An Elsevier Indexed Journal ISSN-2230-7346

Journal of Global Trends in Pharmaceutical Sciences

NANOSPONGES: A NOVEL DRUG DELIVERY SYSTEM – REVIEW

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ARTICLE INFO

Key Words
Nanosponge, Controlled release, Solubility enhancement, Cyclodextrin

ABSTRACT

Nanosponges are tiny mesh-like structures with a size range of bellow 1µm. Due to their small size and porous structure they can easily bind poorly-soluble drugs, which leads to improve the solubility and ultimately the bioavailability of the same drugs. Both lipophilic and hydrophilic drugs can be loaded into nanosponges. Nanosponges play a major role in targeting drug delivery system. These 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. The nanosponges are solid in nature and can be formulated as oral, parenteral, topical or inhalational dosage forms.In this review article, application of nanosponges, its preparation methods and evaluation parameters have been discussed.

INTRODUCTION

The term "Nanosponge" means the nanoparticles having porous structures. It provides solution for several formulation related problems. Nanosponges are tiny sponges with a size of a virus with an average diameter below 1µm.Owing to their small size and porous nature they can bind poorly- soluble drugs within the matrix and improve their bioavailability by modifying the pharmacokinetic parameters of actives. 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. Nanosponges are used for improvement in dissolution rate, solubility and stability of drugs, masking unpleasant flavors, converting liquid substances to solids and prolonging the release of drug. Nanosponges have emerged as one of the most promising fields of life science because of their application in controlled drug delivery. Nanosponge technology offers entrapment of ingredients and is believed to contribute towards reduced side effects, improved stability, increased elegance and enhanced formulation flexibility. Nanosponges are non-irritating, non-mutagenic, non-allergenic and non-toxic. Nanosponges are a novel class of hyper-cross-linked polymer based colloidal structures consisting of solid nanoparticles with colloidal sizes and nanosized cavities. Nanosponges embraces nanotechnology which is applied to pharmacy as nanomaterials, diagnosing and focusing right place in the body and controlling release of the drug. Nanosponges obtained from natural

derivatives such as alginate provide a 3D structure and because of its selective nature expertise its regenerated properties by following washing with eco-compatible solvents, stripping with inert hot gases, changing pH and ionic strength. Due to their soluble nature they mix with water and utilize transport fluid without breaking up convert liquid substances to solids. The nanosponges are solid in nature and can be formulated as oral, parenteral, topical or inhalational dosage forms. [1]

Characteristics of Nanosponges

- Nanosponges are porous particles having high aqueous solubility, used mainly to encapsulate the poor soluble drugs.
- These Nanosponges are capable of carrying both lipophilic and hydrophilic drugs.
- Nanosponges as formulations are stable over the pH range of 1 to 11 and temperature up to 130 °C.
- Nanosponges are non irritating and non-mutagenic, non-allergic and nontoxic.
- They protect the drug from physicochemical degradation.
- Nano sponges can encapsulate various types of molecules by forming inclusion and non inclusion complexes.
- They are able to remove the organic impurities from water.[1]

Advantages

- It provides improved elegance, stability and formulation flexibility.
- The drug is protected from degradation.
- It is non-mutagenic.
- Non-irritating, non-toxic.
- Improve aqueous solubility of lipophilic drugs.
- In this technology provide entrapment of active contents and side effects are less.
- It can be used to mask unpleasant flavours and to convert liquid substances to solids.
- Nanosponge particles are soluble in water and encapsulation can be done within the nanosponge.
- Nanosponges can significantly reduce the irritation of drugs without reducing their efficacy.
- To improve patient compliance by prolonging dosing intervals.
- Biodegradable.
- Predictable release.
- Easy scale-up for commercial production.[2]

Disadvantages

- Nanosponges include only small molecules.
- Depend only upon loading capacities.[1, 2]

PREPARATION OF NANOSPONGES

Solvent method: Mix the polymer with a suitable solvent, in particular in a polar aprotic solvent such as dimethylformamide, dimethylsulfoxide. Then add this mixture to excess quantity of the cross-linker, preferably in crosslinker/polymer molar ratio of 4 to 16. Carry out the reaction at temperature ranging from 10°C to the reflux temperature of the solvent, for time ranging from 1 to 48h. Preferred crosslinkers are carbonyl compounds (Dimethylcarbonate&Carbonyldiimidazole). After completion of the reaction, allow the solution to cool at room temperature, then add the product to large excess of bid stilled water and recover the product by filtration under vacuum and subsequently purify by prolonged soxhletextraction with ethanol. Dry the product under vacuum and grind in a mechanical mill to obtain homogeneous powder.

