A REVIEW OF THE METHODS INVOLVED IN THE PREPARATION OF NANOSPONGES

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***ABSTRACT:** Pharmaceutical nanotechnology is comprised of nano-sized products which can be transformed in numerous ways to improve their characteristics. A Nanosponge is a novel and emerging technology, which offers targeted and controlled drug delivery for topical as well as oral use. The tiny sponges will circulate the body. They touch and adhere to the surface of the particular target site and begin to release the drug in a regulated and predictable way.Nanosponges are tiny in size with a 3-dimensional network and a nanometric cavity size. Nanosponges are highly porous having the unique ability to entrap active moieties and offer a unique advantage of programmable release. The discovery of nanosponge has become a significant step in overcoming certain problems such as drug toxicity, poor bioavailability, and the release of drugs in a predictable fashion as they can accommodate both hydrophilic and hydrophobic drugs. They are biologically safe and simple to produce.Nanosponges can also be used as a carrier for biocatalysts in the delivery and release of enzymes, proteins, vaccines, and antibodies.*

***Keywords:**Nanosponge,Pharmaceutical nanotechnology,Emerging technology, Methods.*

I. INTRODUCTION

Nanotechnology involves the design and modification of materials on a nanoscale to produce products with enhanced properties. A nanometre is one billionth of a meter, and nanomaterials are physical substances with at least one dimension in the range of 1–100 nm.[1]Nanotechnology enables precise control at the nanometre scale, allowing for the engineered synthesis and assembly of substrates with specific chemical and physical properties.[2] This molecular precision facilitates the encapsulation of diverse substances such as antineoplastic agents, proteins, peptides, volatile oils, and DNA within colloidal structures known as NSs, offering a broad range of applications.These particles possess the capability to transport both lipophilic and hydrophilic substances, enhancing the solubility of poorly water-soluble molecules.[3]Nanosponges have a limitation in accommodating only small molecules and can exist in either paracrystalline or crystalline forms. Their loading capacity is primarily influenced by the degree of crystallization. Paracrystalline nanosponges exhibit varying loading capacities. These structures can be synthesized with specific sizes, allowing controlled drug release by adjusting the cross-linker to polymer ratio. [4] The engineering feasibility of nanosponges stems from the straightforward chemistry of their polyesters and cross-linking peptides, distinguishing them from more complex nanoscale drug delivery systems.[5]Various nanoparticle configurations, including polymeric nanoparticles, hard-phospholipid nanoparticles, nanoemulsions, nanosponges (NSs), carbon nanotubes, micellar systems, and dendrimers, are accessible.

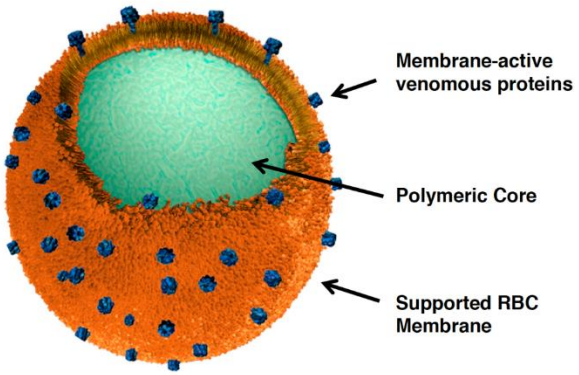

Fig-1: Nanosponges

Nano sponges, characterized by their solid nature, can be formulated into various dosage forms, including Oral, Parenteral, Topical, or Inhalation formulations. In the case of oral administration, these complexes can be dispersed within a matrix comprising excipients, diluents, lubricants, and anticaking agents. This formulation is well-suited for the preparation of capsules or tablets.[6]Nanosponges are intricate formations typically crafted from elongated molecules that undergo folding through cross-linking, resulting in a more or less spherical structure comparable in size to a protein. The construction of nanosponges commonly involves the crosslinking of cyclodextrins with organic carbonates.[7]

Advantages of nanosponges[8]

- Increase aqueous solubility of the poorly water-soluble drug.
- Nanosponges can release the drug molecules in a predictable fashion.
- Nanosponges drug delivery systems are non-irritating, non-mutagenic, and non-toxic.
- Nanosponges help to remove the toxic and venom substances from the body.
- Nanosponges drug delivery system minimizes side effects.
- Increase formulation stability and enhance the flexibility of the formulation.
- Reduce dosing frequency.
- Better patient compliance.
- Nanosponges complexes are stable over wide range of pH (i.e. 1-11) and a temperature of 130 °C.

