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NANOSPONGES IN PHARMACEUTICALS: OVERCOMING SOLUBILITY BARRIERS VIA NANOTECHNOLOGY

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ABSTRACT:

Nano materials are being produced by the pharmaceutical and healthcare industries to address major issues with recently developed chemical entities, such as low water solubility and pharmacokinetic effects. The hydrophobic nature of the majority of pharmaceuticals makes successful invivo distribution difficult. The drug's effectiveness has increased thanks to the nanoscale conversion of the components.[1] Nanosponges are a type of nanotechnology that have properties that are both hydrophilic and hydrophobic. They are composed of tiny particles having chambers that are only a few nanometers broad and can enclose a variety of substances. These particles have the capacity to transport both hydrophilic and lipophilic molecules, improving the solubility of medications that dissolve poorly in water. Nanotechnology research shows that the tiny mesh- like structures known as nanosponges could revolutionise the way that many diseases are treated.[2] Targeted drug distribution is greatly facilitated by nanosponges. This article has examined the applications, formulation process, influences on nanosponge production, evaluation, and potential future uses of nanosponges.

KEYWORDS: Nanosponges, targeted drug delivery, Controlled drug delivery, polymers, and Oral bioavailability.

1. INTRODUCTION:

The drug molecules are contained within the core of the encasing nanoparticles known as nanosponges. The bioavailability of a drug may be impacted by the formulation of a poorly

watersoluble medication in a standard dose form. The inadequacies of such formulation-related issues can be overcome by nanosponge formulations. To create regulated oral delivery and topical medication distribution, nanosponges are composed of water soluble and bioerodible polymers[3].

The Nanosponges are solid in nature and can be administered orally, parenterally, topically, or inhaled. These can be mixed into a matrix of excipients, diluents, lubricants, and anti-caking agents to create tablets or capsules for oral delivery. These can easily be combined with sterile water, saline, or other aqueous solutions for parenteral delivery. They are integrated into hydrogel for topical delivery. [4]

Nanoformulations are superior than traditional ones[5,6]. Nanoemulsions, Nanogels, Polymeric Nanoparticles, Solid Nanoparticles, and Nanosponges (NSs) are examples of nanoformulations. This review mostly focuses on NSs and the uses for them. Since they successfully give many formulations new life, NSs, which are microscopic mesh-like structures with a spongy look, have generated a lot of interest in the pharmaceutical industry[12–14]. The paper provides a thorough explanation of nanosponge and illustrates how it can be utilised as a drug delivery method to improve patient compliance. In addition to their potential usage in the pharmaceutical industry, they also have a wide range of non-pharmaceutical applications, such as agrochemistry, biomedicine, bioremediation procedures, catalysis, and cosmetics[15,16].

1.1. Nanosponges

Unlike other nanoparticles, they are porous, non-toxic, and stable at high temperatures up to 300°C. They are also insoluble in both water and organic solvents. Because of their 3D structure with Nanosize cavities and programmable polarity, they are capable of carrying, transporting, and target releasing a variety of pharmacological molecules. In addition, Nanosponges have more benefits than regular Nanoparticles since they are easily regenerable using a variety of processes, including washing with environmentally friendly solvents, gentle heating, stripping with relatively inert hot gases, or altering ionic strength or pH. 5

The Nanosponges are either crystalline or paracrystalline in structure. The degree of crystallisation affects the loading capacity of nanosponges. Different Paracrystalline Nanosponges have various loading capabilities. By adjusting the ratio of cross linker to polymer, nanosponges can be created in a specified size and release medications over a longer period of time. When there are substances present with magnetic properties, these Nanosponges can be created and magnetised. The small size of Nanosponges is used in the

regulated distribution of medications through the lungs and veins. [18-21]

1.2. Targeting sites by Nanosponges:

Nanosponges' "targeting" assures that the targeted pharmacological reaction will only occur in diseased cells and will not have an adverse effect on healthy cells. Drugs Improved drug stability and protection against premature deterioration are provided by the nanosponge. The nanosponge's microscopic mesh-like structure circulates in the blood until it reaches the target region, where it adheres to the surface to release the medicine in a regulated and predictable manner.7

1.3. Difference between Nanoparticles and Nanosponges:

The main difference between the Nanoparticles and Nanosponges are porosity and size. Nanoparticles have size in Nanometer whereas Nanosponges have pores in Nanometer their overall size can extend up to micrometer smaller than 5µm. Nanosponges has diverse domains in their structure, they have both hydrophobic and hydrophilic groups.

