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Review Article

A Review on Nanosponges

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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 towards overcoming 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. Nanosponges can be referred to as solid porous particles having a capacity to load drugs and other actives into their nanocavity; they can be formulated as oral, parenteral, topical or inhalation dosage forms. 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. Another important character of these sponges is their aqueous solubility; this allows the use of these systems effectively for drugs with poor solubility. In this, application of nanosponges, methods of preparation, evaluation parameter have been discussed.

Key words: Nanosponges; Nanocavity; Inhalation dosage forms

INTRODUCTION

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 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. [1] Nanosponges are tiny mesh-like structures that may revolutionize 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] The nanosponge is about the size of a virus with a 'backbone' (a scaffold structure) of naturally degradable polyester. The long length polyester strands are mixed in solution with small molecules

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called cross-linkers that have an affinity for certain portions of the polyester. They 'cross link' segments of the polyester to form a spherical shape that has many pockets (orcavities) where drugs can be stored. The polyester is predictably biodegradable, which means that when it breaks up in the body, the drug can be released on a known schedule. [2] The nanosponges are encapsulating type of nanoparticles which encapsulates the drug molecules within its core. By the method of associating with drugs, the nanoparticles can be classified into encapsulating nanoparticles, complexing nanoparticles and conjugating nanoparticles. The first type is represented by nanosponges and Nanocapsules. Nanosponges such as alginate nanosponge, which are sponge like nanoparticles containing many holes that carry the drug molecules. Nanocapsules such as poly (isobutyl-cyanoacrylate) (IBCA) are also encapsulating nanoparticles. They can entrap drug molecules in their aqueous core. The second category is Complexing nanoparticle, which attracts the molecules by electrostatic charges. The third type is Conjugating nanoparticle, which links to drugs through covalent bonds. [3] These nanosponges represent a novel class of nanoparticles usually obtained by natural derivatives. As compared to the other nanoparticles, they are insoluble both in water and organic solvents, porous, non-toxic and stable at high temperatures up to 300°C. They are able to capture, transport and selectively release a huge variety of substances because of their 3D structure containing cavities of nanometric size and tunable polarity. Furthermore, nanosponges show a remarkableadvantage in comparison with the common nanoparticles: indeed, they can be easily regenerated by different treatments, such as washing with eco-compatible solvents, stripping with moderately inert hot gases, mild heating, or changing pH or ionic strength. For all these characteristics, nanosponges have been already employed in different applied fields, such as cosmetic and pharmaceutical sectors. [4] Nanosponges can be used as a vessel for pharmaceutical principles to improve aqueous solubility of lipophilic drugs, to protect degradable molecules and to formulate drug delivery systems for various administration routes besides the oral one. The simple chemistry of polymers and cross linkers does not pose many problems in the preparation and this technology can be easily ramp up to commercial production levels. Nanosponges are water soluble but does not breakup chemically in water. They mix with water and use as a transport fluid. They can be used to mask unpleasant flavours, to convert liquid substances to solids. The chemical linkers enable the nanosponges to bind preferentially to the target site. The main disadvantage of these nanosponges is their ability to include only small molecules. 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 nanosponges can be synthesized to be of specific size and to release drugs over time by varying the proportion of cross linker to polymer. The engineering capacity of nanosponge is due to the relatively simple chemistry of its polyesters and cross-linking peptides, compared to many other nanoscale drug delivery systems. [2] These nanosponges can be magnetized when they are prepared in the presence of compounds having magnetic properties. [5] The tiny shape of enables the pulmonary and venous delivery of nanosponges. [1] The lists of polymers and cross linking agents used for the synthesis of nanosponges Chemicals used for the synthesis of nanosponges

Polymers

Hyper cross-linked Polystyrenes, Cyclodextrins and its derivatives like Methyl β-Cyclodextrin, Alkyloxycarbonyl Cyclodextrins, 2-Hydroxy Propyl βCyclodextrins and

Copolymers

likePoly(valerolactoneallylvalerolactone)& Poly(valerolactoneallylvalerolactoneoxepanedione) and Ethyl Cellulose & PVA Cross linkers Diphenyl Carbonate, Diarylcarbonates, Diisocyanates, Pyromellitic anhydride, Carbonyldiimidazoles, Epichloridrine, Glutarldehyde, Carboxylic acid dianhydrides, 2,2bis(acrylamido) Acetic acid and Dichloromethane Advantages of Nanosponges Improve aqueous solubility of lipophilic drug.

