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RECENT ADVANCES IN NANOSPONGES AS DRUG DELIVERY SYSTEM: A REVIEW ARTICLE

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ABSTRACT

Topical drug delivery system faced many problems like poor permeability, skin irritation, allergic reactions etc. The new developed colloidal system called nanosponge has potential to overcome these problems. Nanosponges are tiny sponges with a size of about a virus (250nm-1µm), which consist of cavities that can be filled with a wide variety of drugs. 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 pharmaceutics.

KEYWORDS: Nanosponge; Topical Delivery; Controlled Release.

INTRODUCTION

Nanosponges are porous polymeric delivery systems that are small spherical particles with large porous surface. These are used for the passive targeting of cosmetic agents to skin, there by achieving major benefits such as reduction of total dose, retention of dosage form on the skin and avoidance of Systemic absorption. These nanosponges can be effectively incorporated onto topical systems for prolonged release and skin retention thus reducing the variability in drug absorption, toxicity and improving patient compliance by prolonging dosing intervals.

Nanosponges can significantly reduce the irritation of drugs without reducing their efficacy. The nanosponges are solid in nature and can be formulated as Oral, Parenteral, Topical or Inhalation dosage forms. 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. For topical administration they can be effectively incorporated into topical hydrogel. Effective targeted drug delivery systems have been a dream for long time, now but it has been largely frustrated by the complex chemistry that is involved in 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.

Advantages

- Nanospongesparticles are soluble in water and encapsulation can be done with in the nanosponge.
- Nanosponges can be significantly reduce the irritation of drugs without reducing their efficacy.
- To improving patient compliance by prolonging dosing intervals.
- Biodegradable.
- Easy scale up for commerical production.

Materials used in Nanosponge Preparation

A. Polymers

Hyper cross linked Polystyrenes, Cyclodextrines and its derivatives like Alkyloxycarbonyl Cyclodextrins, Methyl β- Cyclodextrin, Hydroxy Propyl β-Cyclodextrins, Ethyl Cellulose, Poly valerolactone, Eudrgit RS 100, Acrylic polymers.

B. Copolymers

Poly (valerolactone allylvalerolactone), Poly (valerolactone-allylvalerolactone oxepanedione), Ethyl Cellulose, Poly vinyl alcohol.

C. Cross linkers

Carbonyl di imidazoles, Carboxylic acid di anhydrides, Di arylcarbonates, Di chloromethane. Di isocyanates, Di phenyl Carbonate, Epichloridine, Gluteraldehyde, Pyromellitic anhydride, 2,2-bis (acrylamido) Acetic acid.

Preparation Methods of Nanosponge Solvent Method

Dissolve the polymer in suitable solvent. Then add this to excess quantity of cross- linker. Reflux the mixture for

48 hours at a temperature of 10˚C. Then allow this solution to cool at room temperature. Add this to excess quantity of bi-distilled water and filter the product. Then purify by prolonged soxhlet extraction with ethanol. Dry the product and grind in mechanical mill to get homogenous powder.

Emulsion Solvent Diffusion Method
Nanosponges can be prepared by using ethyl cellulose (EC) and polyvinyl alcohol (PVA). Ethyl cellulose is dissolved in dichloromethane. Add this mixture into aqueous solution of polyvinyl alcohol. Stir the mixture at 1000 rpm for 2 hours in a magnetic stirrer. Then filter the product and dry it in an oven at 40^0c for 24 hours.

Ultrasound- Assisted Synthesis
In this method, polymers react with cross- linkers in absence of solvent and under sonication. Here, mix the polymer and cross- linker in a flask. Place the flask in an ultrasound bath filled with water and heat it to 90^0c and sonicate for 5 hours. Allow it to cool and wash with water to remove the unreacted polymer. Purify by prolonged soxhlet extraction with ethanol. Dry the product under vacuum and store at 25^0C.

From Hyper Cross- Linked B- Cyclodextrins Here, β-cyclodextrin (β- CD) can be used as carrier for drug delivery. Nanosponges can be obtained by reacting cyclodextrin with a cross- linker. Nanosponges can be synthesized in neutral or acid forms. The average diameter of a Nanosponge is below 1 μm but fractions below 500 nm can beselected.