While nanosponges offer many advantages, they also face some potential limitations and challenges compared to other nanoparticle-based drug delivery systems.

1. **Limited Drug Loading Capacity:** One significant limitation of nanosponges is their ability to entrap only small amounts of drug molecules. This could be a disadvantage compared to some other nanoparticle systems that may offer higher drug loading capacities.
2. **Complexity in Formulation:** The preparation of nanosponges can be complex, involving multiple factors that need to be carefully controlled. These include the type of polymer, crosslinker, drug characteristics, temperature, and method of preparation. This complexity may make large-scale production more challenging compared to simpler nanoparticle systems.
3. **Polymer and Crosslinker Limitations:** The choice of polymer and crosslinker is crucial in nanosponge formulation. Not all drugs may be compatible with the available polymer and crosslinker combinations, potentially limiting the range of drugs that can be effectively delivered using nanosponges.
4. **Size Control:** While the pore size of nanosponges is in the nanometer range, their overall size can extend to the micrometer range. This larger size might limit their use in certain applications where strictly nano-sized particles are required, such as crossing the blood- brain barrier.
5. **Stability Concerns:** Although nanosponges are generally stable, factors like

temperature, degree of substitution, and method of preparation can affect their stability and drug complexation capacity. This may require more stringent storage and handling conditions compared to some other nanoparticle systems.

6. **Limited Research:** While promising, nanosponges are a relatively new technology compared to some other nanoparticle-based systems. There is still a need for more extensive research, particularly in areas such as long-term safety, in vivo behavior, and large- scale production.

7. **Regulatory Challenges:** As a novel drug delivery system, nanosponges may face additional regulatory scrutiny and challenges in gaining approval for clinical use compared to more established nanoparticle systems.

Despite these challenges, ongoing research and development in nanosponge technology may address many of these limitations in the future, potentially expanding their applications in drug delivery.

1.4. Advantages of Nanosponges:

- They are Amphiphilic in nature,Nanosponges carry the both hydrophobic and hydrophilic drugs. Hydrophobic drugs can be loaded into the Nanosponge are consequently increase their solubility.
- Nanosponges have the ability to produce predictable/controlled drug release.[1]
- Nanosponges can bind with specific linkers to target diseased cells and achieving a high efficacy there by reducing the side-effects, reduce the dose and dosing frequency and increasing the patient compliance.
- The superior properties of Nanosponges have been attributes to 'Tunability', and ability to control the structure of particles, nature and size of aperture.
- Nanosponges can also reduce the irritation of drugs without reducing the efficacy. • Biodegradable in nature and easy production.[8]

1.5. Disadvantages:

Nanosponges has ability to entrap only small amount of the molecules.

1.6. Characteristics Features of Nanosponges:[9]

- Nanosponges of specific size can be synthesised by changing the crosslinker to polymer proportions.
- They are nontoxic, porous, insoluble in most of the organic solvents and stable

up to 300°C temperature. They are stable at the pH range of 1-11.

- They produce clear and opalescent suspension in water.
- They can be reproduced by simple thermal desorption, extraction with solvents, by using microwaves and ultrasounds.
- Their three-dimensional structure cancapture, transportation and selective release of a variety of drugs.
- Chemical linkers are increases the ability of Nanosponges to bind preferably to the target site.
- By complexing with different drugs, Nanosponges produce the inclusion and non-inclusion complexes.
- By adding magnetic particles into the reaction mixture, magnetic properties can also be imparted to Nanosponges.

2. POLYMERS USED IN NANOSPONGE PREPARATION:[11]

These are various polymers and cross linkers are used in the preparation of Nanosponges.

Polymers: Hyper crosslinked Polystyrenes, Cyclodextrines and its derivatives like Methyl β-Cyclodextrin, AlkyloxycarbonylCyclodextrins, 2-Hydroxy Propyl β-Cyclodextrins.

