



NANOSPONGES - AN EFFICIENT AND EFFECTIVE DRUG DELIVERY SYSTEM

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ABSTRACT

Effective targeted drug delivery systems have been a dream for a long time, but it has been largely frustrated by the complex chemistry that is involved in the development of new systems. The invention of nanosponges has become a significant step toward overcoming these problems. Nanosponges are solid, porous, bio-compatible, nano-particulate three dimensional structures which form complexes with different types of lipophilic or hydrophilic drug molecules and have been used as drug carrier for different drugs. They are tiny sponges with a size of about a virus, which can be filled with a wide variety of drugs and circulate around the body until they encounter the specific target site and stick on the surface and begin to release the drug in a controlled and predictable manner. In this review article application of nanosponges, method of preparation, evaluation parameter and added recent patent have been discussed.

KEYWORDS: Cyclodextrin nanosponges, targeted drug delivery, solubility enhancement.

INTRODUCTION

DeQuan Li and Min Ma in 1998 were the first who used the term cyclodextrin nanosponges (CDNS) to indicate a cross-linked β -cyclodextrin with organic diisocyanates leading to the formation of an insoluble network which indicate high inclusion constant with various organic pollutants. CDNS are suggested as a new nanosized drug delivery system with cross-linked polymers of cyclodextrin nanostructured within a three-dimensional network. CD polymer can form porous insoluble nanoparticles with crystalline or amorphous structure and spherical shape with tunable polarity and dimension by changing the crosslinker and degree of cross-linking.^[1,2]

CDNS are a new class of amorphous cross-linked polymers obtained by reacting CD with a suitable polyfunctional agent such as carbonyldiimidazole (CDI) or pyromellitic anhydride. The reaction products turned out to be highly cross-linked, nanoporous polymers showing interesting inclusion/release properties. The presence of the lipophilic cavities of CD units and hydrophilic channels within the porous structure provides the CDNS with the capability of encapsulating a large variety of compounds. Moreover, the type and the amount of crosslinking agent may dramatically regulate the various parameters like the swelling index and hydrophilicity/hydrophobicity of the final product. These properties make CDNS highly attractive for several applications in biocatalysis, agriculture and environmental protection and drug-delivery.^[3]

Nanosponges (NS) are nanosized hyper-crosslinked β -CD within a three dimensional network, which form insoluble porous nanoparticles with a crystalline or amorphous structure. CDNS have the capacity of complexation with different types of lipophilic and hydrophilic drug molecules and to achieve the prolonged release kinetics, the release of the entrapped molecules can be improved by modifying the structure. The NS could be used to enhance the water solubility of poorly water-soluble molecules, stability, protect degradable substances, sustained delivery systems and drug carriers for nanomedicine.^[4]

NS are tiny sponges having size of about a virus which consist of cavities filled with variety of drugs. These sponges circulate around the body until they find the specific target site and attached on the surface and begin to release the drug in a controlled manner. They are non-irritating, non-mutagenic, non-allergic and non-toxic and are five times more effective at delivering drugs for breast cancer than conventional methods. NS are solid in nature and capable of carrying both lipophilic and hydrophilic substance and also improve the solubility of poorly water soluble molecules. They are insoluble in water and other organic solvents, porous, non-toxic and stable upto the temperature 300 degree Celsius. A number of polymers and cross-linkers are used in the preparation of nanosponges. They can be used as carrier for gases like oxygen and carbon dioxide and also act as a carrier for the release and delivery of enzymes, proteins and peptides in biomedical field.^[5]

Different Polymers for the Nanosponges Formulation

Polymers: Hyper-cross linked polystyrenes, CDs and its derivatives like Alkyloxycarbonyl Cyclodextrin, Methyl beta-cyclodextrin, Hydroxy Propyl betacyclodextrin.

Copolymers: Poly (Valero lactone, allyl valerolactone) Ethyl cellulose, Poly vinyl alcohol.

