

NANOSPONGES: AN INNOVATIVE DRUG DELIVERY SYSTEM***Neha Richhariya, Dr. Sunil Kumar Prajapati, Dr. Upendra Kumar Sharma**

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Author****Neha Richhariya**Institute of Pharmacy,
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India.**ABSTRACT**

Site- specific drug delivery system had been an aspiration for long time. The inventiveness of nanotechnology lead to breakthrough of numerous dosage forms to prevail assorted predicaments. After some time, discrete functionalized particles were advanced that are entitled nanosponges. Nanosponges are small molecular sized particle. These particles can spread all over the body up to the time that they combat the specific site and bind to the surface and set about to release the drug in a controlled and predictable manner. Nanosponges are non-irritating, non-mutagenic, non-allergic and non-toxic. Both lipophilic as well as hydrophilic drugs can be packed in nanosponges. The rationale of this write-up is to talk about nanosponges in addition to

their prominent peculiarities, preparation approaches; polymer used as well as execution in miscellaneous disciplines.

KEYWORDS: Nanosponges, Polymers, cross- linker, emulsion- solvent evaporation method, application.

INTRODUCTION

Nanosponge is a resourceful approach that provides controlled drug delivery for topical use, [1] Nanosponges are tiny sponges with a size of about a virus. [2] The mean diameter of nanosponges is lesser than 1 μm although fractions below 500 nm. [3] Nanosponges could be either paracrystalline or crystalline form. The loading capacity of nanosponges hinges primarily on the degree of crystallization. The paracrystalline nanosponges have different loading capacity. [4]

These tiny sponges can be stocked with a multiplicity of drugs and swirl all over the body up to the time that they come across the specific target site and bind to the surface and begin to release the drug in a controlled and predictable manner.^[1] These particles are competent to transport together lipophilic and hydrophilic substance. Moreover, in progressing the solubility of poorly water soluble molecules.^[5]

Nanosponges are obtained by different organic and inorganic materials and also by suitable cross linking process. Nanosponges can entrap several types of molecules by forming inclusion and non-inclusion complexes.^[2]

Nanosponges are tiny mesh like structure which have the capacity of treating many diseases (most effective in Breast cancer).^[6]

Nanosponges have three dimensional structure. The backbone is long-length polyester, they are mixed in solution having cross-linkers to form the polymer. The polyester is biodegradable so it breaks down gradually. As it breaks down, it releases the drug in a predictable manner.^[4]

The nanosponges are solid in nature and can be formulated as different routes of administrations such as oral, topical, parenteral, inhalation dosage forms. For oral administrations, these may be dispersed throughout a matrix of excipients, diluents, lubricants and anticaking agents which is suitable for the preparation of tablets or capsules. For topical administration, they can be effectively incorporated into topical hydrogel,^[8, 9] For parenteral administration, these can be simply mixed with sterile water, saline or other aqueous solutions.^[7]

IMPORTANT CHARACTERISTICS OF NANOSPONGES

1. Nanosponges have 3D structure that enables capture, transportation and selective release of a variety of substances.^[10]
2. They form clear and transparent suspensions in water.^[11]
3. They could be either para-crystalline or crystalline in form.^[12]
4. They form inclusion and non-inclusion complexes with different drugs.^[10]
5. They are non toxic, porous particles, insoluble in most organic solvents and stable at high temperatures up to 300°C.^[13]

ADVANTAGES OF NANOSPONGES.^[14, 15, 1]

1. Particles size can be changed into smaller or larger by changing the ratio of cross- linker to polymer.
2. They are biodegradable.
3. They can be used to mask unpleasant flavors and to change liquid substances into solids.
4. Possible predictable release.
5. These are capable of carrying both lipophilic as well as hydrophilic drugs.
6. These are used to remove pollutants from contaminated water.
7. These are used as nano carriers for biomedical applications.
8. These could be used to increase aqueous solubility of poorly water soluble drugs.
9. Easy scale up for commercial production.

DISADVANTAGES OF NANOSPONGES

1. The main disadvantage of nanosponges is their ability to include only small molecules.
2. The nanosponges could be either crystalline or paracrystalline form. The loading capacity of nanosponges counts principally on the degree of crystallization. Paracrystalline nanosponges can show different loading capacities. The nanosponges can be synthesized to be of particular size and the release drug overtime by varying the proportion of cross-linker to polymer.

MATERIALS USED IN SYNTHESIS OF NANOSPONGES.^[1]

There are some important materials used for synthesis of nanosponges. These are as follows:

Polymer

Hyper cross- linked polystyrene, cyclodextrin and its derivatives like Alkyloxy carbonyl cyclodextrin, Methyl β -cyclodextrin, hydroxypropyl β -cyclodextrin.

