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An Emerging Era for Targeted Drug Delivery: Nanosponges

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Authors' contributions

This work was carried out in collaboration among all authors. Author AAS wrote the first draft of the manuscript. Author EOK managed the literature searches. Author JP designed the study, managed the literature searches, guided authors for drafting the manuscript according to the author guidelines, publishing the review article and being corresponding author for the manuscript. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Many forms of Pharmaceutical product like nanosponge, nanoemulsion, nano-micelles, and nanosomes have been developed using nanotechnology. The size of Nanosponges is like that of a virus. They are very tiny in size and can permeate through the skin easily. Nanosponges can be distributed throughout the body until they reach their specific target area, where they adhere to the surface and the drug is released in a controlled manner, rather than circulating throughout the body. Nanosponge is a promising strategy to overcome problems associated with formulations such as poor bioavailability, drug toxicity, drug degradation, drug solubility and site specificity of drug. Both lipophillic and hydrophilic drug are incorporated in nanosponge. They can also act as biocatalysts and carrier for enzymes, antibodies, protein and vaccines. The use of a biodegradable polymer can help to maintain a constant drug level by allowing the drug to be released in a controlled way. Technologies employed in nanosponge formulations have been widely studied for drug delivery by topical, oral as well as parenteral administration. Improvement of solubility of poorly water soluble drug is another significant characteristic of Nanosponges. The primary goal of this review article is to provide a basic understanding of nanosponges, including their preparation process, advantages and disadvantages, as well as methods of evaluation and applications.

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Keywords: Nanosponge; targeted drug delivery; controlled drug release; biodegradable polymer; hydrophobic-hydrophilic drug.

1. INTRODUCTION

- Nanotechnology has received a lot of attention recently as a result of the discovery of new chemical entities, as well as its use in diagnosis and treatment of a variety of ailments.
- There has been a lot of progress in nanomedicine, such as the advancement of drug delivery systems such as nanoemulsion, nanoparticles, nanosponges, and nanosuspension, of which nanosponges, as an advanced drug delivery system, provides a number of advantages over other options, one of which is increased drug bioavailability. It has also impacted the health-care sector positively as an offshoot called nanomedicine. The development of targetted drug delivery system is as a result of advancement in nanotechnology to get an intended result**.**
- The size of nanosponges is like that of a virus. They are very tiny in size and can permeate through the skin easily.
- It's a new type of material made up of extremely small particles with a nanometer-wide cavity.
- Both water soluble and lipid soluble drug substances could possibly be loaded in nanosponges and thereby the solubility of poorly water soluble drug substance is been enhanced [1,2].
- The fact that nanosponge is a three-dimensional scaffold (backbone) or network of polyester that can naturally degrade is one of its advantages.
- To make nanosponges, these polyesters are combined with a cross-linker in a solution.
- In this situation, biodegradable polyester is commonly used, and it degrades slowly in the body.
- When administered orally, They'll be dispersed across a matrix of additives, lubricants, diluents, and anti-caking agents that are better suited to tablet and capsule formulation [3].

The figure of nanosponges is illustrated in Fig. 1 [4].

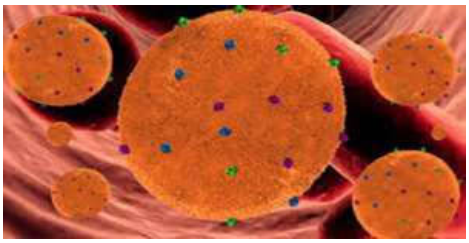

Fig. 1. Nanosponges [4]

1.1 Difference between Nanoparticles and Nanosponges

The disparity in size and porosity is the thin line that distinguishes nanoparticles from nanosponges. Nanoparticles have nanometer-sized pores, while nanosponges have nanometer-sized pores with an overall size that can vary from micrometre to micrometre and is typically less than 5 µm. Nanosponges have been defined as nanoporous nanoparticles / microparticles on several occasions. Due to the presence of both hydrophobic and hydrophilic groups, nanosponges have a structure with a variety of domains. The figure of polymer based nanosponge is illustrated in Fig. 2 [5]

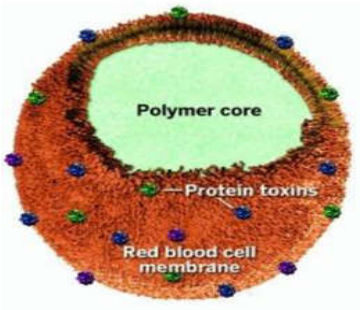

Fig. 2. Polymer based nanosponges [5]

