International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 5(6): November-December 2015

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences

Review Article……!!!

Received: 11-11-2015; Revised: 18-11-2015; Accepted: 19-11-2015

NANOSPONGES - AN EMERGING DRUG DELIVERY SYSTEM

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Keywords:

Nanosponge, Targeted drug delivery, Solubility Enhancement, Controlled drug delivery

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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 as well as 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 provide 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.

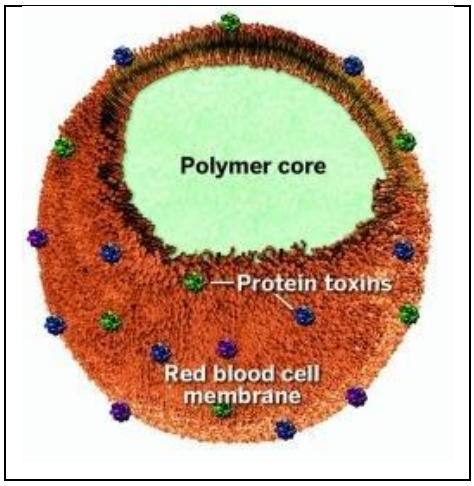

Fig.1- Structure of Nanosponge

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. [(1)] 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. Cyclodextrin based nanosponges is also the new concept to formulate the nanosponges by using cyclodextrin as a cross linking polymer. 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.[(2,3)] Nanosponges are a novel class of hyper-cross-linked polymer based colloidal structures consisting of solid nanoparticles with colloidal sizes and nanosized cavities.[(4)] 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. [5]

Characteristics of Nanosponges [4, 6, 7, 8]

- 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.

Advantages [5, 2, 9, 10]

- Nanosponge particles are soluble in water, so the hydrophobic drugs can be encapsulated within the Nanosponge.
- Targeted site specific drug delivery
- Less harmful side effects (since smaller quantities of the drug have contact with healthy tissue)
- These formulations are stable over range of pH 1 to 11.
- These formulations are stable at the temperature up to 130°C
- It can be used to mask unpleasant flavours and to convert liquid substances to solids.
- Biodegradable.
- Particles can be made smaller or larger by varying the proportion of cross-linker to polymer.
- Predictable release
- These are self sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate.
- Improved stability, increased elegance and enhanced formulation flexibility

Disadvantages [11]

- It depends upon loading capacities.
- It includes only small molecules, not large molecules

Polymers Used in Nanosponge Preparation [7, 12, 13, 14, 15]

Polymers	Copolymers	Cross linkers
• Hyper cross linked Polystyrenes • Cyclodextrins and its derivatives like Alkyloxycarbonyl Cyclodextrins,Methyl ß-Cyclodextrin, Hydroxy Propyl ß-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 1- Polymers used in Nanosponge formulation

List of drugs formulated as Nanosponges [17-24]

Various drugs which are formulated as Nanosponges are given in table 2

Drugs	Nanosponge vehicle	Therapeutic activity
Econazole nitrate	Ethyl cellulose Polyvinyl alcohol	Antifungal
Camptothecin	β-Cyclodextrin	Cancer
Paclitaxel	β-Cyclodextrin	Cancer
Resveratrol	β-Cyclodextrin	Fever Dermatitis Cardiovascular diseases
Acyclovir	Carbonyldiimidazole β-Cyclodextrin	Antiviral
Dexamethazone	β-Cyclodextrin	Brain tumors
Ciprofloxacin	Ethyl cellulose Polyvinyl alcohol	Antiulcer
Itraconazole	β-Cyclodextrin copolyvidonum	Antifungal
Tamoxifen	β-Cyclodextrin	Cancer
Isoniazid	Ethyl cellulose Polyvinyl alcohol	Ant tubercular

Table 2- Drugs formulated as Nanosponges

FACTORS AFFECTING NANOSPONGE FORMULATION [28-32]

Some factors which influence the formulation of Nanosponges are given bellow

- Type of Drug
- Type of Polymer
- Temperature

Type of Drug

The drug molecules to be complexed with nanosponges should have certain characteristics given bellow:

1. Solubility in water is less than 10 mg/ml.(BCS class II drugs are most commonly used)
2. Molecular weight between 100 and 400 gm/mole.
3. The structure of the drug molecule should contain not more than five condensed rings.
4. Melting point of the drug should be below 250°C.

