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A REVIEW ON TARGETED DRUG DELIVERY OF NANOSPONGES

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ABSTRACT

Effective targeted drug delivery system have been possibility to perform the exact function to control the release rates and have a better compliance on the health care system. But the invention of nanosponges has given a importance approach toward solving this problem. Nanosponges contain tiny sponges having size of about a virus and can be filled with variety of drugs. This sponges can circulate throughtout the body until interact with particular target site and stick on surface and start releasing drug in a controlled manner. Based nanosponges proposed nano delivery system and form porous insoluble nanoparticle having crystalline and unformed nature in cyclodextrin nanosponge. Important feature of these sponges is their solubility in aqueous form and give a effect to the drugs with poor solubility.

KEYWORDS

Nanosponges, Controlled release, Emulsion solvent diffusion method, Resilency and Breast cancer.

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INTRODUCTON

An ideal drug therapy achieve concentration of drug at the targeted site for a specific preiod of time in order to minimize general and local sideeffects. The correct amount of drug should be transported and delivered to the site of action in order to obtain a desirable therapeutic response. The distribution of drug to other tissues thereforre seems unnecessary, waste ful and a potential cause of toxicity.

Effective targeted drug delivery systems have been adream for a long time now but it hasbeen largely frustrated by the complex chemistry that is involved how to get them to the right place in the body and how tocontrol the release of the drug to prevent over doses. The development of new and complex molecules

called nanosponges have the potential to solve these problems[1].

Nanosponges are made of microscopic particles with few nanometers wide cavities.These are new class of materials in which a large variety of substances can be encapsulated[2]. These particles are capable of carrying both lipophilic and hydrophilic substances and of improving the solubility of poor water soluble molecules[3]. Nanosponges contain tiny mesh-like structures. These are used in 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 having with an average diameter below 4µm and with a 'backbone' (a scaffold structure) of naturally degradable polyester[2]. The long length polyester strands are mixed with crosslinkers solution which are small molecules that have an affinity for certain portions of the polyester.

The spherical shape of crosslinking segments which are having many pockets or cavities are made up of polysters. where drugs can be stored,which are predictably biodegradable, which means that when it breaks up in the body, the drug can be released on a known schedule[3].

Advantages[4-7]

1. This technology provide entrapment of active contents and side effects are less.
2. It improves the stability, elegance and flexiblity of formulation.
3. It is non-mutagenic.
4. Non-irritating, non-toxic.
5. It provide extended release condition which is continuous action up to 12hr.
6. Drug is protected from degradation.
7. Therapeutic provide onset of action.Formulations are cost effective.
8. It can be used to mask unpleasant flavours and to convert liquid substances to solids.
9. Nanosponge particles are soluble in water.
10. Particles can be made smaller or larger by varying the proportion of cross-linker to polymer.
11. Easy scale-up for commercial production.
12. In case of dosing therapy The drug profiles can be vary from fast, medium to slow release .
13. Predictable release.
14. Biodegradable.

Disadvantages of Nanosponges

Nanosponges have the capacity of encapsulating small molecules, not suitable for larger molecules.

Dose dumping may occur at times[8].

Characteristic Features of Nanosponges

1. Nanosponges provide a range of dimensions (1µm or less) with tunable polarity of the cavities.
2. Nanosponges are specific size can be synthesized by changing the cross linker to polymer ratio.
3. Drug loading capacity depends on the degree of crystallization.
4. They are nontoxic, porous particles, insoluble in most organic solvents and stable up to 300°C.
5. They are stable at the pH range of 1-11.
6. They form clear and opalescent suspension in water.
7. They can be reproduced by simple thermal desorption, extraction with solvents, by using microwaves and ultrasounds.
8. Their three-dimensional structure allows capture, transportation and selective release of a variety of substances.
9. They can be sited to different target sites because of their capacity to link with different functional groups.
10. Chemical linkers permit nanosponges to bind preferably to the target site.
11. By complexing with different drugs nanosponges can form inclusion and non-inclusion complexes.
12. By adding magnetic particles into the reaction mixture, magnetic properties can also be imparted to nanosponges[9].

