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NANOSPONGES: A PROMISING APROACH FOR DRUG DELIVERY SYSTEM

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Abstract : The perfect delivery system will make the medicine soluble, transport the therapy to the desired location, and then release the therapy as needed to meet the specific needs of the patient and stage of the disease. One such efficient drug delivery system that overcomes the issues of drug toxicity and poor bioavailability is the use of nanosponges, which can carry both hydrophilic and hydrophobic medicines. Nanosponges have a nanometric cavity size, a 3-dimensional network, and are extremely small in size. Highly porous nanosponges have a special ability to entrap active molecules and have the advantage of programmable release. They are easy to make and safe for biological use. Different kinds of cyclodextrins can be cross-linked using a carbonyl or a dicarboxylate chemical as a cross-linker to create nanosponges. The use of nanosponge technology has been investigated for a number of purposes, including increasing the bioavailability of drug molecules and delivering medications via oral, topical, and parenteral routes. Enzymes, proteins, vaccines, and antibodies can all be delivered and released using nanosponges as a carrier for biocatalysts.

Keywords: Nanosponges, cross-linkers, controlled release, cyclodextrins, bioavailability.

I.INTRODUCTION:

The practise of giving a pharmacological chemical to people or animals in order to elicit a therapeutic response is known as drug delivery. Clinical treatments for acute and chronic illnesses include a variety of pharmaceutical dose forms, known as conventional dosage forms, such as tablets, capsules, pills, creams, liquids, ointments, aerosols, injectables, and suppositories. [1] It is frequently necessary to administer the medication multiple times to maintain the drug's effective plasma concentration. If effective concentration is not kept at the optimum levels, medication levels will fluctuate and patient compliance will be low. The traditional dose forms occasionally have a tendency to circulate in the general population at higher concentrations, which can have undesirable side effects. To avoid these adverse effects and increase the safety and effectiveness of medications, numerous attempts have been undertaken to deliver active moieties at the desired concentration. The developed technologies for regulating the discharge of therapeutic substances to the desired site that gave rise to the creation of drug delivery systems. The rate at which medications are released into the targeted bodily part is under the control of the drug delivery system. The "controlled release system" and "sustained release system" categories are used to categorise the devices utilised in the novel medication delivery method. Sustained release systems are defined as delivery methods designed to delay the release of a therapeutic agent so that the drug's entry into the systemic circulation is postponed or prolonged. Regulated release systems are those that have been designed to release medicinal moieties in a predictable, controlled manner. Oral administration is the preferred method of administration for most controlled release systems[2]. Novel Drug Delivery Systems are made to deliver a precise therapeutic dose of medication to the right spot quickly and to keep the desired drug concentration in the body[3].

1.1 Nanosponges

Early studies reveal that the technology of nanosponges, which are tiny mesh-like structures, is up to five times more successful at delivering medications for breast cancer than traditional approaches. Nanosponges may revolutionise the treatment of various diseases.The nanosponge has a "backbone" (a scaffold structure) made of naturally biodegradable polyester and is around the size of a virus. Long polyester strands are combined in a solution with tiny molecules known as cross-linkers, which have a preference for particular regions of the polyester. They "cross connect" various sections of the Polyester is used to create a spherical shape with numerous pockets (or cavities) where medications can be kept. Because the polyester degrades predictably in the body, the medicine can be released on a predetermined timetable as it does so.[4]The drug molecules are contained within the centre of the encapsulating nanoparticles known as nanosponges. The nanoparticles can be categorised into encapsulating, complexing, and conjugating nanoparticles based on how they interact with pharmaceuticals. Nanosponges and Nanocapsules are examples of the first category. Alginate nanosponges, which are sponge-like nanoparticles with numerous pores that transport drug molecules, are examples of nanosponges. Nanoparticles are also enclosed in nanocapsules like poly (isobutyl-cyanoacrylate, or IBCA). They have an aqueous core where drug molecules can be trapped. The molecules are drawn to complexing nanoparticles in the second group by electrostatic charges. Conjugating nanoparticles, which connect to pharmaceuticals by covalent bonds, are the third type. [5]

