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Nanosponges: Novel Approach for Controlled Release Drug Delivery System

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ABSTRACT

For effective controlled drug delivery system nanosponges has shown significant approach Nanosponge is a novel and emerging technology which plays a vital role in targeting drug delivery in a controlled manner. Nanosponges are tiny sponges having size of about a virus and can easily penetrate through skin. Tiny sponges circulate around the body until they reach to specific target site and stick on the surface and start to release drug in controlled manner drug release at specific site instead of circulating overall body it is more effective for targeted drug delivery system they enhance bioavailability, solubility and reduces side effects. Nanosponges prevent drug and protein degradation. Both lipophilic and hydrophilic drugs are incorporated in Nanosponge. Nanosponges are capable of providing solutions for several formulation related Problems.The objective of this review article is to provide brief knowledge of nanosponges, its advantages and disadvantages, its method of preparation, evaluation and applications.

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INTRODUCTION

Nanosponges are novel class of hyper-cross linked polymer based colloidal structures consisting of solid nanoparticles with colloidal sizes and nanosized cavities. Nanosponge is a novel and emerging technology which plays a vital role in targeting drug delivery in a controlled manner the system, known as "nanosponges," uses a nanoparticles-sized system to deliver the drug payload. Nanosponges were originally developed for topical delivery of drugs. Nanosponges are tiny sponges with a size of about a virus with an average diameter below 1µm. Nanosponges are tiny sponges with a size of about a virus with an average diameter below 1µm. They cross-link segments of the polyester to form a spherical shape that has many pockets/cavities where drug can be stored. Filling them with drugs and attaching special chemical linkers that bind preferentially to the features found only on the surface of tumor cells these tiny sponges can circulate around the body until they encounter the specific target site and stick on the surface and began 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. They can be used for targeting drugs to specific sites, prevent drug and protein degradation. However, only a few nano-preparations, like abraxane, have reached the market. Proteins, peptides, genes, anti-cancer agents and biomolecules have been loaded in nanoparticulate delivery systems and are widely studied so that the unwanted effects may be lowered and efficacy may be improved. The polyester is biodegradable, so it breaks down gradually in the body. The Nanoscale materials are small enough to be effective in attaching to or passing through cell membranes as compared to other nanoparticles, nanosponges are porous, non-toxic and stable at high temperatures up to 300^{o}C.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. Releases its drug payload in a predictable fashion. For topical administration, they can be effectively incorporated into topical hydrogel. The dimensions of nanosponges in nanometric form improve drugs bioavailability and modify pharmacokinetic parameters. Nanosponges are encapsulating types of nanoparticles which encapsulate drug molecule within a core by method of association with drug nanoparticles can be classified into encapsulating nanoparticle, complexing nanoparticles, conjugating nanoparticles. Great advantage of nanosponges over nanoparticle is, former can be easily regenerated by different treatments e.g. washing with eco-compatible solvents tripping with moderately inert glasses. [1, 2, 3]

Advantages [1, 2, 3, 4,5]

1. Targeted site specific drug delivery.

2. Used to mask unpleasant flavors and to convert liquid substances to solids.

3. Less harmful side effects since smaller quantities of the drug come in contact with healthy tissues.

4. Compatible with most vehicles and ingredients. 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 the polymer.

6. Production through fairly simple chemistry called "click chemistry" (methods for making the nanosponges 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.

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

10. Improved stability, increased elegance and enhanced formulation flexibility.

11. Enhances solubility of poorly soluble drug.

12. Nanosponges systems are non-irritating, non-mutagenic, non-allergenic and non-toxic.

13. These formulations are stable over range of pH 1 to 11.

14. These formulations are stable at the temperature up to 130^0C.

15. These are self-sterilizing as their average pore size is 0.25µm, where bacteria cannot penetrate.

16. Extended release - continuous action up to 12 h.

17. Biodegradable.

Disadvantages [6]

1) Nanosponges include only small molecules.

