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RESEARCH ARTICLE

Nanosponges: A Novel Approach of Drug Delivery System

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ABSTRACT

Targeted drug delivery to specific sites is the significant problem which is being faced by the researchers. The development of new colloidal carrier called nanosponges has the potential to solve these problems. Nanosponge is a novel and emerging technology which offers controlled drug delivery for topical use. In this review article, application of nanosponges, its preparation methods by Emulsion solvent diffusion method, and by using hyper crosslinked cyclodextrin and evaluation have been discussed. Nanosponge play vital role in targeting drug delivery in a controlled manner. Both lipophilic and hydrophilic drugs are incorporated in nanosponge. The outer surface is typically porous, allowing controlled release of drug. They enhanced solubility, bioavailability reduce side effects and modify drug release. Nanosponge drug delivery system has emerged as one of the most promising fields in life science used in chemotherapy nowadays.

INTRODUCTION

Targeting the delivery of drugs has long been a problem for medical researchers - how to get them to the right place in the body and how to control the release of the drug to prevent overdoses. The developments of new and complex molecules called nanosponges have the potential to solve these problems. Nanosponges are a new class of materials and made of microscopic particles with few nanometers wide cavities, in which a large variety of substances can be encapsulated. These particles are capable of carrying both lipophilic and hydrophilic substances and of improving the solubility of poorly water soluble molecules. [1] Nanosponges are tiny mesh-like structures that may revolutionise the treatment of many diseases and early trials suggest this technology is up to five times more effective at delivering drugs for breast cancer than conventional methods. [2] The nanosponge is about the size of a virus with a 'backbone' (a scaffold structure) of naturally degradable polyester. The long length polyester strands are mixed in solution with small molecules called cross-linkers that have an affinity for certain portions of the polyester. They 'cross link' segments of the polyester to form a spherical shape that has many pockets (or cavities) where drugs can be stored. The polyester is predictably biodegradable, which means that when it breaks up in the body, the drug can be released on a known schedule [2]. The nanosponges are encapsulating type of nanoparticles which encapsulates the drug molecules within its core. By the method of associating with drugs, the nanoparticles can be classified into encapsulating nanoparticles, complexing nanoparticles and conjugating nanoparticles. The first type is represented by nanosponges and nanocapsules. Nanosponges such as alginate nanosponge, which are spongelike nanoparticles containing many holes that carry the drug molecules. Nanocapsules such as poly(isobutyl-cyanoacrylate) (IBCA) are also encapsulating nanoparticles. They can entrap drug molecules in their aqueous core. The second category is Complexing nanoparticle, which attracts the molecules by electrostatic charges.

The third type is Conjugating nanoparticle, which links to drugs through covalent bonds. [3] These nanosponges represent a novel class of nanoparticles usually obtained by natural derivatives. As compared to the other nanoparticles, they are insoluble both in water and organic solvents, porous, non toxic and stable at high temperatures up to 300°C.

They are able to capture, transport and selectively release a huge variety of substances because of their 3D structure containing cavities

of nanometric size and tunable polarity. Furthermore, nanosponges show a remarkable advantage in comparison with the common nanoparticles: indeed, they can be easily regenerated by different treatments, such as washing with eco-compatible solvents, stripping with moderately inert hot gases, mild heating, or changing pH or ionic strength. For all these characteristics, nanosponges have been already employed in different applied fields, such as cosmetic and pharmaceutical sectors. [4]

Nanosponges can be used as a vessel for pharmaceutical principles to improve aqueous solubility of lipophilic drugs, to protect degradable molecules and to formulate drug delivery systems for various administration routes besides the oral one. The simple chemistry of polymers and cross linkers does not pose many problems in the preparation and this technology can be easily ramp up to commercial production levels. Nanosponges are water soluble but does not breakup chemically in water. They mix with water and use as a transport fluid. They can be used to mask unpleasant flavours, to convert liquid substances to solids. The chemical linkers enable the nanosponges to bind preferentially to the target site. The main disadvantage of these nanosponges is their ability to include only small molecules. The nanosponges could be either paracrystalline or in crystalline form. The loading capacity of nanosponges depends mainly on degree of crystallisation. Paracrystalline nanosponges can show different loading capacities. The nanosponges can be synthesized to be of specific size and to release drugs over time by varying the proportion of cross linker to polymer. The engineering capacity of nanosponge is due to the relatively simple chemistry of its polyesters and cross-linking peptides, compared to many other nanoscale drug delivery systems. [2] These nanosponges can be magnetized when they are prepared in the presence of compounds having magnetic properties. [5] The tiny shape of nanosponges enables the pulmonary and venous delivery of nanosponges. [1]

ADVANTAGES OF NANOSPONGES [13, 14]

- This technology offers entrapment of ingredients and reduces side effects.
- Improved stability, increased elegance and enhanced formulation flexibility.
- These formulations are stable over range of pH 1 to 11.
- These formulations are stable at the temperature up to 1300C.
- 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.
- These modify the release of drug.
- They increase the solubility of poorly soluble drug.
- They increase the bioavailability of drug.

