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REVIEW ON NANOSPONGE: A NOVEL DRUG DELIVERY SYSTEM

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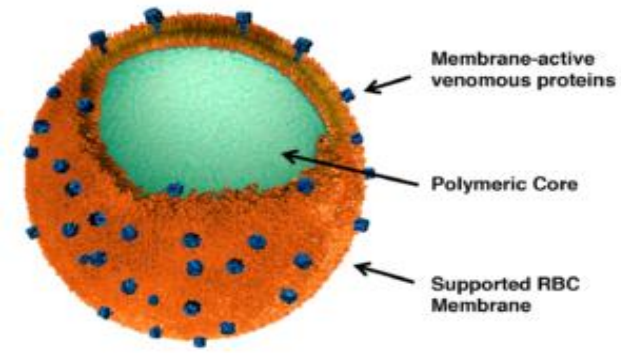
ABSTRACT
Nanosponges are a novel class of hyper-crosslinked polymer based on colloidal structures consisting of solid nanoparticles with colloidal sizes and nanosized cavities. These are nano-sized colloidal carriers have been recently developed and proposed for drug delivery, since their use can solubilize poorly water-soluble drugs and provide prolonged release as well as improve a drugs bioavailability by modifying the pharmacokinetic parameters of actives. Nanotechnology attacked increasing attention during recent year it can resolve the problem associated with solubility and bioavailability. The development of new and complex molecules Nanosponges has potential to solve these problems. Nanosponges is tiny sponges size of about the virus which is filled with drug and complex molecule. It can circulate around the body until they encounter the specific targeted site and stick on the surface and being release the drug in controlled manner. Because the drug can be released at the specific targeted site instead of circulating throughout the body it will be more effective for particular given dosage. This review is focusing on the preparation method, application of Nanosponges in the field of drug delivery.

KEYWORDS: Nanotechnology, Nanosponges, poorly solubility of drug, controlled manner.

INTRODUCTION
The drug delivery technology has certainly a new interest for drugs by providing them new life through their therapeutic targets. Nowadays, targeting drug delivery is the major problem which is being faced by the researchers. Targeted drug delivery implies for selective and effective localization of pharmacologically active moiety at predefined target in therapeutic concentration, while restricting its access to non-target normal cellular linings and thus minimizing toxic effects and maximizing therapeutic index of the drug.

The development of new and complex molecule called Nanosponges has the potential to solve this problem. Nanosponges are a new class of materials and made of microscopic particles with few nanometer wide cavities, in which a large variety of substances can be encapsulated. These particles are capable of carrying both lipophilic and bydrophilic substances and improving the solubility of poorly water soluble molecules. Nanosponges are tiny mesh like structures that may revolutionize the treatment of many disease and early trials suggest this technology is up to five times more effective at delivering drugs for breast cancer than conventional methods.

Nanosponges are tiny sponges with a size of about a virus with an average diameter below 1µm. The sponges acts as a three- dimensional network or scaffold, which consist of the backbone known as long-length polyester. Filling them with a "drug" and attaching special chemical "linker" these Nanoparticle circulate in the body until they encounter the surface of a tumor cell, where they adhere to the surface and start releasing the drug in a controlled and predictable manner. The Nanosponges are solid in nature and can be formulated as oral, parenteral, topical or inhalation dosages forms. Nanosponges is a novel and emerging technology which play a vital role in targeting drug delivery in a controlled manner.



Characteristic features of Nanosponges
i. Nanosponges exhibit a range of dimensions (1µm or less) with tunable polarity of the cavities. Nanosponges of specific size and adjustable polarity

can be synthesized by varying the cross linker to polymer proportion.

ii. They are nontoxic, porous particles insoluble in most organic solvents and stable at high temperature up to 300ºc.

iii. Nanosponges as formulation stable over the pH range of 1 to 11 and temperature up to 130ºc.

iv. They could be either Para-crystalline or in crystalline form, depending on the process conditions. Crystal structure of Nanosponges plays a very important role in their complexation with drugs. The drug loading capacity of Nanosponges mainly depends on the degree of crystallization. Para-crystalline Nanosponges have shown various drug loading capacities.

v. They form clear and opalescent suspensions in water and can be regenerated by simple thermal desorption, extraction with solvents, by the use of microwaves and ultrasounds.

