Scholars Academic Journal of Pharmacy
Abbreviated Key Title: Sch Acad J Pharm
ISSN 2347-9531 (Print) | ISSN 2320-4206 (Online)
Journal homepage: http://saspublisher.com/sajp/

OPEN ACCESS

Pharmaceutical Technology

Nanosponge as a Novel Carrier System: Applications and Emerging Trends

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DOI: 10.36347/SAJP.2019.v08i12.001 | **Received:** 27.11.2019 | **Accepted:** 04.12.2019 | **Published:** 09.12.2019

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Abstract **Review Article**

Nanocarriers deliver drugs to site-specific targets, allowing drugs to be delivered in specific organs or cells without affecting other unwanted one**.** Nanosponges are porous tiny spherical particles with a size of about a virus with an average diameter below 1µm. The Nanosponges are solid in nature and can be formulated as oral, topical, parenteral, and ocular or inhalation dosage forms. Nanosponges are prepared by solvent method, ultra-sound assisted synthesis method, hyper cross linked β- cyclodextrins method and Emulsion solvent diffusion method. Due to their biocompatibility and versatility, nanosponges have wide applications in the pharmaceutical field. For topical administration they can be effectively incorporated into topical hydrogel. For the parenteral administration the complex may be simply carried in sterile water, saline or other aqueous solutions. Nanosponges have wide clinical application in cancer, diabetes, peptides, protein and macromolecules delivery. NS can also serve as an effective carrier for enzymes, proteins, vaccine & antibodies. Nanosponges have been also used for improving the solubility and dissolution rate of poorly soluble drugs. In this review, an attempt has been made to highlight the advantages, characteristics, methods of preparation of nanosponges along with the recent clinical application of nanosponges.

Keywords: Nanosponge, Carrier system, Nanocarrier, β-cyclodextrin, Solubility enhancement.

INTRODUCTION

Targeting a molecule to a specific site requires a specialized drug delivery system. The discovery of nanocarrier has become a significant step in overcoming certain problems such as drug toxicity, poor bioavailability and unpredictable release[1].Nanocarriers are breakthrough in the drug delivery process because they can deliver drugs to specific targets, allowing drugs to be delivered in specific organs or cells without affecting other the unwanted one[2].

Based on associating with drugs, the nanoparticles can be classified as Encapsulating Nanoparticles, Complexing Nanoparticles and Conjugating Nanoparticles. Encapsulating nanoparticles consist of many holes that carry the drug molecule in their aqueous core. Complexing nanoparticles are nanoparticle that attracts the molecule by electrostatic charges and conjugating nanoparticles are the nanoparticles that link the drug through covalent bond [3].

Nanosponges (NS) are porous tiny spherical particles with a size of about a virus with an average diameter below 1µm [4].On account of smaller size and porous nature, NS improves the bioavailability of poorly soluble drug by their ability to bind with the poorly soluble drugs within the matrix.

The nanosponge is about the size of a virus with backbone of biodegradable polyester. The long length polyester strands are mixed in solution cross-linkers that have an affinity for certain portions of the polyester [5].As polyester are biodegradable, they release the drug inpredetermined time.NS can encapsulate various types of molecules by forming inclusion and non-inclusion complexes [6].

These tiny porous particles have capability to accommodate both hydrophilic and lipophilic drug substance, thus leads to increase the stability of poorly water-soluble drug substance [7, 8].

These sponges during circulation encounter with the definite target site, stick onto the surface and then release the drug in a predetermined and sustained

manner which leads to increase in the efficacy and effectivity [9].The NS could be either paracrystalline or in crystalline form. The loading capacity of nanosponges depends mainly on degree of crystallization.The Nanosponges are solid in nature and can be formulated as oral, Topical, parenteral, ocularor inhalation dosage forms [10,11]. NS's are obtained by suitable crosslinking process and also by different organic and inorganic materials. Nanosponges can encapsulate various types of molecules by forming inclusion and non-inclusion complexes. Nanosponges can also serve as an effective carrier for enzyme, proteins, vaccine and antibodies [12].

Advantages of nanosponges [13-15]

- Increase aqueous solubility of the poorly water-soluble drug.
- Predictable release of drug.
- Free flowing.
- Self sterilizer because of non-penetration of bacteria (average pore size is 0.25µm).
- Nanosponges drug delivery system are non-irritating, non-mutagenicand non-toxic.
- Nanosponges help to remove the toxic and venom substancefrom the body.
- Minimize side effect.
- Improved stability, increased elegance and enhanced formulation flexibility.
- Reduction in quantity and frequency of dose.
- Better patient compliance.
- Incorporation of immiscible liquids is possible.
- Stable over wide range of pH (1-11) and temperature of 130 °C.
- Easy scale-up for commercial production.

