Review Article

Nanosponges: A Miracle Nanocarrier for Targeted Drug Delivery

S.Shameem, N.Nithish Kumar Reddy, M.Bhavitha, M.Suman Kumar, M.Balaji Ramaiah, K.Sahithya
Department of Pharmaceutics, P.Rami Reddy Memorial College of Pharmacy, Kadapa, A.P, India.
***Corresponding author's E-mail:** shameemshaiks86@gmail.com

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ABSTRACT

The recent advance in nanotechnology leads to the development of targeted drug delivery system. However effective drug delivery system has been a dream for a long time to overcome problems related to targeted drug delivery like low solubility, low bioavailability, drug degradation, drug toxicity. In order to overcome the drawbacks, a novel carrier is developed which has been termed as a nanosponge. Nanosponge is a novel and emerging nanocarrier to control the release rates of controlled drug delivery for topical use. Nanosponges are small mesh structures less than 1 µm in size. Due to their porous structure and small size, they can easily bind to drugs which are poorly soluble leading to better bioavailability and solubility and capable of loading both hydrophilic and lipophilic drugs. This nanocarrier increases the solubility of water-insoluble drugs, increases the bioavailability, reduces drug toxicity, avoiding drug degradation and targeting the drug to a specific site, which facilitates control release. Nanosponges are formulated in to different dosage forms like parenteral, topical, oral or inhalational. In this review an attempt has been made to highlight the advantages, characteristics, factors affecting, method of preparation, characterization and application in drug delivery system.

Keywords: Nanosponges, Nanocarrier, Targeted delivery, Bioavailability, Controlled release.

INTRODUCTION

The development of new systems. Targeting drug delivery has long been a problem for medical researchers i.e., how to get them to the right place in the body and how to control the release of the drug to prevent overdoses. The development of new and complex molecule called nanosponges, has the potential to solve this problem.[1]

Nanosponge is a novel and emerging technology which play a vital role in targeting drug delivery in a controlled manner. These are new class of materials and made up of microscopic particles with few nanometers (250nm-1um) wide cavities in which a large variety of substances can be encapsulated. The net effect is to form spherically shaped particles filled with cavities drug molecules can be stored. The polyester is biodegradable, so it breaks down gradually in where the body. As it breaks down, it releases its drug payload in a predictable fashion. The nanosponges can be synthesized to be specific size and to release drugs over time by varying proportions of cross-linker to polymer.[2]

A wide variety of drugs can be loaded into nanosponge for targeted drug delivery. This particle is capable of loading both hydrophilic and lipophilic substances and of improving the solubility of poorly water soluble drugs, increases bioavailability, reduces drug toxicity, avoiding drug degradation and targeting the drug to specific site. As compared to other nanoparticles, nanosponges are porous, nontoxic and stable at high temperature up to 300°c. These nanosponges are solid in nature and can be formulated as an oral, parenteral, topical or inhalational dosage forms.

For oral administration, these can be dispersed in an array of Excipients, diluents, lubricants, which is suitable for the preparation of tablets or capsules.

For parenteral administration, these can simply be mixed with sterile water, saline or other aqueous solutions. For topical administration they can be incorporated into the topical hydrogel.

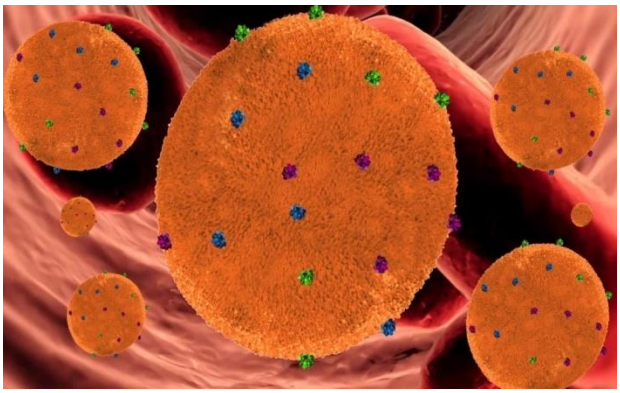

Figure 1: Structure of nanosponges

Advantages of nanosponges [1, 4, 5]

- Targeted site specific drug delivery.
- Biodegradable.
- Nanosponge formulations are stable over range of ph 1 to 11.
- Nanosponge formulations are stable at the temperature up to 130°C

- These formulations are compatible with most vehicles and ingredients.
- These are self-sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate.
- These formulations are free flowing and can be cost effective
- Improved stability, increased elegance and enhanced formulation flexibility.
- Increases aqueous solubility of the purely water soluble drugs.
- Non-irritating, non-mutagenic and non-toxic.
- Reduce dosing frequency and better patient compliance.