Cross Linkers: Carbonyldiimidazole, carboxylic acid dianhydride, diary carbonates, dichloromethane, diisocyanate, diphenyl carbonate, epichloridine, gluteraldehyde, pyromellectic anhydride, 2,2-bis (acrylamido) Acetic acid.^[6]

Advantages of Nanosponges

- Improve aqueous solubility of lipophilic drugs.
- To protect the molecules and to develop drug delivery systems for various administration routes.
- They mix with water and are used as a transport for fluid.
- To mask unpleasant flavors.
- The chemical linkers enable the NSs to bind specifically at the target site.
- The engineering capacity of NS is due to the presence of comparatively simple chemistry of polyesters and cross-linking peptides.^[5,6]

Characteristic Features of Nanosponges

- NS exhibit a range of dimensions (1 μm or less) with tunable polarity of the cavities. NS of specific size and adjustable polarity can be synthesized by varying the crosslinker to polymer proportion.^[8]
- 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 (Swaminathan *et al.* 2009).
- They are nontoxic, porous particles insoluble in most organic solvents and stable at high temperatures up to 300 $^{\circ}\text{C}$.^[10]
- NS as formulations are stable over the pH range of 1 to 11 and temperature up to 130 $^{\circ}\text{C}$.
- They form clear and opalescent suspensions in water and can be regenerated by simple thermal desorption, extraction with solvents, by the use of microwave and ultrasounds.^[11]
- Their 3D structure enables capture, transportation and selective release of a vast variety of substances. They can be targeted to different sites due to their ability to be linked with different functional groups. Chemical linkers enable nanosponges to bind specifically to the target site. Magnetic properties can be also imparted to nanosponges (by adding magnetic particles into the reaction mixture).^[12]

Methods of Nanosponges Preparation: Cyclodextrin nanosponges are prepared by following methods.

1. Solvent Method

In solvent method, the polymers are mixed with suitable polar aprotic solvent such as dimethyl formamide (DMF), dimethyl sulfoxide (DMSO). After this step, the mixture is poured to excess quantity of the cross-linker, in molar ratio of 1:4 (polymer and crosslinker).

Then reaction is carried out at temperature ranging from 10 $^{\circ}\text{C}$ to the reflux temperature of the used solvent, for 1 to 48 hr. When the reaction get complete, it is allowed to cool at room temperature and washed with excess bi-distilled water and recovered by vacuum filtration and purification of product is done by soxhlet extraction with ethanol. Product drying under vacuum completes the process of preparation.^[7]

2. Ultrasound-Assisted Synthesis

In this method, NS are prepared by sonication of polymer and cross linker in the absence of solvent, the particles obtained will be uniformly spherical. The method starts by mixing polymer and cross-linker in a particular molar ratio in a flask and placed in an ultrasound bath for sonication at 90 $^{\circ}\text{C}$ for few hours. After completion of the reaction, the mixture is cooled and the product is roughly ground and washed with water to remove the unreacted polymer and subsequently purified by prolonged soxhlet extraction with ethanol. Further drying will give the nanosponges.^[8]

3. From Hyper Cross- Linked Beta-Cyclodextrins

Here, β - cyclodextrin (β - CD) can be used as carrier for drug delivery. Nanosponges can be obtained by allowing reaction between cyclodextrin and cross- linker. Nanosponges can be synthesized in neutral or acid forms. The mean diameter of a nanosponge will be below 1 μm . The different crosslinking agents modulate the important parameters like swellability and hydrophilicity/hydrophobicity of the final nanoporous polymer.^[10]

4. Emulsion Solvent Diffusion Method

Nanosponges can be prepared by using ethyl cellulose and polyvinyl alcohol. 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 400C for 24 hours.^[13]

Loading of Drug in Nanosponges

Drug molecules can be inserted into the nano-cavities of beta-CD and due to further crosslinking, interactions of the guest molecules with more β -CD units might be observed. Moreover, the presence of a crosslinked network might also cause nano-channels to be formed in the NS structure. This particular structural organization may be responsible for the increased solubilization and protection capacities of NSs compared to the parent CD. Nanosponges so developed are suspended within drug dispersions and freeze dried along with the drug candidate. Drug loading may be also carried out by the solvent evaporation technique, in which the drug is

dissolved in a suitable organic solvent. Prepared NSs are added to the above drug dispersion and triturated until the solvent evaporates. Drug/NS ratio is determined based on the solubility of the drug.^[10,17]

Application of Cyclodextrin Nanosponges

Some specific applications of CD based nanosponges include the following.