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 crosslinking peptides. [6,7]

Characteristic Features of Nanosponges

Nanosponges exhibit a range of dimensions (1 μm 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.[9] 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.[10] They are nontoxic, porous particles insoluble in most organic solvents and stable at high temperatures up to 300 °C.[11] Nanosponges as formulations are stable over the pH range of 1 to 11 and temperature up to 130 °C.[12]

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.[13] 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 preferentially to the target site. They form inclusion and non-inclusion complexes with different drugs.[14] Magnetic properties can be also imparted to nanosponges.

Composition of Nanosponges

Polymer: The selection of polymer can influence the formation along with the performance of Nano sponges. The cavity size must be suitable to incorporate the particular drug molecule. The polymer selection is based upon the required release and drug to be enclosed. The selected polymer should have the property to attach with specific ligands. [15]

Cross linking agent

The cross linking agent selection can be carried out depending upon the structure of polymer and the drug which is to be formulated. The different examples include Diphenyl carbonate, Dichloromethane, Diaryl carbonates, Diisocyanates.

Drug substance

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

METHOD OF PREPARATION

Nanosponges made from hyper cross-linked β-cyclodextrins

Nanosponges are made from materials that make non-porous molecules that are carriers called cyclodextrins for drug release. These cyclodextrins are a hyper-cross-linking agents that forms a numerous networks in nano networks, or can be even a spherical shaped with many networks of protein channels, pores etc. These cross linkers stabilizes the sponge with specific surface charge density, porosity and pore sizes based on the molecules contained in them. The cross linkers help to retain the Nano sponges at different acidic and even

Emulsion solvent method

The main polymers used in this method are ethyl cellulose and polyvinyl alcohol in varying proportions. The dispersed phase is formed by adding ethyl cellulose and the available drug which is dissolved in 20ml of dichloromethane. The drop wise addition of continuous phase is by prepared by dissolving polyvinyl alcohol in 150 ml of distilled water. Then the mixture is allowed to stir for 1000rpm for about 2 hrs. The obtained Nano sponges are collected, filtered and dried in oven for around 1 day and stored in desiccators. [17]

Solvent used method

The above used polymer can be used along with some suitable polar aprotic solvent such as Dimethylformamide, dimethylsulfoxide and mix proportionally. Then to this mixture, cross-linkers available are added with a ratio of 4: 16. A temperature is maintained from 10°C for reaction of polymers for 2 days. Most of the carbonyl cross linkers (Dimethyl carbonate and Carbonyl diimidazole) are used. After the reaction is complete the product kept to cool at room temperature, then add the mixture with distilled water for recovering and filtered under air oven and purification is done by soxhchlet apparatus added with ethanol for further extraction. Again go for drying under vacuum and powdered mechanically to get a homogeneous white powder. [18]

Ultrasound-assisted synthesis

In this procedure Nano sponges can be obtained by using polymers with carbonyl cross linkers in the absence of solvent and kept for sonication. These developed Nano sponges will have uniform spherical dimension .Mix the polymer and the cross-linker in a sufficient quantity and is taken in a flask. The flask is filled with water and heats it to 90°C for ultrasonication. The mixture is kept for 5 hours for continuous sonication. Then the mixture is cooled and washed the product with distilled water and allowed to purify it with soxhchlet extractor using ethanol. The final product obtained is dried at 25˚c and whitish powder is collected and store from humidity.

Loading of drug into nanosponge

The nanosponges formulated for the drug delivery first of all should be pretreated to obtain a mean particle size below 500nm. The nanosponges are then suspended in water for some time and subjected to sonication so as to avoid the formation

of aggregates. The obtained product suspension is subjected to centrifugation to obtain a colloidal fraction. The obtained product supernatant is separated and sample is dried by freeze drying. [20] In other way a nanosponge aqueous suspension is prepared and dispersed it with constant stirring for a specific period of time. The nanosponge solid crystals are obtained by the solvent evaporation or either by freeze drying. The nanosponge crystal structure plays a very important rule in the complexation with the drug. The drug loading is high in crystalline nanosponge than the paracrystalline one. In nanosponges which contain poor crystalline structure the drug loading occurs as a mechanical mixture rather than forming inclusion complex.