Advantages of Nanosponges

- Non-irritating, non toxic.
- It is non-mutagenic.
- It provides improved stability, elegance and formulation flexibility.
- This technology provides entrapment of active contents and side effect are less.
- Drug is protected from degradation.
- Therapeutic provide onset of action. Formulation are cost effective.
- It can be used to mask unpleasant flavors and to convert liquid substances to solids. Less harmful side effect.
- Easy scale-up for commercial production.
- It provide extended release condition which is continuous action up to 12hr.
- Nanosponges particles are soluble in water, so encapsulation can be done within the Nanosponges, by the addition of chemical called an adjuvant reagent.
- Predictable release.
- Biodegradable
- Drug profiles can be vary from fast, medium to slow release in case of dosing therapy.
- Particles can be made smaller or larger by varying the proportion of cross-linker to polymer.

Disadvantages of Nanosponges

- Nanosponges include only small molecules.
- It depends upon only loading capacities.

Materials used in Nanosponge preparation

A. Polymers

Hyper cross linked polystyrenes, cyclodextrins and its derivatives like hydroxy propyl β- cyclodextrins, alkyloxycarbonyl cyclodextrins, methyl β-cylclodextrins, ethyl cellulose, acrylic polymer,

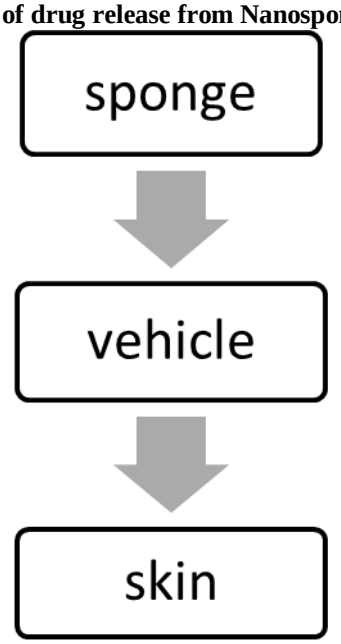
B. Copolymer

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

C. Cross linkers

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

Mechanism of drug release from Nanosponges:



Factors influencing the formation of Nanosponges

Following are the factors which can affect the formulation of Nanosponges,

i. Type of polymer
ii. Type of drugs
iii. Temperature
iv. Method of preparation
v. Degree of substitution

i. 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 particle size.

ii. Type of drugs

Molecule to be complexed with Nanosponges should have certain characteristics mentioned below,

- Drug molecule consists of less than five condensed rings.
- Molecular weight between 100-400 Da
- Solubility in water is less than 10mg\ml
- Melting point of substance is below 250ºc

iii. Temperature

When the temperature increase the stability of the drug\Nanosponge complex decreases, may be due to the

result of possible reduction of drug\Nanosponge interaction forces.

iv. Method of preparation

The method of loading the drug into the Nanosponges can affect drug\Nanosponge complexation**.**

