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Nanosponges: A versatile drug delivery system

Naga Silpa J.*, Srinath Nissankararao, Ramadevi Bhimavarapu, Lakshmi Sravanthi S., Vinusha K. and Renuka K.
Sri Siddhartha Pharmacy College, Nuzvid-India

Abstract
Effective targeted drug delivery systems have been a dream for long time. The invention of nanosponges has become a significant step towards overcoming these problems. These small sponges can circulate around the body until they encounter the target site and stick on the surface and began to release the drug in a controlled and predictable manner which is more effective for a particular given dosage. Owing to their small size and porous nature they can bind poorly-soluble drugs within their matrix and improve their bioavailability. They can be crafted for targeting drugs to specific site, prevent drug and protein degradation and prolong the drug release in a controlled manner. This review attempts to elaborate the interesting features of nanosponges, preparation, Characterization, applications and recent updates of nanosponges in drug delivery.

Key-Words: Nanosponge [Ns], Salient features, Future prospects

Introduction
Effective targeted drug delivery systems have been a dream for long time, but it has been largely frustrated by the complex chemistry that is invovled in the development of the new systems. The invention of the nanosponges has become a significant step step towards overcoming these problems [1]. Nanosponge were originally developed for topical delivery of drugs [2]. Nanosponges are tiny sponges with a size of about a virus [1] with an average diameter below 1µm [2]. These tiny sponges can circulate around the body until they encounter the specific target site and stick on the surface and began to release the drug in a controlled and predictable manner. Because the drug can be released at the specific target site instead of circulating throughout the body it will be more effective for a particular given dosage [1]. Nanosponges are capable of providing solutions for several formulation related problems. Owing to their small size and porous nature they can bind poorly- soluble drugs within the matrix and improve their bioavailability. They can be crafted for targeting drugs to specific sites, prevent drug and protein degradation and prolong drug release in a controlled manner [3].

Nanosponges are obtained by suitable cross linking process and also by different organic and inorganic materials. Nano sponges can encapsulate various types of molecules by forming inclusion and non inclusion complexes.

*** Corresponding Author**
E.mail: junganaga.silpa@gmail.com

Cross linking process: Highly cross linked cyclodextrins and highly cross linked polystyrene (natural derivative of starch)are used for the fabrication of nanosponges insoluble in water and commonest organic solvents,nontoxic,porous,stable above 300˚c which may be used to encapsulate, carry and /or selectively release a great variety of substances [1].

Organic and inorganic materials

Some examples of Nanosponges formed by using Organic and inorganic materials are Titanium or other metal oxide based nanosponges, silicon nanosponge particles. Carbon coated metallic Nanosponges [1].

Interesting features of nanosponges

An important character of these sponges is their aqueous solubility; this allows The use of these systems effectively for drugs with poor solubility [1].

The Nanosponges are capable of carrying both lipophilic and hydrophilic drugs. . Nanosponges could be used to increase aqueous solubility of poorly water-soluble drugs, to remove pollutants from contaminated water, or as nano carriers for biomedical applications. Nanosponges have been used for removal of organic impurities in water [4, 5].

This technology offers entrapment of ingredients and reduced side effects, improved stability, increased elegance, and enhanced formulation flexibility. Nanosponge and Nanosponge systems are non irritating and non-mutagenic, non-allergic and non-toxic.

Extended release-continuous release up to 12h allows incorporation of immiscible liquid improves material

processing-liquid can be converted to powders. They can be formed in a sub microns spherical particle. They can be obtained in a wide range of dimensions, from 1micron to 10 microns. The cavities of the framework have a tunable polarity. Different functional groups can be linked to the structure due to sub micron dimensions of the particle. Nanosponge can disperse at molecular level, highly insoluble principles, stabilizing and protecting their structures, from chemicals, light, oxygen, etc. efficacy and shelf life of drugs can be prolonged if compared to the non-complexed form. By using Nanosponge as drug delivery system, higher therapeutic activities are observed being the concentration of the active molecule the same [6, 14].

