Nano sponges: A targeted drug delivery system and its applications

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Abstract

The recent innovative advance in nanotechnology has led to the development of targeted drug delivery system. Targeting a molecule to a particular site with the help of a drug delivery system efficiently requires the use of specialized drug delivery systems. The invention of Nano sponges has become a significant step in overcoming the problems associated with conventional drug delivery systems. These are able to carry both hydrophilic and hydrophobic drugs. Nano sponge technology widely provide the controlled and predictable release of the drug to the targeted site. The Nano sponge particles circulate around the body and get attached with the target site and release the drug. A wide variety of drugs can be incorporated in the Nano sponge formulation since it possess a porous structure in nature. Nano sponge technology has been studied widely for the drug delivery by oral administration, topical administration and parenteral administration. Nano sponges can be used to prevent drug and protein degradation. Another important characteristic of Nano sponge is that they can improve the solubility of poorly water soluble drug. In this review advantages, composition, method of preparation, evaluation and application of different formulations of drugs and recent studies on Nano sponge have been discussed.

Keywords: Nano sponges; Targeted drug delivery; Solubility enhancement; Controlled drug delivery

1. Introduction

Nanosponge technology is a newer and emerging technology which uses the targeted drug delivery system to release the drug in a controlled manner to the targeted site. Nano sponges are class of materials made up of tiny sponge like structure with narrow cavity of few Nano meter, with an average diameter below 1µm. They cross-link the segments of polyester to form a spherical shape which has many cavities where the drug can be stored. Those narrow cavities can be filled with different type of substance .These are able to carry both hydrophilic and lipophilic drug substances and thereby increasing the solubility of poorly water soluble drug substance [1]. This technology is considered to be a novel approach which offers controlled drug delivery system for topical use. It efficiently offers the entrapment of ingredients with reduced side effects, improved stability, increased elegance and enhanced formulation flexibility [2].

Nanosponges are type of encapsulating nanoparticles which encapsulate the drug molecule within the core by different method of association and it can be classified into encapsulating nanoparticle, complexing nanoparticles, conjugating nanoparticles. When comparing with other nanoparticle, Nano sponges are insoluble in water and organic solvents. Nano sponges are mostly in solid form and it can also be formulated as oral, parenteral, topical or inhalation dosage form. Proteins, peptides, genes, anti-cancer agents and biomolecules have been widely studied using the nanoparticulate system which helps to lower undesired effects and to increase the efficacy.

When orally administrating these may be dispersed within a matrix of excipients, diluents and lubricants and anti-caking agents which are more suitable for the formulation of either capsule or tablet. Saline or other aqueous solution or simply mixing with sterile water can be used for parenteral administrations [3].
1.1. Advantages

- Efficient entrapment of ingredients and reduced side effects.
- Improved stability, increased elegance and enhanced formulation flexibility.
- These formulations are stable up to a temperature of 130°C.
- These formulations are compatible with most vehicles and ingredients.
- These are self-sterilizing as their average pore size is 0.25µm which makes the bacteria unable to penetrate.
- These are free flowing and can be cost effective.
- These formulations modify the release of the drug.
- They increase the solubility of poorly soluble drug.
- It can be used to mask flavours and to convert liquid substance to solids.
- These formulations increase the bioavailability of the drug.
- They are non-irritating. Non mutagenic, nontoxic and non-allergic.
- It has an extended release which provide continuous action up to 12 hrs.
- Easy scale up for commercial production
- Biodegradable
- The material used in this system can provide a protective barrier that shields the drug from premature destruction within the body [4].

1.2. Disadvantages

- They include only small molecule.
- They depend only upon the loading capacities [4].

2. Composition of nanospogens

2.1. 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 [5].

2.2. Cross linking agent

The crosslinking 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 [5].

2.3. Drug substance

- Molecular weight between 100 and 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 [5].

3. Method of preparation

3.1. Nano sponges made from hyper cross-linked β-cyclodextrins

Nano sponges are made from materials that makes a 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 neutral pH [6].
3.2. 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 [7].

3.3. 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 soxhlet apparatus added with ethanol for further extraction. Again go for drying under vacuum and and powdered mechanically to get a homogeneous white powder [8].

3.4. 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 soxhlet extractor using ethanol. The final product obtained is dried at 25˚c and whitish powder is collected and store from humidity [9].

