

Review Article

Nanosponge - A Novel Drug Delivery System

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Abstract

Nanosponge was originally developed for topical delivery of drugs. They are colloidal carriers have recently been developed and proposed for drug delivery, since their use can solubilize poorly water soluble drug and provide prolonged release as well as improving drugs bioavailability and in some case modifying its pharmacokinetics parameters. The average diameter of a nanosponge is below 1µm but fractions below 500 nm can be selected, micro sponges are 10-25 microns in diameter. They can also decrease side effect and protect drug from degradation. 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.

Keywords: Ethosomes, Transdermal, Skin permeation, enhanced drug delivery, Hydroethanolic solution.

1. Introduction

Nanosponge was originally developed for topical delivery of drugs. They are colloidal carriers have recently been developed and proposed for drug delivery, since their use can solubilize poorly water soluble drug and provide prolonged release as well as improving drugs bioavailability and in some case modifying its pharmacokinetics parameters. The average diameter of a nanosponge is below 1 µm as shown in Figure No. 1 but fractions below 500 nm can be selected, micro sponges are 10-25 microns in diameter. They can also decrease side effect and protect drug from degradation¹. 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.

The nanosponges are solid in nature and can be formulated as oral, parenteral, topical or inhalational dosage forms. For oral administration, these may be dispersed in a matrix of excipients, diluents, lubricants and anticaking agents which is suitable for the preparation of tablets or capsules². For parenteral administration, these can be simply mixed with sterile water, saline or other aqueous solutions². For topical administration, they can be effectively incorporated into topical hydrogel^{3,4}. The researchers at Vanderbilt University and Emory University recently reported on a controlled – release nanoparticle drug delivery system, which may be an improved delivery method for delivering anticancer therapies, including direct injection into tumour site. These nanoparticle circulate in the body until they encounter the surface of a tumour cell, where they adhere to the surface and start releasing the drug in a controlled and predictable manner⁵. Targeted drug delivery systems of this type have several basic advantages. As the drug is released at the tumor site instead of circulating widely through the body, it should be more effective

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for a given dosage. They also should have fewer harmful adverse effects because smaller amounts of the drug come into contact with healthy tissue. Another advantage is that the Nanosponge particles are soluble in water. Encapsulating the anticancer drug in Nanosponge allows the use of hydrophobic drugs that do not dissolve readily in water. Recently, these drugs must be mixed with adjuvant reagents, which potentially can

reduce the efficacy of the drug or cause adverse effects^{5,6}.

Polymers Used in Nanosponge Preparation⁷

There are various polymers and cross linkers are used in the preparation of nanosponges, listed in table 1.

Drugs Formulated as Nanosponges

Some drugs formulated as nanosponges are given in Table 2.

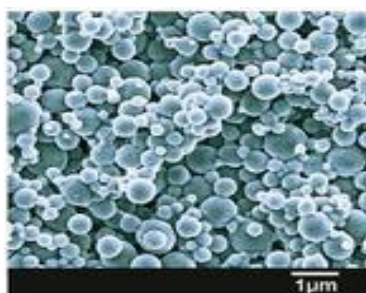


Fig.1: Porous Nanosponges.

Table 1: Different polymers for nanosponge formulation.

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

Table 2: drugs formulated as nanosponges⁸⁻¹⁷.

Drugs	Nanosponge vehicles	Therapeutic Use
Antisense oligonucleotides	Sodium alginate Poly L-lysine	Cancer therapy Viral infection Pathologic disorders
Camptothecin Dexamethazone Econazole nitrate	β-Cyclodextrin β-Cyclodextrin Ethyl Cellulose Polyvinyl alcohol	Cancer Brain tumors Antifungal
Itraconazole	β-Cyclodextrin Copolyvidonum	Antifungal
Paclitaxel	β-Cyclodextrin	Cancer 16, 17 Inflammation Cardiovascular diseases Dermatitis
Resveratrol	β-Cyclodextrin	Gonorrhea Fever Hyperlipidemi
Tamoxifen	β-Cyclodextrin	

Temozolamide	Poly (valerolactone-allylvalerolactone)	Breast Cancer
	Poly(valerolactone-allylvalerolactone-oxepanedione)	Brain tumors

Advantages of Nanosponge

1. Targeted site specific drug delivery.
2. Can be used to mask unpleasant flavour and to convert liquid substances to solids¹¹.
3. Less harmful side effects (since smaller quantities of the drug have contact with healthy tissue).
4. 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 polymer.
6. Production through fairly simple chemistry called "click chemistry" (methods for making the nanosponge 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 therapy¹⁸.
9. Predictable release.
10. Biodegradable.