Copolymers: Poly(valerolactone-allylvalerolactone)& Poly(valerolactoneallylvalerolactoneoxepanedione)and Ethyl Cellulose & PVA.

Cross linkers: Carbonyl diimidazoles, Carboxylic acid dianhydrides,Diarylcarbonates, Dichloromethane,Diisocyanates, DiphenylCabonate,Epichloridine, Pyromellitic anhydride, 2,2-bis (acrylamido) Acetic acid.

Table 1: Biopharmaceutical classification class II drugs:

Category	Drugs
Antianxiety drugs	Lorazepam.
Antibiotics	Ciprofloxacin, Ofloxacin, Azithromycin, Erythromyzin, Sulfomethoxazole.
Anticonvulsants	Clonazepam, Primidone, Carbamazepine,Oxycarbamazipine.
Antidiabetic drugs	Glibenclamide, Glipizide
Antihyperlipidemic drugs	Atorvastatin, Lovastatin.
Antifungal drugs	Ketoconazole, Vericonazole, Lansoprazole, Griseofulvin.
Antihypertensive drugs	Nebivolol, Carvedilol, Nicardipine, Nifedipine, Felodipine, Nisoldipine.
Antiepileptic drugs	Phenytoin.

Anticancer drugs	Docetaxol, Etoposide, Flutamide, Camptothecin.
Antipsychotic drugs	Chlorpromazine hydrochloride.
Antiviral drugs	Ritonavir, Indinavir, Saquinavir, Nelfinavir.
Antiulcer drugs	Omeprazole, Lansoprazole.
Diuretics	Spirinilactone, Chlorthalidone.
NSAIDS	Dapsone, Ibuprofen, Diclofenac, Piroxicam, Naproxen, Nimesulide, Ketoprofen, Etoricoxib, Mefenamic acid.
Antihistamines	Erfenadine.
Antioxidants	Resveratrol.
Gastroprokinetics	Cisapride.
Immunosuppressant's	Cyclosporine, Tacrolimus, Sirolimus.
Anticoagulant	Warfarin.

Table 2: list of drugs entrapped in the nanosponge formulation

Category	Drugs	Nanosponge Vehicle
Antifungal drugs	Econazole nitrate	Ethyl cellulose, PVA
Anticancer drugs	Paclitaxel, Camptothecin.	β -Cyclodextrin
Inflammation	Resveratrol	β -Cyclodextrin
Viral infection, pathological disorder.	Oligonucleotide	Poly-L-lysine.
Breast cancer	Tamoxifen	β –Cyclodextrin.
Brain tumour	Dexamethazone	β –Cyclodextrin.
Antibacterial drugs	Norfloxacin	β –Cyclodextrin.

3. PREPARATION OF NANOSPONGES:

Nanosponges are prepared mainly on the criteria of delivery system, polymer and nature of drug and solvents.

1. Solvent method:

In this method polymer is mixed with suitable solvent, particularly polar aprotic solvent such as dimethylformamide, dimethyl sulfoxide. Then add this mixture to excess quantity of the cross-linker, preferably in crosslinker/polymer molar ratio of 4 to 16. Carry out the reaction at temperature ranging from 10° C to the reflux temperature of the solvent, for time ranging from 1 to 48h. Preferred crosslinkers are carbonyl compounds (Dimethyl carbonate &Carbonyl diimidazole). After completion of the reaction, allow. the solution to cool at room temperature, then add the product to large excess of distilled water and recover the product by filtration under vacuum and subsequently purify by prolonged soxhlet extraction with ethanol. Dry the product under vacuum and grind in a mechanical mill to obtain homogeneous powder[22].

