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Nanosponges: The Promising Carriers for the Targeted Delivery of Drugs

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Abstract: *For a Long time, There has been a desire for an effective targeted drug delivery system, But the chemistry's complex Form has made things difficult but the development of noval colloidal carriers Known as nanosponges (NSs) is Anticipated to solve these Issues. Nanosponges are the nanoporous particles that can entangle a wide range of materials and then be included into a suitable formulation depending on the route of administration. They Delay drug release in a controlled manner, stop drug protein breakdown, and release the medication at the desired Location. They can move around the body and attach on the surface and Releasing the Medication at the precise targeted place in a controlled and predictable manner. Due to their fine aqueous solubility, they act as a barrier for medications with low water solubility. The ideal candidates for this kind of carrier system are medications with low bioavailability. Both hydrophillic and lipophilic drugs can be loaded in Nanosponges. Nanosponges are a better candidate for targeted drug administration because to their numerous uses in recovering the bioavailability of active ingredient molecules and delivering the active ingredient via oral, topical, parenteral, and nasal routes. It can be used as a carrier for biocatalysts in the transport and release of enzymes, proteins, vaccines, and antibodies. They can be prepared by Various methods such as emulsion solvent diffusion method, melt method, ultrasound-assisted method, Quasi emulsion solvent diffusion method.*

Keyword*: Nanosponges, Targeted Delivery, Controlled release, Polymers*

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I. INTRODUCTION

Pharmaceutical and Healthcare industries created nanoscale materials for the treatment of diseases caused by chemical and biological issues.[1]. Nanotechnology has so far Produced a Number of variations, including nanoparticles, nanocapsules, nanospheres, nanosuspensions, nanocrystals, and nanoerythosomes, All of these systems help Deliver drugs to specific areas of body.[2]. The term "Targeted drug delivery system" also known as smart drug delivery system Refer to a Method of administering medication to patients that increase the concentration of the drug in targeted organ.[3]. A controlled and predictable method of delivering drugs to the target place is provided by Nanosponges. They are non-mutagenic, non-irritant, non- allergenic, and nontoxic [4]. Nanosponges are Tiny sponges With a size of a virus, which can be filled with a wide variety of drugs [5]. Nanosponges can swell Significantly depending on crosslinker to polymer ratio and They are synthesized as an acidic or neutral in nature [6]. Cyclodextrin Based Nanosponges can be created by hypercross-linking of cyclodextrin polymer with the proper crosslinking agent [7,8]. Both hydrophilic and lipophilic drug molecules can be carried by them because of their outside hydrophilic branching and inside lipophilic cavities. The crosslinkers used in the Nanosponges enables them to combine to the target site. They are solid in character and can be found harmless for various routes [9]. Depending on the route of administration, they can be originated as oral, topical, parenteral, and inhalational formulations [10,11].

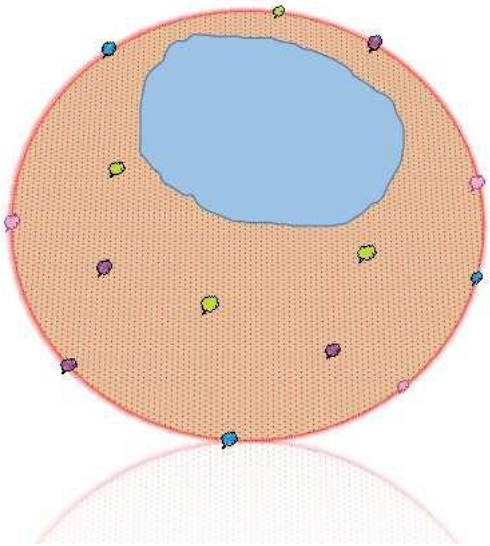

Figure No.1: Structure of a Nanosponge

ADVANTAGES OF NANOSPONGES[12,16]

- Improve aqueous solubility of the poorly water-soluble drug.
- The drug molecules can be released via Nanosponges in a controlled manner.
- The Nanosponges function as a self-sterilizer since bacteria cannot pass through their tiny pore sizes.
- Nanosponges drug delivery system are biodegradable, non-irritating, and non-toxic.
- Nanosponges drug delivery system minimize side effect.
- Increase formulation stability and enhance the flexibility of the formulation.
- Reduce dosing frequency.
- Better patient compliance.
- Easy scale up for industrial manufacturing.
- Nanosponges complexes are stable over wide range of pH (i.e. 1 to 11) and a temperature of 300 °C.