These nanosponges are a novel class of nanoparticles that are often made from natural compounds. They differ from other nanoparticles in that they are porous, nontoxic, insoluble in both water and organic solvents, and stable at temperatures up to 300 °C. They possess a 3D structure with nanometric-sized voids and variable polarity that enables them to catch, transport, and selectively release a wide range of chemicals. In addition, nanosponges exhibit a unique advantage over typical nanoparticles in that they are easily regenerable using a variety of processes, including washing with environmentally friendly solvents, stripping with relatively innocuous hot gases, light heating, or altering pH or ionic strength. Nanosponges have already been used in a variety of applicable domains, including the cosmetic and pharmaceutical industries, due to all these qualities.[6]

In order to protect degradable molecules, increase the water solubility of lipophilic pharmaceuticals, and provide drug delivery systems for routes other than oral administration, nanosponges can be employed as a vehicle for pharmacological principles. The preparation of polymers and cross linkers is not complicated by their simple chemistry, and this method is straightforward to scale up to commercial production levels. Although soluble in water, nanosponges do not chemically degrade in it. They are dissolved in water and used as a transportation fluid. They can be used to cover up bad tastes,to transform liquids into solids. The nanosponges are able to connect to the target site preferentially thanks to the chemical linkers. These nanosponges' ability to contain only tiny molecules is their biggest drawback. The nanosponges may be crystalline or paracrystalline in nature. The degree of crystallisation has a significant impact on the loading capacity of nanosponges.Different loading capacities can be seen in paracrystalline nanosponges. By adjusting the ratio of cross linker to polymer, it is possible to create nanosponges with a desired size and drug release over time. In contrast to many other nanoscale drug delivery systems, the comparatively straightforward chemistry of the polyesters and cross-linking peptides in nanosponge contributes to its engineering potential. [4]When these nanosponges are made in the presence of substances with magnetic characteristics, they can be magnetised. [7] The microscopic form of allows for the transport of nanosponges into the lungs and veins. [8]

1.2 Advantages of nanosponges:

- Increase aqueous solubility of the poorly water-soluble drug.
- Nanosponges can release the drug molecules in a predictable fashion.
- Because of their tiny pore size (0.25 µm), bacteria cannot penetrate the nanosponges and they act like a self-sterilizer.
- Nanosponges drug delivery system are non-irritating, nonmutagenic and non-toxic.
- Nanosponges help to remove the toxic and venom substance from the body.
- Nanosponges drug delivery system minimize side effect.
- 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 [9-11].

1.3 Disadvantages of nanosponges :

- Nanosponges have the capacity of encapsulating small molecules, not suitable for larger molecules.
- Dose dumping may occur at times [12].

1.4 Composition and structure of nanosponges:[13,14]

Nanosponges are intricate structures made of long, linear molecules that are folded into a spherical shape roughly the size of a protein by cross-linkers. The five primary components of nanosponges are listed. A. Polymer B. Cross linking agent C. Surfactant D. Drug substance and E. Solvent

A. Polymer: The kind of polymer used can affect how quickly nanosponges form and release material. The polymers are utilised to interact with the medicinal material or to encapsulate the active drug moiety. The nanosponge's cavity should be large enough to admit a drug molecule of a specific size for complexation. The substitution of functional and active groups affects the polymer's capacity for cross-linking. The polymer needs to be able to bind to the right ligands in order to deliver drugs to the right places at the right times.Examples include Polymethyl methacrylate, Eudragit, and Ethyl cellulose.

B. Crosslinking agent: The drug of choice and the chemical makeup of the polymer both influence the choice of crosslinking agent. For topical treatments, dichloromethane is the most often utilised crosslinker. Due to the decrease in internal phase viscosity, drug entrapment in the polymers and particle size increased as internal phase volume rose without any discernible pattern. 20 mL of dichloromethane was utilised to create the nanosponges that had the best trapping efficiency.Examples include ethanol, dichloromethane, and methanol.