Type of Drug

Method of Preparation

The method of loading drug into the nanosponges can affect drug/nanosponge complexation. However, the effectiveness of a method depends on the nature of the drug and polymer, in many cases

freeze drying was found to Drug molecules to be complexes with nanosponges. Molecular weight of drug should be in the range of 100 to 400 Daltons. The structure of the drug molecule should contain not more than five condensed rings. Water solubility should be less than 10 mg/ml. Melting point of the substance should be less than 250°C[10].

Temperature

Temperature changes can affect drug/nanosponges complexation. In general, increase in the temperature decreases with the magnitude. The apparent stability constant of the drug/nanosponges complex may be a result of possible reduction of drug/nanosponges interaction forces, such as van-der Waal forces and hydrophobic forces with rise of temperature[11].

Degree of Substitution

The complexation ability of the nanosponges may be greatly affected by type, number and position of the substituent on the parent molecule[11].

Chemicals used for the Synthesis of Nanosponges

Some of the polymers that are used for the synthesis of nanosponges are cyclodextrins (such as Methyl β-cyclodextrin (Mβ-CD), 2-hydroxy propyl β-CDs (2HPβ-CD), and alkyloxy carbonyl cyclodextrins), copolymers (like poly valero lactoneallylvalero lactone and poly valero lactone-allyl valero lactone oxepanedione), hyper cross linked polystyrenes, and ethyl cellulose and poly vinyl alcohol[11].

Conjugating nanoparticles

Which links to drugs through covalent bonds Nanosponges are capable of carrying both lipophilic and hydrophilic substances and of improving solubility of poorly water soluble molecules. Nanosponges increases aqueous solubility and poorly water soluble drugs, to remove pollutants from contaminated water, or as nano-carriers for biomedical applications[12,13]. The technology increases entrapment and reduces side effects, improved stability, increased elegance and enhanced formulation flexibility. Nanosponge systems are non-irritating and non mutagenic, non-allergic and nontoxic[14,15]. As compared to the other nanoparticles, they are soluble both in water and organic solvents, porous, non-toxic and stable at high temperatures up to 300°C. Due to its 3D structure containing cavities of nanomeric size, tunable polarity and high solubility they are able to capture transport and selectively release a wide variety of substances to protect degradable molecules and to formulate drug delivery systems for various administration routes besides the oral one. In water Nanosponges are soluble, but does not breakup chemically in water. When they mix with water and then they are use as a transport fluid. They can be used to mask unpleasant flavors, to convert liquid substances to solids. Nanosponges are ability to include only small molecules. The nanosponges could be either par crystalline or in crystalline form. Para crystalline nanosponges can show different loading capacities. The shape of nanosponges enables the pulmonary and venous delivery of nanosponges[16].

Preparation Methods of Nanosponge

Solvent Method

Dissolve the polymer in suitable solvent. Then add this to excess quantity of cross- linker. Reflux the mixture for 48 hours at a temperature of 10ºC. After completion of this mixture then solution are kept under the room temperature and cool it. And then finally add this to excess quantity of bi-distilled water and filter the product then purify by prolonged soxhlet extraction with ethanol. Dry the product and grind in mechanical mill to get homogenous powder[17,16].

Emulsion solvent diffusion method

In nanosponges formulation method two phases are used in different proportion of organic phase and aqueous phase. The dispersed phase having ethyl cellulose (aq. phase) and drug get dissolved in to dichloromethane (20ml) and a definite amount of polyvinyl alcohol is added in to 150ml of aqueous continuous phase. Then, this mixture is properly stirred at 1000 rpm for 2hr and after formation of nanosponges were collected by using filtration process then washed and then dried at room temperature or in oven at 40ºC for 24hr. Dried nanosponges were stored in desiccators[17].

Ultrasound-Assisted synthesis

In this method when the polymers are reacted with cross-linkers in the absence of solvent and under sonication, the nanosponges are formed. The

nanosponges which are obtained by this method are spherical and uniform in size. The polymer and the cross-linker are mixed in a particular molar ratio in a flask. Now the flask is placed in an ultrasound bath which is filled with water and heats it to 90°C. The mixture is sonicated for 5hours and then the mixture to cool and break the product roughly. The product is washed with water to remove the non reacted polymer and subsequently purified by prolonged soxhlet extraction with ethanol. The obtained product is dried under vacuum and store at 25°C until further use[2,18].