2. Emulsion Solvent Diffusion Method:

Nanosponges can be prepared by using different ratio of Ethyl cellulose and Polyvinyl alcohol. The dispersed phase was Ethyl cellulose and drug was dissolved in 20ml

dichloromethane and slowly added to a definite amount of Polyvinyl alcohol in 150ml of aqueous continuous phase. This mixture was stirred at 1000 rpm for 2hrs in a magnetic stirrer. The Nanosponges formed were collected by filtration and dried in oven at 40˚C for 24hrs. the dried Nanosponges was stored in vacuum desiccator to ensure the residual solvents.[11]

3. Quasi-Emulsion Solvent Diffusion Method:

The inner phase was prepared using Ethyl cellulose in suitable solvent. Drug to be incorporated is made into a solution and dissolved under Ultrasonication at 35˚C. This inner phase added into external phase containing Polyvinyl alcohol which acts as emulsifying agent. The mixture is stirred at 1000-2000 rpm for 3hrs at room temperature and dried in hot air oven at 40.C for 12hrs.

4. Ultrasound- assisted synthesis:

In this method, the polymers react with cross- linkers without solvent and under sonication. Here, the polymer and cross- linker are mixed in a flask and place the flasks in Ultrasound bath filled with water and heated up to 90˚C and then sonicate for 5hrs. Then allow to cool and wash with water to remove the unreacted polymer. Dry the product under thevacuum and store at 25˚C.[2]

Loading of drug into Nanosponges:

Suspend the Prepared Nanosponges in water and sonicate to avoid the presence of aggregates and then centrifuge the suspension to collect the colloidal fraction. Separate the supernatant and dry the sample by freeze drying. The aqueous suspension of Nanosponges was prepared and dispersed the amount of the drug to be loaded. Maintain the suspension under constant stirring for specific time for Complexation. After completion of Complexation, separate the uncomplexed drug from complexed drug by centrifugation. Then obtained solid crystals of Nanosponges recovered by solvent evaporation or by freeze drying[23].

4. CHALLENGES IN FORMULATION OF NANOSPONGES:

- Polymer type
- Type of drugs
- Melting point
- Temperature
- Preparation method
- Degree of replacement.

Polymer type:

The formulation as well as the effectiveness of Nanosponges depends up on polymer. The pore size of the Nanosponges should be able to accommodate the drug molecule of suitable size.

Type of drug:

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

Melting point:

The loading capacity of the drug is influenced by the melting point. Low loading capacity of drug is observed with molecules having high melting point. This low loading capacity may be contributed to the structural rigidity of the molecule and also due to the formation of unstable nanosponge complexes[3].

Temperature:

The change in temperature can affect the drug Complexation. The increase in the temperature decreases the apparent stability of the Nanosponge complex which may occur due to possible reduction of drug Nanosponge interaction forces, van der waals force and hydrophobic force.

Method of preparation:

The loading of drug into the Nanosponge can affect the Complexation. The nature of the drug and polymer can affect the Complexation. Freeze drying was more effective method for drug complexation.

Degree of substitution:

The Nanosponge formulation highly affected by the type, number and position of substitution on the parent molecules.[24]

5. CHARACTERIZATION OF NANOSPONGES:

Solubility studies:

Phase solubility study is used approach to study the inclusion complexation which describe the effect of a nanosponge on the solubility of the drug by Higuchi and Conners. Nanosponges

are confirmed by insolubility in water and organic solvents like DMF (Dimethyl Formamide) and DMSO (Dimethyl Sulfoxide) ([5]). Phase solubility diagram describe the degree of complexation[25].

Particle size Determination:

The particle sizes are maintained during polymerization for the formation of free flowing powders have fine aesthetic appearance. Particle size analysis of loaded and unloaded Nanosponges can be carried out by laser light Diffractometry or Malvern Zetasizer[2].

Determination of loading efficiency:[11]

The loading efficiency of Nanosponges are determined by substracting the un-entrapped drug from the total amount of drug. The un-entrapped drug must be estimated by any suitable method of analysis. The method used for separation of un-entrapped drug by gel filtration, Dialysis and Ultracentrifugation. The loading efficiency is calculated as:

CompatibilityStudies:

$$\% \, Drug \; loading = \frac{Actual \; drug \; content}{Theretical \; drug \; content} \times 100$$

The drug should be compatible with the polymers which are used for the preparation of Nanosponges. The compatibility of drug with adjuvants can be determined by thin layer chromatography (TLC) and Fourier

transform infra-red spectroscopy (FT-IR). Crystalline characteristics studied by powder X-ray Diffraction (XRD) and Differential Scanning Colorimetry (DSC)[3].

