IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
October 2016 Vol.:7, Issue:3

Nanosponges: A New Approach for Drug Targetting

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

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Submission: 10 October 2016
Accepted: 15 October 2016
Published: 25 October 2016

www.ijppr.humanjournals.com

Keywords: Biodegradable, Crosslinking, Nanosponges, Pharmaceutical applications, Targeted drug delivery

ABSTRACT

Recent advances in nanotechnology paved path for design of new biomaterials based on nanoscale with many potential applications in the field of nanomedicine. Nanosponges are tiny sponges with a size of about a virus and have a three-dimensional network, which can be filled with a wide variety of drugs to form porous insoluble nanoparticles with a crystalline or amorphous structure and spherical shape or swelling properties. The polarity and dimension of the polymer mesh can be easily tuned by varying the type of cross-linker and degree of cross-linking. Nanosponge fictionalization for site-specific targeting can be achieved by conjugating various ligands on their surface. 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 are a safe and biodegradable material with negligible toxicity on cell cultures. The release of the entrapped molecules can be varied by modifying the structure to achieve prolonged release kinetics or a faster release. The nanosponge could be used to improve the aqueous solubility of poorly water-soluble molecules, protect degradable substances, obtain sustained delivery systems or design innovative drug carriers for nanomedicine. Thus, nanosponges are capable of providing solutions for several formulation related problems.

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[1]. Nanotech materials can be easier to target for specific cells such as those in cancerous tumors. Nanotech materials can be shaped into containers minuscule pockets to contain drugs, especially those for cancer that are toxic to healthy tissues and need to be encapsulated until they reach the target. Both of these conditions are relevant to a new nanotechnology configuration developed by Eva Harth, professor of chemistry at Vanderbilt University (Tennessee, USA). The configuration is called a nanosponge, which is evocative, but not quite accurate as the shape isn't really sponge-like (spongiform) but more like a network of molecules in three dimensions. The point is though that the nanosponge can use its shape to attach to cancer cells and to contain drugs[2].

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[3].

The average diameter of a nanosponge is below 1 μm, but fractions below 500 nm can be selected[4]. The nanosponge is about the size of a virus with a 'backbone' (a scaffold structure) of naturally degradable polyester. The long polyester strands are mixed with small molecules 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 or cavities 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[1]. The nanosponge can be engineered to be of specific size and to release drugs over time and not in the burst mode common with other delivery methods[2]. 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[3]. These nanosponges can be magnetized when they are

prepared in the presence of compounds having magnetic properties[5]. The tiny shape of nanosponges enables the pulmonary and venous delivery of nanosponges[1].

The list of polymers and crosslinking agents used for the synthesis of nanosponges are presented in Table-1.

Table 1. Polymers and crosslinking agents used for the synthesis of nanosponges

Polymers	**Crosslinkers**
Hyper cross-linked Polystyrenes, Cyclodextrins and its derivatives like Methyl β-Cyclodextrin, Alkyloxycarbonyl Cyclodextrins, 2-Hydroxy Propyl β-Cyclodextrins and Copolymers like Poly(valerolactone-allyl valerolactone) & Poly(valerolactone allyl valerolactone oxepanedione) and Ethyl Cellulose & PVA	Diphenyl Carbonate, Diaryl carbonates, Diisocyanates, Pyromellitic anhydride, Carbonyl diimidazoles, Epichloridrine, Glutaraldehyde, Carboxylic acid dianhydrides, 2,2-bis(acrylamido) Acetic acid and Dichloromethane

The nanosponges are encapsulating type of nanoparticles which encapsulates the drug molecules within its core. Depending on the method of associating with drugs, the nanoparticles can be classified into 3 types.

1. Encapsulating nanoparticles:

This type is represented by nanosponges and nanocapsules. Nanosponges such as alginate nanosponge, which are spongelike 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.

2. Complexing nanoparticles:

This category includes complexing nanoparticle, which attracts the molecules by electrostatic charges.

3. Conjugating nanoparticles:

These conjugating nanoparticles link to drugs through covalent bonds[1].

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 300^0C. 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 remarkable advantage 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 gasses, 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[6].

