IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

CREATING NANOSPONGES: A COMPREHENSIVE INSIGHT ON NANOSPONGES PREPARATION LINE AND APPLICATION

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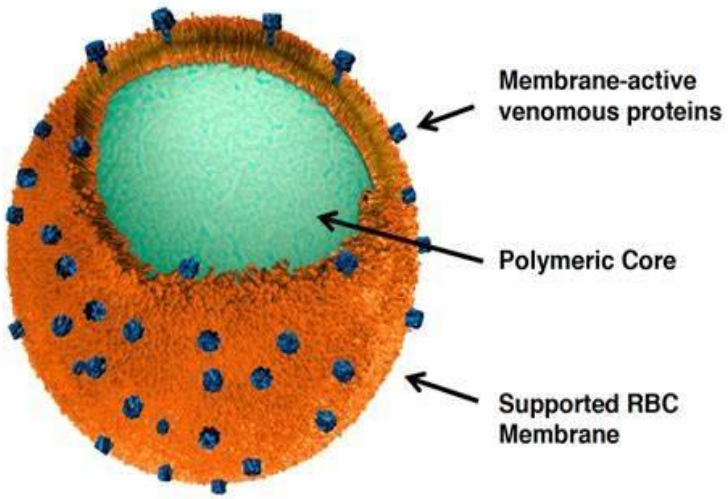
Abstract: The advancement of nanotechnology in the pharmaceutical field has piloted to the development of targeted drug delivery systems (TDDS). Effective drug delivery to the target site helps to reduce issues like such drug toxicity, low bioavailability and making drug release in a predictable manner. Furthermore, employing a drug delivery system to successfully target a drug molecule to a specific site necessitates a specialized drug delivery system. The discovery of one such nanosized drug delivery system called Nanosponges has proved a key step towards conquering many undesired drug effects by increasing the formulation flexibility. Nanosponges are porous structures having about a size of virus and can contain within them various hydrophilic and lipophilic drugs. These tiny sponges travel throughout the body until they encounter any previously determined spot, attach onto its surface, and begin the drug discharge in a controlled and expected fashion. This review attempts to emphasize the advantages, characteristics, preparation methods and application of Nanosponges.

Keywords: Targeted drug delivery systems (TDDS), porous structures, nanosponges, hydrophilic and lipophilic drugs.

I. INTRODUCTION: Pharmaceutical nanotechnology is a growing field of study with enormous promise as a delivery system for several powerful drugs and diagnostics. It is recognized as a specialized field for the delivery of drugs, as well as for the diagnosis, prognosis and treatment of illness employing nanoengineered instruments [1]. Nano drug carriers possess the advantage of traversing across the blood brain barrier, passing through pulmonary system, cross tumor endothelium and tight endothelial cell junctions [2]. Various nanoscale systems for drug delivery have been widely explored; they include liposomes, dendrimers, quantum dots, nanotubes,

polymeric biodegradable nanoparticles, nanosponges and nano capsules [3]. Among these, porous polymeric colloidal drug carriers called Nanosponges have been gaining tremendous importance from a past few years.

Nanosponge has a size range of around 50 nm – 100 nm [4]. These are 3-Dimensional polyester scaffold or a network that can break down naturally, thus derogatorily releasing the drug molecules loaded within it. To create Nanosponges, these polyesters are combined with a crosslinker in a solution [5]. A prime quality of Nanosponges is aqueous solubility, which makes them useful for drugs with limited solubility, this increases the flexibility of the formulation [6]. Nanosponges exhibit marketed benefits than other nanoparticles in terms of its size, porosity and easy engineering capability.



"Fig no.1: Polymer-based Nanosponges"

ADVANTAGES OF NANOSPONGES

1) Nanosponges show predictable and controlled drug release [7].
2) Due to sustained release, they show less variation in plasma drug concentration
3) As drug administration frequency is decreased, patient compliance increases.

4) Since the drug is entrapped into the core, the drug degradation can be avoided.

5) The engineering capacity is simple thus, easy scaleup.

6) The pore size is 0.25 micrometre rendering the bacteria helpless to pass through it, they have a self-sterilizing tendency.