Nanosponges prepared from hyper cross-linked β-cyclodextrins

Nanosponges were prepared from β-cyclodextrins; non-porous materials are used as carriers for drug delivery. By reacting cyclodextrin with a cross-linkers such as diisocianates, diarylcarbonates and carbonyl diimidazoles, carboxylic acid dianhydrides and 2, 2 bis (acrylamido) acetic acid they can form hyperlinked cyclodextrin polymer nanosponge. Surface charge density, porosity and pore sizes of sponges can be controlled in order to attach different molecules. Nanosponges can be synthesized in neutral or acidic form depending in on the agent used as cross linker. Nanosponges are the solid nanoparticles and can be prepared in crystalline form with spherical shape using an ultrasound-assisted preparation method. The average diameter of a Nanosponge is below 1μm but sometimes those below 500nm can also be selected. Various types of molecules can be entrapped in nanosponges by forming inclusion and non-inclusion complexes. Nanosponges have the capacity to incorporate molecules within their structure and are evaluated using drugs with different structures and solubility. Both the lipophilic and hydrophilic drugs can be entrapped in the nanosponges. To increase aqueous solubility of poorly water-soluble drugs and remove pollutants from contaminated water, or as nano carriers for biomedical applications in nanosponge. These are also been used for removal of organic impurities in water[13,10].

Loading of drug into Nanosponges

Nanosponges are targeted drug delivery the drug should be pretreated to obtain a mean particle size below 500nm. The nanosponges are suspend in water and sonicate to avoid the presence of aggregates and then centrifuge the suspension to obtain the colloidal fraction. Separate the supernatant and dry the sample by freeze drying[18]. After completion of freeze drying and Prepare the aqueous suspension of Nanosponge and disperse the excess amount of the drug and maintain the suspension under constant stirring for specific time required for complexation. After complexation, separate the un complexes (undissolved) drug from complexes drug by centrifugation. Then obtain the solid crystals of nanosponges by solvent evaporation or by freeze drying[19,18]. Crystal structure of nanosponge plays a very important role in complexation with drug. A study revealed that par crystalline nanosponges showed different loading capacities when compared to crystalline nanosponges. The drug loading is greater in crystalline nanosponges than par crystalline one. In poorly crystalline nanosponges, the drug loading occurs as a mechanical mixture rather than inclusion complex[20].

Evaluation of Nanosponges

Solubility studies

The most important method used 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[17].

Loading efficiency / Entrapment efficiency

Weighed required amount of loaded nanosponge complexes is to be dissolved in suitable solvent, and then sonicated to break the complex; the breaked nanosponges are diluted suitable solvent. And then analyzed by UV spectrophotometer or HPLC methods[21].

Fourier Transform Infrared (FTIR)

In this (FTIR) Spectroscopy to confirm the formation of nanosponges. Potassium Bromide pellet method was used to study the spectra. The conformational changes of optimized drug can be

study when compared with the pure drug and pure excipients spectrums. The (FTIR) spectrum was recorded in the wave number region of 4000-500cm-1[22].

Determination of Particle Size Distribution

This method was determined by using Dynamic Light Scattering (DLS) technique. This equipment was used for the determination of particle size distribution is HORIBA particle size analyzer. In this technique the particle sizes of a batch of the nanosponges were observed and from the standard deviation and mean particle size of nanosponges, the Poly Dispersity Index (PDI) was calculated. The poly dispersity index is the indication for the nature of dispersity[23].

Zeta potential

Zeta seizer can be used to measure zeta potential, which is the measure of surface charge of Nanosponges. Zeta potential is mostly used for quantification of the magnitude of the electrical surface charge at the double layer. The importance of zeta potential is that its value can be related to the stability of formulation. More than 30 mV zeta potential value in water indicates good stability of Nanosponge[24].

Compatibility Studies

Compatibility in drug and polymer is the main issue in the formulation. The drug should be compatible with polymers which are being used. The compatibility of drug with adjuvant can be determined by Thin Layer Chromatography (TLC) and Fourier Transform Infra-red Spectroscopy (FT-IR)[25].

Resiliency

To determine the viscoelastic properties of nanosponges. Viscoelastic properties of sponges are modified to produce beadlets which are softer and firmer when needed for final formulation. The cross linking are used this formulation to get increased and tends to slow down rate of release. Resiliency is studied according to requirement by releasing function of cross-linking with time[26].