Preparation of nanospoges [4, 7]

Nanosponges are prepared by using hyper cross-linked β-cyclodextrins and Emulsion Solvent Diffusion method.

a) Hyper Cross Linked β- Cyclodextrins.

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, dimethly 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.

b) Emulsion Solvent Diffusion Method

This method uses different proportion of ethyl cellulose and polyvinyl alcohol. The dispersed phase containing ethyl cellulose and drug was dissolved in 20ml dichloromethane and slowly added to a definite amount of polyvinyl alcohol in 150ml of aqueous continuous phase. The reaction mixture was stirred at 1000rpm for 2 hrs. Then Nanosponge formed were collected by filtration and dried in the oven at 400 c for 24 hrs. The dried Nanosponge was stored in vacuum desiccators to ensure the removal of residual solvent.

Evaluation

Nanosponge were evaluated by particle size determination, morphology and surface topography, loading efficiency and production yield, true density, polymer or monomer composition, resiliency, compatibility studies, dissolution tests.

Particle Size Determination

Free-flowing powders with fine aesthetic attributes are possible to obtain by controlling the size of particles during polymerization. Particle size analysis of loaded and unloaded nano and can be performed by laser light diffractometryor Malvern zeta seizer. Cumulative percentage drug release from nano sponges of different particle size will be plotted against time to study the effect of particle size on drug release. Particles larger than 30 microns can impart gritty feeling and hence particles of sizes between 10 and 25 microns are preferred to use in final topical formulation [7, 8].

Morphology and Surface Topography of Nanosponges

For morphology and surface topography, the prepared Nanosponges can be coated with gold–palladium under an argon atmosphere at room temperature and then the surface morphology of the nano and Nanosponge can be studied by scanning electron microscopy [9].

Determination of Loading Efficiency and Production yield

The loading efficiency (%) of the Nanosponges can be calculated according to the following equation.

Loading Efficiency=Actual Drug Content in Nanosponge/ Theoretical Drug Content ×100

The production yield of the Nanosponges can be determined by calculating accurately the initial weight of the raw materials and the last weight of the Nanosponge are obtained [10].

Determination of True Density

The true density of nano particles can be determined using an ultra-pycnometer under helium gas [11].

Polymer/ monomer composition

Polymers with varying electrical charges or degrees of hydrophobicity or lipophilicity may be prepared to provide flexibility in the release of active ingredients. Various monomer combinations will be screened for their suitability with the drugs by studying their drug release profile. Selection of monomer is dictated both by ultimately to be entrapped and by the vehicle into which it will be dispersed [12].

Resiliency (Viscoelastic properties)

Resiliency of sponges can be modified to produce beadlets that is softer or firmer according to the needs of the final formulation. Increased crosslinking tends to slow down the rate of release. Hence resiliency of sponges will be studied and optimized as per the requirement by considering the release as a function of cross-linking with time [12].

Compatibility studies

Thin layer chromatography (TLC) and Fourier transform infra-red spectroscopy (FT-IR) are used to study the Compatibility of drug with reaction adjuncts .Effect of polymerization on crystalinity of the drug can be studied by powder x-ray diffraction (XRD) and Differential Scanning Colorimeter (DSC). For DSC, approximately 5 mg samples can be accurately weighed into aluminum pans and sealed and can be run

at a heating rate of 15 c/min over a temperature range 25–430 c in atmosphere of nitrogen [13].

Dissolution profile

Dissolution profile of Nanosponge can be studied by use of the dissolution apparatus usp xxiii with a modified basket consisted of 5m stainless steel mesh. Speed of the rotation is 150 rpm. The dissolution medium is selected while considering solubility of actives to ensure sink conditions. Samples from the dissolution medium can be analyzed by a suitable analytical method studied by use of the dissolution apparatus usp xxiii with a modified basket consisted of 5m stainless steel mesh. Speed of the rotation is 150 rpm. The dissolution medium is selected while considering solubility of actives to ensure sink conditions. Samples from the dissolution medium can be analyzed by a suitable analytical method [13].