2) Depend only upon loading capacities

MECHANISM OF DRUG RELEASE [5]

The sponge particles have an open structure and the action is free to move in and out from the particles and into the vehicle until equilibrium is reached. In case of topical delivery, once the finished product is applied to the skin, the active that is already in the vehicle will be absorbed into the skin, depleting the vehicle, which will become unsaturated, therefore disturbing the equilibrium. This will start a flow of the action from the sponge particle into the vehicle and from it to the skin until the vehicle is either dried or absorbed. Even after that the sponge particles retained on the surface of stratum corneum will continue to gradually release the active to the skin, providing prolonged release over time

POLYMERS USED IN PREPARATION OF NANOSPONGES [1,4]

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

A. Polymers: Hyper cross-linked Polystyrenes, Cyclodextrins and its derivatives like AlkyloxycarbonylCyclodextrins, Methyl β-Cyclodextrin, Hydroxy Propyl β-Cyclodextrins.

B. Copolymers: Poly (valerolactoneallylvalerolactone), Poly (valerolactone-allylvalerolactoneoxepanedione), Ethyl Cellulose, Polyvinyl alcohol.

C. Crosslinkers: Carbonyl diimidazoles, Carboxylic acid dianhydrides, Diaryl carbonates, Dichloromethane.Diisocyanates, Diphenyl Carbonate, Epichloridine, Glutaraldehyde, Pyromellitic anhydride, 2,2-bis (acrylamido) Acetic acid

PREPARATION OF NANOSPONGE [1, 2, 3]

a. Emulsion solvent diffusion method

Nanosponges prepared by using different proportion of ethyl cellulose and polyvinyl alcohol. The dispersed phase containing ethyl cellulose and drug is dissolved in 20 ml dichloromethane and definite amount of polyvinyl alcohol is slowly added in 150ml of aqueous continuous phase. The reaction mixture is then stirred at 1000 rpm for 2 hrs. The nanosponges formed is collected by filtration and dried in an oven at 40ºC for 24 hrs. The dried nanosponges were stored in vacuum desiccators to ensure the removal of residual solvent.

b. Nanosponges prepared from hyper cross-linked cyclodextrins

In the melt method, the crosslinker is melt along with CDs. All ingredients are finely homogenized and placed in a 250 ml flask heated at 100°C and the reaction is carried out for 5 hrs under magnetic stirring. The reaction mixture is allowed to cool and the obtained product is broken down followed by repeated washing with suitable solvents to remove unreacted excipients and byproducts.

In the solvent method, the melting step is eliminated and the crosslinker is solubilized in solvents like dimethylformamide or dimethylsulfoxide (DMF/DMSO). The polymer is generally mixed with a suitable solvent, particularly polar aprotic solvent, followed by addition of this mixture to an excess quantity of the crosslinker. Optimization of the process is performed by varying the crosslinker/polymer molar ratio. The reaction is carried out at temperatures ranging from 10°C to the reflux temperature of the solvent, for 1 to 48 hrs. Preferred crosslinkers for this reaction are the carbonyl compounds diphenyl carbonate (DPC), dimethyl carbonate (DMC) or carbonyl diimidazole (CDI). The product is obtained by adding the cooled solution to a large excess of bi-distilled water. Recovery of the product is done by filtration under vacuum and the product is further purified by prolonged Soxhlet extraction.

c. Ultrasound- Assisted Synthesis

In this method, polymers react with cross- linkers in absence of solvent and under sonication. Here, polymer and cross- linker are mixed in a flask. Flask is placed in an ultrasound bath filled with water and heat it to 90^{o}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 stored at 25^{o}C.

FACTORS INFLUENCING NANOSPONGES FORMATION [1, 2]

1. Type of Polymer

Type of polymer used can influence the formation as well as the performance of nanosponges. For complexation, the cavity size of nanosponges should be suitable to accommodate a drug molecule of particular size.

2. Type of Drug

Drug molecules to be complexed with nanosponges should have certain characteristics as mentioned below.

- ✓ Molecular weight of drug should be in between 100 to 400 Daltons.
- ✓ The structure of the drug molecule should contain not more than five condensed rings.
- ✓ Solubility in water should be less than 10 mg/ml.
- ✓ Melting point of the substance should be less than 250°C.

3. Temperature

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

4. 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 be most effective method for drug complexation.

5. Degree of Substitution

The complexation ability of the nanosponges may be greatly affected by type, number and position of the substituentOn the parent molecule.