Limitations[2, 4]

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

Characteristic Features of Nanosponges[5, 6]

- ✓ Nanosponges provide a range of dimensions (1 µm or less) with tunable polarity of the cavities.
- ✓ Nanosponges of specific size can be synthesized by changing the cross linker to polymer ratio.
- ✓ They exhibit paracrystalline or crystalline forms, depending on the process conditions.
- ✓ They can be sited to different target sites because of their capacity to link with different functional groups.
- ✓ Chemical linkers permit nanosponges to bind preferably to the target site.
- ✓ By complexing with different drugs nanosponges can form inclusion and non-inclusion complexes.
- ✓ By adding magnetic particles into the reaction mixture, magnetic properties can also be imparted to nanosponges.

Types of Nanosponges[8, 9, 15]

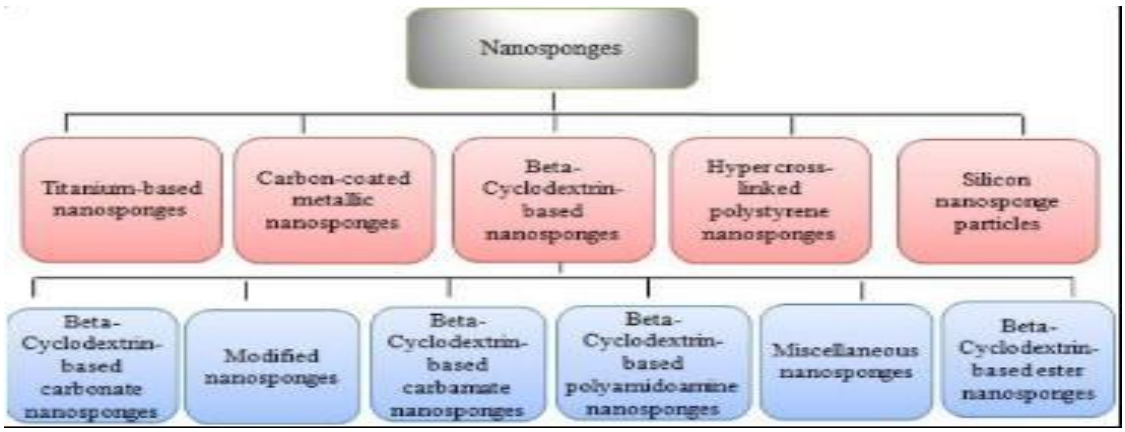

Figure 2: Flow Diagram for the types of Nano Sponges

Factors Influence Nanosponge Formation[10, 11, 14]

Polymer type

The type of polymer used can affect the formation and performance of nanosponges.

Type of drugs

Drug molecules that are complexed with nanosponges must have some characteristics, which are mentioned below.

- Molecular weight between 100 and 400
- The drug molecule is made up of less than five condensed rings
- Solubility in water is less than 10 mg / ml
- The melting point of the substance is below 250°C

Temperature

Temperature changes can affect drug / nanosponge formation. In general, the increase in temperature decreases the amount of the apparent stability constant of the drug / nanosponge complex may be due to a possible reduction of the drug / interaction forces. Nanosponge, such as Van-der Waal forces and hydrophobic forces with increasing temperature.

Preparation method

The method of loading the drug onto the nanosponge can affect the complexation of the drug / nanosponge. However, the effectiveness of a method depends on the nature of the drug and the polymer, in many cases freeze-drying has been more effective for the formation of pharmacological complexes.

Degree of replacement

The complexing capacity of the nanosponge can be greatly influenced by the type, number and position of the substituent on the original molecule.