Drugs Reported to be Best Suitable In Nanosponge Formulation [22]

1. Doxorubicin Ns complex[2] drug formulation is a controlled drug delivery system. It is cross linked by cross linking β-cd with diphenyl carbomate and encapsulated by incubation followed by lyophilization.
2. Dexamethasone and flurbiprofen[2] drug formulations have enhanced drug solubility, and they are cross linked using linking β-cd with diphenyl carbomate and encapsulated by incubation followed by lyophilization.
3. Carbamazepine, nelfinavir, oxcarbamazepine, and danazol[16] drug formulations have enhanced drug solubility. And are crosses linked using dimethyl carbomate and encapsulated by incubation followed by lyophilization.
4. Itraconozole[4] drug formulation enhances drug solubility by use of temary complexation. It is cross linked by carbomate and encapsulated by incubation followed by lyophilization and drying. ternary component used is copolyvidinum.
5. Camptothecin formulation has enhanced drug stability, cytotoxicity and controlled release. And it is cross linked by linking β-cd with diphenyl carbonate and encapsulated by incubation followed by lyophilization.
6. Resveratrol[13] drug formulation has enhanced drug stability, cytotoxicity and controlled release. And it is cross linked by β-cd with carbonyl di imidazole and encapsulated by incubation followed by lyophilization.
7. Tamoxifen[11] drug formulation has enhanced bioavailability and solubility. And it is cross linked by β-cd with carbonyl diimidazole and encapsulated by incubation followed by lyophilization
8. Curcumin[12] drug formulation has enhanced activity and solubilization. It is cross linked by carbomate and encapsulated by incubation followed by lyophilization and drying.
9. Oxygen[15] drug formulation stores oxygen and it is a sustained released formulation. Oxygen entrapment by β-cd with carbonyl diimidazole and encapsulated by incubation followed by lyophilization.
10. Paclitaxel[10] drug formulation has enhanced bio-availability, cytotoxicity and solubilization. And cross linked β-cd with diphenyl carbonate, encapsulated by incubation followed by lyophilization.
11. Albumin[14] drug formulation is a swellable drug delivery system of bovine serum albumin for controlled release, β cyclodextrins are cross linked with 2-2 bisacrylamido acetic acid or 2- methylpiperazine.

Applications

Nanosponges have been explored for primary application in topical and buccal delivery of drugs.

Resveratrol, a polyphenolic phytoalexin, has been used to treat conditions such as cardiovascular diseases, cancer, hyperlipidemia, inflammation, gonorrhoea, dermatitis, and fever. In addition, because of its antibacterial and antifungal properties, it is used on human skin infections. The Ns formulation of Resveratrol has shown significantly better permeation, stability, and cytotoxicity against hcpc-i cells, a continuous cell line derived from a chemically induced cancer in the buccal mucosa of Syrian hamsters. Hence, Ns formulations can be used for topical and buccal applications [23].

Topical agents

Nanosponge delivery system is a unique technology for the controlled release of topical agents of prolonged drug release and retention of drug form on skin. Conventional dermatological and personal-care products typically provide active ingredients in relatively high concentrations but with a short duration of action. This may lead to a cycle of short term over medication followed by long term under medication. Rashes or more serious side effects can occur when active ingredients penetrate the skin. In contrast, this technology allows an even and sustained rate of release, reducing irritation while maintaining efficiency. a wide variety of substances can be incorporated into a formulated product such as gel, lotion, cream, ointment, liquid, or powder [14]. Econazole nitrate, an antifungal used topically to relive the symptoms of superficial candidasis, dermatophytosis, versicolor and skin infections available in cream, ointment, lotion and solution. Adsorption is not significant when econazole nitrate is applied to skin and required high concentration of active agents to be incorporated for effective therapy. Thus, econazole nitrates Nanosponge were fabricated

by emulsion solvent diffusion method, and these Nanosponges were loaded in hydrogel as a local depot for sustained drug release [7].