Zeta potential:

Zeta potential is a measurement of the surface charge. Zeta potential value indicates the stability of nanosponge formulaion. More than 30mV zetapotential value using water as medium indicate the better stability of nanosponges. The surface charge of Nanosponge can be determined by using Zetasizer[19].

Drug release kinetics:

To investigate the mechanism of drug release from the Nanosponge the release data was analysed using zero order, first order, Higuchi, korsemeyer- peppas models. The data can be analysed using DD solver software. The software estimates the parameters of a non-linear

function that provides the closest fit between experimental observations and non-linear function[26].

In vitro release studies:

In vitro release kinetics experiments are carried out by using a multi compartment rotating cell. An aqueous dispersion of Nanosponges containing the drug is placed in the donor compartment, while the receptor compartment separated by a hydrophobic dialysis membrane is filled with phosphate buffer with suitable pH. The experiment is carried out for 24hrs. At specific time intervals the receptor buffer is completely withdrawn and replace with fresh buffer solution. The amount of drug in the medium is determined by analytical method and drug release is calculated to determine the release pattern[26].

Microscopic studies:

Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) can be used to study the microscope structure and surface nature of Nanosponges. The difference in crystallization state of the raw materials and the product seen under electron microscope indicates the formation of the inclusion complexes[26].

6. APPLICATIONS:

Nanosponges have many applications in the pharmaceutical field due to their biocompatibility and versatility. Such as

Nanosponges in Solubility Enhancement:

Presence of crosslinking agent and cavities in the Nanosponge structure helps interaction with active molecules. These features are suitable for several substances and get solubilized in the cavities. The Hydrophobic hydroxyl groups on the surface exposed to the environment, while the hydrophobic nature of the complex hides in the interior cavity of the Cyclodextrin the net effect of watersoluble complex is formed[27].

Nanosponges in Drug Delivery:

Nanosponges have spherical shape and Nanometer in size making them ideal in various dosage forms like topical, parenteral, aerosol, tablets and capsules. It is found that used for higher solubility and *invitro* drug release is observed in inclusion complex.

Nanosponges for Protein Delivery:

The major problem in protein formulation development is the maintenance of the native protein structure during the formulation process and the longterm storage. The Nanosponges were found to be stable at 300˚C and high protein complexation capacity also observed.

Ocular delivery:

Glaucoma is a chronic disease associated with the risk of vision loss. The efficacy of NSs encapsulated compounds was studied in glaucoma therapy by Lambert et al., concluding that one injection of NSs could convey ocular antihypertensive molecules effectively in a continuous, linear fashion for around thirty-two days. They even reported that these formulations are effective at targeting retinal ganglion cell (RGC) that get degenerated in glaucoma patients[28].

In the topical drug delivery:

The nanosponge based drug delivery is widely used for the treatment of various topical infections like bacterial and fungal infections. There are various examples of drug which are widely used for the topical drug delivery in various treatment conditions. The adsorption of econazole nitrate, an antifungal agent, was found to be insignificant, Econazole nitrate loaded NSs hence formulated was found to be highly effective. This was produced by emulsion solvent diffusion method followed by loading those NSs in the hydrogel, that produce facilitated sustained release action Voriconazole nanosponges incorporated in the gel was used for the treatment of topical infections. Cephalexin loaded into the nanosponges and incorporated into the hydrogel was found to be useful in different topical problems such as diabetic foot infection, urinary tract information and soft and skin tissue infection[29-32].

To provide stability:

NSs can selectively trap a few families of protein molecules from the blood, hence can be used in safeguarding those proteins from undergoing enzymatic degradation[33].