Disadvantages of nanosponges [16]

- Not suitable for larger molecules.
- Dose dumping.

Chemicals used for the Synthesis of Nanosponges [17-19]

The polymers, copolymers and crosslinkers are used to prepare and synthesize Nanosponges as depicted in fig. 1.

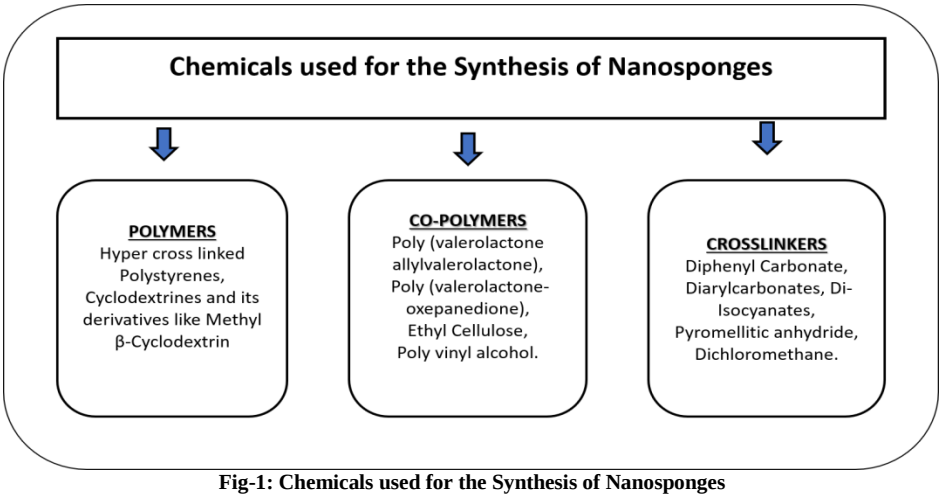

Fig-1: Chemicals used for the Synthesis of Nanosponges

Loading of Drug into Nanosponges

Nanosponges for drug delivery should be pre-treated to obtain a mean particle size below 500nm. For this, nanosponges is suspended in water and then sonicated to avoid the aggregation of particles.The suspension is then centrifuged to produce a colloidal fraction. Thesupernatant is separated and the sample is to be dried by freeze drying. Aqueous suspension of nanosponge is prepared and dispersed in the excess amount of the drug and the suspension is maintained under constant stirring for specific time (required for complexation). After complexation, the uncomplexed (undissolved) drug from complexed drug is separated by centrifugation. Then, the solid crystals of nanosponges are obtained by solvent evaporation or by freeze drying. Crystal structure of nanosponge plays a very important role in complexation with drug. A study revealed that paracrystallinenanosponges showed different loading capacities when compared to crystalline nanosponges. The drug loading is greater in crystalline nanosponges than paracrystalline one. In poorly crystalline nanosponges, the drug loading occurs as a mechanical mixture rather than inclusion complex [20-22]. Then process is as depicted in Fig.2.

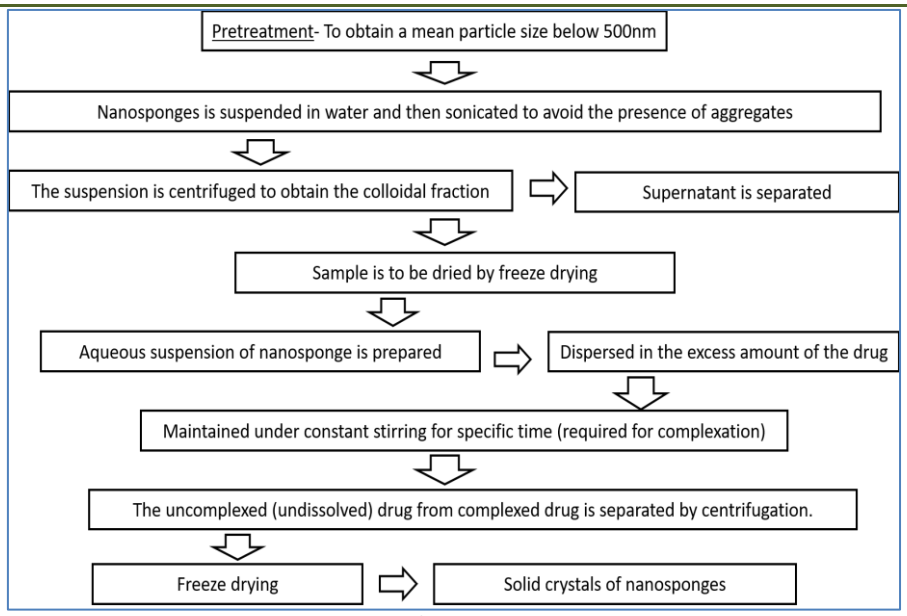

Fig-2: Loading of Drug into Nanosponges

Methods of preparation

Solvent method [11, 21]