II. METHODS OF PREPARATION

1. Melt method

Melt technique In melt technique cyclodextrin is react with a suitable crosslinker such as dimethyl carbonate, diphenyl carbonate, isocyanates, diaryl carbonates, carbonyldiimidazole (C7H6N40), carboxylic acid anhydrides, and 2, 2-bis (acrylamide) acetic acid. All ingredient are delicately integrated and put in a 250 mL flask warmth at 100°C, and the reaction is conceded out for 5 h using magnetic stirrer. The mixture is endorsed to cool and the prepared product is bust down and to eradicate unreacted excipients the product is washed with a proper solvent.[17,18]

2. Solvent diffusion method

- ***Emulsion Solvent diffusion technique***

In this technique, two diverse extents of organic and aqueous phases are used. In organic phase, drug and polymer are integrated, and in aqueous phase, polyvinyl alcohol (PVA) is used. After dissolving drug and polymer to the right organic solvent, this phase is slowly mixed to the aqueous phase and agitates for 2 or more h at 1000 rpm using magnetic stirrer. Then, the ready NSs are composed by filtration washed and then dried in air at room temp or in vacuum oven 40°C for 24 h.[19-21]

- ***Quasi Emulsion Solvent diffusion***

In this process, the polymer is dispersed in an acceptable solvent, and this phase is called an inner phase. In ultrasonication at 35°C, drug is mixed to this solution. Then, the inner phase is poured into the outer phase, which contains a mixture of PVA in water. Then, the suspension is agitated for 60 min using magnetic stirrer at 1000 rpm. Then, the produced NSs are filtered and dried in a hot air oven at 40°C for 2 h.[22-25]

3. Solvent Method

In this type, the polar aprotic solvent such as dimethylformamide, dimethyl sulfoxide is added with a suitable polymer. Then, this blend is mixed to a huge amount of the crosslinker in the molar proportion of 4–16. The

response is conceded out at a temperature ranging from 10°C to the reflux temperature of the solvent, for time vary from 1 to 48 h. Favored crosslinkers are carbonyl compounds dimethyl carbonate and carbonyldiimidazole (C7H6N4O) etc. After finishing of the reaction, the mixture is sanctioned to cool at room temperature, then the compound is mixed to an overload of distilled water and improved the compound by percolation under vacuum and instantly purified by long-lasting Soxhlet extraction with ethanol, and finally the product is dried out under vacuum. To obtain a fine powder, the dried product is grinded in a mechanical mill.[26-28]

4. Ultrasound Assisted Technique

In this method, the polymer is reacted with crosslinkers in the dearth of solvent and under sonication. The formed NSs will be spherical, uniform in size and smaller than 5 µm. In this technique, diphenyl carbonate or pyromellitic anhydride is utilized as crosslinker. A sufficient quantity of anhydrous cyclodextrin is a place to act in melted di-phenyl carbonate at 90°C for time interval of 5 h. Permit the combination to refrigerate and smash the formulation roughly. Then give washing to the product with water and Soxhlet extracted with ethanol to get rid of both unwanted and unreacted diphenyl carbonate. Later than decontamination, NSs is stored at 25°C until extra use. [29-33]

III. MECHANISM OF DRUG RELEASE FROM NANOSPONGES

Since the nanosponges have an open structure (in the surrounding 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 is able to 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 to epidermis until the vehicle is either absorbed or dried. Even after the retention of the nanosponge particles on the surface of skin i.e. the stratum corneum, the release of active substance continues to skin for a long period of time.