Nanosponges in Enzyme Immobilization:

The enzyme immobilization is particularly relevant for lipases and it improves their stability and modifies properties like enantioselectivity as well as the reaction rates. As a consequence, the demand for new solid supports, suitable for family of enzymes is constantly growing.[18]

Nanosponges as a Carrier for Delivery of Gases:

Nanosponges are prepared by encapsulating gamma-oryzanol showing a good protection from Photodegradation. Gamma-oryzanol (a ferulic acid ester mixture), an anti-oxidant and usually employed to stabilize food and pharmaceutical raw materials, also used as a sunscreen in the cosmetics industry. Its applications are less due to its high instability and photodegradation. With the gamma Oryzanol loaded Nanosponges a gel and an o\w emulsion are formulated.[20]

As a carrier for calcium delivery:

Most of the marketly available phosphate binders used for the treating hyper phosphatemia produce more toxic effects, like bone disease, soft tissue calcification, and hypercalcemia. Pravin Shende et al. formulated and characterized enteric-coated cyclodextrin-based calcium carbonate NSs that could bind efficiently to free phosphate ions and release calcium in a controlled manner. According to the report, the cross-linking enhances the stability and helps achieve controlled release of calcium. All these conclude it is better suitable way to treat hyperphosphatemia without any side effects[34].

Modulating Drug Release:

A drug loaded into the Nanosponge is retain and release slowly over the time. Hydrophilic Nanosponges are employed to enhance the drug absorption across biological barriers, to modify the drug release rate and as a potent drug carrier in immediate release formulations. Hydrophobic nanosponges are utilized as sustained release carriers for water soluble drugs, including peptide and protein drugs and they protect the drug during the passage through the stomach. This drug is released very slowly at pH 1.1, whereas release is faster if pH is raised to 7.4.

Effective delivery carriers:

Anticancer drugs such as paclitaxel, Camptothecin and Tamoxifen has bioavailability problem (because of poor solubility) hence Nanosponges can be used as vehicles in order to enhance the solubility as well as bioavailability. Complexes show high effect than the drug alone. After loading the drug in to Nanosponges the bioavailability of paclitaxel was increased and found to be 2.5 fold higher than the plain drug[34].

Non pharmaceutical applications:

Water waste treatment:

β-cyclodextrin based nanosponges strongly bind to the organic pollutants which is present in water and the polymers has the ability to remove the pollutants 10000 times effective than the conventional methods[35].

Biomedical application:

Nanosponges are used as a marker in cancer treatment and carrier for oxygen which are employed in supply of oxygen to the hypoxic tissue associated with various disease like COPD. Polyionicnanosponge also applied on fractinalization of peptides in mass spectroscopy by MALDI technique for proteomic applications[36].

7. FUTURE PROSPECTS:

Nanosponges are effective drug carriers for targeted delivery of drugs to lungs, liver and spleen. A simple approach for formulating Palladium\Silver and Palladium\Silver\Aluminium Nanosponges, which contain network of nanowires has been reported. This strategy establishes the first time preparation of alloy Nanosponges with network nanowire via self-regulated reduction of sodium deodecylsulfate (SDS) and adding the second or third metal salt during synthesis without reducing agent. Further studies on kinetics and biochemical interactions of nanosponges within organisms are vital. These studies are mainly focus on research on Nanosponges translocation pathways, its accumulation in the targeted area, short and long-term toxicity, their interactions with cells, the receptors and signalling pathways involved, cytotoxicity, and their surface functionalization for an effective phagocytosis[37]. There is only a sparse knowledge about the effects of Nanosponges exposure on the lymphatic and immune system, as well as various organs. In order to clarify the possible role of nanosponges in disease recently associated with them (such as crohn's disease, neurodegenerative disease, autoimmune disease, and cancer), Nanoscale characterization technique should be used to a larger extend to identify Nanosponges at disease sites in affected organs or tissues, and to establish relevant interaction mechanisms[38].

8. CONCLUSION:

Nanosponge have been recognized as drug delivery system for encapsulating both hydrophilic and hydrophobic drug to form a complex. Nanosponges are increase the solubility, improve the loading capacity, reduce the side effects, protect the drug from degradation and release the drug at targeted site. Different factors like polymer,

crosslinkers,method of preparation, degree of substitution, temperature, and type of drug mainly affect the formation of nanosponges. Nanosponges offer applications in cosmetics, agrochemistry, biomedicines and catalysis etc. the current research clinical studies indicates nanosponges based products in pharmaceutical markets in future mitigation of fatal diseases like HIV, tuberculosis and cancer etc.

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