Copolymer

Poly (Valerolactone- allylvalerolactone oxypanedione), Ethyl Cellulose, PVA.

Cross-linkers

Diphenyl Carbonate, Diaryl carbonates, Diisocyanates, pyromellitic anhydride, carbonyl diimidazoles, Epichloridrine, glutaraldehyde, carboxylic acid dianhydrides, Dichloro methane.

Appolar Solvents

Methanol, Ethanol, Dimethyl formamide, Dimethyl acetamide.

PREPARATION OF NANOSPONGES BY DIFFERENT METHODS

1. Nanosponges prepared by emulsion solvent evaporation method

Emulsion solvent evaporation method involves different ratios of PVA and ethylcellulose. Then ethyl cellulose and dichloromethane are mixed together. This mixture is added to aqueous solution of PVA. Then the mixture is stirred at 1000 rpm for 2 hours. Nanosponges are collected by filtration method. Dry this product in an oven at 40⁰C for 24 hours. ^[8]

2. Nanosponges prepared by hyper cross-linked β -cyclodextrin

Nanosponges are prepared by reacting cyclodextrin with a cross- linker like dimethyl carbonate, diphenyl carbonate, diisocyanates, diaryl carbonates, carbonyl diimidazoles, carboxylic acid anhydrides and 2, 2-bis (acrylamido) acetic acid. The porosity, pore sizes and surface charge density of nanosponges can be controlled to attach different molecules. ^[11]

3. Nanosponges Prepared by ultrasound assisted synthesis

Nanosponges were prepared by mixing polymers and cross- linkers in the absence of solvent under sonication. The nanosponges thus prepared are spherical and uniform in size. The polymer and the cross- linker were mixed in a particular ratio in the flask. Then the flask was put in an ultrasound bath filled with water and heated upto 90⁰C. This mixture was sonicated for 5 hours. Then this mixture was cooled, and the product was broken roughly. The product was washed with water and purified by soxhlet extraction with ethanol. The product thus obtained was dried under vacuum and stored at 25⁰C. ^[5, 7]

4. Loading of drug into nanosponges

Nanosponges for drug delivery should be pretreated to get a mean particles size below 500 nm. First of all; nanosponges are suspended in water and then sonicated to avoid the presence of aggregates. Following that, the suspension is centrifuged to get the colloidal fraction. The supernatant is separated, and the sample is dried by freeze drying. ^[7]

The prepared aqueous suspension of nanosponges is then dispersed in the excess amount of the drug. This suspension is maintained under constant stirring for specific time. After complexation, the undissolved drug is separated from dissolved drug by centrifugation method. Then, the solid crystals of nanosponges were obtained by solvent evaporation method. ^[5, 16]

The crystal structure of nanosponges plays a very important role in complexation with drug. The loading of drug is greater in crystalline nanosponges than paracrystalline nanosponges. [17]

CHARACTERIZATION OF NANOSPONGES

1. Solubility studies

The phase solubility method is the most widely used method to study about inclusion complexation, which examines the effect of nanosponges on the solubility of drug. [5, 18]

In this method, the drug was placed into an Erlenmeyer flask. This flask contains an aqueous solution of various percentages of nanosponges. Then the Erlenmeyer flask was stirred on a mechanical shaker at room temperature. On reaching the steady state, the suspension was filtered by centrifugation using a 3000 Dalton molecular filter. The solution thus obtained was analyzed to determine the concentration of drug by HPLC. [19]

2. Microscopy Studies

For the study of microscopic aspects of drug, nanosponges and the product, scanning electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) can be used. [12]

3. Determination of loading efficiency

The measured quantity of loaded nanosponges complexes is dissolved in suitable solvent, sonicated to break the complex, diluted and after that analyzed by UV spectrophotometer, [13]

Loading efficiency can be estimated by following formula –

$$\text{Loading efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

4. Infrared spectroscopy

For estimating the interaction between nanosponges and drug molecules in the solid state, infra red spectroscopy is used. Nanosponges bands generally change only slightly upon complex formation. If the fraction of the guest molecules that is encapsulated in the complex is not more than 25%, bands which could be assigned to the included part of the guest molecules are simply masked by the bands of the spectrum of nanosponges. This technique is not suitable to find the inclusion complexes and also is less clarifying than other methods. [20]

5. Determination of zeta potential

Zeta potential is the measurement of surface charge. It can be measured by using additional electrode in the particle size equipment. ^[21]

