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REVIW ARTICLE

NANOSPONGES: A BOON TO THE TARGETED DRUG DELIVERY SYSTEM

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ABSTRACT:

Site specific or targeted drug delivery is used to treat many diseases like cardiovascular disease, Osteo-diseases, hormonal deficiency diseases like Parkinson's disease, auto-immune diseases like arthritis, diabetes. However, the most important application of targeted drug delivery system is to treat cancer. The unregulated cell growth and non-specific nature of the treatment makes Cancer difficult to treat by conventional drug delivery system. Hence targeted drug delivery system can be used to treat various cancers like multiple myeloma, breast cancer, prostate cancer, melanoma, lymphoma and other cancers. The following article emphasizes on one of such system named 'nanosponges'. The objective of the article is to discuss nanosponges with their method of preparation, characterization, and applications.

Keywords: Nanosponges, Cancer, Ultrasound-assisted synthesis,Polydispersity index, Mas Option.

INTRODUCTION:

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. Targeting drug delivery has long been a problem for medical researchers i.e., how to get them to the right place in the body and how to control the release of the drug to prevent overdoses. The development of new and complex molecule called 'nanosponges' has the potential to solve this problem.

The system, known as "nanosponge," uses a nanoparticle -sized system to deliver the drug payload. These nanoparticles circulate in the body until they encounter the surface of a tumor cell, where they adhere to the surface and begin releasing the drug in a controllable and predictable fashion. The controlled-release nanoparticle drug-delivery system uses a targeting peptide that can recognize a radiation-induced cell-surface receptor. The average diameter of a nanosponge is below 1 µm but fractions below 500 nm can be selected[1]. The nanosponges could be either paracrystalline or in crystalline form. The loading capacity of nanosponges depends mainly on degree of crystallization. Paracrystalline nanosponges can show different loading capacities.

The sponge acts as a three-dimensional network or scaffold. The backbone is long-length polyester. It is mixed in solution with cross-linkers to form the polymer. The net effect is to form spherically shaped particles filled with cavities where drug molecules can be stored. The polyester is biodegradable, so it breaks down gradually in the body. As it breaks down, it releases its drug payload in a predictable fashion. The nanosponges can be synthesized to be specific size and to release drugs over time by varying proportions of cross-linker to polymer. The main limitation of nanosponges is their ability to include only small molecules[2].

Advantages:

1. Targeted site specific drug delivery.
2. Can be used to mask unpleasant flavours and to convert liquid substances to solids[2].
3. Less harmful side effects (since smaller quantities of the drug have contact with healthy tissue).
4. Nanosponge particles are soluble in water, so the hydrophobic drugs can be encapsulated within the nanosponge, after mixing with a chemical called an adjuvant reagent.
5. Particles can be made smaller or larger by varying the proportion of cross-linker to polymer.
6. Production through fairly simple chemistry called "click chemistry" (methods for making the nanosponge particles and for attaching the linkers).
7. Easy scale-up for commercial production.
8. The drug profiles can be tailored from fast, medium to slow release, preventing over- or under-dosing of the therapy[3].
9. Predictable release.
10. Biodegradable.

The material used in this system can provide a protective barrier that shields the drug from premature destruction within the body.

MATERIALS USED FOR PREPARATION OF NANOSPONGES:

There are some important components that can be used for the preparation of nanosponges which can be summarized as follows:

Table 1: Chemicals Used For the Preparation of Nanosponges[2]

Polymers	Hyper cross linked Polystyrenes, Cyclodextrins and its derivatives like Methyl β-Cyclodextrin, Alkyloxy-carbonyl Cyclodextrins, 2-Hydroxy Propyl β-Cyclodextrins andCopolymers like Poly (valerolactone – allylvalerolactone) & Poly (valerolactone-oxepanedione) and Ethyl Cellulose & Poly vinyl acetate.
Cross-linkers	Diphenyl Carbonate, Di-aryl carbonates, Di-isocyanates, Pyromellitic anhydride,Carbonyldi-imidazoles, Epi-chloridrine, Glutraldehyde, Carboxylic acid di-anhydrides, 2, 2- bis (acrylamido), Acetic acid and Dichloromethane

METHOD OF PREPARATION:

1. Solvent method:

In this method, the polymer can be mixed with a suitable solvent like polar aprotic solvent such as dimethyl formamide (DMF), dimethyl sulfoxide (DMSO). Further, this mixture is added to excess quantity of the cross-linker, preferably in cross-linker/polymer molar ratio of 1:4. Thereaction is carried out at temperature ranging from 10°C to the reflux temperature of the solvent, for time ranging from 1 to 48hour[7]. After completion of the reaction, the solution is cooled at room temperature and the product is added to large excess of bi-distilled water. The recovery of the product is done by filtration under vacuum and subsequent purification by prolonged soxhlet extraction with ethanol. Drying the product under vacuum completes the process[5].

2. Ultrasound-Assisted synthesis:

In this method, nanosponges can be obtained by reacting polymers with cross-linkers in the absence of solvent and under sonication. The nanosponges obtained by this method will be spherical and uniform in size. In this method, the polymer is mixed with the cross-linker in a particular molar ratio in a flask. The flask is then placed in an ultrasound bath, filled with water and heated to 90°C. Sonication of the mixture is donefor few hours. Then, the mixture is to be cooled and the product is broken roughly. Washing the product with water to remove the non-reacted polymer and subsequently purifying byprolonged soxhlet extraction with ethanol with further drying will give the nanosponges[5, 6].

3. Loading of drug into nanosponges:

Nanosponges for drug delivery should be pretreated to obtain a mean particle size below 500nm. For this, nanosponges is suspended in water and then sonicated to avoid the presence of aggregates. Further, the suspension is centrifuged to obtain the colloidal fraction. Thesupernatent is separated and the sample is to be dried by freeze drying [6]. Aqueous suspension of nanosponge is prepared and dispersed in the excess amount of the drug and the suspension is maintained under constant stirring for specific time (required for complexation). After complexation, the uncomplexed (undissolved) drug from complexed drug is separated by centrifugation. Then, the solid crystals of nanosponges are obtained by solvent evaporation or by freeze drying[5, 7].

Crystal structure of nanosponge plays a very important role in complexation with drug. A study revealed that paracrystalline nanosponges showed different loading capacities when compared to crystalline nanosponges. The drug loading is greater in crystalline nanosponges than paracrystalline one. In poorly crystalline nanosponges, the drug loading occurs as a mechanical mixture rather than inclusion complex[8].

CHARACTERIZATION OF NANOSPONGES:

1. 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].

2. Loading efficiency / Entrapment efficiency:

Weighed amount of loaded nanosponge complexes is to be dissolved in suitable solvent, sonicated to break the complex, diluted suitably and then analyzed by UV spectrophotometer or HPLC methods[13].

3. 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/nanosponge complex). The difference in crystallization state of the raw materials and the product seen under electron microscope indicates the formation of the inclusion complexes[8, 9].

4. Polydispersity index& particle size:

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[2]. The particle size can be determined by scanning electron microscopy (SEM), transmission electron microscopy (TEM), atomic force microscopy (AFM), and freeze fracture electron microscopy (FFEM)[10].

5. Zeta potential determination:

Zeta potential measurements can be made by using an additional electrode in particle size instruments[2]. Also, Laser Doppler anemometry, zeta potential meter can be used[10].

6. 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 isless than 25%, bands which could be assigned to the included part of the guest molecules are easily masked by the bands of the

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spectrum ofnanosponges. The technique is generally not suitable to detect the inclusion complexes and isless clarifying than other methods[9].

The application of the Infra-red spectroscopy is limited to the drugs having some characteristic bands, such as carbonyl or sulfonyl groups. Infrared spectral studies give information regarding the involvement of hydrogen in various functional groups. This generally shifts the absorbance bands to the lower frequency, increases the intensity and widens the band caused by stretching vibration of the group involved in the formation of the hydrogen bonds. Hydrogen bond at the hydroxyl group causes the largest shift of the stretching vibration band[9].

7. X-ray diffractometry:

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), 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 madebetween 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 differentdiffractograms. Diffraction peaks for a mixture of compounds are useful in determining the chemical decomposition and complex formation.The complex formation of drug withnanosponges alters the diffraction patterns and also changes the crystalline nature of the drug. The complex formation leads to the sharpening of the existing peaks, appearance of a few new peaks and shifting of certain peaks[9].