1.2 Advantages: [6-11,12,13]

- At pH 1-11, the formulation are very stable.
- Nanosponges does not cause irritation, They are also, non-toxic, non-allergenic and biodegradable.
- Nanosponge formulations have compatibility with most excipient, ingredient as well as vehicles.
- Encapsulation can be done within the nanosponge by adding adjuvant reagents, or it can be done outside the nanosponge because nanosponges are water soluble.
- The proportion of crosslinker to polymer can be changed to alter the size of nanosponges.
- Depending on the dosing requirement, the release profiles of drug can be varied from quick, intermediate to lastly slow release.
- Predictable release.
- Because the drug has less contact with healthy tissue, there are less adverse side effect.
- Entrapment of ingredients as well as a minimal side effect can be achieved using this technology, increase stability, increase elegance, and as well as formulation flexibility.
- Since their pore size on average 0.25 micrometer, they are self-sterilizing and there for bacteria can not penetrate.
- Provides extended-release up to twelve hours.
- The active ingredient is safe from degradation.
- Unpleasant flavors should be hidden.

1.3 Disadvantages: [14]

- Depends upon only the capacities of loading.
- Small molecules are involved and not large molecules.
- There can be occurance of dose dumping.
- Release may be retarded.

1.4 Characteristics of Nanosponge: [15]

- Nanosponges provided a range of dimension (1μm or less than that) cavities with tunable polarity.
- By altering cross linker to polymer ratio nanosponges of a specific size can be synthesized.
- Para crystalline nanosponge may demonstrate a variety of drug loading capacities; they are nontoxic in nature, porous particles that are poorly soluble in most organic solvents, and have a stability of up to 300°C elsius.
- Stability is preserved at a pH range of 1-11.
- They shape an opalescent and transparent suspension in water.
- They have three-dimensional structures that allow for the capture, transport, and selective release of a wide range of substances, and they can be replicated using basic thermal desorption, solvent extraction, ultrasounds, and microwaves.
- Nanosponge can bind preferably to the targeted site through chemical linkers.
- Using a variety of drugs to form complexes Inclusion and non-inclusion complexes can be formed by nano sponges.
- Nanosponges can acquire magnetic properties when magnetic particles are added to the reaction mixture.

1.5 Materials Used for Preparation of Nanosponges: [16,17]

- Polymers: cellulose of ethyl, 2-hydroxy proply βeta–cyclodextrins, Hyper crosslinked polystyrenes polyvalerol acetone, Eudragit Rs100, acrylicpolymers.
- Co-Polymers: poly (valero lactone allyl valero lactone), poly (valerol acetone – allyivalerol act oneoxepanedione), Poly vinyl Alcohol and ethyl cellulose.
- Crosslinkers: Carbonyl dimidazoles, Carboxylic acid dianhydrides Diarylcarbonates, Di-isocyanates, Di phenyl Carbonate, Epichloridine, Gluteraldehyde, Pyromellitic anhydride, 2, 2-bis (acrylamido) Acetic acid.

1.6 Mechanism of Drug Release: [18,17]

- The movement will freely travel in and out of the particles and into the vehicle before they enter a state of equilibrium. Until the finished product is added to the skin, as in topical distribution, the vehicle's active component can penetrate the skin, depleting the vehicle, causing it to become unsaturated and disrupting the balance.
- Until the vehicle is either absorbed or dried, the action will flow from the sponge particle into the vehicle and then to the skin.
- There will also be constant release after the sponge particles are held on the stratum corneum's surface.

1.7 Method of Nanosponges preparation: [19,20]

- ✓ Solvent method
- ✓ Hyper crosslinked β –cyclodextrin
- ✓ Emulsion solvent diffusion method
- ✓ Ultrasound-assisted synthesis

1.8 Solvent Method: [19,20]

- The polymer is mixed with solvent which is suitable such as dimethyl salfoxide, dimethyl formamide, etc.
- It is then incorporated to the excess amount of crosslinker in crosslinker/ polymer molar ratio of 4 – 16.
- Mostly used crosslinkers are carbonyl compounds such as diphenyl carbonatedimenthy carbonate and carbonyldiimidazole.
- The reaction is performed at the ranging from 10°C to the solvent's reflux temperature for 1 to 48 hours.
- Excess amount of distilled water is added after reaction is complete and permitted to cool at room temperature.
- Filtration under vacuum is used to recover product and soxhlet extraction with ethanol is used for purification.
- Under vacuum, product is dried and mechanical mill to is used to get a homogenous powder by grounding.

1.9 Hyper cross-linked beta cyclodextrins: [18]

- Nanosponges with a carbonyl as a crosslinker can be made by crosslinking different forms of cyclodextrins.
- They're made by combining cyclodextrin with a cross-linker like diphenyl carbonate diisocyanates.
- A transparent block of hyper cross-linked cyclodextrin is coarsely ground, and the solvent is removed with excess water.
- Soxhlet extraction with ethanol is used to purify the product obtained and obtained product is dried in at 60℃ in an oven overnight.