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 crosslinkers 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 break up chemically in water. They mix with water and use as a transport fluid. They can be used to mask unpleasant flavors, to convert liquid substances to solids. The chemical linkers enable the nanosponges to bind preferentially to the target site[1].

Advantages

1. These formulations are stable over range of pH 1 to 11.
2. These formulations are stable at higher temperatures.
3. These formulations are compatible with most vehicles and ingredients.
4. These are self-sterilizing as their average pore size is 0.25μm where bacteria cannot penetrate.
5. These formulations are free flowing and can be cost effective.
6. This technology offers entrapment of ingredients and reduced side effects, improved stability, increased elegance, and enhanced formulation flexibility.
7. Nanosponges are non-irritating, non-mutagenic, non-allergenic, and non-toxic.

8. Extended release action up to 12 hrs can be attained.
9. Allows incorporation of immiscible liquid, Improves material processing as liquid can be converted to powders[7,8,9].

Disadvantages

1. Nanosponges have ability to include only small molecules.
2. Nanosponges could be either paracrystalline or in crystalline form.
3. The loading capacity of nanosponges depends mainly on degree of crystallization.
4. Paracrystalline nanosponges can show different loading capacities[1].

PREPARATION OF NANOSPONGES

1. 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 10^0C to the reflux temperature of the solvent, for time ranging from 1 to 48hrs. Preferred crosslinkers are carbonyl compounds (Dimethyl carbonate & Carbonyldi imidazole)[5]. After completion of the reaction, allow the solution to cool at room temperature, then add the product to large excess of bidistilled water and recover the product by filtration under vacuum and subsequently purify by prolonged soxhlet[10].

2. Emulsion solvent diffusion method

Nanosponges prepared by using different proportion of ethyl cellulose and polyvinyl alcohol. The dispersed phase containing ethyl cellulose and drug was dissolved in 20ml dichloromethane and slowly added to a definite amount of polyvinyl alcohol in 150 ml of aqueous continuous phase. The reaction mixture was stirred at 1000 rpm for 2 hrs. The nanosponges formed were collected by filtration and dried in oven at 40^0C for 24 hrs. The dried nanosponges were stored in vacuum desiccators to ensure the removal of residual solvent[11].

3. Ultrasound-Assisted synthesis

In this method, nanosponge 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 90^0C. Sonicate the mixture for 5hrs. 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 25^0C until further use[1,10].

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[5,10].

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 complex[12].

Factors influence nanosponge formation

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 nanosponge should be suitable to accommodate a drug molecule of particular size[13].

2. Type of drugs

Drug molecules to be complexed with nanosponges should have certain characteristics mentioned below[13].

- 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.

3. Temperature

Temperature changes can affect Drug/Nanosponge complexation. In general, increasing 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 temperature[14].

4. 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[14].

5. 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[14].

Characterization and Evaluation of Nanosponges

1. Particle size and polydispersity index

The particle size can be determined by dynamic light scattering using 90 Plus particle sizer equipped with MAS OPTION particle sizing software or laser light diffractometry or Malvern Zeta sizer. From this, the mean diameter and polydispersity index can be determined[12].

2. Morphology and surface topography

Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) can be used to study the morphology and surface topography of the drug, nanosponges and the product (drug/nanosponge complex) by coating with gold–palladium under an argon atmosphere at room temperature. The difference in crystallization state of the raw materials and the product seen under electron microscope indicates the formation of the inclusion complexes[12,15].

3. Thermoanalytical methods

Thermoanalytical 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 complexes[15].

4. 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. The complex formation of drug in 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. 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. Diffraction peaks for a mixture of compounds are useful in determining the chemical decomposition and complex formation[15].

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 established[15].

5. 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 methods[15].

6. 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 nanosponge[15].

7. Loading efficiency and production yield

The loading efficiency (%) of the nanosponges can be calculated according to the following equation.

$$\text{Loading Efficiency} = \frac{\text{Actual drug content in nanosponges}}{\text{Theoretical drug content}} \text{X100}$$

The production yield of the nanosponges can be calculated by following equation after determining accurate initial weight of the raw materials and final weight of the nanosponge obtained[16].

$$\text{Production yield (PY)} = \frac{\text{Practical mass of nanosponges}}{\text{Theoretical mass (polymer+drug)}} \text{X100}$$

8. Resiliency

Resiliency (viscoelastic properties) of sponges can be modified to produce beadlets that are softer or firmer according to the needs of the 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[18].