8. Single crystal X-ray structure analysis:

Itmaybe used to determine the detailed inclusion structure and mode of interaction. The interaction between the host and guest molecules can be identified and the precise geometrical relationship can be established[9].

9. In Vitro release studies:

The release of the drug from the optimized nanosponge formulation can be studied using multi-compartment rotating cell with dialysis membrane (cut-off 12,000 Da). The donor phase consists of drug-loaded nanosponge complex in distilled water. The receptor phase also contains the same medium. The receptor phase is withdrawn completely after fixed time intervals, suitably diluted with distilled water and then analyzed by UV spectrophotometer[12]. Also, USP II can be used in many cases depending upon the formulation [10].

10. Photo-degradation study:

The photo-degradation of drug loaded nanosponge complex is performed under UV lamp. The samples are kept at distance of 10 cm from the lamp for 1 hr. stirring under dark; simultaneously the samples are quantitatively analyzed by HPLC[12].

11. 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 [19].

APPLICATION:

1. Cancer:

Oftentimes, the drugs injected by doctors in cancer patients are rendered inefficient. This happens mainly for two reasons – either they can't get to the tumor site, or they are attacked and dismembered by the immune system. This obstacle has now been solved by the use of nanosponge to certain extent. Experts proposed that fixing drugs into nanosponge ensures that the chemicals reach their destination in large amounts[15, 16].One of the important drug formulated as nanosponge is paclitaxel, the active ingredient in the anti-cancer therapy Taxol.

The researchers have recorded the response of two different tumor types in animal studies — slow-growing human breast cancer and fast-acting mouse glioma - to single injections. In both cases, they found that the delivery through nanosponges increased the death of cancer cells and delayed tumor growth compared with other chemotherapy approaches [4].

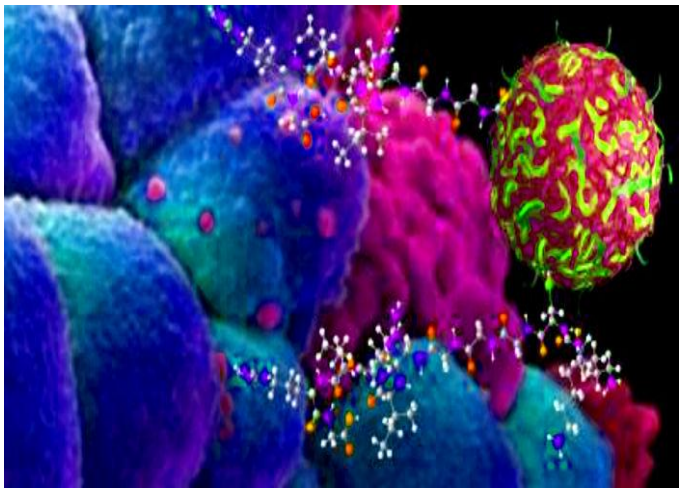

Figure 1: The illustration shows a nanosponge particle attaching to human breast cancer cells.

(The particle holds an anticancer drug that it releases gradually as the particle decomposes. Peptide linkers are shown with the ball and stick representation. Although only two are shown in the illustration, about three dozen are attached to the surface of actual particles. The linkers

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are specially configured to bind to the surface of irradiated cancer cells.)

2. Oxygen delivery systems:

Cyclodextrin nanosponges have also been developed as oxygen delivery system. For this purpose, the three types of nanosponges made up of α, β and γ – cyclodextrin is suspended in water, saturated with oxygen and in vitro characterized. Oxygen permeation through a silicone membrane can also be obtained using a β-cyclodextrin nanosponge/hydrogel combination system[6.] 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 [17].

3. As a carrier for biocatalysts and in the delivery and release of enzymes, proteins, vaccines and antibodies:

Many industrial processes involving chemical transformation are associated with operational disadvantages. Non-specific reactions lead to low yields, and the frequent need to operate at high temperatures and pressures requires consumption of large amounts of energy, and very large amounts of cooling water in the down-stream process. All these drawbacks can be eliminated or significantly reduced by using enzymes as biocatalysts. These enzymes operate under mild reaction conditions, have high reaction speed, and are highly specific. The administration of these molecules presents various problems.