Nanosponges are broadly classified in to five types. They are titanium-based nanosponges, carbon-coated metallic nanosponges, β -cyclodextrins based nanosponges, hyper cross-linked polystyrene nanosponges, silicon nanosponge particles. Among all the types β-cyclodextrins based nanosponges shows greater significant properties.

Cyclodextrin based nanosponges are proposed as a new nano sized delivery system. These are safe and effective nanosponges. These are a class of cyclic glucopyranose oligomers and are synthesized by enzymatic action on hydrolysis starch. The main common native cyclodextrins are α, β, γ, which composes six, seven and eight glucopyranose units. These polymers can be obtained by reacting native cyclodextrins with cross-linking agent, which result in formation of chains, in between this chains drug is loaded.

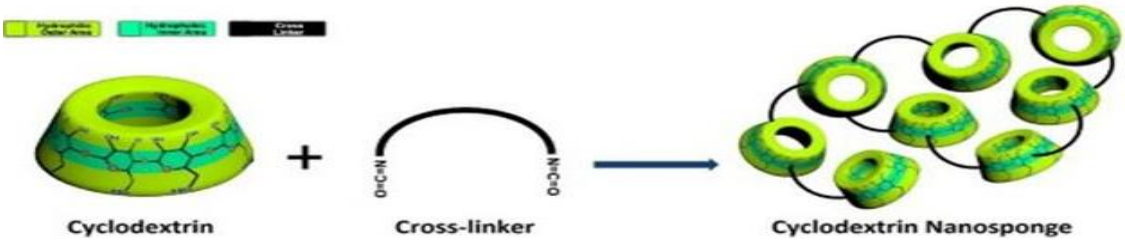

Figure 3: Cyclodextrin Nanosponges

These type of nanosponges play a important role to improve aqueous solubility of poorly water soluble drugs and release the drug in a controlled manner. Cyclodextrin nanosponges further divided in to six types. They are:

- β –cyclodextrin based carbonate nanosponges
- β –cyclodextrin based carbamate nanosponges
- β – cyclodextrin based polyamidoamine nanosponges
- β – cyclodextrin based ester nanosponges
- Modified nanosponges
- Miscellaneous nanosponges

The information regarding the types of cyclodextrin nanosponges are shown in (table 1)

Table 1: Fabrication requirements for various types of β – cyclodextrin nanosponges[11]

Type of β-CD Nanosponges	Cross linker	Temperature (°c)	Method	Solvent	Reaction time(h)	Type of drug to be included
CD-based carbonate nanosponges	Carbonyl or dicarboxylate compound Diphenyl carbonate, Dimethyl carbonate	100 10 to the reflux temperature of solvent	Melt method	None DMF/ DMSO	5 1-48	Any drug Any drug
CD-based carbamate nanosponges	Diisocyanates like HDI,TDI	70	Solvent method	DMF/ DMSO	16-24	Any drug
CD-based ester nanosponges	Dianhydride such as pyromellitic anhydride	Room temperature	Solvent method	DMF/ DMSO	Completed within a few minutes	
CD-based polyamidoamine	Acetic acid 2,20-bis(acrylamide)	Room temperature	Solvent method	Water	96	Peptides and proteins to be seperated
Modified type	Fluorescein isothiocyanate and carbonate nanosponge	90	Solvent method	DMF/ DMSO	A few hours	Cancer therapeutics

Materials Used In Preparation of Nanosponges[13]

Table 2: Materials required for nanosponges preparation

Polymer	Hypercross-linked polystyrens, Cyclodextrin and its derivatives like methyl β-cyclodextrin, 2-hydroxypropyl β- cyclodextrin.
Co-polymer	Ethyl cellulose, Polyvinyl alcohol, poly (valerolactone allylvalerolactone).
Crosslinker	Diphenyl carbonate, Diaryl carbonates, Diisocyanate, Carbonyl diimidazoles, Dichloromethane.