7) Nanosponges can dramatically lessen drug sensitivity without compromising their effectiveness.
8) They are readily regenerable using techniques like washing, breaking with somewhat inert gases, using liquids that are beneficial to the environment, mildly increase the temperature, or varying the ionic or pH value.
9) Due to the inclusion of crosslinkers and other components in the manufacture of NSs, the encapsulated medication is shielded from first pass metabolism.

DISADVANTAGES OF NANOSPONGES

1) Only small therapeutic molecules can be incorporated by the NSPs.
2) The degree of crosslinking has an impact on the ability to load drugs because it controls the amount of empty space in NSs that is accessible for loading.
3) Due to the swift breakdown of crosslinker, there is a chance of dosage dumping.

CHARACTERISTICS OF NANOSPONGES:

Many features of nanosponges make them different from other nanoparticles. Some of them are as discussed below:

- They have a tiny size dispersion and a mean diameter that is less than 1μm.
- It is a kind of encasing nanoparticle that can keep the therapeutic molecule inside its core [8].
- NSs are non-lethal and are stable upto temperatures of approximately 300 °C [9].
- Since carbonate NSs have a greater zeta potential, they generate stable water suspensions which does not agglomerate over time. Their zeta potential is around 25 mV.
- Their three-dimensional design enables the collection, transport, and controlled release of several chemicals**.**
- Nanosponges can connect more effectively to the target region owing to chemical linkers.
- Nanosponges can create inclusion- and non-inclusion-containing complexes by combining with various drugs [10].
- NSs exist in both crystalline and para-crystalline form which mainly depend on the processing conditions. This crystallization property of NSPs helps in determining its drug loading capacity.
- They have excellent aqueous solubility, making it possible to give medications that are not well soluble in water. Both water loving and oil loving drug molecules can be caged in NSs for drug delivery purposes [11].
- Nanosponges can also acquire magnetic qualities by including magnetic particles in the reaction mixture.

COMPONENTS OF NANOSPONGES: [12]

Numerous substances have produced promising results and can be utilized to create NSIIs, depending on the desired kind of NS and the required degree of crosslinking.

Polymers: - Hyper Cross-linked Polystyrene, Cyclodextrins, and their derivatives such as Methyl β-Cyclodextrin, Hydroxy Propyl β-Cyclodextrin, and Alkyloxy carbonyl Cyclodextrins.

Copolymers: -Poly(valerolactoneallylvalerolactone) and Poly (valerolactoneallylvalero- lactone Oxepanedione), Ethyl Cellulose, Poly Vinyl Alcohol.

Cross-linkers: - Carboxylic acid dianhydrides and carbonyl diimidazoles, Diisocyanates, Diphenyl Carbonate, Diarylcarbonates, Dichloromethane, Glutaraldehyde, Pyromellitic anhydride, 2,2-bis (acrylamido) Acetic acid, Epichloridine

II. METHODS OF FORMULATING NANOSPONGES:

The preparation of nanosponges is mostly based on the delivery method, polymer, nature of the medication, and solvents.

1) **Nanosponges prepared from hyper-cross linked β-cyclodextrins**:

Hyper-cross linked β-cyclodextrin nanosponges were made by adding 17.42g of anhydrous -CD to 100ml of dimethyl formamide (DMF) in a flask with a round bottom flask and shaking the mixture to accomplish full dissolution. The solution was then combined with 9.96g of carbonyl diimidazole (61.42m mol) and allowed to react for 4 hours at 1000°C. The block of hyper cross-linked cyclodextrin was roughly crushed when condensation polymerization was finished, and more deionized water was added to remove DMF. Finally, Soxhlet extraction with ethanol was used to thoroughly eliminate any remaining by-products or unreacted chemicals [13]. The resulting white powder was then dried throughout the whole night at 600°C. The obtained fine powder was dissolved in water. The colloidal component that was still floating in the water was retrieved and lyophilized. The produced nanosponges have a spherical form and are sub-micron in size [14].

2) Ultrasound assisted synthesis:

In this method, the polymer and the crosslinker are allowed to react with each other while they are subjected to sonication for 5 hours without the addition of a solvent, in a flask. The product thus obtained is washed with water to remove any unreacted polymer contained in it. After allowing it to cool, the unreacted polymer was rinsed away with water. Store the product at 250°C after vacuum-drying it [13].