6. X-ray diffractometry

For detecting inclusion complexation in the solid state, powder x-ray diffractometry is used. When the drug molecule is in liquid form, the diffraction pattern of a newly formed substance differs from uncomplexed nanosponge. This difference of diffraction pattern shows the complex formation. When the drug is in the solid form, a comparison can be made between the diffractogram of the assumed complex and mechanical mixture of the drug and polymer. ^[18]

7. Single crystal x-ray structure

For determining the detailed inclusion structure and mode of interaction, single crystal x-ray structure analysis is used. The interaction between the host and guest molecules may be identified and the precise geometrical relation can be established. ^[18]

8. Determination of Particle size

For optimization process, the particle size of nanosponges is an important factor. Particle size can be estimated by laser light diffractometry or zeta sizer. Particles size greater than 30 m can appear gritty feeling while particles sizes range from 10 - 25 m are preferred for final topical formulation. ^[8, 22]

9. In vitro release studies

The releasing of drug from the optimized Nanosponge formulation can be studied by using multi compartment rotating cell with dialysis membrane. The donor phase as well as the receptor phase have drug loaded nanosponge complex in distilled water. The receptor phase is withdrawn after limited period of time, diluted with distilled water and analyzed by UV spectrophotometer. ^[23]

10. Photo degradation studies

The photo degradation of drug loaded nanosponge is done under UV lamp. All the samples are put at distance of 10 cm from the lamp for 1 hour stirring under dark, and then the samples are analyzed by HPLC. ^[23]

11. Thermoanalytical Method

These methods determine whether the changes occurs in drug substance before the thermal degradation of the nanosponges. These changes may be melting, oxidation, decomposition & evaporation. The thermogram prepared by DTA and DSC can be observed for broadening, shifting and appearance of new peak or disappearance of definite peaks.^[18]

APPLICATION OF NANOSPONGES

There are some important applications of nanosponges which are given below:

1. Nanosponges in topical drug delivery Systems

The categories of drug that can be easily formulated as topical nanosponges are local anesthetics, antifungals and antibiotics. Nanosponges can be prepared by various methods like emulsion solvent evaporation method.^[23] For ex. – Econazole nitrate, topically used antifungal relieves the symptoms of superficial infection, is available in cream, lotion, ointment and solution.^[8]

2. Nanosponges in oral drug delivery system

Oral delivery of drugs involves the use of bio erodible polymers especially for colon specific delivery and controlled release drug delivery system. Thus it reduces the toxicity of drug and improves patient compliance by providing site particular drug delivery system and dosage intervals.^[8, 24] Earlier studies include Carbamazipine, danazol, dexamethasone, itraconazole, nelfinavir, flurbiprofen and oxycarbamazipine. These all are bcs 2nd class drugs that have low solubility and a dissolution rate limited poor bioavailability.^[25]

3. Nanosponges in protein delivery

In the successful development of pharmaceuticals, long term stability is a critical point, including macromolecules such as proteins.^[26] Nevertheless, proteins can reversibly or sometimes irreversibly denature on lyophilization and adopt confirmation markedly distinct from the natives.^[27] In context of nanosponge, protein like BSA (Bovine Serum Albumin) are encapsulated in a swellable cyclodextrin based polyamidoamine nanosponge to enhance the stability of proteins.^[10]

4. Nanosponges in sustained delivery

For the treatment of herpes simplex virus infections, acyclovir is the most commonly used antiviral agent due to its efficacy. Anyhow, neither the parenteral nor the oral administration of acyclovir is able to result in suitable concentrations of the agent reaching at target sites.

Absorption of acyclovir in the gastrointestinal tract is slow and incomplete, what is more, its pharmacokinetics following oral medication is highly variable. The in-vitro release profiles of acyclovir from the two types of nanosponges showed a sustained release of the drug from the two types of nanosponges showing the encapsulation of acyclovir within the nanostructures. The percentages of acyclovir released from carb-nanosponges and nanosponges after 3 hours were approx. 22% and 70% respectively.^[28]

5. Nanosponges used in enzyme immobilization

The main concern of enzyme immobilization is suitable for lipases because it enhances their stability and adjusts properties like enantio selectivity and reaction rates.^[29] As a consequence, the demand of new solid supports, relevant for this family of enzymes is continuously growing.^[30]

6. Nanosponges as a carrier for biocatalysts

The industrial processes that involve chemical transformation are associated with operational disadvantages. Non-specific reactions lead to low yields and the frequent demand to perform at high temperatures and pressures needs consumption of large amounts of energy and cooling water in the downstream process. All these drawbacks can be reduced by using enzymes as biocatalysts. These enzymes work under mild reaction conditions, have high reaction rate and are highly specific. The conducting of these molecules presents many problem.