The list of polymers and crosslinking agents used for the synthesis of nanosponges are presented in Table-1.

Table 1. **Chemicals used for the synthesis of nanosponges**

Polymers	Hyper cross linked Polystyrenes, Cyclodextrines and its derivatives like Methyl β-Cyclodextrin,Alkyloxycarbonyl Cyclodextrins, 2-Hydroxy Propyl β-Cyclodextrins and Copolymers like Poly(valerolactone-allylvalerolactone) & Poly(valerolactone-allylvalerolactoneoxepanedione) and Ethyl Cellulose & PVA
Crosslinkers	Diphenyl Carbonate, Diarylcarbonates, Diisocyanates, Pyromellitic anhydride,Carbonyldiimidazoles, Epichloridrine, Glutarldehyde, Carboxylic acid dianhydrides, 2,2-is(acrylamido) Acetic acid and Dichloromethane

Drugs which are particularly critical for formulation in terms of their solubility can be successfully delivered by loading into the nanosponges. List of some BCS Class II dugs which can be developed as nanosponges are given in Table 2.

Table 2. Biopharmaceutical Classification System Class II drugs [6]

Drug Category	**List of Drugs**
Antianxiety drugs	Lorazepam
Antiarrhythmic agents	Amiodarone hydrochloride
Antibiotics	Azithromycin, Ciprofloxacin, Erythromycin, Ofloxacin, Sulfamethoxazole
Anticoagulant	Warfarin
Anticonvulsants	Carbamazepine, Clonazepam, Felbamate, Oxycarbazepine, Primidone
Antidiabetic and Antihyperlipidemic drugs	Atorvastatin, Fenofibrate, Glibenclamide, Glipizide, Lovastatin, Troglitazone
Antiepileptic drugs Phenytoin Antifungal agents	Econazole nitrate, Griseofulvin, Itraconazole, Ketoconazole, Lansoprazole,Vericonazole
Antihistamines	Terfenadine
Antihypertensive drugs	Felodipine, Nicardipine, Nifedipine, Nisoldipine
Antineoplastic agents	Camptothecin, Docetaxel, Etoposide, Exemestane, Flutamide, Irinotecan,

	Paclitaxel, Raloxifene, Tamoxifen, Temozolamide, Topotecan
Antioxidants	Resveratrol
Antipsychotic drugs	Chlorpromazine Hydrochloride
Antiretrovirals	Indinavir, Nelfinavir, Ritonavir, Saquinavir
Antiulcer drugs	Lansoprazole, Omeprazole
Anthelmintics	Albendazole, Mebendazole, Praziquantel
Cardiac drugs	Carvedilol, Digoxin, Talinolol
Diuretics	Chlorthalidone, Spironolactone
Gastroprokinetic agent	Cisapride
Immunosupressants	Cyclosporine, Sirolimus, Tacrolimus

NSAIDs	Dapsone, Diclofenac, Diflunisal, Etodolac, Etoricoxib, Flurbiprofen, Ibuprofen, Piroxicam Indomethacin, Ketoprofen, Mefenamic acid, Naproxen, Nimesulide, Oxaprozin,
Steroids	Danazol, Dexamethazone,
Miscellaneous	Melarsoprol, Phenazopyridine, Ziprasidone,

Table 3. Examples of nanosponges

Drug	**Nanosponge vehicle**	**Indication**	**Study**	**In vitro / in vivo / Mathematical Model**	**Reference**
Paclitaxel	β-cyclodextrin	Cancer	Bio-availability	Sprague Dawley rats MCF7 cell line	9 10

Camptothecin	β-cyclodextrin	Cancer	Haemolytic activity Cytotoxicty	Diluted blood HT-29 cell line	11 12
Tamoxifen	β-Cyclodextrin	Breast cancer	Cytotoxicty	MCF-7 cell line	5
Econazole nitrate	Ethyl cellulose Polyvinyl alcohol	Antifungal	Irritation study	Rat	7,8

PREPARATION OF NANOSPONGE

a. *Emulsion solvent diffusion method*

Nanosponges prepared by using 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. The nanosponges formed were collected by filtration and dried in oven at 400 c for 24 hrs.The dried nanosponges were stored in vacuum desiccators to ensure the removal of residual solvent.[15]

b. Nanosponge prepared from hyper crosslinked cyclodextrin

In the melt method, the crosslinker is melted along with CDs. All ingredients are finely homogenized and placed in a 250 ml flask heated at 100 °C and the reaction is carried out for 5 hrs under magnetic stirring. The reaction mixture is allowed to cool and the obtained product is broken down followed by repeated washing with suitable solvents to remove unreacted excipients and byproducts.