Disadvantages of nanosponges[9]

- Nanosponges have the capacity of encapsulating small molecules, not suitable for larger molecules.
- Dose dumping may occur at times

II. MECHANISM OF DRUG RELEASE FROM NANOSPONGES

Since the nanosponges have an open structure (in the surroundings of nanosponges they do not have any continuous membrane), the active substance is added to the vehicle in an encapsulated form. The encapsulated active substance can move freely from the particles into the vehicle until the vehicle gets saturated and the equilibrium is obtained. As soon as the product is applied on to the skin, the vehicle containing the active ingredient gets unsaturated causing a disturbance in the equilibrium. Thus, the flow of active substances from nanosponge particles into vehicles starts inthe epidermis until the vehicle is either absorbed or dried. Even after the retention of the nanosponge particles on the surface of the skin i.e. the stratum corneum, the release of active substance continues to the skin for a long period.[10]

Factors Affecting Formulation of Nano sponge

Degree of substitution:[11]

The complexation ability of the nanosponge may be strongly influenced by the kind, quantity, and location of the substituent on the parent molecule.

Method of preparation:[12]

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.

Temperature:[13]

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:[14]

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.

Type of polymer and crosslinkers:[15]

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. Crosslinkers aid in the formation of a 3D structure of nanosponges. The amount of crosslinker utilized affects drug entrapment as well as organ targeting. The crosslinker utilized 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 utilizing hydrophilic nanosponges in drug delivery is that theyenhance drug absorption across biological

membranes and are a valuable transporter for pharmaceuticals to produce quick-release formulations.

III. Preparation Methods

Solvent method:[16]

Mix the polymer with a suitable solvent, in particular like as dimethylformamidedimethylsulfoxide, a polar aprotic solvent. Then apply this mixture to the cross-excess linker's amount, preferably 4 to 16 in the crosslinker/polymer molar ratio. The reaction is carried out at a temperature varying from 10 °C to a solvent reflux temperature ranging from 1 to 48h. Cross-linkers that are favoured**.**

Polymer is mixed with a suitable solvent like polar aprotic solvent.This mixture is added to quantity of the cross linker preferably in cross linker /polymer molar ratio of 1:4.Action is carried at temperature ranging from 10°C to the reflex temperature of the solvent, for time ranging from 1-8 hours.After completion of the reaction, the solution is cooled at room temperature and the product is added to large excess of distilled water.This recovery of the product is done by filtration under vacuum.

Hyper cross-linked b - Cyclodextrin:[17]

Nanosponges were prepared from β-cyclodextrins as nanoporous materials used as carriers for drug delivery. Nanosponges are recently developed hyper-cross-linked cyclodextrin polymers nano structured to form 3-dimensional networks. A roughly spherical structure, about the size of a protein, with channels and pores inside. They have been obtained by reacting cyclodextrin with a cross-linker such as diisocianates, diarylcarbonates and carbonyl diimidazoles, carboxylic acid dianhydrides and 2, 2-bis (acrylamido) acetic acid. The surface charge density, porosity and pore sizes of sponges can be controlled to attach different molecules. In the neutral or acidic forms, nanosponges can be synthesized in one-step or two-step processes depending on the physico-chemical properties of the drug to be loaded. If the drug is normally an inert non-polar substance, it is called porogen, which produces the porous structure. Porogen drug is stuck with onset, which does not impact and activated by polymerization, even stable to free radicals.

Ultrasound-assisted synthesis:[18]

In this method, the nanosponge has been obtained by reacting polymers with the cross-linker in the absence of the solvents and sonication. It is obtained by this method, it will be spherical and uniform in size. The mix of the polymers and cross-linkers in a particular molar ratio in the flask and placed the flask in ultrasound bath and filtered with water. It is heated at 90°C. Sonicated the mixture 5 hours. Then allow the mixture to cool and breaking the product and wash the product with water to remove the polymers. The prolonged soxhlet extraction with ethanol and dry obtained the products.

Loading of drug into nanosponges:[19]

Suspend the nanosponge in water and sonicated to avoid the presence of aggregates and then centrifuge the suspension to obtained the colloidal fraction. Separate supernatant and dry the sample by freeze drying. The amount of drug and maintain the suspension under the stirring for specific time required for complexation. After complexation, Separate the undissolved drug from complex drug by centrifugation. Then obtained of the solid crystal of nanosponge by solvent evaporation or freeze drying and formed nanosponge.

Characterization

Solubility studies:

Inclusion complexes is a technique by which can determine the solubility and bioavailability of the drug. This technique is the most widely approached technique for analysis of the inclusion complexes of nanosponges. Degree of completion can be known by the plot of phase solubility. Solubility studies are conducted to access the pH of the drug, solubilization outline and to evaluate the factors affecting drug solubility. [21]

Microscopic study:

Microscopic studies of nanosponges/drug can be conducted by using scanning electron microscope and transmission electron microscope. Inclusion complex formation is indicated by the difference in the crystallization state and the product seen under an electron microscope. [22]

Zeta potential determination:

Zeta potential can be defined as the difference of potential between two layers (dispersion medium and immobile layer) of fluid locked up with dispersed particles. Zeta potential is the major key indicator for the stability of the colloidal dispersion. By adding an extra electrode on particle size equipment or zeta seizer, the zeta potential can be measured. The higher the value of the zeta potential of a colloidal dispersion more is its stability. [23]

Particle size and polydispersity:

Particles size is determined by the process of dynamic light scattering using 90Plus particle size determining software. Dynamic light scattering (DLS) is defined as a technique used to find out the size distribution profile of

nanoparticles. At last, the final diameter of the particles and poly-dispersity index (PDI) can be found. [24]

Loading efficiency:

The loading efficiency of a nanosponge particle can be determined by the estimation of drug loaded into the nanosponge using UV spectrophotometer and high-performance liquid chromatography method for the nanosponges.[25]The loading efficiency of nanosponges can be calculated by using the following equation.