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. Mix the polymer and the cross-linker in a particular molar ratio in a flask. Place the flask in an ultrasound bath filled with water and heat it to 90°C. Sonicate the mixture for 5hours. Then allow the mixture to cool and break the product roughly. Wash the product with water to remove the nonreacted polymer and subsequently purify by prolonged soxhlet extraction with ethanol. Dry the obtained product under vacuum and store at 25°C until further use.

Loading of drug into nanosponges

Nanosponges for drug delivery should be pretreated to obtain a mean particle size below 500nm. Suspend the nanosponges 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. 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 uncomplexed (undissolved) drug from complexed drug by centrifugation. Then obtain the solid crystals of nanosponges by solvent evaporation or by freeze drying. [3]

FACTORS INFLUENCING NANOSPONGE FORMATION

Type of polymer

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

Type of drugs

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

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

Temperature: Temperature changes can affect Drug/Nanosponge complexation. In general, increasing in the temperature decreases the magnitude of the apparent stability constant of the Drug/Nanosponge complex may be due to a result of possible reduction of drug/nanosponge interaction forces, such as vanderWaal forces and hydrophobic forces with rise of temperature.

Method of preparation

The method of loading the drug into the nanosponge 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 for drug complexation.

Degree of substitution

The complexation ability of the nanosponge may be greatly affected by type, number and position of the substituent on the parent molecule. [1, 3]

EVALUATION OF NANOSPONGES:

1. Particle size determination: Particle size of the drug can affect the solubility as well as release pattern of the drug. Particle size can be determined by laser light diffractometry or Zeta sizer. Particles larger than 30 microns can impart gritty feeling and hence particles of sizes between 10 and 25 microns are preferred to use in final topical formulation Cumulative percentage drug release from nanosponges of different particle size can be plotted against time to study effect of particle size on drug release.

2. Polydispersibility index (PDI): The polydispersibility index (PDI) is an index of width or spread or variation within the particle size distribution. PDI can be

determined by dynamic light scattering instrument. Suspend the Nanosponges in water ↓ Sonicate to avoid the presence of aggregates ↓ Centrifuge the suspension to obtain the colloidal fractions (10min) ↓ Separate the supernatant & dry the sample by freeze drying ↓ Prepare the aq. suspension of Nanosponges ↓ Disperse excess of drug & maintain the suspension under constant stirring For specific time required for complexation ↓ Separate the uncomplexed (undissolved) drug by centrifugation ↓ Obtained the solid crystals of Nanosponges by solvent evaporation or freeze drying. Monodisperse samples have a lower PDI value, whereas higher PDI value indicates a wider particle size distribution and the polydisperse nature of the sample. PDI can be calculated by following equation: PDI = Δd/d avg Where, d is the width of distribution denoted by SD, and d avg is the average particle size denoted by MV (nm) in particle size data sheet.

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.

4. Zeta potential: Zeta sizer can be used to measure zeta potential, which is the measure of surface charge of Nanosponges. Zeta potential is widely used for quantification of the magnitude of the electrical surface charge at the double layer. The significance 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.

5. 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 adjuvants can be determined by Thin Layer Chromatography (TLC) and Fourier Transform Infra-red Spectroscopy (FT-IR).

6. Solubility studies: Solubility problem affect the performance of the drug.Higuchi and Connors explained the method to study the inclusion complexation known as phase solubility method. This method used to know the effect of Nanosponge on the solubility of drug, which indicates the degree of complexation.

7. Loading Efficiency / Entrapment Efficiency: The weighed amount of drug loaded nanosponges dispersed in suitable solvent and after sonication for specific period of time, diluted suitably. Sonication required to break the complexes. After dilution, it is analyzed by UV spectrophotometer or HPLC method.

8. Production yield: The production yield (PY) can be determined by calculating initial weight of raw materials and final weight of drug loaded nanosponges.

Production Yield = Practical mass of Nanosponge/ Theoretical mass (polymer + drug) X 100

9. Thermo-analytical methods : The most commonly used methods are DSC and DTA to observe the peak broadening, peak shifting and appearance and disappearance of certain peaks with the help of thermogram. These thermo-analytical methods determine whether the drug substance undergoes some change before the thermal degradation of the nanosponge. This degradation may be melting, evaporation, decomposition, oxidation or polymorphic transition. The change of the drug substance indicates the complex formation.

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.

11. X-ray diffractiometry: Powder X-ray diffractometry can be used to detect inclusion complexation in the solid state. The complex formation of drug with nanosponges alters the diffraction patterns and also changes the crystalline nature of the drug. 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. The complex formation leads to the sharpening of the existing peaks, appearance of a few new peaks and shifting of certain peaks.