A number of systems for carrying enzymes and proteins have been developed, such as nano and microparticles, liposomes and hydrogels. Carriage in a particular system can protect proteins from breakdown, modify their pharmacokinetics and improve their stability in-vivo. Now, it has been found that Cyclodextrin based nanosponges are particularly suitable as carrier to adsorb proteins, enzymes, antibodies and macromolecules. In particular when enzymes are used, it is possible to maintain their activity, efficiency, prolong their operation and extends the pH and temperature range of activity and allows the conduct of continuous flow processes. Moreover, proteins and other macromolecules can be carried by adsorbing or encapsulating them in cyclodextrin nanosponges[2].

4. Harvesting of rare Cancer Marker from Blood:

It has been seen that a new type of nanoparticle, whose interiors is decorated with different types of 'bait' molecules, is used to selectively trap specific families of proteins from blood and protect them from degradation by enzymes in blood[4].

5. In the removal of organic matter to produce ultrapure water for power regeneration:

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 in the removal of natural organics (volatile component), dissolved organic carbon (DOC) and total organic carbon (TOC) from water collected at a specific power plant has been reported in the literature. The CD - polymers also has demonstrated the ability to remove dissolved organic carbon (DOC) from raw water by as much as 84%, whilst total organic carbon (TOC) removal was relatively low[9].

6. Solubility enhancement:

Nanosponges have been also used for improving the solubility and dissolution rate of poorly soluble drugs as well as providing controlled release profile. However the molecular dimensions and conformation are critical parameters influencing inclusion complexation within nanosponges and thus may not be universally applicable to all molecules. Nanosponges of Cefpodoxime proxetil (CP) have been prepared to improve dissolution rate of CP [10].

7. Novel flame retardants containing cyclodextrin nanosponges and phosphorus compounds to enhance EVA combustion properties:

A novel flame retardant in tumescent system, aimed to improve the fire stability of ethylene vinyl acetate copolymer (EVA), has been prepared by melt blending of the copolymer and a complex of cyclodextrin nanosponge-phosphorus compounds. As compared to traditional systems, this complex which is stable in processing conditions, has the advantage that nanosponges act as both carbon sources and foam forming agents while the phosphorus compounds are able to directly generate phosphoric acid *in situ*. In this context, cyclodextrin nanosponges undergo dehydration in presence of the acid source, generating water vapour and char, and thus protecting the copolymer against combustion[11].

8. Topical drug delivery system:

Local anesthetics, antifungals and antibiotics are among the category of the drugs that can be easily formulated as topical nanosponges. In this context, nanosponges can be prepared by various methods like emulsion solvent diffusion method, etc. The nanosponges of econazole nitrate were prepared, which are discrete free flowing nanosized particles with perforated orange peel like morphology as visualized by SEM in the literature[12].

9. Antiviral application:

Nanosponges can be useful in the ocular, nasal, pulmonary administration routes. The selective delivery of antiviral drugs or small interfering RNA (siRNA) to the nasal epithelia & lungs can be accomplished by nanocarriers in order to target viruses that infect the RTI such as respiratory sinctial virus, influenza virus & rhinovirus. They can also be used for HIV, HBV, and HSV. The drugs which are currently in use as nano delivery system are zidovudine, saquinavir, interferon- α, acyclovir (Eudragit based)[12].

10. More effectiveness than direct injection:

Recent research suggests that nanosponge could be up to five times more effective at reducing tumor growth than direct injection. The drug delivery system is likened to be filling virus-sized sponges with an anti-cancer drug, attaching chemical linkers that bond to a receptor on the

surface of tumor cells, then injecting the sponges into the body. When the sponges come into contact with a tumor cell, they either attach to the surface or are sucked into the cell, where they off-load their deadly contents in a predictable and controlled manner [14, 18].

11. Floriculture:

Nanosponges have been recently developed and proposed for delivering preservative and anti - ethylene compounds in order to improve cut flower vase life [18].

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. Thus, the nanosponge drug delivery system is a boon in the area of targeted and site specific drug delivery system. Although, more developmental studies are required to make this drug delivery useful to mankind.

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