- **Improvement of drug stability:** β -CD units are complexed with a polymer, where a number of β -CD units are bound to the same polymer chain. Several β -CD units increase the stability of the drug complex. Further, the polymer may cooperate with the β -CD moieties in stabilizing the complexes. Such studies have been carried out for proteins and peptides because of their insufficient stability, costly production, immunogenic and allergic potential as well as poor bioavailability and sensitivity towards proteases.^[14]

- Nanosponges as carriers for biocatalysts and in the release and delivery of proteins, enzymes, antibodies and vaccines. – Proteins, peptides, enzymes and derivatives there of are used in the biomedical and therapeutic fields. Proteolytic enzymes are used to treat cancer or type I mucopolysaccharidosis, whereas oligonucleotides and DNA are used in gene therapy. Proteins and other macromolecules are carried and delivered across a biological barrier, targeting them towards the site by adsorbing or encapsulating them in CDNS.^[15]

- **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.^[3,8]

- **Solubility enhancement:** The presence of cross-linking and cyclodextrin cavities in the structure favors interaction with active molecules. These characteristics enable several substances to be included and get solubilized in the formed cavities. Inclusion complexation or solid dispersions with CDs can improve drug solubility or rate of dissolution of poorly water-soluble drugs due to the reduction in drug crystallinity. The resulting complex hides most of hydrophobic functionality in the inner cavity of the CD while hydrophilic hydroxyl groups on the outside surface which remain exposed to the environment; the net result is that a water soluble complex is formed.^[16]

- **Topical drug delivery system:** Local anesthetics, antibiotics and antifungals are easily developed into topical nanosponges by using several methods like emulsion solvent diffusion method, etc. The prepared nanosponges of econazole nitrate are discrete free flowing nanosized particles with perforated orange peel like morphology as confirmed by SEM.^[6,17]

Characterization of Nanosponges

Inclusion complexes formed between the drug and nanosponges can be characterized by following methods.

Thermo-analytical methods

Thermo-analytical methods determine whether the drug substance undergoes some change before the thermal degradation of the nanosponge. The change of the drug substance may be melting, evaporation, decomposition, oxidation or polymorphic transition. The change of the drug substance indicates the complex formation. The thermogram obtained by DTA and DSC can be observed for broadening, shifting and appearance of new peaks or disappearance of certain peaks. Changes in the weight loss also can provide supporting evidence for the formation of inclusion complexes.^[9]

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. The difference in crystallization state of the raw materials and the product seen under electron microscope indicates the formation of the inclusion complexes.^[9,10]

X-ray diffractometry and single crystal X-ray structure analysis

Powder X-ray diffractometry can be used to detect inclusion complexation in the solid state.

When the drug molecule is liquid since liquid have no diffraction pattern of their own, then the diffraction pattern of a newly formed substance clearly differs from that of uncomplexed nanosponge. This difference of diffraction pattern indicates the complex formation. When the drug compound is a solid substance, a comparison has to be made between the diffractogram of the assumed complex and that of the mechanical mixture of the drug and polymer molecules. A diffraction pattern of a physical mixture is often the sum of those of each component, while the diffraction pattern of complexes are apparently different from each constituent and lead to a “new” solid phase with different diffractograms. Diffraction peaks for a mixture of compounds are useful in determining the chemical decomposition and complex formation.^[8,9]

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]

Infra-Red spectroscopy

Infra-Red spectroscopy is used to estimate the interaction between nanosponges and the drug molecules in the solid state. Nanosponge bands often change only slightly upon complex formation and if the fraction of the guest molecules encapsulated in the complex is less than 25%,

bands which could be assigned to the included part of the guest molecules are easily masked by the bands of the spectrum of nanosponges. The technique is not generally suitable to detect the inclusion complexes and is less clarifying than other methods.^[9,17]

Thin Layer Chromatography: In Thin Layer Chromatography, the R_f values of a drug molecule diminishes to considerable extent and this helps in identifying the complex formation between the drug and nanosponge.

Loading efficiency: The loading efficiency of nanosponges can be determined by the quantitative estimation of drug loaded into nanosponges by UV spectrophotometer & HPLC methods.^[17]

Zeta potential: Zeta potential is a measure of surface charge. It can be measured by using additional electrode in the particle size equipment.

Particle size and polydispersity: The particle size can be determined by dynamic light scattering using 90 Plus particle sizer equipped with MAS OPTION particle sizing software. From this the mean diameter and polydispersity index can be determined.

CONCLUSION

The nanosponges have the ability to include either lipophilic or hydrophilic drugs and release them in a controlled and predictable manner at the target site. By controlling the ratio of polymer to the cross-linker the particle size and release rate can be modulated. Nanosponges enable the insoluble drugs and protect the active moieties from physicochemical degradation and controlled release. Because of their small size and spherical shape nanosponges can be developed as different dosage forms like parenteral, aerosol, topical, tablets and capsules.

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