In this method, the polymer mixed with a like polar aprotic solvent (dimethyl formamide, dimethyl sulfoxide). And the mixture is added to required quantity of the cross-linker in molar ratio of 1:4. Thereaction is carried out at temperature 10°C to reflux the temperature of the solvent for the time ranging from 1 to 48hr. At the end of the reaction, the solution is cooled at room temperature and large excess of bi-distilled water added to the product. Filtrationcarried out undervaccumfor the recovery of the product and subsequent purification by soxhlet extraction with ethanol followed by complete drying. As shown in Fig.3.

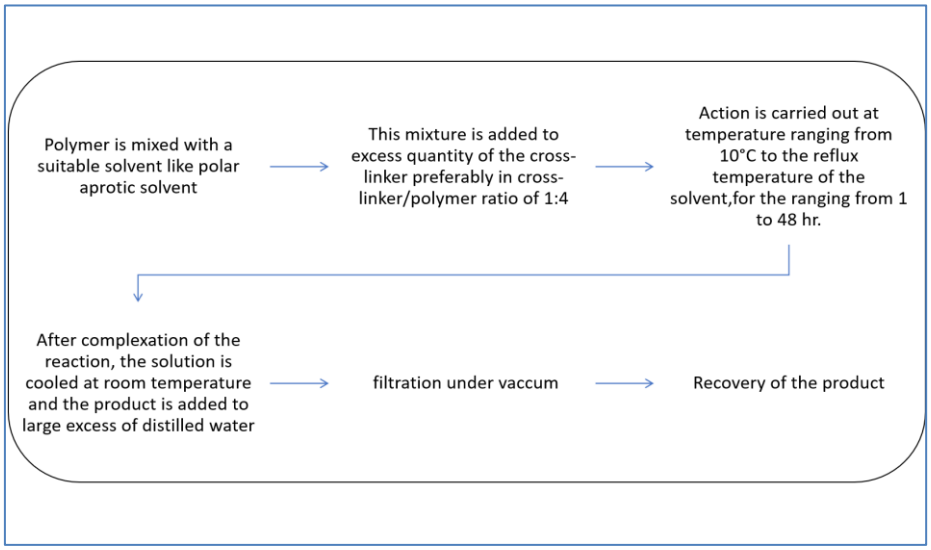

Fig-3: Solvent method

Ultra-sound assisted synthesis [22]

Polymers are made to react with crosslinkers in a flask without the solvent. Then, flask is placed in an ultrasound bath which is filled with water and heated up to 90˚C and the mixture is sonicated for 5 hr. Then the mixture is cooled down to room temperature and then the product is broken into rough pieces. At last, the non-reacting polymer is removed by washing the product with water and refining is done using soxhlet apparatus (ethanol) to obtain nanosponges. As shown in Fig.4.

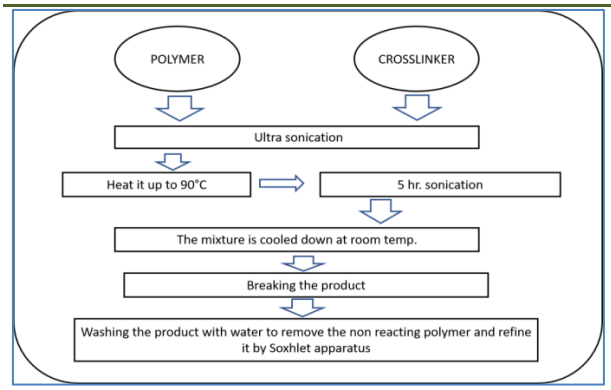

Fig-4: Ultra-sound assisted synthesis

Hyper cross linked β- Cyclodextrins [23]

Nanosponge has been recently developed hyper cross linked cyclodextrin polymers nano structured to form 3-dimensional networks; a roughly spherical structure, about the size of a protein, with channels and pores inside. They are obtained by reacting cyclodextrin with a cross-linker such as di-isocianates, diaryl carbonates, dimethyl carbonate, diphenyl carbonate, and carbonyl diimidazoles, carboxylic acid dianhydrides and 2, 2-bis(acrylamido)acetic acid. The surface charge density, porosity and pore sizes of sponges can be controlled to attach different molecules. Nanosponge with low cross linking gives a fast drug release.