1.10 Emulsion Solvent Diffusion Methods: [21]

- Aqueous and organic phases are prepared, with the aqueous phase containing copolymer and the organic phase containing medication and polymer.
- The organic phase was gradually incorporated into the aqueous phase.
- The mixture is then stirred at room temperature for 3 hours at 1000-2000 rpm.
- The Nanosponges formed were filtered, washed & dried at room temperature.

1.11 Ultrasound-Assisted Synthesis: [6,9]

- In a flask, a specific molar ratio of polymer to crosslinker is mixed.
- The flask is heated to 90°C in a water-filled ultrasound bath.
- After cooling, the resulting mixture was sonicated for 5 hours.
- There is a rough breakdown of the commodity.
- Washing the substance with water removes non-reacted polymer.
- The substance is purified by adding ethanol to the soxhlet extraction.
- The final product is vacuum-sealed and stored at 250°C.

1.2 Factors Influencing the Formation of Nanosponges: [20,22]

1.2.1 Type of polymer: [23]

- Formation and performance of nanosponges can be influenced by type of product used.
- The nanosponge cavity must be large enough to hold a drug molecule of a specific size for complexation.

1.2.2 Type of drugs: [23]

- Molecules that will be complexed with nanosponges must possess certain features. They consist of:
- Molecular weight between range of 100 – 400 Da.
- A drug molecule with less than five condensed rings.
- Water solubilityis less than ten milligrammes per milliliter.
- The substance’s melting point is less than 250°C elsius.

1.2.3 Temperature: [24]

- Changes in the temperature can affect the complexation of drug/ nanosponges.
- The drug/ nanosponge complex becomes less stable as the temperature rises,

possibly due to a decrease in drug/nanosponge interaction forces.

1.2.4 Method of preparation: [24]

The method of drug loading into nanosponge will affect drug/ Nanosponge complexation. However, the nature of the drug and the polymer play an important role in the method's effectiveness; in many cases, freeze drying is the most effective method for drug complexation.

1.2.5 Degree of substitution:

The type, number, and function of the substituent on the parent molecule can also have a significant impact on the nanosponge's ability to complex [24].

1.2.6 Loading of drug into nanosponges

When pre-treating nano-sponges for drug delivery, the average particle size should be less than 500 nm. To avoid the presence of aggregates, nanosponges are suspended in water and centrifuged to extract the colloidal fraction.The sample is freeze dried after the supernatant is removed. Another method is to distribute excess amounts of the drug in an aqueous suspension of nanosponge that has been prepared with constant stirring for the time needed for complexation, and then centrifugation is used to isolate the uncomplexed (undissolved) drug. Solvent evaporation or freeze drying is used to obtain the solid crystals of nanosponges. For complexation with drug, the crystal structure of nanosponge plays a significant role. Study has unconcealed that para crystalline nanosponge showed completely in comparison to crystalline nanosponges. The loading of drug is smaller amount in paracrystallinenanosponge than crystalline one [22].

2. EVALUATION PARAMETERS

2.1 Particle Size Determination: [18]

Particle size can be determined using laser light diffractometry or a Zeta sizer. Plotting cumulative percentage drug release from nanosponges of different molecule sizes against time can be used to investigate the effect of particle size on drug release.

2.2 Loading Efficiency: [20]

The loading efficiency of nanosponge can be calculated by subtracting un-entrapped drug from the total amount of drug. A suitable method of analysis can be used to estimate the amount of untrapped drug. Dialysis, gel filtration, and ultra centrifugation are some of the techniques used to isolate unentrapped drugs. The loading efficiency is measured as follows:

$$\text{Loadingefficiency} = \frac{\text{Actual drug content}}{\text{Theoritical drug content}} \times 100$$

2.3 Porosity: [20]

The equation for percent porosity is,

$$\%\ \text{porosity (E)} = \frac{\text{Bulk volume} - \text{True volume}}{\text{Bulk volume}} \times 100$$

2.4 Zeta potential: [25]

Zeta sizer is used to determine the surface charge of nanosponge.

2.5 SEM and TEM: [25]

Used for morphological characterization and to determine shape of particles.

2.6 Fouriertransforms – infrared spectroscopy (FTIR): [20]

The presence of functional group can be determined using this tool.

2.7 Production Yield: [25]

$$\text{Production yield} = \frac{\text{Practical mass of nanosponges}}{\text{Theoritical mass of nanosponges}} \times 100$$

2.8 Solubility Studies: [20]

Higuchi and Connors model has described the phase solubility method used to study inclusion complexation, in which effect of a nanospongecan be examined, on the drug solubility. Degree complexation is indicated by phase solubility diagram.

2.9 In Vitro Release Studies [20]

A dissolution apparatus USP xxiii with a modified basket made of 5m stainless steel rotating at 150 rpm can be used to determine drug release from nanosponge. The dissolution medium is chosen after considering the solubility of the actives to ensure sink condition. A sample from the dissolution medium may be analysed using a suitable analytical process. In most cases Franz diffusion cell can also be used depending upon the formulation.