Loading of drug into nanosponges
Nanosponges for drug delivery should be pretreated to obtain a mean particle size below 500nm. Suspend the nanosponges in water and sonicate to avoid the presence of aggregates and then centrifuge the suspension to obtain the colloidal fraction. Separate the supernatant and dry the sample by freeze drying. Prepare the aqueous suspension of Nanosponges disperse the excess amount of the drug and maintain the suspension under constant stirring for specific time required for complexation. After complexation, separate the uncomplexed (undissolved) drug from complexed drug by centrifugation. Then obtain the solid crystals of nanosponges by solvent evaporation or by freeze drying Crystal structure of nanosponges plays a very important role in complexation with drug. A study revealed that paracrystalline nanosponges 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. (Susmitha Bezawada et al., 2014)

FACTORS INFLUENCE NANOSPONGE FORMATION

Type of polymer
Type of polymer used can influence the formation as well as the performance of Nanosponges. for complexation, the cavity size of nanosponge should be suitable to accommodate a drug molecule of particular size (amber et al., 2008)

Type of drugs
Drug molecules to be complexed with nanosponges should have certain characteristics mentioned below (amber et al., 2008)

- Molecular weight of drug should be in between 100 to 400 Daltons.
- Drug molecule consists of less than five condensed rings.
- Solubility in water should be less than 10mg/ml.
- Melting point of the substance should be less than 250°C.

Temperature
Temperature changes can affect Drug/Nanosponge complexation. In general, increasing in the temperature decreases the magnitude of the apparent stability constant of the Drug/Nanosponge complex may be due to a result of possible reduction of drug/nanosponge interaction forces, such as van-der Waal forces and hydrophobic forces with rise of temperature (Rajeswari et al., 2005).

Method of preparation
The method of loading the drug into the nanosponge can affect Drug/Nanosponge complexation. However, the effectiveness of a method depends on the nature of the drug and polymer, in many cases freeze drying was found to be most effective for drug complexation (Rajeswari et al., 2005).

Degree of substitution
The complexation ability of the nanosponge may be greatly affected by type, number and position of the substituent on the parent molecule.

Characterization of nanosponges

1. Particle size determination
The size of particles are maintained during polymerization for the formation of free-following powders having fine aesthetic attributes. Particle size analysis of loaded and unloaded nanosponges performed by laser light diffractometry or malvern zeta sizer. Cumulative graph is maintained or ploted as particle size against time to study effect of particle size on drug release. Particle size larger than 30 m can show gritty feeling and particle size range from 10 –25 m can be preferred for topical drug delivery.

2. Determination of loading efficiency
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:
Loading efficiency = Actual drug content in nanosponge / Theoretical drug × 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:
% 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:
% Swelling = Marking of cylinder at a specified 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 with time.

6. Compatibility Studies
The drug should be compatible with the polymers which are used for the preparation of nanosponges. The compatibility of drug with adjuvants can be determined by Thin Layer Chromatography (TLC) and Fourier Transform Infra-red Spectroscopy (FT-IR). Crystalline characteristics can be studied by powder X-ray diffraction (XRD) and Differential Scanning Colorimetry (DSC).

7. Zeta Potential
Zeta potential is a measure of surface charge. The surface charge of Nanosponge can be determined by using Zeta sizer.

8. Solubility studies
The most widely used approach to study inclusion complexation is the phase solubility method described by Higuchi and Connors, which examines the effect of a nanosponge, on the solubility of drug. Phase solubility diagrams indicate the degree of complexation.

9. Drug release kinetics
To investigate the mechanism of drug release from the Nanosponge the release data was analysed using Zero order, First order, Higuchi, Korsemeyer-Peppas, Hixon Crowell, Kopcha and Makoid-Banakar models.

The data can be analysed using graph pad prism software. The software estimates the parameters of a non-linear function that provides the closest fit between experimental observations and non- linear function.

10. In vitro release studies
In vitro release kinetics experiments are perfomed using a multi compartment rotating cell. An aqueous dispersion of nanosponges (1ml) containing the drug is placed in the doner compartment, while the receptor compartment separated by a hydrophillic dialysis membrane is filled with phosphate buffer at pH 7.4 or pH.

1.2. Each experiment is carried out for 24hr. At fixed times, the receptor buffer is completely withdrawn and replaced with fresh buffer. The amount of drug in the medium is determined by the a suitable analytical method and drug release is calculated to determine the release pattern.

11. 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.

12. Microscopy studies
Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) can be used to study the microscopic aspects of the drug, nanosponges and the product (drug/nanosponge complex). The difference in crystallization state of the raw materials and the product seen under electron microscope indicates the formation of the inclusion complexes.