Emulsion solvent diffusion method [24]

In this method, different proportion or amount of ethyl celluloseand polyvinyl alcohol are used to prepare nanosponges. Twophases are used in this methoddispersed and continuous. Thedispersed phase consists of ethyl cellulose and the drug, which isthen dissolved in 20 ml of dichloromethane and some amount ofpolyvinyl alcohol (PVA) is added to 150 ml of the continuousphase (aqueous). Then, the mixture is stirred at the speed of1000-2000 rpm for about 2 hr. The product i.e. the nanosponge's arecollected by filtration. Finally, the product is dried inanoven at a temperature of 400˚C. As shown in Fig.5.

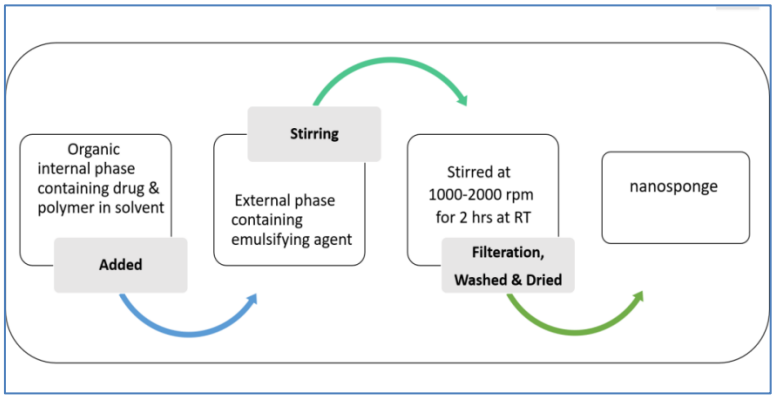

Fig-5: Emulsion solvent diffusion method

Application

Due to their biocompatibility and versatility, nanosponges have wide applications in the pharmaceutical field. NS can act as multifunctional carriers for enhanced product performance and elegancy, improved thermal, physical and chemical stability of product. Following are the application of nanosponges which shows versatility of nanosponges.

Nanosponges for drug delivery

As NS are generally solid in nature these can be formulated as Oral, Parenteral, Topical or Inhalation dosage forms. Nanosponges have several properties that enhance the product performance and elegance, controlled release, sustained release, decrease skin irritation, improve solubility and increase product flexibility.

Oral Drug Delivery

For the oral administration, the complexes may be dispersed in a matrix of excipients, diluents, lubricants and anticaking agents suitable for the preparation of capsules or tablets. Because of their nanoporous structure, NSs can accommodate water insoluble drugs. These complexes can be used to increase the dissolution rate, solubility and stability of drugs, to mask unpleasant flavours and to convert liquid substances to solids.

β-Cyclodextrin based nanosponges are reported to deliver the drug to the target site three to five times more effectively than injectable[25].

In oral application it forms the nanosponge system consist of pores which increase the rate of solubilization of poorly watersoluble drugs which get entrapped the drug in pores. The surface area is increased due to nanosize form and increase rate of solubilization[26].

Many researchers prepared oral Nanosponges of low solubility drugs such as, traconazole, flurbiprofen, dexamethasone, danazol, nelfinavir, carbamazepine using bio-erodible polymers, especially for colon specific delivery and controlled release drug

delivery system thereby, reducing drug toxicity and bioavalibity[26].

Topical Delivery

For topical administration they can be effectively incorporated into topical hydrogel [27]. Various categories of drugs that can be formulated as topical nanosponges are: Local anaesthetics, antifungals and antibiotics [28].

NanospongeTopical delivery system is a unique technology for the controlled release of topical agents for prolonged drug release and retention of drug form on skin. A wide variety of substances can be incorporated into a formulated product such as gel, lotion, cream, ointment, liquid, or powder [29].

Econazole nitrate cream, ointment, lotion and solution showed poor andinsignificant adsorption but econazole nitrates Nanosponge when loaded in hydrogelas a local depot for sustained drug release showed better adsorption [30].

Parenteral Delivery

For the parenteral administration the complex may be simply carried in sterile water, saline or other aqueous solutions [20].

Ocular delivery system

Eyes, undisputedly remains the most accessible organ of the body, at the same time the most sensitive. A carrierbased system like NS helps to increase the residence time of NS in the eye and also could release the drug in a controlled manner thereby also reducing the associated side effects [32].