Preparation of Nanosponges

Emulsion Solvent Diffusion Method

Two phases are used in this method–dispersed and continuous. The dispersed phase consists of ethyl cellulose and the drug, which is then dissolved in 20 ml of dichloromethane and some amount of polyvinyl alcohol (PVA) is added to 150 ml of the continuous phase (aqueous). Then, the mixture is stirred at the speed of 1000 rpm for about 2hrs. The product i.e. the nanosponges are collected by filtration. Finally, the product is dried in an oven at a temperature of 40°c for 24hrs. The resulting nanosponges are stored in desiccator in order to remove residual solvent.[1]

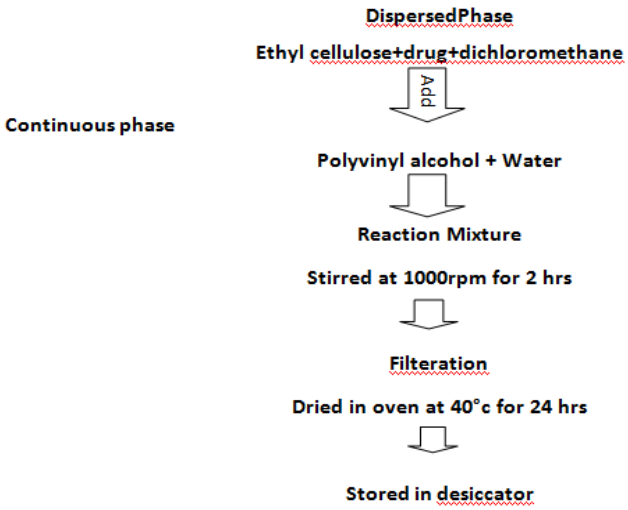

Figure 4: Flow diagram for the preparation of nanosponges by emulsion solvent diffusion method

Solvent Method

Using solvent method, Nanosponges are prepared by mixing polar aprotic solvents like Dimethyl sulfoxide (DMSO), Dimethylformamide (DMF) with the polymer. A crosslinker is then added to this mixture in the ratio of 1:4. The above reaction should be proceeded at temperature 10˚C to reflux the temperature of the solvent for the time ranging from 1 to 48 hr. Once the reaction has completed, the solution is cooled down at room temperature and then obtained a product is added to bi-distilled water. The product is recovered by filtering the product under vacuum and refining by soxhlet extraction with ethanol followed by drying.[3]

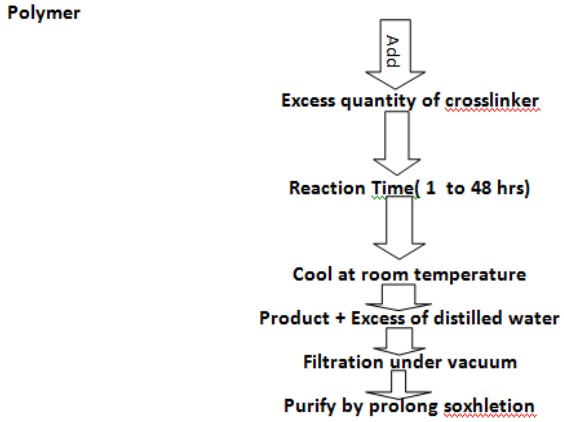

Figure 5: Flow diagram for the preparation nanosponges by solvent method

Ultra Sound Assisted Synthesis

The polymers are reacted with cross linkers in a solvent-free flask. The flask is placed in an ultrasonic bath which is filled with water and heated to 90 ° C and the mixture is sonicated for 5 hours. Then the mixture is cooled to room temperature and then the product is divided into rough pieces. Finally, the non-reacting polymer is removed by washing the product with water and the refining is carried out using a Soxhlet apparatus (ethanol) to obtain nanosponges. [20]

Melt Method

Nanosponges are prepared by reacting cyclodextrin with a cross linker such as: dimethyl carbonate, diphenyl carbonate, diisocyanates, diaryl carbonates, carbonyl diimidazoles, carboxylic acid anhydrides and acetic acid 2,2-bis (acrylamide). All the ingredients are finely homogeniszed, placed in a 250 ml flask and heated at 100˚ C. The Reaction was carried out for about 5 hrs by using magnetic stirrer. The mixture was allowed to cool and broken down the product. The obtained product was

washed with suitable solvent to remove extra unreacted excipients.[4, 25]