IV. FACTORS INFLUCING FORMULATION OF NANOSPONGES

1. Nature of Polymer

The polymer used in the preparation of nanosponges can influence its formation and can also affect the pre-formulation. The size of the cavity of a nanosponge should be big enough to entrap a drug molecule of a particular size into it for complexation [34].

2. Drug

To be complex with nanosponges, the drug molecules should have some specific characteristics as mentioned below:

- The molecular weight of the drug molecule should be in range ranging from 100-400 Daltons.
- Structure of drug molecule should not consist of more than 5 condensed ring.
- The solubility of the drug in water should be<10 mg/ml.
- The melting point of the drug should be <250 ˚ C.

3. ***Temprature***

Changes in the temperature can affect the complexation of drug or nanosponges. Increasing the temperature generally decreases the extent of the stability constant of the drug or the nanosponge complex which may be due to the reduction of interaction forces such as hydrophobic forces and Van der Waal forces of drug/nanosponges with an increase in the temperature [35].

4. ***Degree of Substitution***

The number, position, and type of the substituent of the parent molecule can affect the ability of complexation of the nanosponges to a greater extent [36].

5. ***Method of Prepration***

The method of drug loading into the nanosponges can cause a change in the complexation of drug and the nanosponges. Although, the success of a method mainly depends on the nature or the characteristics of the drug and polymer; in some cases, freeze drying has also been known to affect the drug and nanosponge complexation.

V. CHARACTERIZATION OF NANOSPONGES

The characterization methods for the complexed drug/nanosponges are listed below:

1. 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[37].

2. ***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.

3. 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 extra electrode on particle size equipment or zeta seizer, the zeta potential can be measured. Higher the value of zeta potential of a colloidal dispersion more is its stability.

4. Thermodynamical method

If any changes occur in drug molecules or particles undergoes some changes earlier then the thermal degradation of nanosponges it can be determined by the thermo-chemical method. The changes of drug particles can be melting, evaporation, oxidation and decomposition and polymeric changes. The changes in the drug molecules indicate the formation of a good complex.

5. 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.

6. Thin layer chromatography (TLC)

TLC can be defined as a technique which can be used to separate the non-volatile or evaporative mixture. In this technique, if the Rf value of a particular drug molecule is of an acceptable range then it is helpful in recognizing the formation of a complex between drug and nanosponges.

7. Infrared spectroscopy

The interaction between nanosponges and the drug in the solid state can be determined by using infrared spectroscopy. Nanosponge bands can slightly change during formation of complexes. Few guest molecules attached in the complexes which are less than 25%, the drug spectrum can be easily masked by the spectrum of nanosponges. The technique is not appropriate to identify the inclusion complex over the other methods [38].

8. Entrapment efficiency

Weighed amount of drug loaded NSs are dispersed in methanol, centrifuged at 1000 rpm for half an hour, the supernatant withdrawn, suitably diluted with methanol and are subjected to ultraviolet (UV) spectroscopy for taking absorbance of the sample against blank methanol. The percentage of drug entrapment is calculated by the following equation. The entrapment efficiency (%) of NSs can be resolute by [39-41]

$$\textbf{Entrapment efficiency} = \frac{\textbf{Actual drug content}}{\textbf{Theoretical drug content}} \times \textbf{100}$$

VI. APPLICATION OF NANOSPONGES

Nanosponges have a wide range of application in the pharmaceutical field, because of its biocompatibility and versatility. In the pharmaceutical industry, nanosponges can be used as an excipient for the formulation of tablets, capsules, granules, pallets, suspensions, solid dispersions and topical dosage forms. Nanosponges can accommodate both lipophilic and hydrophilic drug molecules, basically, those drugs substances which belong to the biopharmaceutical classification system (BCS-class II) as well as the poorly water-soluble drug [42].