6. Loading of Drug into Nanosponges

Nanosponges for drug delivery should be pre-treated to obtain a mean particle size below 500 nm. Nanosponges are suspended in water and sonicated to avoid the presence of aggregates and then suspension centrifuged to obtain the colloidal fraction. Supernatant is separated and sample is dried by freeze drying. Another way, an aqueous suspension of nanosponges is prepared and an excess amount of drug is dispersed in it with constant stirring for specific time required for complexation. After complexation, the uncomplexed (undissolved) drug from complexed drug separated by centrifugation. Then solid crystals of nanosponges are obtained by solvent evaporation or by freeze drying. The crystal structure of nanosponges 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.

EVALUATION OF NANOSPONGES [4, 7]

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

Solubility Studies

The most widely used approach to study inclusion complex 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. In the solubility studies changes in solubility of the guest are plotted as a function of the cyclodextrins concentration, if the solubility of a potential guest increases with increasing cyclodextrin concentration; complex formation in solution is indicated. Solubility studies were performed to evaluate the drug pH solubilization profile and to assess the effect of multi-component complexation on drug solubility.

Particle Size and Polydispersity

The particle size can be determined by Dynamic Light Scattering Instrument (DLSI) equipped with particle sizing software. From this, the mean diameter and Polydispersity

Index (PDI) can be determined. PDI is an index width or spread or variation within the particle size distribution. Mono-dispersed samples have a lower PDI value, whereas higher value of PDI indicates a wider particle size distribution and the poly-dispersed nature of the sample.

The particle size can also be determined by Scanning Electron Microscopy (SEM), Transmission ElectronMicroscopy (TEM), Atomic Force Microscopy (AFM) and Freeze-Fracture Electron Microscopy (FFEM).

Zeta Potential

Zeta potential is a measure of surface charge. It can be measured by using additional electrode in the particle size equipment. Also, laser Doppler anemometry, zeta potential meter can be used.

Microscopy Studies

Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) can be used to study morphology, surface topography and microscopic aspects of the drug, nanosponges and the product (drug/nanosponges complex). The difference in crystallization state of the raw materials and the product seen under electron microscope indicates formation of the inclusion complexes, even if there is a clear difference in crystallization state of the raw material and the product obtained by co-precipitation.

Thin Layer Chromatography

In Thin Layer Chromatography (TLC), the Rf values of a drug molecule diminish to considerable extent and this helps in identifying the complex formation between the drug and nanosponges. Inclusion complexation between guest and host molecules is a reversible process. Consequently, the complex may separate completely in guest and host molecules during the chromatographic process and only the spots of the guest and host molecules are found on the TLC-plate.

Infra-Red Spectroscopy

Infra-Red spectroscopy is used to estimate the interaction between nanosponges and the drug molecules in the solid state. 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.

Analytical Methods

Thermoanalytical methods determine whether drug substance undergoes some change before the thermal degradation of the nanosponges. The change of the drug substance may be melting, evaporation, decomposition.

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 has no diffraction pattern of their own) the diffraction pattern of a newly formed substance clearly differs from that of uncomplexed nanosponges. 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.

The complex formation of drug with nanosponges 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.

Single Crystal X-ray Structure Analysis

This method 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. This information obtained from the analysis leads to know about the formation of inclusion complexes.

Loading Efficiency and Production Yield

The loading efficiency (%) of nanosponges can be determined by the quantitative estimation of drug loaded into nanosponges by UV spectrophotometer, HPLC methods and calculations according to the following equation:

Loading Efficiency = Actual drug content in nanosponge/ Theoretical drug content × 100

The production yield of the nanosponges can be determined by calculating accurately the initial weight of the raw materials and the final weight of the nanosponge obtained.

Photo-degradation Study

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

***In-vitro* Drug Release**

Drug release from the nanosponges can be measured across the dialysis membrane using Franz Diffusion Cell. The dialysis membrane soaked in receptor medium for 8 hrs is used as a barrier between the donor and receptor compartment. A one gram Nanosponge is placed on the membrane surface in the donor compartment that is sealed from the atmosphere with aluminum foil. The receptor compartment is filled with specific volume of phosphate buffer of suitable pH (6.8 skin pH). During the experiment, the solution of receptor side compartment is kept at

37±0.5^{o}C and stirred at 100 rpm with Teflon-coated magnetic stirring bars. Aliquots are collected from the receptor compartment at designated time intervals and replaced by the same volume of fresh receptor solution to maintain sink condition and constant volume. The sample is analyzed using UV-spectrophotometer. Even, USP type II dissolution apparatus can be used in many cases depending upon the formulation.