12. Single Crystal X-Ray Structure Analysis: The detailed inclusion structure and mode of interaction can be determined by Single Crystal X-Ray Structure Analysis. It can also help to determine the interactions between the host and guest molecules.

13. *In-vitro* release studies: The In-vitro release study can be carrying out with optimize formulation of nanosponges by using multi-compartment rotating cell with dialysis membrane. The donor phase consists of drug loaded nanosponge complex in distilled water. The receptor phase also contains the same medium. After fixed time intervals, the receptor phase is withdrawn completely, diluted with water and analyzed by UV spectrophotometer. Also, USP II can be used in many cases depending upon the formulation.

14. Accelerated stability study: The stability playing major role in the any type of formulation. Therefore, stability study carries out for nanosponge formulation by placing the freshly prepared samples in stability chamber as per the ICH guidelines. [1, 2]

APPLICATIONS:

1. Nanosponges for drug delivery:

Because of their nanoporous structure, nanosponges can advantageously carry water insoluble drugs (Biopharmaceutical Classification System class-II drugs). These complexes can be used to increase the dissolution rate, solubility and stability of drugs, to mask unpleasant flavours and to convert liquid substances to solids. β-Cyclodextrin based nanosponges are reported to deliver the drug to the target site three to five times more effectively than direct injection.

2. Cancer Therapy: Nanosponges can be used as anticancer drug delivery system for tumors. They claim that the method is three to five times more effective at reducing tumor growth than direct injection of the drugs. The tiny nanosponges are filled with a drug load and expose a targeting peptide that binds to radiation- induced cell surface receptors on the tumor. When the sponges encounter tumor cells they stick to the surface and are triggered to release their cargo. Benefits of targeted drug delivery include more effective treatment at the same dose and fewer side effects. Studies so far have been carried out in animals with paclitaxel as the sponge load.

3. Enhanced solubility: The nanosponge system has pores that increase the rate of solubilisation of poorly soluble drug by entrapping such drugs in pores. Due to nano size surface area significantly increased and increase rate of solubilisation. BS class-2 drugs having low solubility and a dissolution rate limited poor bioavailability. However, when formulated with Nanosponge they demonstrate enhanced solubilisation efficiency, with desired drug release characteristics.

4. 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 sincytial 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.

5. Encapsulation of gases: Cyclodextrin based carbonate Nanosponge was used to form inclusion complexes with three different gases, i.e. 1-methylcyclopropene, oxygen and carbondioxide. The complexetion of oxygen or carbondioxide could be useful for many biomedical applications. In particular, the oxygen - filled Nanosponge could supply oxygen to the hypoxic tissues which are present in various diseases. Because of its super porous nature; the Nanosponge also has been explored as an effective gas carrier.

6. Nanosponge in protein drug delivery: Bovine serum albumin (BSA) protein is unstable in solution form so stored in lyophilized form. Swellable cyclodextrin based poly(amidoamino) nanosponge enhanced the stability of proteins like BSA. Nanosponges have also been used for enzyme immobilization, protein encapsulation and subsequent controlled delivery and stabilization.

7. Topical agents: Nanosponge delivery system is a unique technology for the controlled release of topical agents of prolonged drug release and retention of drug form on skin. Local anesthetics, antifungal and antibiotics are among the category of the drugs that can be easily formulated as topical nanosponges. Rashes or more serious side effects can occur when active ingredients penetrate the skin. In contrast, this technology allows an even and sustained rate of release, reducing irritation while maintaining efficiency. A wide variety of substances can be incorporated into a formulated product such as gel, lotion, cream, ointment, liquid, or powder. Econazole nitrate, an antifungal used topically to relive the symptoms of superficial candidasis, dermatophytosis, versicolor and skin infections available in cream, ointment, lotion and solution. Adsorption is not significant when econazole nitrate is applied to skin and required high concentration of active agents to be incorporated for effective therapy. Thus, econazole nitrates Nanosponge were fabricated by emulsion solvent diffusion method and these Nanosponges were loaded in hydrogel as a local depot for sustained drug release. [(4)]

CONCLUSION

From the above study it is concluded that the Nanosponges provide drug targeting and drug release rate in controlled and predictable manner. They can also used for carrying both lipophilic and hydrophilic molecules, due to their small particle size and spherical shape. The Nanosponges can be incorporated in to the form of gel, lotion, cream, ointment, liquid, powder and tablet form for oral drug delivery. In this technology offers loading of ingredients and it reduce the side effects, increases elegance, improved stability and increases the formulation flexibility and enhancement the rate of solubilization of poorly water soluble drugs. Nanosponge is an emerging technology for topical drug delivery.

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