C. Drug substance: Drug molecules to be formulated as nanosponges should have certain characteristics mentioned below:

- Molecular weight between 100 and 400 Daltons.
- Drug molecule should have not more than five condensed rings.
- Molecule water solubility should be less than 10 mg/ml.
- Melting point of the active moiety should be below 250°C.

D. Surfactants: Polyvinyl alcohol is a surfactant that is frequently employed in the creation of nanosponges and is essential for the development of nanosponges with smaller particle sizes. It was discovered that the particle size increased as the surfactant concentration rose. Higher surfactant concentrations cause foaming, which leads to the production of aggregates. As the

concentration of surfactant increased, the effectiveness of drug entrapment decreased. This can be because the drug's specific polymer concentrations are insufficient for particle encapsulation. Examples: Polyvinyl alcohol, Ethanol, Dichloromethane

E. Solvent:Water is the only solvent used in the creation of nanosponges. In the last stage of nanosponge synthesis, the amount and temperature of the solvent play crucial roles in pore diameter on the surface of the nanosponges as well as production yield.

1.5 Mechanism of drug release from nanosponges

The active drug moiety travels in and out of the open-structured sponge particles into the vehicle until equilibrium is maintained. When a topical delivery vehicle is used, the active ingredient is already present in the vehicle when the completed dosage form is applied to the skin.will be absorbed into the skin, depleting it and making the vehicle unsaturated, which will upset the balance. Starting from the sponge particles into the vehicle and then from the vehicle into the skin, this will cause a flow of the active medicine until the vehicle is either dry or absorbed. Even after that, the sponge particles will remain on the stratum corneum's surface, where they will continue to release the active ingredient into the skin over time enabling the drug's gradual release over time[15].

1.6 How nanosponges are better than other vesicular systems?

Some colloidal drug delivery methods with a nanometric size are nanosponge, ethosomes, niosomes, ufasomes, bilosomes, and transferosomes. When compared to nanosponges, some of these vesicular systems have certain stability issues. While cholesterol oxidation and phospholipids induce formulation instability in liposomes, medication hydrolysis in niosomes, and chemical instability in transferosomes due to their propensity for oxidative degradation. These are a few of the typical issues vesicular systems run against. Nanosponges are a brand-new class of colloidal structures made of hyper-crosslinked polymers that are composed of solid nanoparticles with colloidal sizes and nanosized voids. They are made up of surfactants, crosslinkers, and polymers.The bioavailability of dosage forms is increased using nanosponges, which also alter medication release and lessen side effects.[16,17]

II.METHOD OF PREPARATION

2.1 Nanosponges made from hyper cross-linked β-cyclodextrins

Materials used to create cyclodextrins, non-porous molecules used as carriers for drug release, are used to create nanosponges. These cyclodextrins are hyper-cross-linking substances that create several nanoscale networks or can even take the form of a sphere with countless networks of protein channels, pores, etc. Based on the chemicals they contain, these cross linkers stabilise the sponge and give it a certain surface charge density, porosity, and pore size. Cross linkers aid in maintaining Nano sponges at various acidic and even neutral pH levels [18].

2.2 Emulsion solvent method

Ethyl cellulose and polyvinyl alcohol, in various ratios, are the two major polymers employed in this process. The available medication is dissolved in 20 ml of dichloromethane before being added to ethyl cellulose to create the dispersed phase. In order to prepare the drop-by-drop continuous phase addition, polyvinyl alcohol is dissolved in 150 ml of distilled water. The mixture is then allowed to agitate for approximately two hours at 1000 rpm. The obtained Nano sponges are gathered, filtered, and baked for about a day before being placed in desiccators. [19]

2.3 Solvent used method

The polymer mentioned above can be combined in a proportional amount with a suitable polar aprotic solvent, such as dimethylformamide or dimethylsulfoxide. Then, available cross-linkers are added to this mixture in a 4: 16 ratio. For two days, a temperature of 10°C is maintained for polymer polymerization. Dimethyl carbonate and carbonyl diimidazole are the two most commonly utilised carbonyl cross linkers. After the reaction is finished, the product is allowed to cool at room temperature before being purified using a soxhlet apparatus with ethanol added for additional extraction. The mixture is then added to distilled water for recovery and filtered under an oven. To obtain a uniform white powder, repeat the mechanical grinding and drying processes under vacuum. [20]