A number of systems have been developed for carrying enzymes and proteins such as nano and microparticles, liposomes and hydrogels carriage in a particular system can protect proteins from breakdown develop their pharmacokinetics and improve their stability.^[4]

7. Nanosponges for solubility enhancement

Nanosponges are used for improving the solubility and dissolution rate of poorly soluble drugs and providing controlled release profile. The molecular dimensions and confirmation are critical parameters that influence inclusion complexation within nanosponges so these may not be universally applicable to all molecules.^[21]

8. Nanosponges used as chemotherapeutic agent

Nanosponges which carries anticancer drugs, slow the growth of tumor. Researcher at Vanderbilt University prepared nanosponges that are used to deliver anticancer drugs to

tumor. They claimed that this method is more effective in reducing tumor growth than direct injection of drugs.^[11] Camptothecin, that is a plant alkaloid and a potent antitumor agent has a limited therapeutic property. Due to its poor aqueous solubility, lactone ring instability and serious side effects.^[24] At physiological pH, the lactone ring opens up and develops the inactive carboxylate form. Cyclodextrin based nanosponges are an innovative class of cross-linked derivatives of cyclodextrins. They are used to enhance the solubility of poorly soluble ingredients, to protect the labile groups and control the release. The fusion of camptothecin in nanosponges lead to a prolonged release profile in an active form, hindering the hydrolysis of the lactone form & resulting in enhanced stability.^[23]

9. Nanosponges as chemical sensor

Metal oxide nanosponges were used as chemical sensors in a very sensitive detection of hydrogen by using nanosponges Titania. In the structure of a nanosponge, there are no any contact points. Therefore, it becomes much less difficulty to electron transports and results in higher sensor stability 3D interconnected nanosponge titania is more sensitive to H₂ gas. 3D interconnected metal oxide nanostructure is a promising class of sensor material through which the ultra high chemical sensitivity of nanostructure can be controlled in practical devices.^[31]

OTHER APPLICATIONS

Besides the above applications there are also some other applications of nanosponges. Which are as follows:

1. Biomedical application of nanosponges

Cyclodextrin based carbonate nanosponges can be used to produce inclusion complexes with three gases that are methyl cyclopropene, oxygen and carbondioxide. The complexation of O₂ and CO₂ may be useful for many biomedical applications and the oxygen filled nanosponges supply O₂ to the hypoxic tissues that are present in several ailments.^[32, 33]

2. Analytical applications of nanosponges

The microporous hyper cross linked nanosponges were used in selective preparation of inorganic electrolytes by size medium exclusion chromatography method. The 3D Nanosponges play a big role in the fractionalization of peptides for proteomic uses.^[34]

3. Nanosponges used in floriculture

Newly developed nanosponges provide nutrients, preservative and anti-ethylene compounds for improving the flower-life.^[35, 36]

4. Nanosponges for water purification

Cyclodextrin nanosponges are used to remove pollutants from contaminated water. As β -cyclodextrin nanosponges are insoluble in water, so they have the character of encapsulating organic pollutants from water. Cyclodextrin based nanosponges strongly bind organic molecules and remove them from water even at very low concentrations.^[37, 35, 38]

5. Nanosponges in food industry

Nanosponges are used in reduction of bitter elements from fruit juices and other food products by selective combination of polymer and cross linker.^[32]

6. Nanosponges for oil cleaning

Nanotechnology creates new materials with advanced and unique characteristics. Some researchers discovered latest nanotechnology in which they found that after adding boron with carbon during nanotube construction creates spongy blocks that have oil absorbing character. Nanosponges are hydrophobic in nature, so they have the natural property to float on the water and not absorb it. Since nanosponges are ferromagnetic so they can be controlled by a magnet. The density of the material is very low, making the available volume for oil uptake very high. It not only soaks up over 100 times its weight in oil as it floats on the water, but also it can store the oil for later time. Then the oil can be squeezed out or burned off, and the sponge can be reused.^[35, 39]

CONCLUSION

The earlier study reveals that nanosponges are innovative class of drug delivery system as it offers controlled drug delivery for topical use. These small particles are capable of carrying both lipophilic and hydrophilic substances and of improving the solubility of poorly soluble molecules. They can be formulated in different routes of administration such as topical, oral parenteral dosage form due to small particle size and spherical shape. Nanosponges have the character to release the drug in a controlled and predictable manner. The nanosponges provide site specific drug delivery and prolonged dosage intervals. They are used in several fields such as food industry, floriculture, and oil cleaning etc. They have been found to have a profound ability to protect essential biomarkers in different ailments such as cancer and biocatalysts from physiochemical degradation. In recent future, nanosponges stand as milestones in drug delivery system.

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