v. Degree of substitution

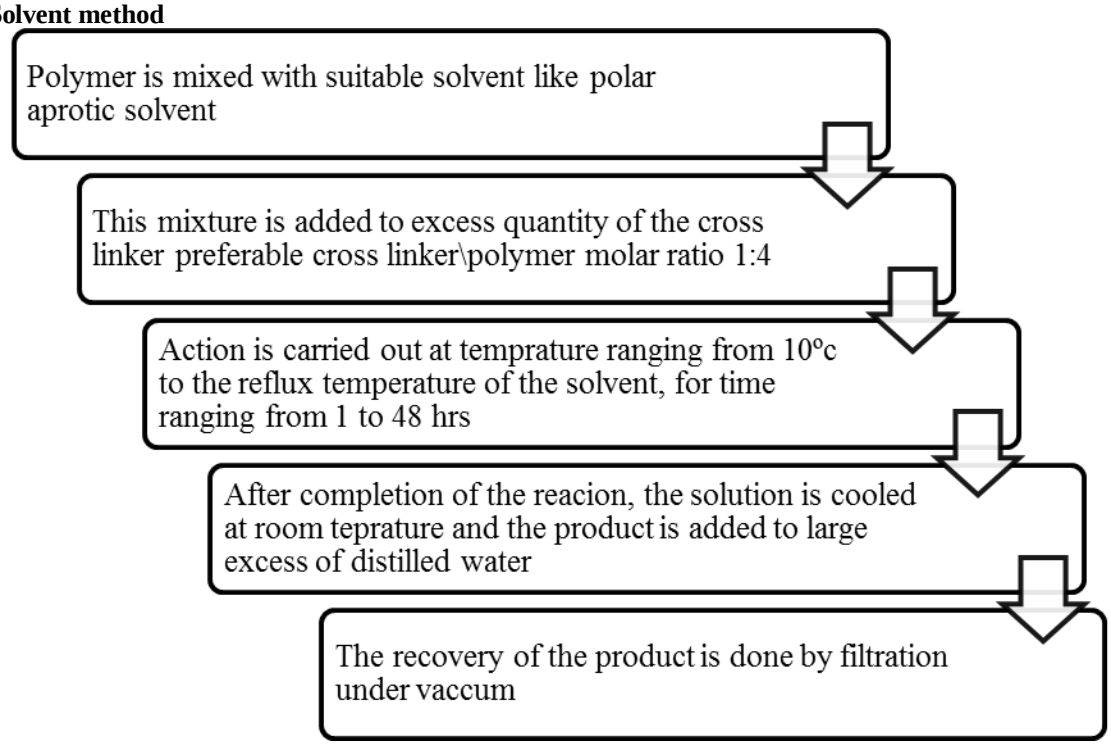
The complexation ability of the Nanosponge may be greatly affected by the, number and position of substituent on the parent molecule.

Preparation methods of Nanosponges

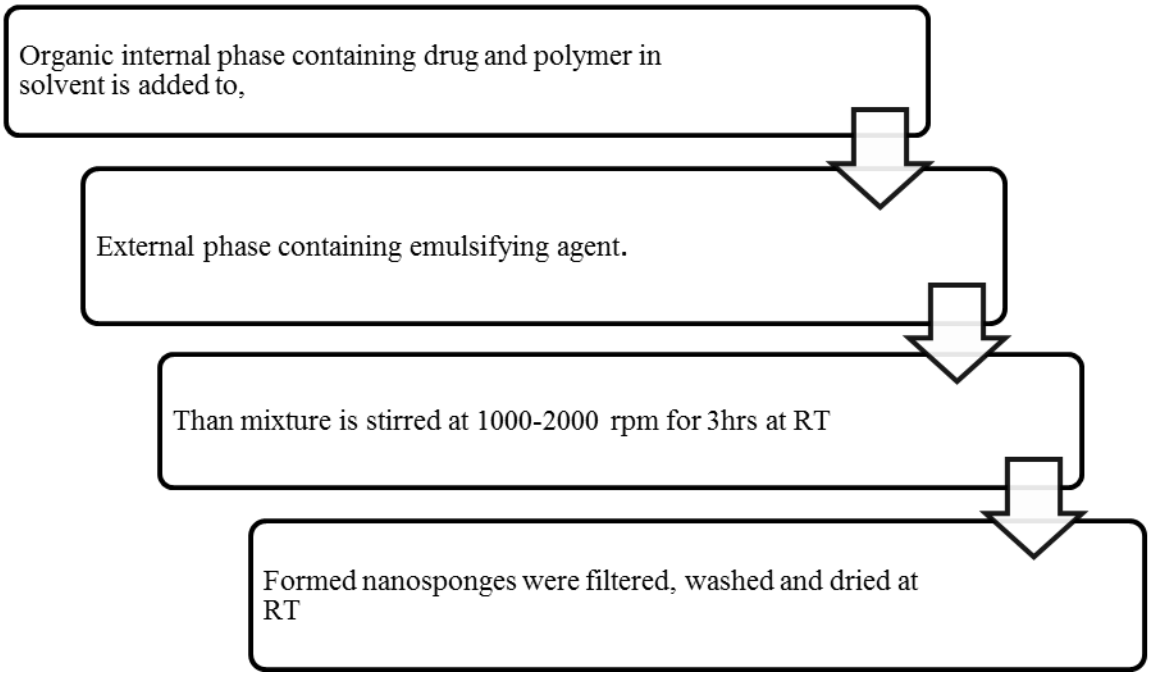
The Nanosponge are prepared by using the following different methods,