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

Applications of Nanosponges

Nanosponges for drug delivery

Because of their nonporous 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 flavors 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 injection¹⁹. Drugs which are particularly critical for formulation in terms of their solubility can be successfully delivered by loading into the nanosponges. The nanosponges are solid in nature and can be formulated as Oral,

Parenteral, Topical or Inhalation dosage forms. For the oral administration, the complexes may be dispersed in a matrix of excipients, diluents, lubricants and anticaking agents suitable for the preparation of capsules or tablets². For the parenteral administration the complex may be simply carried in sterile water, saline or other aqueous solutions². For topical administration they can be effectively incorporated into topical hydrogel^{3,12}.

Nanosponges as a carrier for biocatalysts and in the delivery and release of enzymes, proteins, vaccines and antibodies

Many industrial processes involving chemical transformation are associated with operational disadvantages. Non-specific reactions lead to low yields, and the frequent need to operate at high temperatures and pressures requires consumption of large amounts of energy, and very large amounts of cooling water in the down-stream process. All these drawbacks can be eliminated or significantly reduced by using enzymes as biocatalysts. These enzymes operate under mild reaction conditions, have high reaction speed, and are highly specific. They have a beneficial effect on the environment because they reduce energy consumption and reduce production of pollutants. The catalytic activity of enzyme depends mainly on the correct orientation of the active site²⁰. Proteins, peptides, enzymes and derivatives thereof also can be used in the biomedical and therapeutic field. Proteolytic enzymes can be used to treat cancer or type I mucopolysaccharidosis, while DNA and oligonucleotides are used in gene therapy. The administrations of these molecules present various problems and limitations. Most protein drugs are poorly absorbed through the biological membranes due to the some factors such as large molecular size, hydrophilic nature, degree of ionization, high surface charge, chemical and enzymatic instability and low permeability through mucous membranes. Following intravenous administration, protein molecules may be rapidly cleared from blood,

bind to plasma proteins, and sensitive towards proteolytic enzymes. With oral administration bioavailability is the problem. Various approaches exist for therapeutic use, such as increasing the dose or using absorption promoters, which can cause toxicity problems²⁰. A number of systems for carrying enzymes and proteins have been developed, such as nano and microparticles, liposomes and hydrogels. Carriage in a particular system can protect proteins from breakdown, modify their pharmacokinetics and improve their stability *in vivo*. Now, it has been found that Cyclodextrin based nanosponges are particularly suitable carrier to adsorb proteins, enzymes, antibodies and macromolecules. In particular when enzymes are used, it is possible to maintain their activity, efficiency, prolong their operation and extends the pH and temperature range of activity and allows the conduct of continuous flow processes. Moreover, proteins and other macromolecules can be carried by adsorbing or encapsulating them in cyclodextrin nanosponges²⁰.

Modulating drug release

Frequent administration is the major drawback of most of the conventional, commercially available delivery systems. However, a drug loaded in the nanosponge structure can be retained and released slowly over time. Hydrophilic CD NS can modify the rate of drug release, which can be used for enhancement of drug absorption across biological barriers, serving as a potent drug carrier in immediate release formulations. Hydrophobic CD NS may serve as sustained release carriers for water-soluble drugs, including peptide and protein drugs²¹. Nanosponges can be also used as carriers of drugs such as doxorubicin (an anticancer drug), and they may protect the drug during its passage through the stomach. This drug is released very slowly at pH 1.1, whereas release is faster if pH is raised to 7.4.

Other applications of Nanosponges

Nanosponges based on cyclodextrins can strongly bind organic molecules and remove them from water even at very low concentrations²². The same concept can be useful for elimination of bitter components from grape fruit juice by selective combination of polymer and cross linker. The micro porous

hyper cross linked nanosponges have been used in selective separation of inorganic electrolytes by size exclusion chromatography. The three dimensional nanosponges will play important role in the fractionalization of peptides for proteomic applications²³. Nanosponges can be used as carrier for gases like oxygen and carbon dioxide. These nanosponges could be useful for many biomedical applications. In particular the oxygen-filled nanosponges could supply oxygen to the hypoxic tissues which are present in various diseases²⁴. Nanosponges can selectively soak up biomarkers for the diagnosis. One study concluded that nanosponges can harvest rare cancer marker from blood²⁵.