Type of Polymer

The polymer which is used in the formulation can affect the formation as well as the performance of Nanosponges. The cavity size of Nanosponge should be suitable to accommodate a drug molecule of particular size for the complexation. Hydroxy propyl ß-cyclodextrin possess good affinity to form inclusion complex as compared to a, and γ-cyclodextrin [28]

Temperature

The variation in temperature can affect the formation of Nanosponges. Increase 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, with rise of temperature. [29, 32]

Biopharmaceutical Classification System Class II drugs [26, 27]

Category	Drugs
Antihypertensives	Felodipine, Nicardipine, Nifedipine, Nisoldipine
Antibiotics	Azithromycin, Ciprofloxacin, Erythromycin, Ofloxacin, Sulfamethoxazole
Antiarrhythmic agents	Amiodarone hydrochloride
Antifungal agents	Econazole nitrate, Griseofulvin, Itraconazole, Ketoconazole, Lansoprazole,Vericonazole
Anthelmintics	Albendazole, Mebendazole, Praziquantel
Antidiabetic and Antihyperlipidemic	Atorvastatin, Fenofibrate, Glibenclamide, Glipizide, Lovastatin, Troglitazone

NSAIDs	Dapsone, Diclofenac, Diflunisal, Etodolac, Etoricoxib,Flurbiprofen, Ibuprofen,Indomethacin, Ketoprofen, Mefenamic acid, Naproxen, Nimesulide,Oxaprozin,Piroxicam
Cardiac drugs	Carvedilol, Digoxin, Talinolol
Anticoagulant	Warfarin
Anticonvulsants	Carbamazepine, Clonazepam, Felbamate, Oxycarbazepine, Primidone.
Antipsychotic drugs	Chlorpromazine Hydrochloride
Antiretrovirals	Indinavir, Nelfinavir, Ritonavir, Saquinavir
Antianxiety drugs	Lorazepam
Antiepileptic drugs	Phenytoin
Steroids	Danazol, Dexamethazone
Immunosupressants	Cyclosporine, Sirolimus, Tacrolimus
Antiulcer drugs	Lansoprazole, Omeprazole
Antioxidants	Resveratrol
Diuretics	Chlorthalidone, Spironolactone
Antineoplastic agents	Camptothecin, Docetaxel, Etoposide, Exemestane, Flutamide, Irinotecan,Paclitaxel, Raloxifene, Tamoxifen, Temozolamide

Table 3. Biopharmaceutical Classification System Class II drugs

Method of preparation of Nanosponges [4, 6, 33-36]

1. Emulsion solvent diffusion method :

Preparation of dispersed phase and aqueous continuous phase

Dispersed phase : Ethyl cellulose & dichloromethane

Aqueous continuous phase : Polyvinyl alcohol in water

↓

Reaction mixture was stirred at 1000 RPM

for 2 hrs on magnetic stirrer

↓

Formation of nanosponges

↓ filtration

Obtained product dried in oven at 40ºc

↓

Dried Nanosponges was stored in vacuum

dessicator to ensure the removal of residual solvent.

Fig.2- Nanosponge preparation by Emulsion solvent diffusion method

2. **Ultrasound assisted synthesis :**

Mix the polymers with cross linkers

↓

Place the flask in ultrasound bath filled with water

↓

Heat it to 90ºc and sonicate for 5 hrs

↓

Allow mixture to cool & break the product roughly

↓

Wash the product with water to remove non-reacted polymer

↓

Purify by prolonged soxhlet extraction with ethanol

↓

Dry the product under vacuum & store at 25ºc until further use

Fig.3- Nanosponge preparation by Ultrasound assisted synthesis

3) **Solvent method :**

Polymer dissolved in suitable solvent like Dimethylsulfoxide (DMSO), Dimethylformamide(DMF)

↓

Reaction mixture added to excess quantity of cross linker

↓

Reflux the mixture for 48 hrs at temperature ranging from 10ºc to the reflux temperature

↓

Allow this solution to cool at room temp.