Quasi-emulsion Solvent Diffusion

The nanosponges can also be prepared by quasi-emulsion solvent diffusion method using the different polymer amounts. To prepare the inner phase, eudragit RS100 was dissolved in suitable solvent. Then, drug can be added to the solution and dissolved under ultra sonication at 350c. The inner phase was poured into the PVA solution in water (outer phase) and allowed for stirring for 1 hr, then the mixture is filtered to separate the nanosponges. The nanosponges are dried in an air-heated oven at 40˚c for 12 hrs.[14]

Loading of Drug into Nanosponges

To obtain an average particle size of less than 500 nm, it is necessary to pre-treat the nanosponges for the administration of drugs. Suspend the nanosponges in water and sonic to avoid the presence of aggregates, then centrifuge the suspension to obtain the colloidal fraction. After complexation, separate the complex (undissolved) drug from the complex drug by centrifugation. Then obtain the solid crystals of nanosponges by solvent evaporation or lyophilization.

Mechanism of drug release from nanosponges

Since nanosponges have an open structure (in the environment of nanosponges they do not have a continuous membrane), the active ingredient is added to the vehicle in an encapsulated form. The encapsulated active substance can move freely from the particles towards the vehicle until the vehicle is saturated and balance is achieved. As soon as the product is applied to the skin, the vehicle containing the active ingredient is unsaturated and causes an alteration of the balance. Therefore, the flow of active substances from the nanosponge particles to the vehicles begins in the epidermis until the vehicle is absorbed or dried. Even after retention of the nanosponge particles on the surface of the skin, i.e. the stratum corneum, the release of active substance continues into the skin for a long period of time.[13]

Characterization of nanosponges[3, 5, 20]

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

Solubility studies

The inclusion complexes are a technique that allows you to determine the solubility and bioavailability of the drug. This technique is the most widely used technique for the analysis of nanosponge inclusion complexes. The degree of completion can be known from the phase solubility graph. Solubility studies are performed to access the drug's pH, the solubilization program and to evaluate the factors that influence the drug's solubility.

Microscopic study

Microscopic studies of nanosponges / drugs can be performed using a scanning electron microscope and a transmission electron microscope. The formation of the inclusion complex is indicated by the difference in the crystallization state and by the product seen under the electron microscope.[7]

Zeta's potential determination

The zeta potential can be defined as the difference in potential between two layers (dispersion medium and immobile layer) of fluid enclosed by dispersed particles. Zeta potential is the main key indicator for the stability of colloidal dispersion. By adding an additional electrode to the particle size equipment or the zeta hoarder, the zeta potential can be measured. The higher the value of the zeta potential of a colloidal dispersion, the greater its stability.

Thermodynamic method

If changes occur in the molecules or particles of the drug, some changes occur first, then the thermal degradation of the nanosponges can be determined by the thermo chemical method. The changes in the drug particles can be fusion, evaporation, oxidation and decomposition and polymeric changes. Changes in the drug's molecules indicate the formation of a good complex.

Particle size and polydispersity

Particle size is determined by the dynamic light diffusion process using the 90Plus particle size determination software.

Thin layer chromatography (TLC)

TLC can be defined as a technique that can be used to separate the non-volatile or evaporative mixture. In this technique, if the Rf value of a particular drug molecule falls within an acceptable range, it is useful to recognize the formation of a complex between the drug and the nanosponges.

Infrared spectroscopy

The interaction between nanosponge and the solid state drug can be determined by infrared spectroscopy. Nanosponge bands can change slightly during complex formation. Few host molecules bound in complexes of less than 25%, the spectrum of the drug can be easily masked by the spectrum of nanosponges. The technique is not appropriate for identifying the inclusion complex compared to other methods.

Charging efficiency

The loading efficiency of a nanosponge particle can be determined by estimating the drug loaded on the nanosponge using a UV spectrophotometer and a high performance liquid chromatography method for nanosponges. The charging efficiency of nanosponge can be calculated using the following equation.[7]

$$\text{Loading Efficiency} = \frac{\text{Actual drug content in nanosponges}}{\text{Theoretical drug content}} \times 100$$

Application of nanosponge

Nanosponges have a wide range of applications in the pharmaceutical field, thanks to their biocompatibility and versatility. In the pharmaceutical industry, nanosponges can be used as an excipient for the formulation of tablets, capsules, granules, granules, suspensions, solid dispersions and topical dosage forms.