Dissolution tests

In this method Nanosponges are studied by using dissolution apparatus USP having a modified basket method. It consist of 5ml stainless steel mesh with a speed of rotation around 150rpm. Proper dissolution medium is selected and solubility of active contents is considered to ensure sink conditions. Proper analytical methods are used for the sample form dissolution medium[19].

APPLICATIONS

Cancer

Oftentimes, the drugs injected by doctors in cancer patients are rendered inefficient. They are 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[27]. One of the important drug formulated as nanosponge is paclitaxel, the active ingredient in the anti-cancer therapy Taxols.

The researchers have recorded the response of two different tumor types in animal studies-slow growing human breast cancer and fast-acting mouse gliomas - to single injections. They found that the delivery through nanosponges increased the death of cancer cells and delayed tumor growth occur in two cases when compared with other chemotherapy approaches[28].

Oxygen delivery systems

Cyclodextrin nanosponges are developed as oxygen delivery system. For this reason, the three types of nanosponges made up of α, β and γ - cyclodextrin is suspended in water, saturated with oxygen and *in vitro* characterized. Silicone membrane can also be exist using a β-cyclodextrin nanosponge/hydro gel combination system through a oxygen permeation. 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[18].

Topical drug delivery system

Local anesthetics, antifungal and antibiotics are among the category of the drugs that can be easily formulated as topical nanosponges. In this circumstances, nanosponges can be prepared by various methods like emulsion solvent diffusion method, etc. The nanosponges of econazole nitrate

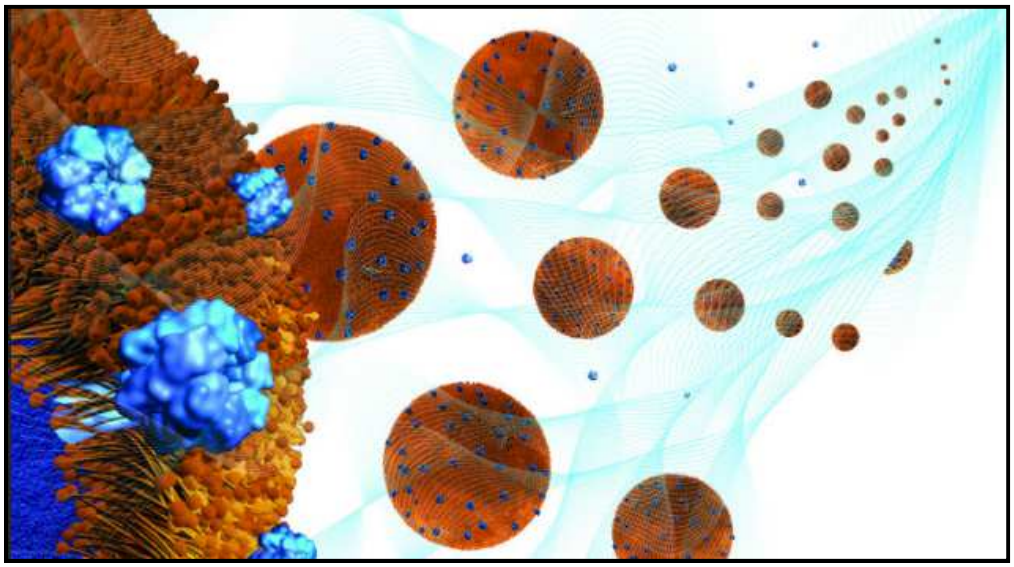
were prepared, which are discrete free flowing nanosized particles with perforated orange peel like morphology as visualized by SEM in the literature[29].

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 and lungs can be accomplished by nanocarriers in order to target viruses that infect the RTI such as respiratory sinctial virus, influenza virus and 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)[30].

More effectiveness than direct injection

Recent research recommended 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. In our body tumor cell when sponges are come and contact with tumour 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[31].



CONCLUSION

Nanosponges carry both hydrophilic and hydrophobic drugs by forming inclusion and non-inclusion complexes and including solubilization, stabilization, and modulation of drug release, cellular internalization, and site targeting. And it is vertasile carrier system. They can deliver drugs by various routes like oral, topical and parenteral in a predictable manner to the target site. Catalysis, among others. Drugs delivered by nanosponges can be proved safe and effective and the pharmaceutical industries will benefit greatly if clinical studies can prove their potential for human use.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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