B-Cyclodextrin based dexamethasone Nanosponges in ocular drug delivery showed enhanced permeation along with high retention as compared to conventional Cyclodextrins [33].

Hayiyana Z *et al*. formulated cyclodextrin-based nanosponge drug delivery system with potential to improve corneal permeation and drug solubility. The result showed that, 75 % permeation of the NS drug was achieved as compared to the 28% of pure drug. The nanosponges provided drug release for approximately an hour.

The ester-based hydrophilic cyclodextrin-based nanosponge derivative can be used as a drug delivery system in topical ocular drug delivery, to improve stability, solubility and corneal permeation [34].

Oxygen delivery systems

The deficiency of adequate oxygen supply (hypoxia), is related to various pathologies, from inflammation to cancer. Cyclodextrin nanosponges developed as oxygen delivery system which has the ability to store and to release oxygen slowly over time. These nanosponges could be useful for many biomedical applications. Oxygen-filled nanosponges could supply oxygen to the hypoxic tissues which are present in various diseases [10]. Developed nanosponges formulations as oxygen delivery systems for topical application which have the ability to store and to release oxygen slowly over time [35].

Clinical application

The anticancer drugs given in cancer patients found to be inefficient due to non-availability of drug in the tumor site.When, prepared in NS it shows better release the drug at the tumor site instead of circulating widely through the body. So, it is more effective for a given dosage and also shows minimum side effects thus, improve the function of the nanosponges in cancer therapy through the attachment of tumor-specific targeting ligands [20].

Most protein drugs are poorly absorbed through the biological membranes due to large molecular size, hydrophilic nature, and high surface charge, chemical and enzymatic instability. On intravenous administration, protein molecules rapidly cleared from blood and bind to plasma proteins. With oral route bioavailability is the problem. Cyclodextrin based nanosponges can besuitable carrier to adsorb proteins, enzymes, antibodies and macromolecules [36].Stability is a critical factor in the successful development of macromolecular like proteins [37].

A major obstacle in protein formulation development is the maintenance of the protein structure during the formulation process and during storage. Reported new swellable cyclodextrin based poly (amidoamine) nanosponges. The formulated β-CD based poly (amidoamine)-nanosponges were found to be stable at high temperature (300°C) and also high protein complexation capacity was observed.

Bovine serum albumin (BSA) protein in solution is not stable; hence it is stored in lyophilized state. However, proteins can reversibly denatured on lyophilisation and adopts conformation markedly different from native structure. Stability of proteins like BSA was reported to increase when encapsulated in swellable cyclodextrin based poly (amidoamine) nanosponges [38].Recently, zidovudine, saquinavir based Nanosponges are used in nasal and pulmonary route of administration. It provides specificity to deliver antiviral drug on RNA to lungs or nasal route through nanocarriers for targeting virus which may cause infection [28,39].

Other application

Nanosponges based on cyclodextrins can strongly bind organic molecules and remove them from water even at very low concentrations [40].

Nanosponges can selectively soak up biomarkers for the diagnosis. One study concluded that nanosponges can harvest rare cancer marker from blood [41].

Nanosponges have been also used for improving the solubility and dissolution rate of poorly soluble drugs. Nanosponges of Cefpodoxime proxetil have been prepared to improve dissolution rate drug [42].

Swaminathan *et al.* [38] studied a formulation of itraconazole in Nanosponges. B-cyclodextrin based nanosponges of itraconazole showed increase in solubility of poorly soluble drug. The solubility increased by 50 folds compared to ternary dispersion system. Nanosponges solubilize drug by masking the hydrophobic groups of itraconazole, by increasing the wetting of the drug.

Gamma-oryzanol is a mixture natural antioxidant and usually employed to stabilize food and pharmaceutical raw materials, moreover as a sunscreen in the cosmetics industry. It ishighly unstable and shows photodegradation. When gel and an O/W emulsion were formulated with the gamma-oryzanol-loaded nanosponges it showed a good protection from photodegradation [43].

CONCLUSIONS

The discovery of nanocarrier specially, Nanosponge has become a significant step in overcoming certain problems such as drug toxicity, poor bioavailability and unpredictable release of drug. They are also capable of carrying both lipophilic and hydrophilic molecules. Due to their spherical and small particle size these can be developed as different dosage forms like oral, parenteral and topical preparations. Nanosponge offers entrapment of drugs and ultimately reduction in side effects, increase in stability, elegance and formulation flexibility. Nanosponge provides site specific drug delivery and improving patient compliance. Besides their application in the drug delivery, they have potential applications in biomedicine, Solubility enhancement, and catalysis.

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