↓

Add this to excess quantity of bi-distilled water

↓Filtration

Obtained product purify by prolonged soxhlet extraction with water

↓

Dry the product & grind in mechanical mill to get homogenous powder

Fig.4- Nanosponge preparation by Solvent method

4) From hypercross-linked β cyclodextrin:

In this method, ß- cyclodextrin (ß- CD) can be used as carrier for drug delivery. Nanosponges can be obtained by reacting cyclodextrin with a cross- linker. Nanosponges can be synthesized in neutral or acid forms. The average diameter of a Nanosponge is below 1 µm but fractions below 500 nm can be selected.

Loading of drug into Nanosponges

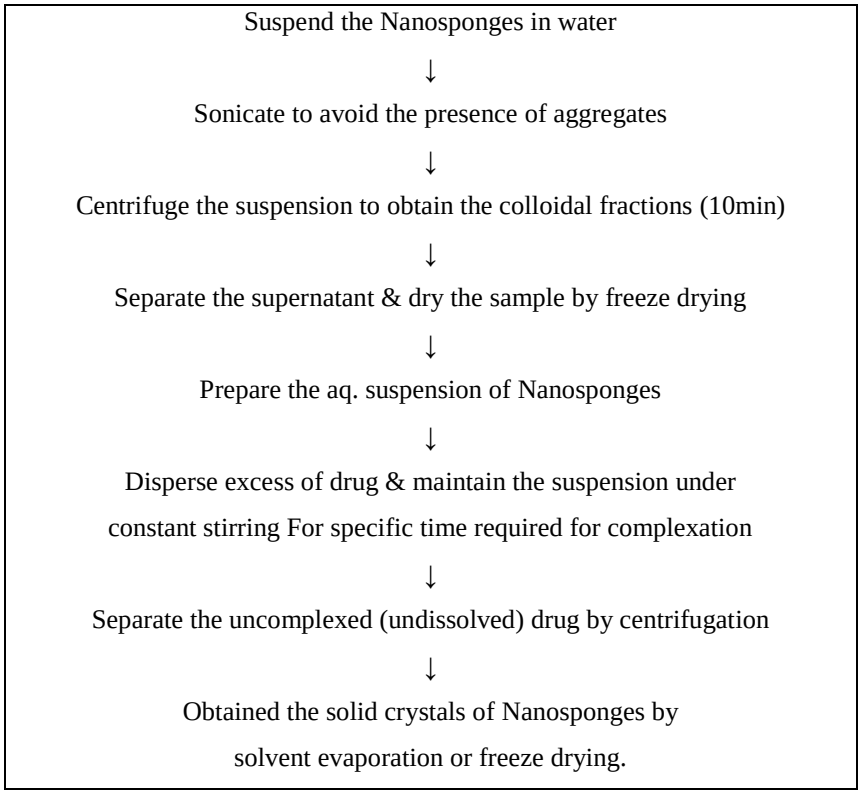

Fig.5- Loading of drug into Nanosponges

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. [43]

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.

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:

$$PDI = \Delta d/d_{avg}$$

Where,

d is the width of distribution denoted by **SD,** and $\mathbf{d_{avg}}$ is the average particle size denoted by **MV(nm)** in particle size data sheet.[9]

Polydispersity Index	Type of dispersion
0-0.05	Monodisperse standard
0.05-0.08	Nearly monodisperse
0.08-0.7	Mid range polydisperse
> 0.7	Very polydisperse

Table 4-Polydispersibility index according to its type of dispersion

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. [22]

4. Zeta potential :

Zeta sizer can be used to measure zeta potential, which is the measure of surface charge of Nansponges. 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. [14]

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). [4]

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. [16]

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]

8. Production yield :

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

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

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. These degradation may be melting, evaporation, decomposition, oxidation or polymorphic transition. The change of the drug substance indicates the complex formation. [35]

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. [42]

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. (26)

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. [26]

13. In-vitro release studies :

The In-vitro release study can be carry 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. [5]

14. Accelerated stability study :

The stability playing major role in the any type of formulation. Therefore, stability study carry out for nanosponge formulation by placing the freshly prepared samples in stability chamber as per the ICH guidelines. [41]

Applications:

1. Solubility Enhancement: [4]

The poorly water soluble drugs can affect the performance of the formulation. Nanosponge is the carrier system, which entrap the drug into its core and provide improved solubility as well as the bioavailability of the formulation. Inclusion complex of cyclodextrin approach is widely used in pharmaceutical field for improvement of solubility and bioavailability of lipophilic drugs.