3. DRUG RELEASE KINETICS [20]

3.1 *In vitro* Diffusion Model

The donor compartment of a multicompartment rotating cell is filled with an aqueous dispersion of drug-loaded nanosponge (1ml), while the receptor compartment is filled with phosphate buffer at pH 7.4 or 1.2, separated by a hydrophilic dialysis membrane.

Each experiment takes 24 hours to complete.

At regular intervals, the receptor buffer is entirely removed and replaced with new buffer. A suitable analytical method is used to determine the amount of drug in the medium, and drug release is measured to determine the release pattern.

3.2 Resiliency: [20]

Sponge resiliency (viscoelastic properties) may be altered to create softer or firmer beadlets, depending on the final formulation's requirements. Increased crosslinking causes the rate of release to slow down. As a result, sponge resiliency will be studied and optimised in accordance with requirements, taking into account release as a function of crosslinking over time.

3.3 True density: [20]

An ultra-pycnometer can be used to determine the true density of nanosponge in helium gas.

4. APPLICATIONS

4.1 Oral Delivery: [17]

The complex can be dispersed in a matrix of diluents, excipients, lubricants, and anti-caking agents for oral administration in the form of capsules or tablets. Acetyl salicylic acid, a nonsteroidal anti-inflammatory drug (NSAID) classified as a BCS class III drug, was used to create nanosponges for use in an oral drug delivery system.

4.2 Topical delivery: [19]

Nanosponge components can be applied topically in the form of a gel or cream. Resveratrol-loaded nanosponges were believed to increase drug permeation in vitro on porcine skin. Nanosponges' ability to increase solubility at the skin's surface may also be attributed to their ability to enhance visitor molecule uptake by the skin.

4.3 Nanosponge as Chemical Sensors [17,26]

In rather sensitive detection of hydrogen nanosponge titania, the nanosponge which are kind of metallic oxides act as a chemical sensor. There is less Nanosponge components can be applied topically in the form of a gel or cream. Resveratrol-loaded nanosponges were believed to increase drug permeation in vitro on porcine skin. Nanosponges' ability to increase solubility at the skin's surface may also be attributed to their ability to enhance visitor molecule uptake by the skin. Hindrance to electron transport because the nanosponge structure has no contact point and it result in higher 3D interconnected nanospongeTitania which is sensitive to H2 gas.

4.4 Enhanced Solubility: [25]

βeta-Cyclodextrin based nanosponge of itraconazole have increase the solubility of insoluble drug. The solubility improvement is by fifty fold in comparison to ternary dispersion system. E.g.copolyvidonum.

4.5 Anti-viral application: [26]

Nanosponge is used in both the pulmonary and nasal delivery systems. It uses nanocarriers to deliver antiviral drugs based on small interfering ribonucleic acid (siRNA) to the nose or lungs, allowing it to treat viruses that cause respiratory tract infections such as rhinoviruses and influenza viruses. Zidovudine and saquinavir were used as nanocarriers.

4.6 Chemotherapy: [26]

Targeting a drug to a specific site while avoiding the immune system's impediment. Affected cancer cells, such as carcinoma or quick-acting glioma, were treated with nanosponges using a single injection dose. The use of cyclodextrins, which are suspended in water and become saturated with it, distinguishes the oxygen delivery system. They will be used to treat hypoxic tissues caused by a variety of illnesses. With the help of a nanosponge/ hydrogel system, a silicon form of membrane can be used for oxygen permeation.

4.7 As a Carrier for Biocatalysts and in the Delivery [23]

Nanosponge is used to transport biocatalysts as well as proteins, enzymes, vaccines, and antibodies. Biocatalysts and the release of proteins, enzymes, vaccines, and antibodies are carried by nanosponge. It requires industry-standard procedures that are linked to operating conditions. Non-specific reactions produce less product and necessitate increased pressures and temperatures, all of which consume a lot of energy and water in the downstream process. These disadvantages can be solved by using biocatalysts such as enzymes, which work in a mild environment and at a high reaction rate. Biocatalysts are carried by nanosponge, which allows proteins, enzymes, vaccines, and antibodies to be released. It involves manufacturing processes that are related to operating conditions. Non-specific reactions produce less product and necessitate increased pressures and temperatures, which lot of energy and water in the downstream process is used. Biocatalysts, such as enzymes, can overcome these disadvantages by operating in mild conditions and at fast reaction speeds.

5. CONCLUSION

Nanosponges can carry both hydrophilic and hydrophobic drug, and they are drug delivery system that allows controlled as well as predictable drug release at the effective target site, thereby improving efficacy and bio-availability. They can be formulated in various formulation such as topical, oral, and parental system.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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