i. Solvent method
ii. Emulsion solvent diffusion method
iii. Ultrasound assisted synthesis
iv. From hyper cross-linked β-cyclodextrins

i. Solvent method



ii. Emulsion solvent diffusion method

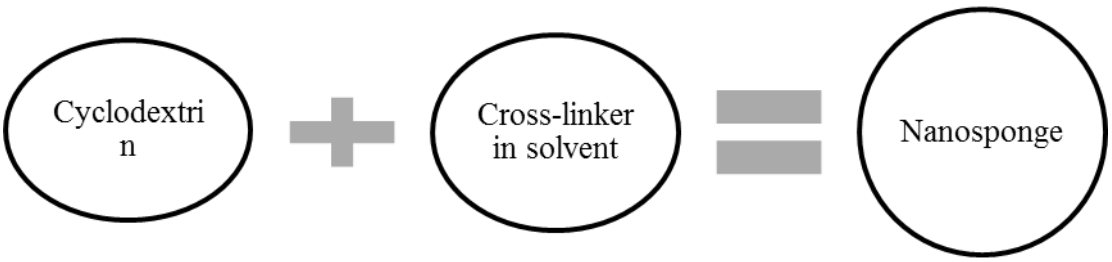


iii. Ultrasound assisted synthesis

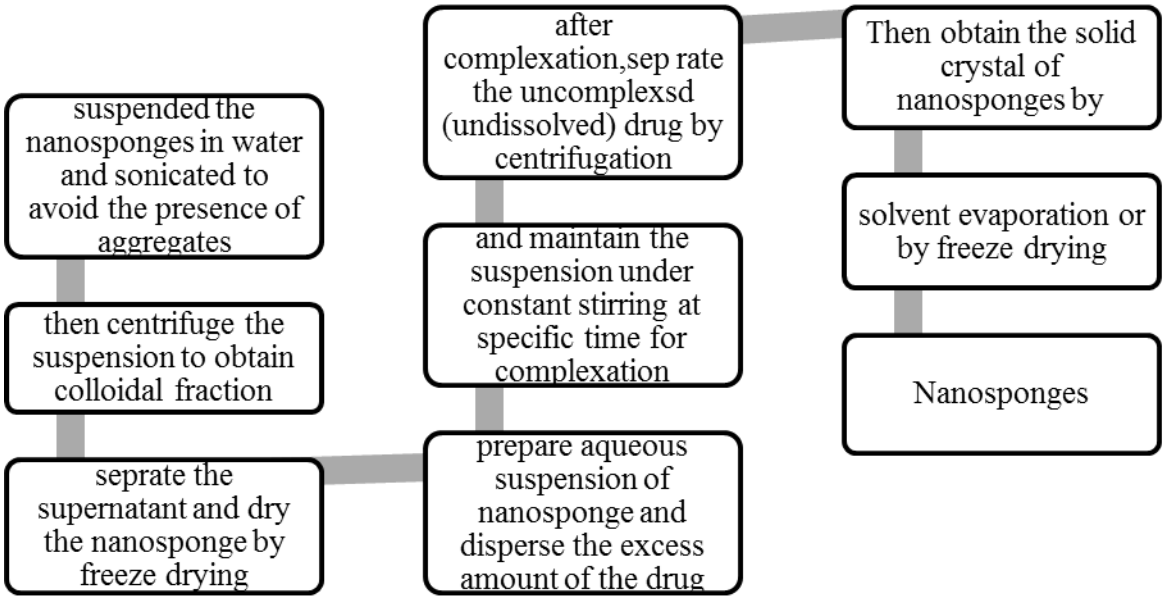
- Nanosponges are obtained by reacting polymer with cross linkers without adding or without using solvent and sonification is maintained.
- The size obtained by this technique will be spherical and uniform.
- The polymer is mix with a cross linkers in balanced ratio in a flask.
- The flask is placed in a molar ratio in an ultrasound bath field with water and temperature maintained at 90ºc.
- The mixture is sonicated for 5hrs.
- Then the mixture is kept to cool and product is break roughly then the product is washed with water to remove non-reacted polymer and subsequently purified by soxhlet extraction with ethanol.
- The product is dried under vaccum at 25ºc until its further use is utilized.

iv. Hyper cross linked β-cyclodextrins:

- Nanosponges are obtained by reacting cyclodextrins with a cross-linker such as isocyanides, diaryl carbonates, dimethyl carbonate, diphenyl carbonate and carbonyl diimidazoles.
- The average diameter of a Nanosponges is below 1μm but fractions below 500nm can be selected.