2.4 Ultrasound-assisted synthesis

By utilising polymers with carbonyl cross linkers in the absence of a solvent and keeping them for sonication, nano sponges can be created using this process. The spherical dimensions of these newly designed Nano sponges will be constant. In a flask, combine the cross-linker and polymer in a enough amount. For ultrasonication, the water in the flask is heated to 90°C. For five hours, the mixture is held for continuous sonication. The product is then permitted to be purified with a soxhlet extractor using ethanol after the mixture has been cooled and rinsed with distilled water. The finished product is dried at 25 degrees Celsius, and whitish powder is collected and stored away from moisture. [21]

The initial step in pretreating the nanosponges designed for drug administration is to reduce the mean particle size to under 500 nm. After being suspended in water for a while, the nanosponges are sonicated to prevent the development of aggregates. A colloidal fraction is obtained by centrifuging the product suspension that has been obtained. The product's supernatant is separated, and the sample is then dried by freeze drying. [22]

Another method is to produce and distribute a nanosponge aqueous suspension while stirring continuously for a set amount of time. The solvent is evaporated to produce the nanosponge solid crystals, or the crystals are frozen dried. The crystal structure of the nanosponge is a key factor in how the drug complexes with it. In comparison to paracrystalline nanosponge, crystalline nanosponge has a higher drug loading. Drug loading happens mechanically rather than as an inclusion complex in nanosponges with inadequate crystalline structure. [23]

III.FACTORS INFLUENCING NANOSPONGE FORMULATION

3.1 Type of polymer

The choice of an appropriate polymer affects both the creation and performance of a nanosponge. A medication molecule of the appropriate size should fit inside the nanosponge's cavity or pores. [24]

3.2 Type of drug

- The molecular weight must be between 100 to 400 Daltons.
- The drug molecule structure should contain no more than five condensed rings.
- The solubility in water should be less than 10 mg/ml.
- The melting point should be less than 250 °C. [24]

3.3 Temperature

The complexation of the medication can be impacted by temperature changes. Due to a potential reduction in drug nanosponge contact forces, Vander Waals forces, and hydrophobic forces with rising temperature, the apparent stability of the nanosponge complex diminishes with temperature. [25]

IV. CHARACTERIZATION OF NANOSPONGES

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

4.1 Solubility studies

Particle size is maintained throughout polymerization to create free-following powders with fine aesthetic qualities. Analysis of the particle size of loaded and unloaded nanosponges using a malvern zeta sizer or laser light diffractometry. To evaluate the impact of particle size on drug release, a cumulative graph is maintained or plotted as particle size against time. Particle sizes between 10 and 25 m can be favoured for topical drug delivery, while those bigger than 30 m may exhibit a gritty feeling.[26]

4.2 Microscopic study

Scanning and transmission electron microscopes can be used to study drugs and nanosponges at the microscopic level. The discrepancy between the crystallisation state and the final product visible under an electron microscope indicates inclusion complex development.

4.3 Zeta potential determination

Zeta potential is the differential in potential between two layers of fluid that are imprisoned with scattered particles (the dispersion medium and immobile layer). The primary indicator for the stability of the colloidal dispersion is zeta potential. The zeta potential can be determined by adding an additional electrode to particle size analysis equipment or a zeta seizer. More stable a colloidal dispersion is, the higher its zeta potential value.

4.4 Thermodynamical method

The thermo-chemical approach can be used to assess whether drug molecules or particle alterations take place before the thermal destruction of nanosponges. Melting, evaporation, oxidation, breakdown, and polymeric modifications are only a few of the possible drug particle alterations. The drug molecules' alterations show that a strong complex has formed.

4.5 Particle size and polydispersity

Using the 90Plus particle size determining programme, the dynamic light scattering technique is used to determine the size of the particles. The definition of dynamic light scattering (DLS) as a method for determining the size distribution profile of nanoparticles. Finally, the poly-dispersity index (PDI) and particle diameter can be calculated.

