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Nanosponge: New Colloidal Drug Delivery System for Topical Delivery

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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. Nanosponge are tiny sponges having size of about a virus and can easily penetrate through skin. 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. The objective of the review article is to discuss nanosponge with their method of preparation, evaluation and applications.

KEYWORDS: Nanosponge; Topical Delivery; Controlled Release; Colloidal Carrier.

INTRODUCTION

Nanosponges are novel class of hyper-crosslinked polymer based colloidal structures consisting of solid nanoparticles with colloidal sizes and nanosized cavities. They enhance stability, reduce side effects and modify drug release. The outer surface is typically porous, allowing sustain release of drug. They are mostly use for topical drug delivery. Size range of nanosponge is 50nm-100nm[1].This technology is being used in cosmetics, over-the-counter skin care, sunscreens and prescribed drugs. Conventional formulation of topical drugs accumulate excessively in epidermis and dermis. Nanosponge prevent the accumulation of active ingredient in dermis and epidermis. Nanosponge system reduce the irritation of effective drug without reduce their efficacy[2].

They can be used for targeting drugs to specific sites, prevent drug and protein degradation. 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[3]. It is possible to control the size of nanosponge. To varying the portion of cross-linkers and polymers, the nanosponge particles can be made larger or smaller[4]. These particles are capable of carrying both lipophilic and hydrophilic substances and of improving the solubility of poorly water soluble molecules[5]. Nanosponge technology offers entrapment of ingredients and is believed to contribute towards reduced side effects, improved stability, increased elegance and enhanced formulation flexibility[2]. Nanosponges are non-irritating, non-mutagenic, nonallergenic and non-toxic[6].Nanosponges are tiny mesh-like structures that used for the treatment of many diseases and this technology is five times more effective at delivering drugs for breast cancer than conventional methods.[4]The nanosponges are solid in nature and can be formulated as oral, parenteral, topical or inhalational dosage forms. For oral administration, these may be dispersed in a matrix of excipients, diluents, lubricants and anticaking agents which is suitable for the preparation of tablets or capsules[7].For parenteral administration, these can be simply mixed with sterile water, saline or other aqueous solutions[6]. For topical administration, they can be effectively incorporated into topical hydrogel[8]. Topical nanosponge can be more patient compliant and provide sufficient patient benefits by reducing repeated doses and side effects.[9]

ADVANTAGES OF NANOSPONGES [10,11]

- 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 130^0C.
- 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.

CHEMICALS USED FOR THE SYNTHESIS OF NANOSPONGES [12]

a. ***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.

b. ***Crosslinkers*:** Diphenyl Carbonate, Diarylcarbonates, Diisocyanates, Pyromellitic anhydride, Carbonyldiimidazoles, Epichloridrine, Glutarldehyde, Carboxylic acid dianhydrides, 2,2-bis(acrylamido) Acetic acid and Dichloromethane

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.[2]

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.[1,14]

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.[2,15]

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[14]:

$$\text{Loading efficiency} = \frac{\text{Actual drug content in nanosponge}}{\text{Theoretical drug content}} \times 100$$

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 **.**

$$\text{Production yield} = \frac{\text{Practical mass of nanosponge}}{\text{Theoretical mass(drug + polymer)}} \times 100$$

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[15]:

$$\%\text{Porosity} = \frac{\text{Bulk volume} - \text{True volume}}{\text{Bulk volume}} \times 100$$

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[15]:

$$\%\ \text{Swelling} = \frac{\text{Marking of cylinder at a specified time point}}{\text{Initial marking before soaking}} \times 100$$

$$\%\ \text{Water uptake} = \frac{\text{Mass of hydrogel after 72 hrs}}{\text{Initial mass of dry polymer}} \times 100$$

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[16].

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[17].

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[18].

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.[6]

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[1]. 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[6].

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[20].

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[20,21].

Biomedical applications

Nanosponge can be used for contaminated water. Nanosponge have been used for the removal of organic impurities in water[21].

Purification of water

The presence of organic pollutants in raw water is a major concern for a number of power plants and industries requiring

ultrapure water such as pharmaceutical and electronics sectors. The effectiveness of water-insoluble cyclodextrin (CD) polymers of nanosponge in the removal of natural organics (volatile component), dissolved organic carbon[5].

Oxygen delivery systems

Cyclodextrin nanosponges have also been developed as oxygen delivery system. Nanosponge has the ability to store and to release oxygen slowly over time. Oxygen-filled nanosponges could supply oxygen to the hypoxic tissues which are present in various diseases.[22]

Antiviral application

Nanosponges can be useful in the ocular, nasal, pulmonary administration routes. The drugs which are currently in use as nano delivery system are zidovudine, saquinavir, interferon- α, acyclovir (Eudragit based)[9].

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[1].

Nanosponge as carrier for biocatalyst

Nanosponge act as carrier for the delivery of enzymes, vaccines, proteins and antibodies for diagnosis purpose. Proteins and other macromolecules are adsorbed and encapsulated in cyclodextrin nanosponge[14].

Comparison of Some Effective Vesicular Systems

Liposome, niosome, ethosome, transferosome and nanosponge are colloidal drug delivery systems. They all are nanometric in size. Liposome, niosome and transferosomes have some stability problems which is discuss below in table but nanosponge enhanced the stability of drug[13,22].

Liposome	**Niosome**	**Ethosome**	**Transferosome**	**Nanosponge**
Liposome consist of one or more concentric lipid bilayers, which enclose an internal aqueous volume.	Niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or other lipids.	Ethosomes are lipid vesicles containing phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water.	Transferosomes are vesicular system consisting of phosphatidylcholine and surfactants.	Nanosponge are novel class of hyper-crosslinked polymer based colloidal structures consisting of solid nanoparticles with colloidal sizes and nanosized cavities.
The compostion of liposomes is phospholipids and cholesterol .	They composed of non-ionic surfactants and cholesterol.	They composed mainly of phospholipids, high concentration of ethanol and water.	They consists of phospholipids and surfactants.	They composed of polymers and cross linkers.
Stability problems: due the formation of ice crystals in liposomes, the subsequent instability of bilayers leads to the leakage of entrapped material. The oxidation of cholesterol and phospholipids also leads to the formulation instability.	Stability problems: fusion, aggregation, sedimentation and leakage on storage. The Hydrolysis of encapsulated drug.	Ethosomes has initiated a new area in vesicular research for transdermal drug delivery which can provide better skin permeation and stability than liposomes. Application of ethosomes provides the advantages such as improved entrapment and physical stability.	Stability problem: chemically unstable because of their predisposition to oxidative degradation.	Nanosponge are chemically and physically stable. They increase the stability and bioavailability, modify drug release and reduce side-effects.

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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