Factors Influencing Nanosponge Formulation

Type of polymer The formation as well as the performance of nanosponge depends upon the selection of suitable polymer. The cavity or pore size of the nanosponge should be able to accommodate the drug molecule of suitable size. [22]

Type of drug

The molecular weight must be between 100 to 400 Daltons. The drug molecule structure should contain no morethan five condensed rings. The solubility in water should be less than 10 mg/ml. The melting point should be less than 250 °C. [22]

Temperature

The change in temperature can affect the drug complexation. The increase in the temperature decreases the magnitude of the apparent stability of the nanosponge complex which may occur due to possible reduction of drug nanosponge interaction forces, Vander Waals force and hydrophobic forces with rise of temperature. [23]

Applications of Nanosponges

Due to their biocompatibility and versatility, nanosponges have many applications relating the pharmaceutical field. Nanosponges can be used as excipients in preparation of tablets, capsules, pellets, granules, suspension, solid dispersion or topical dosage forms.

Nanosponges as a sustained delivery system

Acyclovir is one of the widely used antiviral agents for the treatment of herpes simplex virus infection. Its absorption in the GIT is slow and incomplete and highly variable. The in vitro release profile of the acyclovir from different types of Nano sponges showed sustained release of the drug. The percentage release of acyclovir from carb-nanosponges and nanosponges after the 3 h of administration were about 22% and 70%. The drug was not adsorbed on the nanosponge surface since no initial burst effect was not observed. [25, 26]

Nanosponges in solubility enhancement

Itraconazole is a BCS class II drug which has a dissolution rate limited poor bioavailability. Thus the application of nanosponges improved the solubility of the drug more than 27- fold. The solubility was found to be exceeded to 55fold, when copolyvidonum was added as a Supporting component. Either by masking the hydrophobic groups of itraconazole, by increasing the wetting ‘of the drug or by decreasing the crystallinity of the drug nanosponges improve the solubility of the drug. [27]

Nanosponges in drug delivery

Nanosponges can be formulated by different dosage form like topical, parenteral, aerosol, tablet and capsules. Telmisartan (TEL) is a class II drug with dissolution rate limited bioavailability. TEL was incorporated in nanosponge formulation. The saturation solubility and vitro dissolution of β-CD complex of TEL was compared with plain TEL and the nanosponge complexes of TEL. The highest solubility and in vitro drug release was observed in inclusion complexes prepared from nanosponge and NaHCO3. Paclitaxel is an anticancer drug with poor water solubility. β- CD based nanosponges are an alternative to classical formulation in cremophor because cremophor reduces the paclitaxel tissue penetration. The biological effect of paclitaxel in vitro is highly enhanced by nanosponge formulation. Econazole nitrate is an antifungal agent used for skin infections and dermatophytosis. Adsorption is not significant when econazole is applied to skin. Thus econazole nitrate nanosponges is made up by solvent diffusion method and loaded as hydrogel form. [28]

Nanosponges in enzyme immobilization

Nanosponges have been widely used for stabilizing the enzyme. CD-NS show much higher inclusion constants as compared to CD and is suitable to support for enzyme immobilization. They help to preserve the catalytic proficiency and stability of the immobilized enzymes. Enzyme immobilization is important for enzyme recycling and facilitates the separation and recovery of the formed products along with its increased thermal and operational stability of the biocatalysts. Boscolo et al. also studied about the high catalytic performance of some pseudomonas flurescens lipases adsorbed on cyclodextrin – based nanosponge. Lipases are widely used for catalyzing the hydrolysis of triacylglucerols and trans esterification reactions which are involved in a number of industrial applications. [29]

