, a shortage in oxygen delivery, has been linked to a wide range of diseases, from inflammation to cancer. When applied topically, the nanosponge composition provides oxygen to cells. Vero cells were used to test the safety of nanosponge. A CD–NS hydrogel hybrid system was used to study the penetration of oxygen through a silicone membrane. Carbonildiimidazole cross-linker was used by Trotta et al. to encapsulate 1-methylcyclopropene, oxygen, and carbon dioxide in CD-NS.

**TYPES OF NANOSPONGES**
**CD-based carbonate nano sponges**
Starting with the locally available -cycloextrin and dynamic carbonyl combinations, such as Carbonyl diimidazole, these were combined Cyclodextrin-based carbonate sponges. Consideration edifices were shaped using three unique gases, such as 1-methylcyclopropene, oxygen and carbon dioxide in this study As evidenced by direct reaction, gravimetric inquiry (CO2) and oxymeter, the exemplification of gas was demonstrated (Oxygen). Oxygen or carbon dioxide complexation may be useful in several biomedical applications. Particularly in
cases of hypoxic tissues, the micro sponges packed with oxygen could be used to deliver oxygen. Remembered for cyclodextrin, 1-methylcyclopropene. When compared to the promoted items, nano sponges were found to exhibit more prominent ant ethylenic displays in long-lasting cut flowers.

**Carbamate nano sponges**
Cyclodextrins and cross-linkers, such as hexamethylene diisocyanate and toluene diisocyanate, can be dissolved under an anhydrous/nitrogen atmosphere at ambient temperature to 70°C to form such NS. In 1998, DeQuan Li and Min [created NSs for the purification of water, including the ejection of decomposed natural carbon, such as nitrophenol]. Final advancement is to plan to use diisocyanate cross-linkers in atomically engraved nano sponges to include compounds such as steroids, colours, and dextromethorphan.

**Anhydride Nano sponge**
To speed up the polymerization of anhydride nano sponges, for example, by using crosslinkers, such as pyromellitic diamine ethylene-diamine tetra-acid-corrodive dianhydride of the polydextrins at room temperature, the dissolvable approach can be used. An arrangement is made by using cyclodextrin: molar quantities ranging from 1: 2 to 1: 8 are used. Several studies have found that various drugs, including doxorubicin, meloxicam, ibuprofen, and acetylsalicylic corrosive, have been compared to each other.

**Epichlorohydrin cyclodextrin nano sponges**
They are more hydrophilic in nature because they were formed by dissolving cyclodextrins in an important medium such as sodium hydroxide with cross-connecting specialists, such as epichlorohydrin. Creatinine and cyclodextrin are two examples of nano sponges that have been used to demonstrate strong compound resistance and flexible expansion capacity. However, in certain studies, the molar ratio of up to 1:10 has been explored for cross-connecting with cyclodextrin.

**CD-based ester nano sponges**
Such Nano sponges can be made by using a proper anhydride of the pyromellitic anhydride as a crosslinking agent. It takes just 5 minutes for the crosslinking riposte to lose its heat and CD is dissolved in pyridine at normal temperature. The free carboxylic acidic group in these nano sponges is both anionic and cationic in nature.
Polyamide Nano sponges
Carrying out riposte in acrylamide at normal temperature (94 hours) yields this type of Nano sponge. In both basic and acidic solutions, these blobs appear. When in contact with a water solution, it transforms into a clear gel. Depending on the gel's durability for 80 hours, a time-dependent bulge may occur. Around 95 percent of the albumin protein was used in these formulations, which resulted in substantial protein entrapment. Albumin and other proteins are released at a consistent rate during 24 hours in vitro tests. The SDS page formulation of sodium lauryl sulphate [SDS] was used to determine the stability of the solution. This demonstrates that the product's formulation has been stable for a period of time.[39-40]

CONCLUSION
Hydrophilic and hydrophobic drugs are both transported by nano sponges, which serve as a drug delivery framework. For example, oral, parenteral, and effective frameworks can be considered. In the pharmaceutical sector, nano sponge technology offers a wide range of applications. Medications made with this innovation allow for a controlled and safe delivery of the medicament. Hydrophilic and hydrophobic medicines can both be delivered using nanosponges, making them a versatile drug delivery mechanism. They are available in a variety of forms, including oral, parenteral, and topical. In the pharmaceutical sector, nano sponge technology has a wide range of applications. It is safe and effective to use drugs that have been developed using this technique for a lengthy period of time.

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