3) Emulsion solvent diffusion method:

Polymers like ethyl cellulose and polyvinyl alcohol are mainly employed in Emulsion solvent diffusion method. The inner phase consists of drug-ethyl cellulose dispersion phase, dissolved in 20 ml dichloromethane, it then being added into the continuous phase containing specified amount of aqueous solution of polyvinyl alcohol. Keeping on a magnetic stirrer, the solution is stirred for 2 hours at a rotating speed of about 1000 rpm. The formed nanosponges are then collected by filtration, dried in oven for 24 hours at 40°C. Finally, the dried Nanosponges are stored in desiccators [15].

4) Quasi Emulsion method:

The dispersed phase is produced by Eudragit RS 100 and then mixed with appropriate solvent. The drug intended to be integrated is prepared as a solution and dissolved at 35° by ultrasonic technology. Followed by addition of inner phase into external phase containing polyvinyl alcohol. Mixture is then agitated for 3 hours at a rate of 1000-2000 rpm and in a hot air oven dried for 12 hours at 40°C [16].

5) Bubble electrospinning:

A syringe, syringe pump, a high-voltage power source, together with grounded collector makes majority of a traditional and typical electrospinning design. Polyvinyl alcohol is an additional polymer that may be utilized in bubble electrospinning. It was organized into a 10% polymer solution by adding distilled water to it, which was

then heated to between 80 and 90 °C for two hours to create a one-phase mixture. The polymer solution was then allowed to reach at room temperature before being employed to create nano porous fibers [17].

III. DRUG LOADING CAPABILITY INTO NANOSPONGES:

Nanosponges intended for drug delivery are pre-treated by suspension in water, to avoid the aggregation of particles and then sonication. This gives a particle size below 500 nm. Centrifugation process is done on the Nanosponges to obtain a colloidal solution, on freeze drying separates into supernatant and the Nanosponges are dried. Drug in excess amount is added and constantly stirred and is maintained for specific time to facilitate complexion process. As a result of centrifugation, the undissolved drug from the complexed drug is segregated [18]. Finally, the solid crystals of Nanosponges are obtained by solvent evaporation or by freeze drying [19].

IV. MECHANISM OF RELEASING DRUG FROM NANOSPONGES:

The surface of Nanosponges contain several pores on it. These pores allow the movement of the drug through them. When the fluid has reached the point of drug molecule saturation, the final products are then pressed into the skin or they are ingested. This causes a condition of unsaturation, which upsets the balance by lowering the amount of drug in the vehicle. The process continues until all the drug in the body has been absorbed [20].

V. CRITERIA FOR DRUGS TO BE LOADED INTO NANOSPONGES:

Drugs, to be loaded into Nanosponges formulation must meet certain qualities as mentioned below:

1) The molecular mass of the drug must be in the range of 100 and 400 D.

2) 5 condensed ring structures must be present in drug molecule structure.

3) Melting point must be lower than 250°C

4) Aqueous solubility of drug must be lower than 10 mg/ml. [21].

VI. FACTORS AFFECTING NANOSPONGES DRUG RELEASE:

1) Type of cross-linker and polymer chosen:

The type of the polymer and cross-linker employed effects the drug entrapment and the organ targeting. Depending upon the crosslinker and the polymer type, the Nanosponges become soluble in water or any other solvent [22].

2) Temperature:

Many of the entrapped active molecules may be very viscous to spontaneously flow from sponges onto the skin at ambient temperature, but higher skin or environment temperatures may cause the flow rate to rise and finally cause the medicine to be released [23].

3) Medium used for interaction:

The medium used for the drug loading facilitates the contact between the Nanosponges pores and the drug particle. Depending on it, the drug release occurs. To contain hydrophilic molecules, Nanosponges are formulated in

hydrophilic medium, whereas to unleash organic molecules, organic phase is employed. The polarity of media, size and structural properties determine the interaction between the host-guest molecule [24].

4) Degree of crosslinking:

The Nanosponges complexation ability is chiefly influenced by the presence of substituents on the parent molecule. More the amount of substituent, greater is the degree of crosslinking thus, the final result is a porous, network like Nanosponges [25].