Nanosponges for protein deliver

A major barrier in the protein formulation development is the maintenance of the original protein structure both during the formulation

process and upon long term storage. Swaminathan et al studied about new swellable cyclodextrin based poly nanosponges. Through water uptake studies they observed very good swelling capacity stable for 72 hrs. Bovine serum albumin was used as a model protein and is incorporated into the prepared nanosponge. Enhanced swelling property along with increased stability of protein was observed. At physiological pH, the lactone ring opens up and develops inactive carboxylate form. The fusion of camptothecin in nanosponges lead to a prolonged release profile in an active form which hinders the hydrolysis of the lactone form and resulting enhanced stability. [30]

Nanosponges as protective agent from light or degradation

The Gamma–oryzanol can be encapsulated in the form of nanosponge which shows a good protection from the photodegrdation. Gamma oryzanol is a ferulic acid mixture which is a natural antioxidant and mainly used to stabilize the food and pharmaceutical raw materials. Its application is limited because of its high instability and photogegradation [31] Nanosponges as a carrier for biocatalyst Nanosponges act as carrier for the delivery of enzymes, vaccines, proteins and antibodies for diagnosis purpose. Proteins and other macromolecule are adsorbed and encapsulated in cyclodextrin nanosponge [32]

Nanosponges as gas delivery system

The deficiency of adequate oxygen supply named hypoxia, is related to various pathologies from inflammation to cancer. Cavalli et al developed a nanosponge formulation for oxygen delivery through a topical application. Safety of nanosponge was studied in vero cells. Oxygen penetration through a silicone membrane was studied using a CD –NS hydrogel combination system. Trotta et al. reported CD-NS prepared using carbonildiimidazole cross –linker for encapsulation of 1- methylcyclopropene, oxygen and carbon dioxide. [33

Evaluation of Nanosponges

Microscopic studies

To study the microscopic aspects of a drug, Nano sponge, or the product it can be subjected to Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM). The difference in the crystallization state indicates the formation of inclusion complexes. [24]

Loading efficiency

It can be determined by quantitative estimation of the drug which is loaded into the nanosponge using either by UV spectrophotometer or HPLC method. The loading efficiency can be calculated by [25]

Solubility studies

The most frequently used method includes phase solubility method described by Higuchi and Connors which helps to determine the effects of nanosponge upon the solubility of the drug. The degree of complexation was indicated by phase solubility diagram. [26]

X ray diffraction studies

For the solid state, powder X ray diffractiometry can be used to determine the inclusion complexation. When the drug molecule is liquid and liquid have 0 diffraction pattern of their own the diffraction pattern of a newly formed substance clearly differs from that of uncomplexed nanosponge. This difference in the 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 complex and that of mechanical mixture of the drug and polymer molecules. A diffraction pattern of 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. The complex formation of drug with nanosponge alters the diffraction pattern and also changes the crystalline nature of the drug. The complex formation leads to sharpening of the existing peaks and shifting of certain peaks. [27]

Single crystal x ray structure analysis

Single crystal x ray structure analysis is used to determine the detailed inclusion structure and mode of interaction. The interaction between the host and guest can be identified and precise geometrical relationship can be established. [28]

Infra – red spectroscopy

This spectroscopy method is mainly used to estimate the interaction between nanosponge and drug molecule in the solid state. Upon the complex formation nanosponge bands are tend to change often and if the fraction of 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 spectrum of nanosponges. The application of infra-red spectroscopy is limited to drugs having characteristic bands such as carbonyl or sulfonyl group. Infra-red spectral studies give information regarding the involvement of hydrogen in various functional groups. [29]

Thin layer chromatography

The RF values of the drug molecule diminish to considerable extend in thin layer chromatography and this helps in identifying the complex formation between the drug and nanosponge formulation. [30]

Particle size and polydispersity

The particle size of a nanosponge formulation can be determined by dynamic light scattering using 90 plus particle sizer equipped with MAS OPTION particle sizing software. From the data obtained mean diameter and polydispersity index can be determined. [31]

Zeta potential

Zeta potential is measured to find the surface charge. It can be measured by using additional electrode in particle size equipment. [32]

Production yield

The production yield can be determined by calculating initial weight of raw materials and final weight of nanosponges. [33]

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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