Loading of drug in to Nanosponges



Evaluation 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 seizer. Cumulative graph is maintained or plotted as particle size against time to study effect of particle size on drug release. Particle size larger than 30m can show gritty feeling and particle size range from 10-25m 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 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 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

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 formulations. Increased cross linking 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 Nanosponges can be determined by using zeta seizer.

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 Nanosponges, 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 nanoponge the release data was analyzed using zero order, first order, Higuchi, Korsemeyer-Peppas, Hixson Crowell, Kopcha and Makoid-Banakar models.

The data can be analyzed 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 performed using a multi compartment rotating cell. An aqueous dispersion of Nanosponges (1ml) containing the drug is placed in the donor compartment, while the receptor compartment separated by a hydrophilic dialysis membrane is filled with phosphate buffer at pH 7.4 or pH.

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 in 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 250ml 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 8hrs 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\nanosponges complex). The difference in crystallization state of the raw materials and the product seen under electron microscope indicates the formation of the inclusion complexes.

Application of Nanosponges

The nonporous structure that is formed changes many properties of the native cyclodextrins. This peculiar and versatile structure is suitable for a broad range of potential and actual application.

Some specific application of CD based Nanosponges include the following.

- Improvement of drug stability due to presence of several β-CD units and polymers.
- Function as carriers for biocatalysts and in the delivery and release of enzyme, proteins, vaccines and antibodies.
- Modulate drug release, hydrophilic CDNS can modify the rate of drug release, which can be used for enhancement of drug absorption across biological barriers. Hydrophobic CDNS may serve as sustained release carriers for water-soluble drugs.
- Solubility enhancement, the presence of cross-linking and cyclodextrins cavities in the structure favors interaction with active molecule. These characteristics enable several substances to be included and get solubilized in the formed cavities.
- Effective delivery carriers, CDNS have been used as vehicles for antitumor drugs such as paclitaxel, camptothecin and tamoxifen which present bioavailability problems because their solubility in water is low or non-existent.
- CDNS can strongly bind organic molecules and are therefore used to remove organic matter, flavors and odors from water.
- Hyper-cross linked NS have been used in selective separation of inorganic electrolytes through size exclusion chromatography.

Examples of Nanosponges

Drug	**Nanosponge vehicle**	**Indication**	**Study**	**In vitro\in vivo mathematical model**
Antisense oligonucleotides	Sodium alginate poly L-lysine	Cancer therapy, viral infections, pathologic disorders	Pharmacokinetic studies	Mice
Bovine serum albumin	Cyclodextrins based poly	Protein supplement	Drug release study, stability	In-vitro release modulation and stability
camptothecin	B-cyclodextrin	Cancer	Haemolytic activity, cytotoxicty	Diluted blood HT-29 cell line
Dexamethasone	B-cyclodextrin	Brain tumors	Drug release experiment	Dialysis bag technique in vitro
Econazole nitrate	Ethyl cellulose, polyvinyl alcohol	Antifungal	Irritation study	Rat
Itraconazole	β-cyclodextrin and copolyvidonum	Antifungal	Saturation solubility study	Higuchi model
Paclitaxel	β-cyclodextrin	cancer	Bio-availability	Sprague dawley rats MCF7 cell line

CONCLUSION

It may be concluded that the Nanosponges are nano sized colloidal carrier so they easily penetrate through skin. Due to their small sizes 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. It is include lipophilic or hydrophilic drugs and release drug at target site in controlled manner. Polymer and cross-linker ratio can be balanced and release rate can be modified. Nanosponges permit the insoluble drugs and prevent the physiochemical degradation of active contents and controlled release. Their small size and spherical shaped had provided Nanosponges to develop as different dosage forms like parentral, aerosol, topical, tablets and capsules.

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