9. 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[5,14].

10. Zeta potential

Zeta potential is a measure of surface charge. It can be measured by using additional electrode in the particle size equipment[12].

11. Dissolution test

Dissolution profile of nanosponges can be studied by use of dissolution apparatus USP XXIII with a modified basket consisted of 5m stainless steel mesh, speed of the rotation is 150 rpm. The dissolution medium is selected while considering solubility of actives to ensure sink conditions. Samples from the dissolution medium can be analyzed by suitable analytical method[18].

Mechanism of drug release from nanosponges:

The active ingredient is added to vehicles in the entrapped form since the nanosponges particles have an open structure the active substance is free to move in and out from the particles into the vehicle until equilibrium is reached when the vehicle become saturated. Once product is applied to skin, the active substance that is already in vehicle which will become unsaturated, therefore disturbing the equilibrium. This will start flow of active substance from nanosponge's particle into vehicle from it to skin until vehicle is either dried or absorbed. Even after that nanosponges

particle retained on the surface of stratum corneum will continue to gradually release active substance to skin providing prolonged release over time.

Applications of Nanosponges

Nanosponges have the capacity to incorporate drugs within their structure, either as inclusion complexes or as non-inclusion complexes. By virtue of their biocompatibility and versatility, nanosponges have many potential applications in the pharmaceutical field.

1. Solubility enhancement

One of the greatest limits to the development of various pharmaceuticals is the low water solubility of many drugs. About 40% of new drugs are poorly soluble in water, which hinders their clinical application. The formulation of poorly water-soluble drugs constitutes a problem that is difficult to solve. Nanosponges can improve the wetting and solubility of molecules with very poor solubility in water. The drugs can be molecularly dispersed within the nanosponge structure and then released as molecules, avoiding the dissolution step. Consequently, the apparent solubility of the drug can be increased. Many formulation and bioavailability problems can be solved by enhancing the solubility and dissolution rate of a substance, and nanosponges can greatly enhance the drug solubility.

2. Sustained delivery system

The design of a modified-release product is generally intended to optimize the treatment regimen by providing slow, continuous delivery of the drug over the entire dosing interval. This makes it possible to decrease the dose administered, change the pharmacokinetic profile, and decrease side effects. The drug release kinetics from nanosponges can be obtained with a prolonged release profile over time by using suitable polymers and crosslinking agents. Nanosponges can be used to store and prolong the release of volatile molecules, such as essential oils, following their encapsulation[19].

3. Oral delivery systems

The dissolution rate of a solid drug is a limiting factor for oral bioavailability. For hydrophobic drugs, the dissolution process acts as the rate-controlling step and, therefore, determines the rate

and degree of absorption. As a consequence, many hydrophobic drugs show erratic and incomplete absorption from the gastrointestinal tract[19]. For the oral administration, the complexes may be dispersed in a matrix of excipients, diluents and lubricants suitable for the preparation of capsules or tablets[1].

4. Topical delivery systems

Conventional dermatological and personal care products typically provide active ingredients in relatively high concentrations but with a short duration of action. This may lead to a cycle of short-term overmedication followed by long term under medication. 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 efficacy[20]. Nanosponges can suspend or entrap a wide variety of substances, and then be incorporated into a formulated product such as a gel, lotions, cream, ointments, liquid or powder. Nanosponges can be used in gels or creams for topical application[4]. The ability of nanosponges to increase the uptake of the guest molecule by the skin can be attributed to the capacity to increase solubility at the surface of the skin[19].

5. Protein delivery

Swellable cyclodextrin-based nanosponges were purposely prepared for protein delivery by using a different synthetic route. New swellable cyclodextrin-based poly(amidoamine) nanosponges (PAA-NS) , named NS 10 and NS 11, were synthesized by cross-linking β-cyclodextrins with either 2,2- bis(acryl amidoacetic acid) or a short polyamido-amine chain deriving from 2,2-bis(acryl amidoacetic acid) and 2-methylpiperazine, respectively. PAA-NS were reduced in nanosuspensions by using the high pressure- homogenization technique. These swellable nanosponges were shown to be sensitive to the pH of the surrounding media[19].

