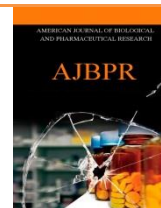




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NANOSPONGES AS INNOVATIVE NANOCARRIERS FOR ENHANCED DRUG DELIVERY AND THERAPEUTIC EFFICACY AN REVIEW

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ABSTRACT

Nanosponges are innovative nanosized porous carriers that have gained significant attention in pharmaceutical research due to their ability to improve drug solubility, stability, bioavailability, and controlled release. These three-dimensional polymeric structures possess a highly porous network capable of encapsulating both hydrophilic and hydrophobic drugs. Nanosponges are commonly prepared using biodegradable polymers such as cyclodextrins and can effectively protect drugs from degradation while enhancing therapeutic efficacy. The unique characteristics of nanosponges, including high drug-loading capacity, biocompatibility, and targeted drug delivery potential, make them suitable for various routes of administration, including oral, topical, parenteral, and pulmonary delivery. Recent studies have demonstrated their applications in the treatment of infectious diseases, cancer, inflammatory disorders, and other chronic conditions. Furthermore, nanosponges offer advantages such as reduced dosing frequency, minimized side effects, and improved patient compliance. This review highlights the preparation methods, characterization techniques, advantages, limitations, and pharmaceutical applications of nanosponges, emphasizing their potential as a promising platform for advanced drug delivery systems.

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. butylated hydroxyanisole (BHA), butylated 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. 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 crosslinkers 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. The nanosponges are encapsulating type

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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. 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. 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 crosslinking peptides, compared to many other nanoscale drug delivery systems. These nanosponges can be

magnetized when they are prepared in the presence of compounds having magnetic properties. The tiny shape of nanosponges enables the pulmonary and venous delivery of nanosponges.

ADVANTAGES OF NANOSPONGES

- 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. Journal of Medical Pharmaceutical and Allied Sciences
- 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.

DISADVANTAGES OF NANOSPONGES

1. Nanosponges have ability to include only small molecules.
2. Nanosponges could be either paracrystalline or in crystalline form.
3. The loading capacity of nanosponges depends mainly on degree of crystallization.
4. Paracrystalline nanosponges can show different loading capacities

TYPES OF NANOSPONGES

1. Cyclodextrin-Based Nanosponges

- Made from cross-linked cyclodextrins (cyclic sugar molecules).
- Most commonly used type.
- Can encapsulate both hydrophilic and hydrophobic drugs.

2. Polymeric Nanosponges

- Prepared using synthetic or natural polymers.
- Examples include polyesters, polyamides, and biodegradable polymers.

3. Ethyl Cellulose Nanosponges

- Composed mainly of ethyl cellulose polymer.
- Often prepared by emulsion-solvent diffusion methods.
- Improved bioavailability of poorly soluble drugs

4. Hyper-Crosslinked Polymer Nanosponges



- Highly porous three-dimensional networks formed through extensive cross-linking.
- Possess very large surface areas.

5. Magnetic Nanosponges

- Incorporate magnetic nanoparticles within the nanosponge structure.
- Can be directed to specific sites using an external magnetic field.

6. Stimuli-Responsive (Smart) Nanosponges

- Respond to environmental triggers such as:
 - pH
 - Temperature
 - Light
 - Enzymes
- Release their payload only under specific conditions.
- Useful for site-specific drug delivery.

7. Protein-Based Nanosponges

- Constructed using proteins or protein-coated materials.
- Biocompatible and biodegradable.

PHYSICOCHEMICAL CHARACTERIZATION OF NANOSPONGES:

Particle size determination

Free flowing powders with fine aesthetic attributes will be possible to obtain by controlling the size of particles during polymerization. Particle size analysis of loaded and unloaded nanosponges will be 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.

Determination of loading efficiency and production yield

The prepared nanosponge loading efficiency is determined by subtracting the untrapped drug from the total amount of drug. The drug entrapment efficiency will be determined by separating untrapped 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 $\text{Loading efficiency} = \frac{\text{Actual drug content in nanosponge}}{\text{Theoretical drug content}} \times 100$. 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. $\text{Production yield} = \frac{\text{Practical mass of}}$

$\text{nanosponge/Theoretical mass (drug + polymer)} \times 100$
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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 can 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

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

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

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

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

.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.