Oral Delivery Of Drugs

Oral delivery of drugs using bioerodible polymers, especially for colon specific delivery and controlled-release drug delivery system thus reducing drug toxicity and improving patient compliance by providing site particular drug delivery system and prolonging dosage intervals [7, 15]. Molecular studies include itraconazole, flurbiprofen, dexamethasone, danazol, nelfinavir, carbamazipine, and oxy carbamazipine. These are bcs class-2 drugs having low solubility, and a dissolution rate limited poor bioavailability. However, when formulated with Nanosponge they demonstrate enhanced solubilisation efficiency, with desired drug release characteristics [16].

Delivery of Proteins

Bovine serum albumin (BSA), protein insolution is not stable. They are stored in a lyophilized state. However, proteins can reversibly denature on lyophilization and adopts conformation markedly different from native structure. Major drawback in protein formulation and development is to maintain its native structure during processing and long-term storage. In the Nanosponge based approach protein like BSA are encapsulated in a swell able cyclodextrin based poly (amidoamine) Nanosponge to increase the stability of proteins [17]. Ns have also been used for enzyme immobilization, protein encapsulation, and subsequent controlled delivery and stabilization. The enzymes studied are from the oxidoreductase, transferase, hydrolase, lyase, isomerase, and ligase classes. The model protein bovine serum albumin has been encapsulated with ns, and studies showed prolonged release of albumin. In addition, encapsulation of albumin in ns protected and stabilized the protein during storage [20].

Encapsulation of gases

Cyclodextrin based carbonate Nanosponge was used to form inclusion complexes with three different gases, i.e. 1-methylcyclopropene, oxygen and carbondioxide. The complexetion of oxygen or carbondioxide could be useful for many biomedical applications. In particular, the oxygen-filled Nanosponge could supply oxygen to the hypoxic tissues which are present in various diseases [18]. Because of its super porous nature, the Nanosponge also has been explored as an effective gas carrier. Nanosponge formulation shows the ability to store and release oxygen in a controlled manner. In future, they could be one useful tool for the delivery of some vital gases [19].

Chemotherapy

Nanosponges have been studied as a potential delivery system for anticancer therapies in which enhancement of bioavailability and activity was seen in molecules such as Paclitaxel and Tamoxifen. In vivo, studies in rats revealed a 2.5-fold improvement in bioavailability for Paclitaxel-loaded Ns compared with plain Paclitaxel; in a Tamoxifen-loaded Ns complex, a 1.44-fold improvement was seen [21]. It has been used in a successful single-injection test, delivering the drug paclitaxel (generic taxol) to mice with glioma (a fast-acting brain cancer) and cells with human breast cancer [1].

Camptothecin (cam), a plant alkaloid and a potent antitumor agent, has a limited therapeutic utility because of its poor aqueous solubility, lactone ring instability and serious side effects [15] the lactone ring at physiological pH opens up and produces the inactive carboxylate form. Cyclodextrin-based Nanosponges (Ns) are a novel class of cross-linked derivatives of cyclodextrins. They have been used to increase the solubility of poorly soluble actives, to protect the labile groups and control the release. Incorporation of camptothecin in Ns has led to a prolonged-release profile in an active form, hindering the hydrolysis of the lactone form and resulting in increased stability.

Curcumin, the extract from the dried roots of rhizome curcuma shown potential application as a tumor treatment. An Ns formulation of curcumin provided efficient delivery of encapsulated curcumin, increasing its solubilization efficiency and improving stability by reducing hydrolytic degradation and biotransformation for longer periods of time [24].

Nano carriers for biomedical applications

Nanosponge could be used to from contaminated water Nanosponge have been used for the removal of organic impurities in water [4].

Conclusion

Nanosponge offers entrapment of ingredients, and thus reduced side effects improved stability, increases elegance and enhanced formulation flexibility. Nanosponge can be effectively incorporated into a topical drug delivery system for retention of dosage form on skin, and also use for oral delivery of drugs using bioerodible polymers, especially for colon specific delivery and controlled-release drug delivery system thus improving patient compliance by providing site specific drug delivery system and prolonging dosage intervals. The next tests will be a series of injections against whole tumors. In parallel to these tests, the approach must also be evaluated for toxicity. Like all nonmedical materials, Nanosponge

will need lengthy phased trials, which means that commercial availability is still years away [1].

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