Drug Release Kinetics

To investigate the mechanism of drug release from nanosponge the release data could be analyzed using Zero order, First order, Higuchi, Peppas, Hixon-Crowell, Kopcha and Makoid-Banakar etc. models. The data can be analyzed using graph pad prism software. The

software estimates the parameters of a non-linear function that provides the closest fit between experimental observations and non-linear function.

Resiliency

Resiliency (viscoelastic properties) of sponges can be modified to produce beadlets that are softer or former according to the need of final formulation. Increased crosslinking tends to slow down the rate of release. Hence resiliency of sponges will be studied and optimized as per the requirement by considering release as a function of cross-linking with time.

True Density

True density of nanosponges can be determined using an ultra-pycnometer under helium gas.

DRUGS REPORTED TO BE BEST SUITABLE IN NANOSPONGE FORMULATION [7]

1. Doxorubicin Ns complex2 drug formulation is a controlled drug delivery system. It is cross-linked by cross-linking _-cd with diphenyl carbonate and encapsulated by incubation followed by lyophilization.

2. Dexamethasone and flurbiprofen2 drug formulations have enhanced drug solubility, and they are crosslinked using linking _-cd with diphenyl carbonate and encapsulated by incubation followed by lyophilization.

3. Carbamazepine, nelfinavir, oxcarbazepine, and danazol 16 drug formulations have enhanced drug solubility. And are crosses linked using dimethyl carbamate and encapsulated by incubation followed by lyophilization.

4. Itraconazole drug formulation enhances drug solubility by use of ternary complexation. It is cross-linked by carbamate and encapsulated by incubation followed by lyophilization and drying. Ternary component used is copolyvidinum.

5. Camptothecin formulation has enhanced drug stability, cytotoxicity and controlled release and it is cross-linked by linking _-cd with diphenyl carbonate and encapsulated by incubation followed by lyophilization.

6. Resveratrol13 drug formulation has enhanced drug stability, cytotoxicity and controlled release. And it is cross-linked by _-cd with carbonyl diimidazole and encapsulated by incubation followed by lyophilization.

7. Tamoxifen11 drug formulation has enhanced bioavailability and solubility. And it is cross-linked by cd with carbonyl diimidazole and encapsulated by incubation followed by lyophilization

8. Curcumin12 drug formulation has enhanced activity and solubilization. It is cross-linked by carbamate.

APPLICATIONS OF NANOSPONGES[1, 3, 5, 6, 7]

1) Nanosponges as chemical sensor

Nanosponges which are the type of "metal oxides" act as a chemical sensor which is used in highly sensitive detection of hydrogen using nanosponge titania. Nanosponge structure initially has no point of contact so there is less hindrance to electron transport and it results in higher 3D interconnect nanosponges titania which is sensitive to H2 gas.

2) Nanosponge for oral delivery

In oral application, it forms the nanosponge system consists of pores which increase the rate of solubilization of poorly water-soluble drugs which get entrapped the drug in pores. The surface area is increased due to nano size form and increase rate of solubilization.

3) Solubility enhancement

β-cyclodextrin based nanosponges of itraconazole have enhanced solubility of poorly soluble drug. The solubility increased by 50 folds compared to ternary dispersion system. e.g. copolyvidonum.

4) Nanosponges as a carrier for biocatalysts

Nanosponges as a carrier for biocatalysts and release of enzymes, proteins, vaccines and antibodies. It includes the process applied in industry which correlates with operational condition. Reactions which are not specific give rise to low yields and require high temperatures and pressures which consume large amount of energy and cooling water in

downstream process. This is the drawbacks can be removed by using enzymes as biocatalysts as this operate under high reaction speed, mild condition.

5) Antiviral application

Nanosponges used in nasal, pulmonary route of administration. It provides specificity to deliver antiviral drug on RNA to lungs or nasal route through nanocarriers for targeting virus which may cause infection to RTI such as influenza virus, rhinovirus. Drugs used as nanocarriers are- Zidovudine, Saquinavir.

