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Nanosponges: A Promising Nanocarrier Systems for Drug Delivery

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ABSTRACT

Nanoengineered drug delivery system is generally used to solubilize the hydrophobic drugs. They also carry the drug to the target site and release the drug according to need of patient. These are very effective drug carriers which minimize and resolve the problems of drug toxicity and poor bioavailability as they can load both hydrophilic and hydrophobic drugs. Nanosponges are tiny in size with three dimensional networks. These are highly porous in nature and entrap active moieties and provide an advantage of programmable release. These are prepared by cross linking using many type of cyclodextrin with carbonyl and dicarboxylate compound like cross linker. Nanosponges are used for enhancing the bioavailability of drug and delivery of drug via oral, topical and parenteral routes. These are also used as a carrier for release of enzyme, protein, vaccines and antibiotics.

Key words: Nanocarrier, Nanosponges, Targeted drug delivery.

1. INTRODUCTION

Nanosponge is a nano sized particle designed to deliver drug to the target site. They are mutagenic, nontoxic, non-irritant and non-allergenic. These are porous spheres which hold active ingredients. They have a high capacity of entrapping active substances such as emollients, fragrances, oil, and sunscreens used as a topically. ¹ Nanosponges are tiny mesh like structure in which a large amount of substances can be encapsulated. ² Nanosponges can solubilize poorly water soluble drug and increase the release rate as well as improve the drug bioavailability. For the nanosponges meant for oral administration, the complex may be dispersed in a matrix system of excipients, diluents, lubricants suitable for the preparation of tablet and capsule form. For parenteral administration, it may be dispersed in sterile water, saline, or aqueous solution. ²

1.1 Advantages of Nanosponges ^{3,4}

There are various advantages of nanosponges like:

- a) These are nontoxic, non-irritant and non-mutagenic because they are composed of biodegradable excipients.
- b) They improve aqueous solubility of lipophilic drug.
- c) They protect drug from degradation.
- d) They can be used for site specific targeting of drug.
- e) Nanosponges can be used to mask unpleasant flavour, odour and to convert liquid substances to solid.

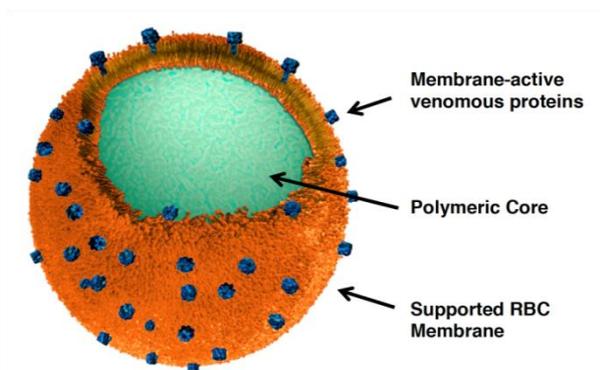


Fig. 1: Structure of nanosponge

1.2 Disadvantages of nanosponges^{5,6}

The disadvantages of nanosponges are as follow:

- a) A nanosponge has ability to load only small molecules.
- b) Dose dumping.
- c) They may retard the release of drug.

2. MATERIALS USED

These are the various materials like polymer, co-polymer and cross-linker are used for the fabrication of nanosponges^{7,10} and represented in table 1.

Table 1: Materials used for fabrication of nanosponges

Excipients	Examples
Polymer	Hyper cross linked polystyrenes, ethyl cellulose, 2-hydroxy propyl beta-cyclodextrins, and poly valerol acetone, and eudragit RS 100, acrylic polymers.
Co-polymer	Poly (Valerol acetone ally valerol acetone), poly (valerol acetone-ally valerol acetone oxepanedione), ethyl cellulose, poly vinyl alcohol.
Cross-linker	Carbonyl diimidazole, carboxylic acid dianhydrides, di aryl carbonates dichloromethane diisocyanate, di phenyl carbonate, epichloridin, glutaraldehyde, pyromellitic anhydride 2, 2-bis (acrylamido) acetic acid. ^{7,10}

3. TECHNIQUES FOR PREPARING NANOSPONGES

There are several techniques for preparing nanosponges. Some of them are discussed as under:

3.1 Solvent method

Solvent method technique is generally used for the preparation of nanosponges. It involves mixing of drug with a suitable solvent like polar aprotic solvent. These are two examples of polar aprotic solvent like dimethylformamide and di-methylsulfoxide used for the preparation of nanosponges. In polymer solution a cross linking agent is also added during solvent method.¹¹

3.2 Hyper cross-linked β -cyclodextrin method

In this method cyclodextrin react with a cross linker agent to obtained nanosponges. These are the various examples of cross linkers used for the preparation of

nanosponges like diisocyanate, diaryl carbonate, dimethyl carbonate, diphenyl carbonate and carbonyl diimidazole, carboxylic acid dianhydrides. Nanosponges which shows poor cross linking provide immediate release of drug.

3.3 Ultrasound assisted synthesis method

In this method the polymer is reacting with cross linker agent obtained a spherical and uniform shape nanosponges. Take an equal amount of polymer and cross linker agent in a flask and mix properly. The mixture of polymer and cross linker is sonicated for 5 h with maintaining a temperature 90 °C then the mixture is cooled and filter. The product is washed properly with distilled water to remove the non reacted polymer and purified by soxhlet extraction process using ethanol.

3.4 Emulsion solvent diffusion method

Take a different proportion of ethyl cellulose and polyvinyl alcohol for the preparation of nanosponges.

Isolated phase contain ethyl cellulose and drug. Isolated ethyl cellulose and drug is dissolve in 20 ml dichloromethane and gradually add polyvinyl alcohol i.e. 150 ml in an aqueous continous phase with continuously stirring at 1000 rpm for 2 h. Then collect the final product and dry in oven at 400 °C for 24 h. The completely dried nanosponges are kept in vaccum dessicator to remove rest amount of solvent.^{12, 14}

4. EVALUATION OF NANOSPONGES

These are several parameters for evaluation of nanosponges like:

4.1 Size and morphology

Mainly two techniques are used to determine the particle size distribution of nanosponges. These are suitable techniques for the sizing of nanosponges.

4.1.1 Scanning electron microscopy (SEM)

Scanning electron microscopy used for the analysis of nanosponges, a random sample is put on an aluminium plate sample is accumulate on sputter coated with gold-palladium alloy to minimize the surface charge of nanosponges.¹⁵

4.1.2 Transmission electron microscopy (TEM)

This test is aimed to find out the size and morphology of nanosponges. Nanosponges are diluted upto (1:1000) with distilled water a one drop of diluted sample directly deposit on waxed paper. Then deposit on a circular copper film grid of 400 mesh and stained with 2% (W/V) phosphotungstic acid for 10s and air dried. Then measure the droplet size of nanosponges.¹⁶

4.2 Loading efficiency

The drug incorporation efficiency is determined by using subtracting the un-entrapped drug from the total amount of drug. These are the various methods used for the separation of un-entrapped drug by gel filtration, dialysis and ultra centrifugation. Calculate the loading efficiency using this equation.¹⁷

$$\text{Loading efficiency} = \frac{\text{Actual drug content in nanosponges}}{\text{theoretical drug content}} \times 100$$

4.3 Zeta potential

Zeta potential is used for the measurement of surface charge using zeta sizer. All the measurement is complete by adding 20 µl of the sample to 10 ml of distilled water.

This mixture is adjusting to a conductivity of 50 µS cm⁻¹ using NaCl solution and analysis a zeta potential.¹⁶

4.4 Porosity

Porosity study is performing to check the extent of nanochannels and nanocavities form. Porosity of nanosponges is assessed through helium pycnometer, since helium gas is able to penetrate inter and intra-particle channel of particulate materials. The true volume of material is determined using the helium displacement method. Calculate the porosity of sample through this equation.¹⁷

$$\% \text{ porosity (E)} = \frac{\text{bulk volume} - \text{true volume}}{\text{bulk volume}} \times 100$$

4.5 Fourier transform-infra red spectroscopy (FTIR)

FTIR is basically used to determine the degradation of polymeric matrix of the nanocarrier system. FTIR provide the information about surface composition of the nanosponges up on using manufacturing procedure and conditions.