2. As a carrier for biocatalyst and in the delivery and release of enzymes, proteins, vaccines and antibodies. [5]

The administration of the proteins, enzymes and antibodies can be possible with the help of nanosponge as the carrier system. When enzymes are used, nanosponge formation can maintain their activity, efficiency, extend their operation, pH and temperature range of activity and allows the conduct of continuous flow processes.

3. Nanosponge for drug delivery: [9]

The nanosponge is the newly found carrier system, which can be formulated in various dosage forms like Topical, Oral, and Parenteral dosage forms. Topical hydrogels can be prepared from nanosponges and administered topically. saline, sterile water can also prepared from nanosponges and delivered parenterally whereas by oral administration tablets or capsules can be administered.

4. More effective than direct injection: [4]

The nanosponges are able to attach to the surface of tumor cells and reduce the tumor growth. When nanosponges are administered to the body, that comes in contact with tumor cells and

adhere on the surface of tumor cells or sucked into the cells, where they off-load their deadly content in controlled manner. They have ability to give more effectiveness than direct injection.

5. Gas drug delivery system: [40]

Various types of gases can be administered to the patient through the nanosponge drug delivery system like oxygen, carbon dioxide, 1-methylcyclopropane etc. Nanosponges are able to store and release oxygen to the hypoxic tissue in various diseased state. The oxygen delivered to the hypoxic tissue by forming inclusion complexation with cyclodextrin based carbonate nanosponges. Generally, among the three types of cyclodextrins like α, β, γ-cyclodextrin, β-cyclodextrin is most commonly used, which previously saturated with oxygen before administration.

6. Water Purification: [35]

It is need to used purified water in various power plants, pharmaceutical industries or other industries. Nanosponges are also used to remove the organic pollutants from the raw water to get ultrapure water and it is possible by using water-insoluble cyclodextrin polymer in nanosponge which remove the natural organics (volatile component), dissolved organic carbon (DOC) and total organic carbon (TOC) from the raw water. These are able to remove dissolved organic carbon (DOC) upto 84%, Total organic carbon (TOC) is relatively low.

7. Blood Purification: [43]

Blood purification can possible with the help of nanosponges. Kidney failure is marked by accumulation of many middle Molecular weight toxins (MMW 10–20 has been long done using haemodialysis. Dialysis Membranes allow permeation of low molecular weight solutes but the removal of potent MMW toxins remains incomplete. Hence, Malik et al. investigated a more specific technique for selectively allowing the MMW toxins to diffuse into the porous matrix while size-excluding serum albumins. They used a membrane emulsification technique having the ability of adsorption of MMW uraemic toxins (size Range 0.5–20 kDa), 2-microglobulin whilst size-excluding larger blood proteins like serum albumin.

8. Antiviral Application: [10]

Some antiviral agents can be administered to the patient by forming a nanocarrier system, which help to give more effectiveness as compared to the other formulations. This nanocarriers are used to target viruses that infect the RTI such as respiratory sinctial virus, influenza virus, and rhinovirus. Drugs which are currently in use as nano delivery system are zidovudine, saquinavir, interferon- a, acyclovir. They can also be used for HIV, HBV, HSV.

9. Cancer Therapy: [42]

The anticancer drugs can be encapsulated with nanosponges. The nanosponge drug delivery system is three to five times more effective than direct injection. In that, the nanosponges are attach to the tumour cells or sucked by cells. The off-load their deadly content in controlled manner. Benefits of targeted drug delivery include more effective treatment at the same dose and fewer side effects. The drugs which are currently used as anticancer agents are paclitaxel, camptothecin etc.

CONCLUSION

From the above review, it can be concluded that, due to their very small size of the particles and its porous structure it provides improved solubility as well as the bioavailability of poorly soluble drugs. Different dosage forms like oral, parenteral and topical can be develop for both types of drug molecules like lipophilic as well as hydrophilic because of spherical shape and tiny size of nanosponges. Nanosponge technology offers entrapment of ingredients and provide reduced side effects, site specific drug delivery, improved stability, increased elegance, enhanced formulation flexibility and prolongs dosage intervals and thus improving patient compliance. Therefore, it could be the best solution to many problems in pharmaceutical industry.

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