4. Factors influencing nano sponge formulation

4.1. Type of polymer

The formation as well as the performance of nanosponge depend 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 [10].

4.2. Type of drug

- The molecular weight must be between 100 to 400 Daltons
- The drug molecule structure should contain not more than five condensed rings.
- The solubility in water should be less than 10 mg/ml
- The melting point should be less than 250 °C [10].

4.3. 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, van der waals force and hydrophobic forces with rise of temperature [11].

4.4. Method of preparation

The loading of drug into the nanosponge formulation can affect the complexation. The nature of the drug and polymer can affect the complexation. In many cases freeze drying was found to be more effective method for the drug complexation [11].

4.5. Degree of substitution

The nanosponge formulation can be highly affected by the type, number and position of substituent on the parent molecule [11].
5. Loading of drug into nanosponge

The nanospores formulated for the drug delivery first of all should be pretreated to obtain a mean particle size below 500nm. The nanospores 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 supernantant is separated and sample is dried by freeze drying [12].

In other way a nanosponge aqueous suspension is prepared and dispersed it with constant stirring for a specific period of time. The nanospore solid crystals are obtained by the solvent evaporation or either by freeze drying. The nanospore crystal structure plays a very important rule in the complexation with the drug. The drug loading is high in crystalline nanospore than the paracrystalline one. In nanospores which contain poor crystalline structure the drug loading occurs as a mechanical mixture rather than forming inclusion complex [13].

6. Evaluation of nanospores

6.1. 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 [14, 15].

6.2. Loading efficiency

It can be determined by quantitative estimation of the drug which is loaded into the nanospore using either by UV spectrophotometer or HPLC method. The loading efficiency can be calculated by [16].

\[
\text{Loading efficiency} = \frac{\text{Actual drug content in nanospore}}{\text{Theoretical drug content}} \times 100
\]

6.3. Solubility studies

The most frequently used method include phase solubility method described by Higuchi and Connors which helps to determine the effects of nanospore upon the solubility of the drug. The degree of complexation was indicated by phase solubility diagram [17, 18].

6.4. 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 nanospore. 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 nanospore 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 [19].

6.5. 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 [20].

6.6. Infra - red spectroscopy

This spectroscopy method is mainly used to estimate the interaction between nanospore and drug molecule in the solid state. Upon the complex formation nanospore 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 gives information regarding the involvement of hydrogen in various functional group [21].

6.7. Thin layer chromatography
The Rf values of the drug molecule diminish to considerable extent in thin layer chromatography and this helps in identifying the complex formation between the drug and nanosponge formulation [21].

6.8. 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 [22].

6.9. Zeta potential
Zeta potential is measured to find the surface charge. It can be measured by using additional electrode in particle size equipment [23].

6.10. Production yield
The production yield can be determined by calculating initial weight of raw materials and final weight of nanosponges [23].

\[ \text{product yield} = \frac{\text{practical mass of nanospone}}{\text{Theoretical mass}} \times 100 \]

7. Pharmaceutical application 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 [24].

7.1. Nanosponges as a sustained delivery system
Acyclovir is one of the widely used antiviral agent 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].

7.2. 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 55-fold, 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].

7.3. 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 complex of TEL. The highest solubility and in vitro drug release was observed in inclusion complexes prepared from nanospone and NaHCO3. Paclitaxel is an anticancer drug with poor water solubility. β-CD based nanosponges is 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].
7.4. 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 fluorescens* lipases adsorbed on cyclodextrin-based nanosponge. Lipases are widely used for catalysing the hydrolysis of triacylglycerols and trans esterification reactions which are involved in a number of industrial applications. [29].

7.5. Nanosponges for protein delivery
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 nanosponge. 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 develop 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].

7.6. 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 photodegradation. 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 photodegradation [31].

7.7. 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].

7.8. 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 carbodiimidazole cross-linker for encapsulation of 1-methylcyclopropene, oxygen and carbon dioxide [33].

8. Conclusion
Nanosponges are drug delivery system which can carry both hydrophilic and hydrophobic drugs. They can be formulated in different formulation such as oral, parenteral and topical system. Nano sponge technology have wide application in Pharmaceutical industry. Drugs developed by this technology provide prolonged and controlled release of the drug in a safe and effective way.

Compliance with ethical standards

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