4.6 Thin layer chromatography (TLC)

TLC can be characterised as a method for separating non-volatile or evaporative mixtures. If a certain drug molecule's Rf value falls within the allowed range in this approach, it can be useful in identifying the development of a complex between the drug and the nanosponges.

4.7 Infrared spectroscopy

Infrared spectroscopy can be used to analyse how the medicine interacts with nanosponges in the solid state. As complexes develop, nanosponge bands can somewhat alter. The drug spectrum can be easily hidden by the spectrum of nanosponges when there are only a few guest molecules bound in complexes that are less than 25%. The method is ineffective for identifying the inclusion complex when compared to other methods [27].

4.8 Loading efficiency

By measuring the amount of drug loaded into a nanosponge using a UV spectrophotometer and high-performance liquid chromatography for nanosponges, one may calculate the loading efficiency of a given nanosponge particle. The following equation can be used to determine the loading effectiveness of nanosponges.

$$L.E. = \frac{Actual\ drug\ content\ in\ nanosponges}{Theoretical\ drug\ content} \text{ x } 100$$

V. APPLICATIONS OF NANOSPONGES

Nanosponges are extremely versatile and have a wide range of uses in the pharmaceutical industry. When making tablets, capsules, pellets, granules, suspensions, solid dispersions, or topical dosage forms, they can be employed as excipients[28]. As indicated in Table 1, they can encapsulate a range of medications. Nanosponges can serve as multifunctional carriers to improve the functionality and aesthetics of a product, as well as its thermal, physical, and chemical stability. They can also provide prolonged release and less irritability. The applications of nanosponges that are listed below demonstrate their adaptability.

5.1 Nanosponges as a sustained delivery system

Due to its effectiveness in treating herpes simplex virus infections, acyclovir is a commonly used antiviral drug[29]. However, neither parenteral nor oral administration of the acyclovir formulations currently on the market can result in the drug reaching target locations in sufficient concentrations. Acyclovir is poorly absorbed in the gastrointestinal tract and has very varied pharmacokinetics after oral administration. A prolonged release of the drug from the two types of nanosponges was seen in the in vitro release profiles of acyclovir, demonstrating that the drug has been enclosed within the nanostructures. After 3 hours in vitro, acyclovir was released from Carb-nanosponges and nanosponges in proportions of around 22% and 70%, respectively. Both formulations did not exhibit an initial burst effect, which demonstrated that the medication was not only marginally adsorbed onto the nanosponge surfaces[30].

5.2 Nanosponges in solubility enhancement

Itraconazole in Nanosponges was examined by Swaminathan et al. Itraconazole is a BCS Class II medication with poor bioavailability and a dissolving rate restriction.The drug's solubility was enhanced more than 27-fold by nanosponges. This increased to 55-fold when copolyvidonum was included in the formulation of the nanosponge as a supportive element. Itraconazole's hydrophobic groups may be concealed by nanosponges, which also increase the drug's wetting and/or reduce the crystallinity of the drug[31].

5.3 Nanosponges in drug delivery

Because of its spherical shape and nanomeric size, nanosponges can be manufactured in a variety of dosage forms, including topical, parenteral, aerosol, tablet, and capsule forms.

A BCS Class II medication with a dissolution rate-restricted bioavailability is telmisartan (TEL). Carbonate bonds were used to cross-link -CD, resulting in -CD-based nanosponges. The nanosponges have TEL integrated into them. The -CD complex of TEL was compared to plain TEL and nanosponge complexes of TEL in terms of its saturation solubility and in vitro dissolution research.

It was discovered that adding NaHCO3 to the drug-nanosponges combination instead of TEL enhanced the solubility of TEL by 8.53 fold in distilled water, 3.35 fold in 1 mol HCl, and 4.66 fold in phosphate buffer pH 6.8. The inclusion complex made from nanosponges and NaHCO3 showed the maximum solubility and in vitro drug release [32].