Loading efficiency= Actual drug content in nanosponges/Theoretical drug content*100

In vitro release studies:

In vitro release kinetics experiments are carried out using a multi compartment rotating cell. An aqueous dispersion of nanosponges (1ml) containing the drug is placed in the donor compartment, while the receptor compartment separated by a hydrophilic dialysis membrane is filled with phosphate buffer of requires pH. The experiment is carried out for 24hr. At fixed time intervals, the receptor buffer is completely withdrawn and replaced with fresh buffer. The amount of drug in the medium is determined by the suitable analytical method and drug release is calculated to determine the release pattern.[26]

Applications of Nanosponges

Solubility enhancement:

Wetting and solubility of molecules with very low water solubility can be enhanced by nanosponges. Within the nanosponge structure, the drugs can be molecularly distributed and then released as molecules, preventing the dissolution stage. It is possible to improve the apparent solubility of the compound. Many problems with formulation and bioavailability can be solved by improving a substance solubility and dissolution rate and nanosponges can significantly increase the solubility of the drug. [27]

Nanosponges for drug delivery:

In nature, the nanosponges are solid and can be formulated as dosage forms of oral, parenteral, topical or inhalation. Complexes may be distributed in a matrix of excipients, thinners, lubricants and anticoagulants appropriate for the preparation of capsules or tablets for oral administration. The complex may be transported simply in sterile water, saline or other aqueous solutions for parenteral administration. They can be incorporated efficiently into topical hydrogel for topical administration.[28]

Topical agents:

A novel technique for the controlled release of extended drug release topical agents and drug form retention on the skin is the nanosponge delivery system. Local anaesthetics, antifungals and antibiotics are included in the category of drugs that can be easily produced as topical nanosponges. When the skin is penetrated by active ingredients, rashes or more serious side effects may occur.[29]

Cancer Therapy:

An a significant thing in cancer is to direct drugs to a particular site, which decreases the side effect and improves bioavailability. Nanosponges, such as breast cancer, colon cancer, brain cancer, lymph carcinoma, lung cancer, are treated for various cancers using a single dose of injections. A plant alkaloid that is used as the antitumor agent, camptothecin (CAM). Owing to its limited therapeutic usefulness and extreme side effects, it has poor aqueous solubility. Nanosponges based on cyclodextrin (NS) are a new class of cross-linked cyclodextrin derivatives used to target anti-cancer drugs. This is used to improve the solubility of the poorly soluble drug, to protect and monitor the release of labile groups.[30]

Antiviral application:

To target nasal and lung drugs, nanosponges are used. It delivers the antiviral drug to target viruses that may cause RTI (Respiratory tract infection) infection such as influenza virus, rhinovirus, through nanocarriers to the lungs or nasal path. Zidovudine and Saquinavir are examples of nanocarriers used in pharmaceutical goods.[31]

Encapsulation of gases:

The inclusion complexes with three different gases i.e. 1-methylcyclopropene, oxygen and carbon dioxide, were developed using cyclodextrin-based carbonate nanosponge. Oxygen or carbon dioxide complexion can be beneficial for many biomedical applications. The oxygen-filled nanosponge could, in particular, supply oxygen to the hypoxic tissues that are present in different diseases. The Nanosponge was also explored as a powerful gas carrier because of its super porous existence. The composition of nanosponge demonstrates the capacity to store and release oxygen in a regulated manner. They may be a helpful method for the distribution of certain essential gases in the future.[32]

Nanosponges as a carrier for biocatalysts:

Cyclodextrin-based nanosponges have been found to be basically efficient carriers for the adsorption of enzymes, antibodies, proteins, and macromolecules. The creation of nanosponge can maintain its activity, efficiency, extend

its operation, activity range of pH and temperature, specifically when enzymes are used, and allow continuous flow processes to be carried out in addition, by adsorbing or encapsulating, proteins and other macromolecules can be transferred to cyclodextrin nanosponges.[33]

IV. 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. This technology provides ingredient capture and thus, decreases side effects, improves stability, increases beauty, and enhances versatility in formulation. Therefore, by offering a site-specific drug delivery system and extending dose intervals to increase patient compliance. For the solution of various nano-related problems in pharmaceutical energy, nanosponge formulation may be best.

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