APPLICATIONS OF NANOSPONGES

Nanosponges for drug delivery
Because of their nanoporous structure, nanosponges can advantageously carry water insoluble drugs (Biopharmaceutical Classification System class-II drugs). These complexes can be used to increase the dissolution rate, solubility and stability of drugs, to mask unpleasant flavors 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 direct injection (David F, 2011).

List of some BCS Class II dugs which can be developed as nanosponges are given below:-

BIOPHARMACEUTICAL CLASSIFICATION SYSTEM CLASS II DRUGS

CATEGORY		**DRUG**
Antianxiety drugs		Lorazepam
Antiarrhythmic agents		Amiodarone hydrochloride
Antibiotics		Azithromycin
		Ciprofloxacin
		Erythromycin
		Ofloxacin
		Sulfamethoxazole
Anticoagulant		Warfarin
Anticonvulsants		Carbamazepine, Clonazepam,
		Felbamate, Oxycarbazepine,
		Primidone
Antidiabetic	and	Atorvastatin, Fenofibrate,
Antihyperlipidemic drugs		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,
		Indomethacin, Ketoprofen,

		Nimesulide, Oxaprozin,
		Piroxicam
		Danazol, Dexamethazone
Steroids		Atovaquone, Melarsoprol,
Miscellaneous		Phenazopyridine, Ziprasidone

The nanosponges are solid in nature and can be formulated as Oral, Parenteral, Topical or Inhalation dosage forms. 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 (jenny et al., 2011).

For the parenteral administration the complex may be simply carried in sterile water, saline or other aqueous solutions. For topical administration they can be effectively incorporated into topical hydrogel (Renuka et al., 2011).

The nanosponges used in the formulation of some drugs are provided in the table.

Drug used in Nanosponges drug delivery

Drug	**Nanosponge Vehicle**	**Indication**	**Study**	***In-Vitro/In- Vivo* Mathematical Model**
	Sodium alginate	Cancer therapy	Pharmacokinetic	Mice
Antisense	Poly L-lysine	Viral infection	studies	
oligonucleotides		Pathological-		
(Isabelle et al,		disorders		
1999)				
Itraconazole (Shankar et al, 2007)	β-cyclodextrin and copolyvidonum	Antifungal	Saturation solubility study	Higuchi model
Bovine serum	Cyclodextrin	Protein	Drug release	*In-vitro*
albumin	based	supplement	study	release
(Swaminathan	Poly		Stability study	modulation
et al, 2010)	(amidoamine)			and stability.
Camptothecin	β-cyclodextrin	Cancer	Haemolytic	Diluted blood
(Shankar et			activity	HT-29 cell
al,2010;				line
Rosalba et al,				
2011)				
Dexamethasone (Lala et al, 2011)	β-cyclodextrin	Brain tumors	Drug release experiment	Dialysis bag technique *In- vitro*
Econazole nitrate (Renuka et al, 2011)	Ethyl cellulose Polyvinyl alcohol	Antifungal	Irritation study	Rat
Paclitaxel	β-cyclodextrin	Cancer	Bioavailability	Sprague
(Torne et al,				dawley rats
2010; Ansari et			Cytotoxicity	MCF7 cell
al, 2011)				line

Resveratrol (Khalid et al, 2011)	β-cyclodextrin	Inflammation Cardiovascular disease, Dermatitis, Gonorrhea, fever and hyperlipidemia Cytotoxicity	Accumulation of drug in the buccal mucosa of rabbit *Ex-vivo* study Permeation study	HCPC-I cell line Rabbit buccal mucosa Pig skin
Tamoxifen (Jennyet al, 2011)	β-cyclodextrin	Breast cancer	Cytotoxicity	MCF7 cell line
Temozolamide (William et al, 2011)	Poly (valerolactoneallyl valerolactone) and poly (valerolactoneallyl valerolactoe-Oxepanedione)	Brain tumors	Drug release study	*In-vitro* and *In-vivo* studies.