The cancer treatment drug paclitaxel has a low water solubility and is utilised. Because cremophor decreases the tissue penetration of paclitaxel, -CD based nanosponges provide an alternative to the traditional formulation in cremophor EL for paclitaxel delivery. The cytotoxicity and intracellular concentration of paclitaxel are both dramatically raised when compared to plain paclitaxel after 72 hours of incubation, thus enhancing the biological action of paclitaxel in vitro[33].

The antifungal drug econazole nitrate, which comes in cream, ointment, lotion, and solution forms, is applied topically to relieve the symptoms of superficial candidiasis, dermatophytosis, and skin infections. When econazole nitrate is applied to the skin, a high concentration of active substances must be used in order to achieve therapeutic success. The emulsion solvent diffusion process was used to create econazole nitrate nanosponges, which were then placed in hydrogel to serve as a local depot for sustained drug release[34].

5.4 Nanosponges for protein delivery

The development of medications, including macromolecular ones like proteins, depends heavily on their long-term stability[35]. However, upon lyophilization, proteins can reversibly (or perhaps even irreversibly) denature and afterwards acquire a conformation distinctly different from the native ones. Therefore, maintaining the natural protein structure both throughout the formulation process and after long-term preservation is a significant challenge in the creation of protein formulations[36].

Nanosponges 10 and 11 were created by crosslinking -CDs with either 2,2-bis-acrylamidoacetic acid or a short polyamido-amine chain derived from 2,2-bis-acrylamidoacetic acid and 2-methyl piperazine, respectively. Swaminathan et al. reported these new swellable cyclodextrin-based poly (amidoamine) nanosponges. High protein complexation ability was noted and the synthesised poly (amidoamine)-nanosponges were proven to be stable at 300 °C[37].

5.5 Nanosponges in enzyme immobilization

Since it increases their stability and controls qualities like enantio selectivity and reaction speeds, enzyme immobilisation is particularly important for lipases[38]. As a result, there is an increasing need for new solid supports that are appropriate for this family of enzymes.

For this, Pseudomonas fluorescens lipase adsorbed on a brand-new variety of cyclodextrin-based nanosponges shown remarkable catalytic performances[39].

5.6 Nanosponges as a carrier for delivery of gases

Gases are used in medicine for both diagnostic and therapeutic purposes. Hypoxia, or a lack of sufficient oxygen supply, is linked to a number of diseases, including cancer and inflammatory diseases. In clinical practise, it can be challenging to administer oxygen in the right form and amount.

As topical oxygen delivery devices, Cavalli et al. created formulations for nanosponges that have the capacity to store and release oxygen gradually over time[40].

5.7 Nanosponges as protective agent from light or degradation

A ferulic acid ester combination known as gamma-oryzanol has recently gained a lot of attention due to its potential as a natural antioxidant. It is typically used to stabilise food and pharmaceutical raw materials as well as a sunscreen in the cosmetics industry. Due to its high instability and photodegradation, its use is restricted. Nanosponges were used to encapsulate gamma-oryzanol, which demonstrated good photoprotection. The nanosponges loaded with gamma-oryzanol were used to create a gel and an O/W emulsion[41].

VI. MARKETED PRODUCTS[49]

List of marketed products

Drug	Administration route	Trade name	Dosage form
Dexamethasone	Dermal	Glymesason	Fujinaga Pharmaceutical Co., Ltd. (Tokyo, Japan)
Iodine	Topical	Mena- gargle	Kyushin pharmaceutical Co., Ltd. (Tokyo, Japan
Piroxicam	Oral	Brexin	Chiesi Pharmaceuticals (Parma, Italy)

VII. CONCLUSION

Because they can transport both hydrophilic and hydrophobic drugs by creating inclusion and non-inclusion complexes, nanosponges are flexible drug delivery systems. They can predictably administer medications to the desired place via a variety of methods, including oral, topical, and parenteral. Other prospective uses include the fields of cosmetics, biomedicine, bioremediation procedures, agrochemistry, and catalysis, in addition to their use in the drug delivery industry. 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. This review summarized various methods of preparation, factors influencing nanosponge formulation and their applications . Nanosponges can be proved as a safe and effective vehicle for drug delivery and other applications.

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