VII. CHARACTERIZATION OF NANOSPONGES:

1) Particle size analysis:

Particle sizes are kept constant throughout polymerization to provide free-following powders with a fine aesthetic look. Malvern zeta sizing or laser light diffractometry can be used to analyze the particle size of loaded and unloaded Nanosponges [26].

2) Determination of entrapment efficiency:

Entrapment efficacy of manufactured Nanosponges is calculated by subtracting the quantity of actives that has not been entrapped from the total amount of drug. Any acceptable method of analysis must be used to estimate the unentrapped medication. Loading efficiency is determined as follows:

$$Entrapment\ Efficiency = \frac{Practical\ drug\ content}{Theoretical\ drug\ content} \times 100$$

3) Drug content determination:

10 mg drug is dissolved is dissolved in 10 ml methanol in 10 ml volumetric flask. The solution is then filtered and the absorbance of the resulting solution was measured using UV-Vis spectrophotometer [27].

The following equation is used to calculate the drug content:

$$Drug\ content = \frac{Actual\ drug\ content}{Theoretical\ drug\ content} \times 100$$

4) Production yield:

The ratio of initial weight of all raw materials and the final weight of obtained Nanosponges gives the production yield [28].

5) Porosity:

The study evaluates the extent of nanopores and nanocavities formed inside the Nanosponges. The gas flow through the channels in Nanosponges is measured by helium pycnometer [29].

Calculated by the formula:

$$\%\ Porosity = \frac{Bulk\ volume - True\ volume}{Bulk\ volume} \times 100$$

6) Fourier Transform Infrared Spectroscopy (FTIR):

FTIR studies are involved in the work to determine the structure elucidation and to know interactions occurring if any. The drug and polymers employed in the fabrication of nanosponges are desired to be compatible with each other. The bands of Nanosponges usually changes moderately upon complex formation [30].

7) Differential Scanning Calorimetry:

DSC studies give a brief knowledge whether the drug has undergone any changes in thermal degradation when are formulated into Nanosponges. Differential scanning calorimetry (DSC) is an effective analytical technique for determining the physical characteristics and thermal transitions of polymeric materials. DSC is used to investigate phase transitions like melting and exothermic decompositions, as well as glass transitions [31,32].

8) Powder X-ray Diffraction Study

The P-XRD studies are carried out to evaluate the crystallinity or the crystalline nature of the compound. The formulations are looked on for the peak sharpening, appearance or disappearance of peaks or peak shifting.

9) Scanning electron microscopy (SEM)

To analyze the surface morphology of the prepared Nanosponges, SEM studies are carried out. Through SEM studies, the external appearance of the Nanosponges can be illustrated.

10) In-vitro drug release studies:

The dissolution pattern of Nanosponges is studied by USP Type-1 (rotating basket) set at 50 RPM and a temperature of 37 ± 5°C. The selection of dissolution medium depends on the solubility of the active moiety. At pre-determined intervals, the sample is withdrawn and replaced with fresh medium. The absorbance of the sample is then analysed by UV spectroscopy [21].

11) Drug release kinetics study [33]

To better understand the release pattern of drugs from nanosponges, the release data is analysed employing the Zero order, First order, Higuchi and Korsmeyer Peppas models. The mathematical equations are as given below:

Zero order:	$Q_t = Q_0 + K_0 t$	(1)
First order	$\text{Log } ct = \log c_0 \frac{-k1t}{2.303}$	(2)
Higuchi model	$Q = K_H - t^{1/2}$	(3)
Korsmeyer-peppas model	$Mt / M\infty = K_m t^n$	(4)

VIII. APPLICATIONS OF NANOSPONGES:

1) Nanosponges in drug delivery:

Attributing to the porous nature of the nanosponges, they can contain within them various hydrophilic and hydrophobic molecules. This quality makes them ideal to carry BCS Class-II drugs having low solubility rate creating a successful delivery of such drugs. Owing to their solid nature, they can be developed as oral, parenteral, topical, and inhalational dosage form [34].