4.6 Powder x-ray diffraction (P-XRD) technique

P-XRD technique is used to detect inclusion complexation in the solid state. When the drug molecule are liquid since liquid have no diffraction pattern of their own, then the diffraction pattern of a newly formed substances clearly differ from that uncomplexed nanosponges. Diffraction peak for a mixture of compound are useful for determining the chemical decomposition during complex formation. A complex formation between drug and excipients change the diffraction pattern and also alter the drug crystalline form.

4.7 Thermo gravimetric analysis (TGA)

This technique is basically used for the determination of melting point, thermo stability and crystalline behaviour of the nanosponges.

4.8 Molecular weight measurement of nanosponges

Molecular weight of the polymer and its distribution in the matrix can be measured through Gel Permeation Chromatography (GPC) using a refractive index detector.

4.9 In vitro release

In vitro release profile can be determined using, Standard dialysis, Diffusion cell, and Ultra filtration techniques.

Measure the *in vitro* drug release profile of nanosponges using diffusion cell. A millipore hydrophilic low protein binding membrane is placed between the two chambers. The donor chamber is filled with nanosponges' suspension and the receptor chamber filled with buffer. The receptor compartment is assayed at different time interval and to check the released of drug using standard procedure.^{18,19}

5. APPLICATIONS OF NANOSPONGES

Due to their biocompatibility and versatility, there are various applications of the nanosponges in the pharmaceutical field. They can be used as excipients in preparing tablets, capsules, pellets, granules, suspension, solid dispersion, or topical dosage forms. These act as multifunctional carrier for improved product performance and, extended release, reduced irritation, improved physical and chemical stability of the drug product.

5.1 In anticancer therapy

Nanosponges can be used as a drug delivery system for anticancer drugs. This method is more effective for reducing the tumor growth than dried injection of the drug.¹

5.2 Antiviral application

Nanosponges administer through nasal and pulmonary route. It is deliver to antiviral drug on RNA to lungs or nasal route through nanocarrier for targeting virus which may cause infection to RTI such as rhinovirus, influenza virus. Drug used as nanocarrier are acyclovir, saquinavir, and zidovudine.¹⁷

5.3 Nanosponges in stability enhancement

Itraconazole is a BCS Class-II drug that has high penetration and poor bioavailability. The nanosponges increase the drug solubility by 27-fold. When using copolyvidonum as a supporting component of nanosponges formulation, these exceeded to 55-fold. Copolyvidonum react with hydrophobic group of Itraconazole, and improves the wetting property of the drug or decreasing the crystallinity of the drug.²

5.4 Nanosponges in drug delivery

These are nonmeric in size and spherical in shape, these can be prepared in different dosage form such as aerosol, parenteral, topical, capsules, and tablets. Econazole nitrate is an antifungal drug for the topical treatment to minimize the symptoms of superficial candidiasis, dermatophytosis and skin infection, available

in cream, ointment, lotion and solution form. Econazole is applied on the skin and requires the high concentration for effective therapy. These are made-up of emulsion solvent diffusion method and these nanosponges loaded in hydrogel used as a local depot for sustained drug release.¹

5.5 Nanosponges as a carrier for delivery of gases

There are various gases playing an important role in medicine, for the treatment or diagnostic purposes. The deficiency of oxygen causes hypoxia which is related to various pathologies, from inflammation to cancer. These are sometime difficult to deliver oxygen and dosages in clinical practice. Nanosponges formulation can be prepared such as oxygen delivery system, which is applied topically having ability to store and release oxygen slowly over a time period.²

5.6 Nanosponges in enzyme immobilization

Enzyme immobilizations are particularly relevant for lipases and increase their stability and modulate properties such as enantio selectivity and reaction rates. These are reported high catalytic performances for pseudomonas fluorescens lipase adsorbed on a new type of cyclodextrin based nanosponges.²⁰

5.7 Nanosponge for oral drug delivery

Nanosponges consist of pores which increase the rate of solubilization of poor water soluble drugs which get enter the drug in pores. Increase the surface area due to nano size form and increase rate of Solubilization.¹⁷

6. CONCLUSION

These are drug carrier system carrying both hydrophilic and hydrophobic drug by forming complexes. The drug can be delivered by various routes such as oral, topical and parenteral to the target site and their applications in the drug delivery field, potential application exist for bioremediation processes, cosmetic and catalysis among other. Drug delivery through nanosponges can be effective and safe. The pharmaceutical industries might get advantage if clinical studies can confirm their potential for human use.

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