Voriconazole **(**Dr. Prathima Srinivas et al, 2013)	Ethyle cellulose(EC), Polymethyl methacrylate (PMMA), PVA	Antifungal	Drug release Experiment	Rat
Clotrimazole (P. Suresh Kumar et al, 2015)	β- Cyclodextrin	Antifungal	diffusion study	mouse skin Higuchi and Peppas model

Cancer Therapy

Nanosponges which can be used as anticancer drug delivery system for tumors. They claim that the method is three to five times more effective at reducing tumor growth than direct injection of the drugs. The tiny nanosponges are filled with a drug load and expose a targeting peptide that binds to radiation- induced cell surface receptors on the tumor. When the sponges encounter tumor cells they stick to the surface and are triggered to release their cargo. Benefits of targeted drug delivery include more effective treatment at the same dose and fewer side effects. Studies so far have been carried out in animals with paclitaxel as the sponge load.

Camptothecin, 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. Cyclodextrin - based nanosponges are a novel class of cross - linked derivatives of cyclodextrin. They have been used to increase the solubility of poorly soluble actives, to protect the labile groups and control the release. This study aimed at formulating complexes of camptothecin with β-cyclodextrin based nanosponges (Swaminathan et al; 2010).

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. 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.

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 solubilisation. 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.

Antiviral application

Nanosponges can be useful in the ocular, nasal, pulmonary administration routes. The selective delivery of antiviral drugs or small interfering RNA (siRNA) to the nasal epithelia & lungs can be accomplished by nanocarriers in order to target viruses that infect the RTI such as respiratory sincytial virus, influenza virus & rhinovirus. They can also be used for HIV, HBV and HSV. The drugs which are currently in use as nano delivery system are zidovudine, saquinavir, interferon- α, acyclovir (Eudragit based) (Ansari K et al; 2011).

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. 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 (Trotta et al; 2011).

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 H_2 gas.

Nanosponge in protein drug delivery

Bovine serum alubin (BSA) protein is unstable in solution form so stored in lyophilized form. swellable cyclodextrin based poly (amidoamino) nanosponge enhaced the stability of proteins like BSA. Nanosponge have also been used for enzyme immobilization, protein encapsulation and subsequent controlled delivery and stabilization (Swaminathan et al; 2010).

Nanosponges as a carrier for biocatalysts

Nanosponges act as carriers in the delivery of enzymes, proteins, vaccines and antibodies. Many industrial processes involving chemical transformation are associated with operational disadvantages. Non-specific reactions lead to low yields and the frequent need to operate at high temperatures and pressures requires consumption of large amounts of energy and very large amounts of cooling water in the down - stream process.

All these drawbacks can be eliminated or significantly reduced by using enzymes as biocatalysts. These enzymes operate under mild reaction conditions, have high reaction speed and are highly specific. They have a beneficial effect on the environment because they reduce energy consumption and reduce production of pollutants. Developments in genetic engineering have increased the stability, economy, specificity of enzymes and number of their industrial applications is continually increasing (Amber V et al; 2012).

Other applications of Nanosponges

Nanosponges based on cyclodextrins can strongly bind organic molecules and remove them from water even at very low concentrations. The same concept can be useful for elimination of bitter components from grape fruit juice by selective combination of polymer and crosslinker. The microporous hyper cross linked Nanosponges have been used in selective separation of inorganic electrolytes by size exclusion chromatography. The three dimensional Nanosponges will play important role in the fractionalization of peptides for proteomic applications. Nanosponges can be used as carrier for gases like oxygen and carbon dioxide.

These Nanosponges could be useful for many biomedical applications. In particular the oxygen-filled Nanosponges could supply oxygen to the hypoxic tissues which are present in various diseases. Nanosponges can selectively soak up biomarkers for the diagnosis. One study concluded that Nanosponges can harvest rare cancer marker from blood.

MARKETED PREPARATION

DRUG	ADMINISTRATION ROUTE	TRADE NAME	DOSAGE FORM
Dexamethasone	Dermal	Glymesason	Tablet
Iodine	Topical	Mena- gargle	Solution
Alprostadil	I.V	Prostavastin	Injection
Piroxicam	Oral	Brexin	Capsule

CONCLUSION

Nanosponge are nano sized colloidal carrier so they easily penetrate through skin. Due to their small size and porousnature. 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.

Nanosponges are based on nano, polymer-based spheres that can suspend or entrap a wide variety of substances and then be incorporated into a formulated product such as a gel, lotions, cream, ointments, liquid or powder. This technology offers entrapment of ingredients and thus reduced side effects improved stability, increases elegance and enhanced formulation flexibility. Nanosponges can be effectively incorporated into topical drug delivery system for retention of dosage form on skin and also use for oral delivery of drugs using bioerodibl 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.

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