2) Nanosponges as Solubility Enhancers:

The crosslinking agent and cavities present in the nanosponge structure facilitates interaction with active chemicals. These characteristics allow many compounds to be incorporated and solubilized in the resulting cavities. Cyclodextrins possess the ability of complex forming with moieties, making them suitable for enhancing the solubility of poor soluble drugs [35].

3) Sustaining the drug release:

Nanosponges show a controlled and a gradual release of drug molecules once entrapped into them. This sustained drug release can overcome the need of frequent drug administration, thus reducing the adverse effects, and increasing the patient compliance [36].

4) Nanosponges as a Photoprotective Agent:

Nanosponges were created by encapsulating gamma-oryzanol and demonstrated good photoprotection. Gamma-oryzanol (a ferulic acid ester combination), an anti-oxidant that is commonly used to stabilize food and pharmaceutical raw materials, is also utilized as a sunscreen in the cosmetics sector. Its uses are limited due to its extreme instability and photodegradation. A gel and an O/W emulsion are created using gamma oryzanol-loaded nanosponges.

5) Nanosponges in Antiviral Treatment:

Medication administered by doctors are sometimes rendered useless in cancer patients as they are either unable to penetrate the tumor location, or the immune system attacks and dismembers them. The usage of NS has helped to overcome this impediment to some extent. According to experts, fixing NS medicines ensured that sufficient amounts of the substance reached their objective. The primary element in Paclitaxel is Taxol, which is beneficial in anticancer treatment and is a successful drug that has been produced as an NS formulation [21].

6) Absorbent in treating poison in blood:

The harmful noxious substances circulating in the blood, that are hazardous to the body can be soaked up by using Nanosponges. In the red blood stream, Nanosponges appears like red blood cells, attracting toxins into targeting them and then consumes it [37].

7) As a gas carrier:

The polymers which are employed to create the Nanosponges, contain within them several chambers that form an inclusion complex. Such inclusion complexes act as gas reservoirs and have the capacity to store enormous volumes of gases like carbon dioxide and oxygen [38].

8) For transportation of biocatalysts, enzymes, proteins and vaccines:

It has recently been shown that CD-based NS are particularly suitable carriers for adsorbing antibodies, enzymes, proteins, and macromolecules. Specifically, the pH and temperature range of activity may be enlarged and continuous flow operations can be carried out when enzymes are utilized. They can also maintain their function, performance, and operation [37].

10) Nanosponges as a protective aid: Gamma-oryzanol is a combination of ferulic acid chemical compounds that is commonly used to stabilize food and pharmaceutical products as well as a sun blocker in the cosmetic industry. High photo instability and degradation limits its use, enclosing into Nanosponges system can be helpful to overcome this drawback [39].

IX. Some of the drugs enclosed into Nanosponges are as:

Table no 1: List of drugs incorporated into nanosponges

Drug	Therapeutic activity	Attributes	Administration route
Itraconazole	Antifungal	Enhanced drug solubility	Oral, topical
Econazole Nitrate	Antifungal	Prolonged drug release	Topical
Resveratrol	Antioxidant	Enhanced stability, permeation, cytotoxicity, controlled drug release	Oral, topical
Curcumin	Antineoplastic	Enhanced activity, solubilization	Parenteral
Camptothecin	Antineoplastic	Improved stability and activity	Parenteral
Dexamethasone	Anti-inflammatory	Enhanced drug solubility	Oral, parenteral
Acyclovir	Antiviral	Enhanced antiviral action prolong release	Oral, topical and parenteral

X. Conclusion:

Pharmaceutical Nanosponges has a new scope of study with better opportunities in different areas of diagnosis and treatment. Nanosponges in drug delivery has the benefit of improving drug absorption via biological membranes and serving as a valuable transporter for pharmaceuticals to create instant release formulations. As they can entrap both hydrophilic and lipophilic molecules, the undesired effects of majority of the drugs like toxicity, less bioavailability and uncontrolled drug release could be overcome. Thus, nanosponges may prove to a potential candidate for safe and effective sustained drug delivery as well as an attempt towards growing interests to manufacture formulations for compliance of elderly patients.

XI. Acknowledgement

I owe my humblest thanks to my guide for his valuable guidance and support throughout this work.

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