6) Cancer

Targeting drug to specific site avoiding the obstacle created by immune system. Different cancer cells had been treated by nanosponges like breast cancer or fast acting glioma type with help of single dose of injections.Oxygen Delivery System Characterized by using α, β and ϒ cyclodextrins and this are suspended in water and get saturated with water. A silicone form of membrane can also be used for oxygen permeation with the help of nanosponge/ hydrogel system. They can also apply it to hypoxic tissues caused in various type of diseases.

Other Applications

7) Biomedical Applications

Cyclodextrin based carbonate nanosponges were used to form inclusion complexes with three different gases i.e. methyl cyclopropane, oxygen and carbon dioxide. The complexation of oxygen or carbon dioxide could be used for many biomedical applications. In particular, the oxygen filled nanosponges could supply oxygen to the hypoxic tissues which are present in various diseases. Nanosponges can selectively soak up biomarkers for the diagnosis. One study concluded that nanosponges can harvest rare cancer marker from blood.

8) Analytical Applications

The microporous hyper cross-linked nanosponges have been used in selective preparation of inorganic electrolytes by size exclusion chromatography. The three dimensional nanosponges will play important role in the fractionalization of peptides for proteomic applications.

9) For Hydrogen Storage

Hydrogen is considered as an alternative energy for the future, but one of the problems to be solved before it achieves the versatility of other fuel sources as oil is how to store it. Recent studies claim to find materials that could act as sponges that absorb hydrogen and store it until ready to use. But until now had not found a material with the capability to store hydrogen under the necessary pressure and temperature. A team of scientists from the Universities of Newcastle and Liverpool has discovered a new class of materials which composed of long carbon chains linked by metal atoms. To crystallize, these molecules form cavities that are less than a nanometer, which is connected by windows" that are even smaller than a molecule of hydrogen. While these cavities are filled, hydrogen fits through the windows, because the carbon chains are flexible. But once filled the cavities, the chains lose their flexibility, thus closing the windows. Consequently, it can be loading the high-pressure hydrogen gas, and when pressure levels drop, forming a sort of molecular size seal. Although so far the materials created by this team of scientists do not have enough capacity for most applications that use fuel cells, their work represents a new approach to the problem and nanosponges could potentially have a key role in the hydrogen storage system in future.

10) In Agriculture

Plants that grow more have a better appearance, what counts is not just the climate, but technology. This is so for functionalized nanosponges (FNS), an agricultural invention that allows plants to grow more and improve their appearance by feeding them with an optimal dosage of micro-nutrients and active ingredients that are necessary for healthy growth. Another notable advantage is that nanosponges allow a significant reduction in the use of herbicides and fertilizers, thereby increasing productivity and improving both the environmental and cultivation quality levels.Nutritive substances (such as iron and zinc), or active ingredients, are encapsulated in the nano-cavities during the synthesis process. The nutritive substances incorporated in the nanosponges are dosed and fed to the plants in a very precise manner, "drop by drop", thereby optimizing photosynthesis. The significant reduction in the use of fertilizers makes their cultivation similar to that of organic products, although production levels are much higher. This means lower production costs and access to healthier food for many more people. For example, FNSs with iron solve one of the most common problems with plants, iron chlorosis (yellowing of leaves), thereby allowing more efficient

photosynthesis conversions and higher plant growth rate. One of the major advantages of this innovative product is the possibility of making ad-hoc formulations for diverse applications.

11) In Floriculture

Nanosponges have been recently developed and proposed for delivering nutrients, preservative and anti-ethylene compounds in order to improve cut off flower life.

12) In Food Industry

Nanosponges are useful for masking, reduction and elimination of bitter components from fruit juices and other dietary products by selective combination of polymer and cross-linker.

13) For Water Purification

Cyclodextrin nanosponges can be used for the removal of organic pollutants from water. β-cyclodextrin nanosponges are completely insoluble in water, have the property of encapsulating organic pollutants from water. Ceramic porous filters can be impregnated with these nanosponges resulting in hybrid organic/inorganic filter modules. These hybrid filter modules were tested for the effective purification of water.

CONCLUSION

Nanosponges are novel class of hyper-cross linked polymer based colloidal structures consisting of solid nanoparticles with colloidal sizes and nanosized cavities. They are small size and porous so easily improves bioavailability of drugs. Nanosponges reduces side effect improves stability, elegance, enhance formulation flexibility. Nanosponges can incorporate many drugs and release it in controlled manner. They are easy to evaluate and having number of applications in many fields.

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