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.

Permeation studies

The diffusion studies of the prepared nanosponge can be carrying Journal of Medical Pharmaceutical and Allied Sciences (June_2016); 78-92 88 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 $37 \pm 1^\circ$ 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 be replaced with equal volume of fresh dissolution medium. Then the samples can analysed for the drug content by using phosphate buffer as blank.

APPLICATIONS OF NANOSPONGES:

1. Solubility enhancement:

Nanosponges can improve the wetting and solubility of molecules with very poor solubility in water. The drugs can be molecularly dispersed within the nanosponge structure and then released as molecules, avoiding the dissolution step. Consequently, the apparent solubility of the drug can be increased. Many formulation and bioavailability problems can be solved by enhancing the solubility and dissolution rate of a substance, and nanosponges can greatly enhance the drug solubility.

2. Nanosponges for drug delivery:

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 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.

3. 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 anaesthetics, 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.

MECHANISM OF DRUG RELEASE FROM NANOSPONGES

The sponge atoms have an open arrangement and the active is free to move in and out from the particles and into the vehicle up to equilibrium is got. In case of topical delivery, once the finished product is

applied to the target tissue, the active that is already in the vehicle will be absorbed into it. Depleting the vehicle, which will become unsaturated, therefore disturbs the equilibrium. This will start a flow of the active from the sponge particle into the vehicle and from it to the target tissue until the vehicle is either dried or absorbed. Even after that the sponge particles retained on the surface of tissue will continue to gradually release the active to it, providing prolonged release over time. Chemicals used for the synthesis of nanosponges.

METHOD OF PREPARATION OF NANOSPONGES

Solvent method

Suitable solvents, like dimethylformamide and dimethyl sulfoxide which are polar aprotic solvents, were used in the process. To this, polymer was added and properly blended. The crosslinker/polymer ratio of 8:2 is ideally used into which the above mixture was added. The mixture got from the above mixing, was then left to react for 48 hours and in a temperature range of 10°C and up to solvent's reflux temperature. On completion of the reaction, the solution was cooled until it reached the room temperature. Excess amount of bi-distilled water was added to obtain the product from the above-cooled solution and the product was recovered under vacuum filtration.

Ultrasound-assisted method

The ultrasound-assisted method of synthesis utilizes polymer ultrasonics junction. Crosslinking is got without using any solvent, and polymer crosslinking occurs due to ultra sonic waves. In a flask, polymer and crosslinker were combined at a reasonable molar ratio. During the ultra-sonication process, ultrasound bath was used to place the flask, at a temperature of 90°C and for a time period of 5h. The temperature of the collected mixture was reduced after sonication, and the product was split harshly and cleaned to extract unreacted polymer and reagents with an excess volume of water. The washed solid was purified with ethyl alcohol by Soxhlet extraction. The filtered NSs acquired were vacuum dried and processed correctly until further loading of drugs.

