Review Article www.pharmaresearchlibrary.com/ajmps **ISSN: 2348-0165**

Asian Journal of Medical and Pharmaceutical Sciences

A Recent Approach of Targeted Drug Delivery System: Nanosponges

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Received: 18 April 2014, Accepted: 19 May 2014, Published Online: 19 June 2014

Abstract

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 tiny sponges with a size of about a virus, which can be filled with a wide variety of drugs. These tiny sponges can 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. Because the drug can be released at the specific target site instead of circulating throughout the body it will be more effective for a particular given dosage. 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 objective of the article is to discuss nanosponges with their advantages, method of preparation, characterization, and applications.

Keywords: Nanosponges, Cancer, Polymers, Targeted Drug Delivery

Contents

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Manuscript ID: AJMPS2149

PAPER QR-CODE

1. Introduction

Nowadays, targeting drug delivery is the major problem which is being faced by the researchers. Target oriented drug administration with improvements in therapeutic efficacy, reduction in side effects and optimized dosing regimen, shall be the leading trends in the area of therapeutics. Targeted drug delivery implies for selective and effective localization of pharmacologically active moiety at pre-identified (preselected) 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 [1, 2].

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[3]. 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[2, 4].

The nanosponges are solid in nature and can be formulated as oral, parenteral, topical or inhalational dosage forms. For oral administration, these may be dispersed in a matrix of excipients, diluents, lubricants and anticaking agents which is suitable for the preparation of tablets or capsules. For parenteral administration, these can be simply mixed with sterile water, saline or other aqueous solutions. For topical administration, they can be effectively incorporated into topical hydrogel[3, 5].

Advantages:

a. 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.
b. Less harmful side effects (since smaller quantities of the drug have contact with healthy tissue).
c. Biodegradable.
d. Predictable release.
e. Targeted site specific drug delivery.
f. Can be used to mask unpleasant flavours and to convert liquid substances to solids.
g. Production through fairly simple chemistry called "click chemistry" (methods for making the nanosponge particles and for attaching the linkers).
h. Particles can be made smaller or larger by varying the proportion of cross-linker to polymer.
i. Easy scale-up for commercial production.
j. The material used in this system can provide a protective barrier that shields the drug from premature destruction within the body.
k. The drug profiles can be tailored from fast, medium to slow release, preventing over- or under-dosing of the therapy[1, 6, 7].

Polymers used in Nanosponge Preparation

There are various polymers, copolymers and cross linkers are used in the preparation of nanosponges.

A. Polymers: Hyper cross linked Polystyrenes, Cyclodextrines and its derivatives like Alkyloxycarbonyl Cyclodextrins, Methyl β-Cyclodextrin, Hydroxy Propyl β-Cyclodextrins.
B. Copolymers: Poly (valerolactone allylvalerolactone), Poly (valerolactone-allylvalerolactone oxepanedione), Ethyl Cellulose, Poly vinyl alcohol.
C. Cross linkers: Carbonyl diimidazoles, Carboxylic acid dianhydrides, Diarylcarbonates, Dichloromethane, Diisocyanates, Diphenyl Carbonate, Epichloridine, Gluteraldehyde, Pyromellitic anhydride, 2,2-bis (acrylamido) Acetic acid [4, 8].

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 10°C. Then allow this solution to cool at room temperature. 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 [2, 9].

Emulsion Solvent Diffusion Method

Nanosponges can be prepared by using ethyl cellulose (EC) and polyvinyl alcohol (PVA). 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 40°C for 24 hours [6, 10].

Ultrasound- Assisted Synthesis

In this method, polymers react with cross- linkers in absence of solvent and under sonication. Here, mix the polymer and cross- linker in a flask. Place the flask in an ultrasound bath filled with water and heat it to 90°C and sonicate for 5 hours. Allow it to cool and wash with water to remove the unreacted polymer. Purify by prolonged soxhlet extraction with ethanol. Dry the product under vacuum and store at 25°C [2, 11].

From Hyper Cross- Linked B- Cyclodextrins

Here, β- cyclodextrin (β- CD) can be used as carrier for drug delivery. Nanosponges can be obtained by reacting cyclodextrin with a cross- linker. Nanosponges can be synthesized in neutral or acid forms. The average diameter of a Nanosponge is below 1 μm but fractions below 500 nm can be selected [5, 7].

Evaluation of Nanosponges[3, 12-14]

1. **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).
2. **Particle Size Determination**
   The particle size of Nanosponge is an important criteria in the optimization process. Particle size can be determined by laser light diffractometry or Zeta sizer. Cumulative percentage drug release from nanosponges of different particle size can be plotted against time to study effect of particle size on drug release. Particle size larger than 30 m can show gritty feeling and particle size range from 10 –25 m can be preferred for topical drug delivery.
3. **Zeta Potential**
4. Zeta potential is a measure of surface charge. The surface charge of Nanosponge can be determined by using Zeta sizer.
5. **Microscopy Studies**
   Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) can be used to study the microscopic aspects of the nanosponges. The morphology of nanosponges can be determined by SEM analysis.
6. **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.
7. **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.
8. **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.
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. Also, USP II can be used in many cases depending upon the formulation.

2. Applications

1. **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. 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 [15, 16].
2. **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. 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 [17].
3. **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 [3, 17].

4. **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 [4, 5, 18].
5. **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 [1, 19].
6. **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 [8, 20].
10. **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 [9, 17].
11. **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, 15].
12. **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 [8,11, 20].
13. **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 [6, 7, 21].

3. Conclusion

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. The nanosponges have the ability to release the drug in a controlled manner to the targeted site. Nanosponge technology offers entrapment of ingredients and thus reduced side effects, improved stability, increases elegance and enhanced formulation flexibility. Thus Nanosponge technology provides site specific drug delivery and prolongs dosage intervals and thus improving patient compliance. Nanosponge drug delivery system has emerged as one of the most promising fields in life science.

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