Nanosponges for drug delivery

Nanosponges can carry the water-insoluble drug because of their tiny porous structure. To increase the dissolution rate, solubility and permeability of drug nanosponges complexes play a major role. This is reported that β-cyclodextrine based nanosponges are three or five times more effective to deliver the drug to the targeted site. Nanosponges are generally solid in nature and can be prepared for oral, parental, topical and inhalation dosage form. For the preparation of tablet, capsule i.e. oral administration the nanosponges complexes are dissolved in a suitable excipient like lubricants, diluents and anti-cracking agent.

Nanosponges for cancer therapy

Most challenging works nowadays in the pharmaceutical field is the delivery of anticancer drug because of their low solubility. In one article they claim that nanosponge's complex is three times more effective to reduce the growth of tumor then direct injection. The nanosponge's complex load with a drug and expose a targeting peptide that fastens tightly with a radiation-induced cell upper layer on the tumor receptor. When nanosponges confront the tumor cell they stuck on the surface of tumor cell and start to release the drug molecules. The advantage of targeting drug delivery is to get a more effective therapeutic effect at the same dose and with minimized side effect[43].

Nanosponges for delivery of protein

To study the encapsulating capacity of β-cyclodextrin-based nanosponges, bovine serum albumin (BSA) was used as a model protein. Protein solution of bovine serum albumin (BSA) is not stable so they are stored in lyophilized form. Proteins can convert to denatured on lyophilization from its native structure. For the formulation and development of protein, the major drawback is that to maintain its native structure and long-term storage during and after processing. For delivery of the protein like Bovine serum albumin (BSA) with the cyclodextrine based, nanosponges can increase the stability of these proteins. Nanosponges have also been used for immobilization of enzyme, encapsulation of protein, for controlled delivery and stabilization [44].

Role of nanosponges for treatment of fungal infections

Fungal infections of the skin are one of the dangerous diseases in worldwide [45]. Topical therapy is an attractive choice for the treatment of the coetaneous infections due to various advantages such as targeting of drugs to the direct site of infection and reduction of systemic side effects. Econazole nitrate (imidazole) is an antifungal or pharmaceutical fungicide used topically to cure athlete's foot, ringworm, tineapityriasis versicolor, jock itch and vaginal thrush. The available products of econazole nitrate present in the market are cream, ointment, lotion, and solution. Adsorption of econazole nitrate is not significant when it is applied to the skin and effective therapy; need a high concentration of active agents to be combined. For this reason, econazole nitrate nanosponges were fabricated by emulsion solvent method and these econazole nitrate nanosponges were loaded in a hydrogel as a topical delivery for sustained release of the drug [46,47]. Itraconazole is also an antifungal drug comes under biopharmaceutical classification system class II and that has a dissolution rate limited and poor bioavailability. So the aim of this study was to increase the solubility of the itraconazole, so that can solve the bioavailability problem. In these nanosponges, if used β-cyclodextrine as cross-linked with carbonate bonds and loaded it with itraconazole than the solubility of itraconazole can be increased.

As absorbent in treating poison in blood

Nanosponges can remove the dangerous poisonous substance from our blood by absorbing the poison. Instead of using antidotes, if we incorporate nanosponges by injection into blood nanosponges can soak up the toxins. In the bloodstream, the nanosponge looks like a red blood cell, tricks toxins into attacking it, and then absorbs it. The number of toxin molecules each nanosponge can absorb depends on the toxin [48].

VII. CONCLUSION

Nanosponges have been identified as drug delivery mechanism that can encapsulate or accumulate both hydrophilic and lipophilic drug by forming a complex. They can successfully deliver the medication at a predetermined target location in a controlled manner. Nanosponges can be incorporated into topical preparation such as lotions, cream, ointments etc. And liquid or powder form. The advantage of this technology offers targeting the drug to specific site reduces side effects, improve stability, and improve formulation flexibility and better patient compliance. Nanosponges offer application in other areas such as cosmetics, biomedicine, bioremediation process, agrochemistry,and catalysis etc.

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