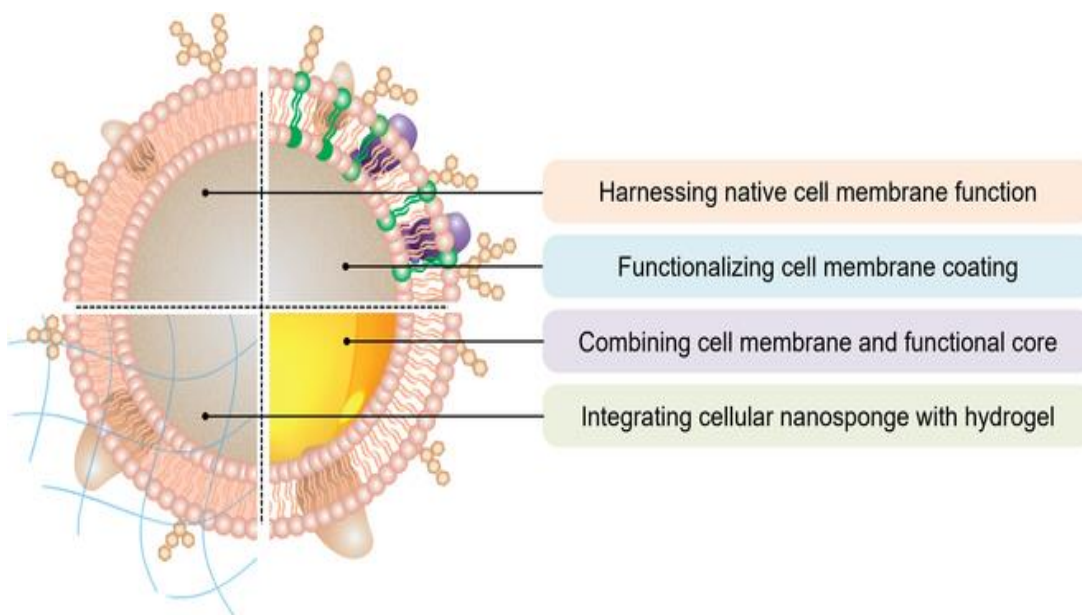
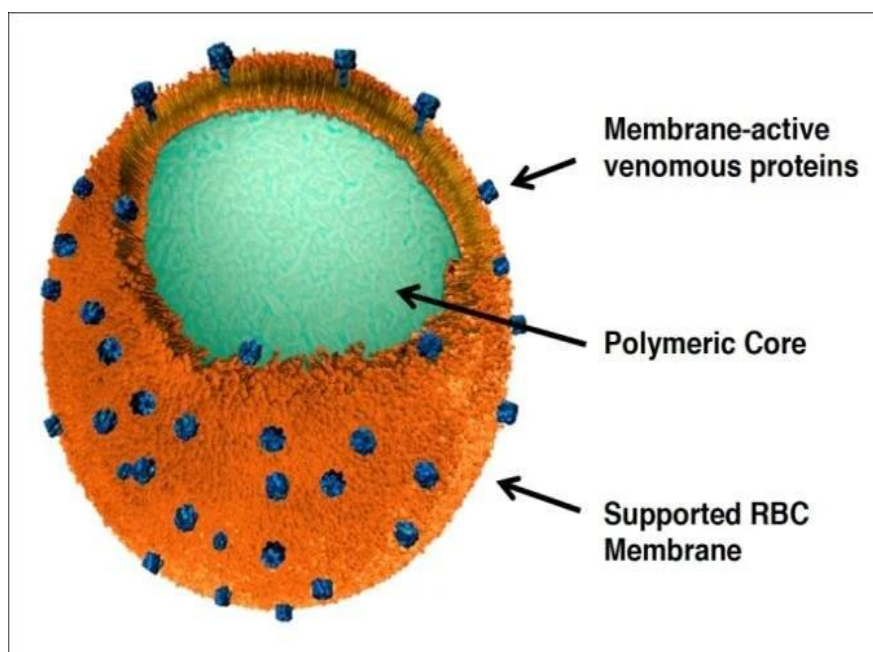
Melt method