In the solvent method, the melting step is eliminated and the crosslinker is solubilise in solvents like dimethylformamide or dimethylsulfoxide (DMF/DMSO). The polymer is generally mixed with a suitable solvent, particularly

a polar aprotic solvent, followed by addition of this mixture to an excess quantity of the crosslinker. Optimization of the process is performed by varying the crosslinker/polymer molar ratio. The reaction is carried out at temperatures ranging from 10 °C to the reflux temperature of the solvent, for 1 to 48 hrs. Preferred crosslinkers for this reaction are the carbonyl compounds diphenyl carbonate (DPC), dimethyl carbonate (DMC) or carbonyldiimidazole (CDI).The product is obtained by adding the cooled solution to a large excess of bidistilled water. Recovery of the product is done by filtration under vacuum and the product is further purified by prolonged Soxhlet extraction. [16, 17]

PHYSICOCHEMICAL CHARACTERIZATION OF NANOSPONGE

1. ***Particle size determination*** Free-flowing powders with fine aesthetic attributes will possible to obtain by controlling the size of particles during polymerization. Particle size analysis of loaded and unloaded nanosponges will performed by laser light diffractometry or Malvern Zeta sizer. Cumulative percentage drug release from nanosponges of different particle size will be plotted against time to study effect of particle size on drug release. Particles larger than 30 m can impart gritty feeling and hence particles of sizes between 10 and 25 m are preferred to use in final topical formulation. [1, 8]

2. ***Determination of loading efficiency and production yield*** The prepared nanosponge loading efficiency is determined by subtracting the un-entrapped drug from the total amount of drug. The drug entrapment efficiency will be determined by separating un-entrapped drug estimated by any suitable method of analysis. The method used for separation of un-entrapped drug by gel filtration, dialysis and ultra centrifugation. The loading efficiency is calculated as [23]:

Loading efficiency=Actual drug content in nanosponge/Theoretical drug content×100

The production yield of the nanosponge can be determined by calculating accurately the initial weight of the raw materials and the last weight of the nanosponge obtained **.**

Production yield=Practical mass of nanosponge/Theoretical mass(drug+polymer)×100

3. *Porosity*

Porosity study is performed to check the extent of nanochannels and nanocavities formed. Porosity of nanosponges is assessed with a helium pycnometer, since helium gas is able to penetrate inter- and intra-particular channels of materials. The true volume of material is determined by the helium displacement method. Owing to their porous nature, nanosponges exhibit higher porosity compared to the parent polymer used to fabricate the system. Percent porosity is given by equation [24]

%Porosity=Bulk volume−True volume/Bulk volume×100

4. ***Swelling and water uptake*** For swellable polymers like polyamidoamine nanosponges, water uptake can be determined by soaking the prepared nanosponges in aqueous solvent. Swelling and water uptake can be calculated using equations [24]

% Swelling=Marking of cylinder at aspecified time point/Initial marking before soaking×100

% Water uptake=Mass of hydrogel after 72 hrs/Initial mass of dry polymer×100

5. *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.

6. *In vitro release studies* 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. [19]

7. *Permeation studies* The diffusion studies of the prepared nanosponge can be carrying

out in Franz diffusion cell for studying the dissolution release of nanosponge through a cellophane membrane. Nanosponge sample (0.5g) can taken in cellophane membrane and the diffusion studies were carried out at 37 ± 1° using 250 ml of phosphate buffer (pH 7.4) as the dissolution medium. 5ml of each sample can withdrawn periodically at 1, 2, 3, 4, 5, 6, 7 and 8 hrs and each sample will replaced with equal volume of fresh dissolution medium. Then the samples can analyzed for the drug content by using phosphate buffer as blank. [25]

APPLICATIONS OF NANOSPONGE

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. Local anesthetics, antifungal and antibiotics are among the category of the drugs that can be easily formulated as topical nanosponges. 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 [20]. 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. [21]

Enhanced solubility The nanosponge system has pores,that increase the rate of solubilisation of poorly soluble drug by entrapping such drugs in pores. Due to nano size surface area significantly increased and increase rate of solubilisation1. BS 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. [21]

Nanosponge as chemical sensors Nanosponges which are the type of "metal oxides" act as a chemical sensors which is used in highly sensitive detection of hydrogen using nanosponge titania. Nanosponge structure intially have no point of contact so there is less hinderance to electron transport and it results in higher 3D interconnect nanosponges titania which is sensitive to H2 gas.[22]

Chemotherapy The tiny sponges are filled with drug and expose a targeting peptide that bind to radation induced cell surface receptor on tumor. When the sponge encounter tumur cell they stick to surface and triggered to release cargo. One of the important drug formulated as nanosponge is paclitaxel, the active ingredient in the anti-cancer therapy Taxol. [2l, 22] ***Biomedical applications*** Nanosponge can be used for contaminated water. Nanosponge have been used for the removal of organic impurities in water. [22]

CONCLUSION

Nanosponge are nano sized colloidal carrier so they easily penetrate through skin. Due to their small size and porous nature they can bind poorly- soluble drugs within the matrix and improve their bioavailability of drug and they also increase the solubility of poorly soluble drugs. The nanosponges have the ability to incorporate many drugs and release them in a controlled and predictable manner at the target site. Topical nanosponge can be more patient compliant and provide sufficient patient benefits by reducing repeated doses and side effects. Nanosponge can be effectively incorporated into topical drug delivery system for retention of dosage form on skin. Nanosponges are tiny mesh-like structures that may revolutionise the treatment of many diseases and this technology is five times more effective at delivering drugs for cancer than conventional methods. These are self sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate.

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