Synthesis 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 (Dimethyl carbonate & Carbonyldiimidazole)². After completion of the reaction, allow the solution to cool at room temperature, then add the product to large excess of distilled water and recover the product by filtration under vacuum and subsequently purify by prolonged soxhlet extraction with ethanol. Dry the product under vacuum and grind in a mechanical mill to obtain homogeneous powder¹¹.

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 size²⁶. 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 5 hours. Then allow the mixture to cool and break the product roughly. Wash the product with water to remove the non reacted polymer and

subsequently purify by prolonged soxhlet extraction with ethanol. Dry the obtained product under vacuum and store at 25°C until further use^{11,26}.

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 drying¹¹. 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^{2,11}. Crystal structure of nanosponge 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 complex²⁷.

Factors Influence 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 below²⁸. Molecular weight between 100 and 400 Drug molecule consists of less than five condensed rings Solubility in water is less than 10mg/m 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 van-der Waal forces and hydrophobic forces with rise of temperature²⁹.

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 complexation²⁹.

Degree of substitution

The complexation ability of the nanosponge may be greatly affected by type, number and position of the substituent on the parent molecule²⁹.

Evaluation of Nanosponges

Particle Size Determination

The particle size of Nanosponge is an important criteria in the optimization process. Particle size can be determined by laser light diffractometry or Zeta sizer. Cumulative percentage drug release from nanosponges of different particle size can be plotted against time to study effect of particle size on drug release. Particle size larger than 30 m can show gritty feeling and particle size range from 10 – 25 m can be preferred for topical drug delivery^{3,30}.

Zeta Potential

Zeta potential is a measure of surface charge. The surface charge of Nanosponge can be determined by using Zeta sizer⁹.

Microscopy Studies

Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) can be used to study the microscopic aspects of the nanosponges^{9,30}. The morphology of nanosponges can be determined by SEM analysis³¹.

Loading Efficiency

The loading efficiency (%) of Nanosponge can be determined by³²

$$\text{Loading Efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Loading efficiency can also be determined by quantitative estimation of drug loaded into nanosponges by UV spectrophotometry and HPLC methods³³.

Production Yield

The production yield (PY) can be determined by calculating initial weight of raw materials and final weight of nanosponges³².

$$\text{Production Yield} = \frac{\text{Practical mass of Nanosponge}}{\text{Theoretical mass (polymer + drug)}} \times 100$$

Thermo-analytical methods

Thermo-analytical methods determine whether the drug substance undergoes some change before the thermal degradation of the nanosponge. The change of the drug substance may be melting, evaporation, decomposition, oxidation or polymorphic transition. The change of the drug substance indicates the complex formation. The thermogram obtained by DTA and DSC can be observed for broadening, shifting and appearance of new peaks or disappearance of certain peaks. Changes in the weight loss also can provide supporting evidence for the formation of inclusion complexes³³.

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^{27,34}.

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 have no diffraction pattern of their own, then the diffraction pattern of a newly formed substance clearly differs from that of uncomplexed nanosponge. 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 molecules³³.

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 formation³³. 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 peaks³³.

Single crystal X-ray structure analysis may be 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 established³³.

Solubility studies

The most widely used approach to study inclusion complexation is the phase solubility method described by Higuchi and Connors, which examines the effect of a nanosponge, on the solubility of drug. Phase solubility diagrams indicate the degree of complexation^{2,29}.

Infra-Red spectroscopy

Infra-Red spectroscopy is used to estimate the interaction between nanosponges and the drug molecules in the solid state. Nanosponge bands often change only slightly upon complex formation and if the fraction of the 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 the spectrum of nanosponges. The technique is not generally suitable to detect the inclusion complexes and is less clarifying than other methods³³. The application of the Infra-red spectroscopy is limited to the drugs having some characteristic bands, such as carbonyl or sulfonyl groups. 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 band³³.

Thin Layer Chromatography

In Thin Layer Chromatography, the Rf values of a drug molecule diminishes to considerable extent and this helps in identifying the complex formation between the drug and nanosponge³³.

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