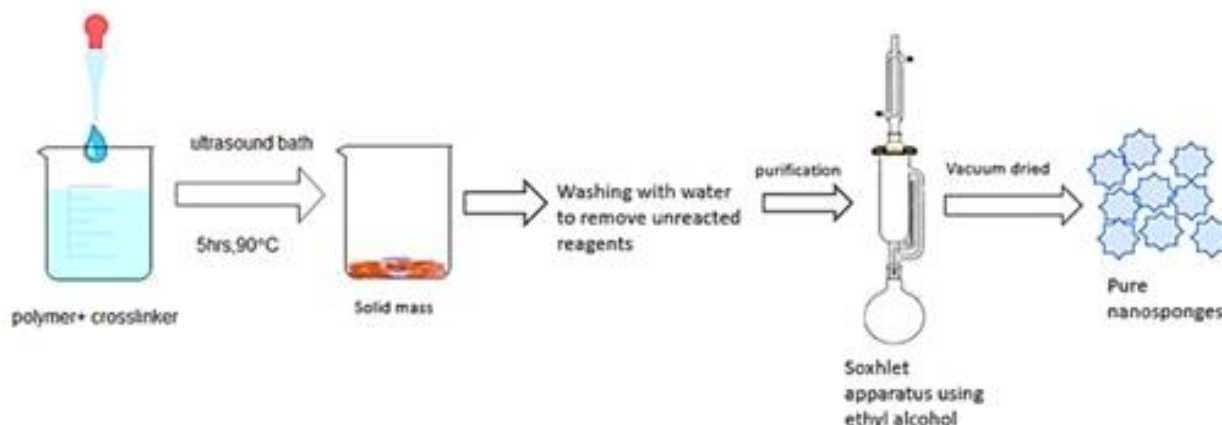
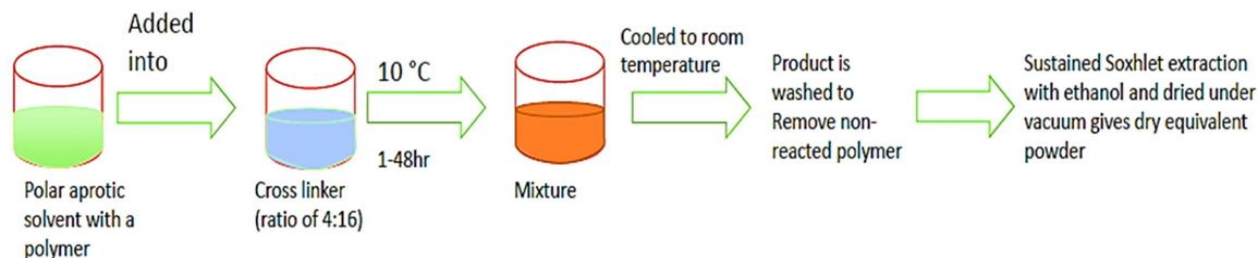
The crosslinker and the polymer are melted together in the melting process. All the ingredients were finely homogenized. NSs were collected by washing the acquired product repeatedly with a suitable liquid. Cleaning the product, extracts the waste polymer and reagents which are unreacted and divides the product into the form of NSs. Such blank NSs were further exposed to the encapsulating of narcotics.



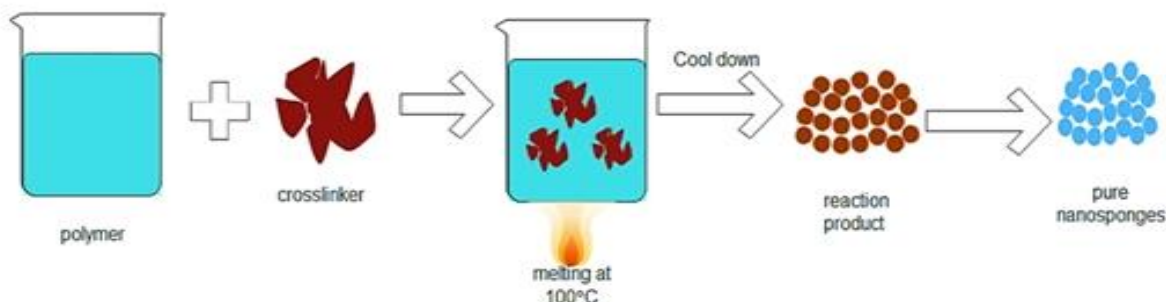
Table 1: Components Used in Preparation of Nanosponges.

POLYMER	COPOLYMER	CROSSLINKER	POLAR SOLVENTS
Hyper Crosslinked Polystyrene cyclodextrin	Poly (valerolactone allyl valerolactone)	Carbonyl diimidazole	Ethanol
Methyl β -cyclodextrin	Poly (valerolactone allyl valerolactone oxypandione)	Carboxylic acid dianhydrides	Dimethylacetamide
Hydroxy propyl β -cyclodextrin	Ethyl cellulose	Diarylcarbonates	Dimethylformamide
Poly-valerolactone	Polyvinyl alcohol	Dichloromethane	





Components Used in Preparation of Nanosponges.



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 meshlike 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 $0.25\mu\text{m}$ where bacteria cannot penetrate.

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