Nanosponges for cancer therapy

The most demanding jobs today in the pharmaceutical field are the delivery of anticancer drugs due to their low solubility. In one article, they claim that the nanosponge complex is three times more effective in reducing tumor growth than direct injection. Complex loading of the nanosponge with a drug exposes a targeted peptide that is firmly attached to a top layer of radiation-induced cells on the tumor receptor. When the nanosponges face the cancer cell, they stick to the surface of the cancer cell and begin to release the drug molecules. The advantage of targeting drug administration is to achieve a more effective therapeutic effect at the same dose and with a minimized side effect.[22]

Role of nanosponges for the treatment of fungal infections

Fungal skin infections are one of the dangerous diseases worldwide. Topical therapy is an interesting option for the treatment of skin infections due to numerous benefits, such as targeting drugs on the direct site of the infection and reducing systemic side effects. Itraconazole is also an antifungal drug that falls under the class II biopharmaceutical classification system and has a limited dissolution rate and poor bioavailability. Therefore, the goal of this study was to increase the solubility of itraconazole, so that it could solve the bioavailability problem. In these nanospong, if β-cyclodextrin is used as a carbon cross linked and loaded with itraconazole, the solubility of itraconazole can be increases.[24]

Nanosponge for protein intake

To study the encapsulation capacity of β-cyclodextrin-based nanosponges, bovine serum albumin (BSA) was used as a model protein. The bovine serum albumin protein (BSA) solution is not stable, therefore they are stored in lyophilized form. Proteins can be denatured in freeze-drying from their native structure. For the formulation and development of proteins, the main disadvantage is to maintain its native structure and long-term storage during and after processing. For the supply of proteins such as bovine serum albumin (BSA) with the cyclodextrin base, nanosponges can increase the stability of these proteins. Nanosponges have also been used for the immobilization of enzymes, the encapsulation of proteins, for controlled release and stabilization.[15]

Nanosponge for drug delivery

Nanosponge can carry the water insoluble drug due to its small porous structure. To increase the dissolution rate, the solubility and permeability of drug nanosponge complexes play an important role. B-cyclodextrin-based nanosponges have been reported to be three to five times more effective at transporting the drug to the target site. Nanosponges are generally solid in nature and can be prepared for the oral, parental, topical and inhalation dosage form. For the preparation of the tablet, the capsule, i.e. the oral administration, the nanosponge complexes are dissolved in a suitable excipient as lubricants, diluents and anti-cracking agents.

Table 3: Molecules Complexed by using nanosponges

Drug	Therapeutic activity	Administration route	References
Progestrone	hormonal	oral	15
Itraconazole	antifungal	Oral, topical	16
Omeprazole	antiulcerative	oral	16
Telmisartan	antihypertensive	oral	17
Resveratrol	antioxidant	Oral, topical	21
Dexamethasone	Anti-inflammatory	Oral, topical	17
Doxorubicin	anti-neoplastic	parenteral	21
Tomoxifen	antiestrogen	oral	21
Acyclovir	anti-viral	Oral, topical, parenteral	18
Flurbiprofen	Anti-inflammatory	oral	17
Acetyl salicylic acid	analgesic	oral	16
Camptothecin	Anti-neoplastic	parenteral	21

As an absorbent in the treatment of blood poison

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 the blood, nanosponges can absorb toxins. In the bloodstream, the nanosponge resembles a red blood cell, causing toxins to attack it and therefore absorb it.[8]

Other applications of nanosponges

Cyclodextrin-based nanosponges bind closely to organic molecules and remove them from water even at very low concentrations. Using a selective combination of polymer and crosslinker, the same concept is useful for removing bitter components from grape fruit juice. The hyperlinked microporous nanosponges can be used in the selective separation of inorganic electrolytes by size exclusion chromatography.[16]

CONCLUSION

Nanosponge is a targeted drug delivery system that prevents the side effects associated with conventional dosage forms and promotes safety and efficacy. They can be formulated in different formulations such as oral, parenteral, topical. They can carry both hydrophilic and lipophilic drugs. Using this nanotechnology to improve solubility, bioavailability and toxicity and to release the drug in a controlled way.

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