6. Gas delivery

Nanosponge formulations can act as a reservoir for various types of gas. β-CD nanosponges have shown an ability to store large amounts of carbon dioxide, 1-methylcyclopropene and oxygen. The complexation of oxygen or carbon dioxide 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 diseases**.** Three different cyclodextrin nanosponges were synthesized cross-linking α-, β- or γ-cyclodextrin with carbonyl diimidazole as oxygen-encapsulating formulations. The nanosponges were able to release oxygen both in the presence and in the absence of ultrasound (US). Oxygen permeation through a silicone membrane was obtained by using a nanosponge/hydrogel combination system[21,22].

7. Protection from light or degradation

Nanosponges can also be used as carriers to protect encapsulated molecules from light or chemical and enzyme induced degradation[19]. Thus improving stability and retaining potency of the molecule.

8. 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, employing a variety of water pollutants. It has been established that polycyclic aromatic hydrocarbons (PAHs) can be removed very efficiently (more than 95%). Representatives of the pollutant group of trihalogen methanes (THMs), monoaromatic hydrocarbons (BTX), and pesticides (simazine) can also be removed (>80%)[23].

The nanosponges used in the formulation of some drugs are listed in Table 2.

Examples of nanosponges				
Drug	**Therapeutic activity**	**Nanosponge vehicle**	**Study**	**Reference**
Paclitaxel	antineoplastic	β-cyclodextrin or carboxylimidazole	Bio-availability	24, 25
Camptothecin	Antineoplastic	β-Cyclodextrin	Stability and solubility	26
Tamoxifen	Antiestrogen	β-Cyclodextrin	Solubility	27
Resveratrol	Antioxidant	β-Cyclodextrin	Drug permeation	28
Econazole nitrate	Antifungal	Ethyl cellulose Polyvinyl alcohol	Adsorption	29

Itraconazole	Antifungal	β-Cyclodextrin and copolyvidonum	Bioavailability and solubility	30
Temozolamide	Antitumor	Poly (valerolactoneallylvalerolactone) and poly (valerolactoneallylvalerolactone oxepanedione)	Drug release	31
Bovine serum albumin (BSA)	Protein	cyclodextrin based poly (amidoamine)	Stability	32
Dexamethasone	Antitumor	β-Cyclodextrin	Drug release	33
Antisense oligonucleotides	Antineoplastic and antiviral	Sodium alginate Poly L-lysine	Pharmacokinetic	34
Gamma-oryzanol	Antioxidant	β-Cyclodextrin	Stability	35
Acetylsalicylic acid	Analgesic	Pyromellitic dianhydride crosslinked β-cyclodextrin	Drug release	36
5-fluorouracile	Antineoplastic	β-Cyclodextrin	Stability	19
Telmisartan	Antihypertensive	Carbonated crosslinkers	Dissolution rate	19
Lysozyme	Enzyme	cyclodextrin-based poly(amidoamine)	Drug release and stability	19
Acyclovir	Antiviral	Carboxylated crosslinkers	Solubility and drug release	37
Nelfinavir mesylate	Antiviral	β-Cyclodextrin	Solubility and drug release	19
Flurbiprofen	anti-inflammatory	β-Cyclodextrin	Drug release	38

CONCLUSION

Nanosponges are a new type of biocompatible cross-linked polymer, whose production is flexible and cost-effective. This technology offers entrapment of ingredients and thus reduced side effects, improved stability and increases elegance. Nanosponges can improve bioavailability of poorly soluble drugs, prevent drug and protein degradation and prolong drug release in a controlled manner. They can suspend or entrap a wide variety of substances and can be developed as different dosage forms like parenteral, aerosol, topical, tablets and capsules. Nanosponges can be effectively incorporated into topical drug delivery system for retention of

dosage form on skin, and also for oral delivery of drugs using bio-erodible polymers, especially for colon specific delivery and controlled release drug delivery system thus improving patient compliance by providing site specific drug delivery system and prolonging dosage intervals. They could be used to delivery two active substances simultaneously for combination therapy, or for simultaneous therapeutic and diagnostic applications. In conclusion, nanosponges can be considered as multifunctional nanoscale systems suitable for the delivery of active molecules in nanomedicine.

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