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NANOSPONGES: A BOON TO FIELD OF PHARMACY

Shobhana. N*, Suma. R

Department of Pharmaceutics, Al-Ameen College of Pharmacy.

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ABSTRACT

Effective targeted drug delivery systems have been a dream for long time. The invention of nanosponges has become a significant step towards overcoming these problems. These small sponges can circulate around the body until they encounter the target site and stick on the surface and began to release the drug in a controlled and predictable manner which is more effective for a particular given dosage. Owing to their small size and porous nature they can bind poorly-soluble drugs within their matrix and improve their bioavailability. They can be crafted for targeting drugs to specific site, prevent drug and protein degradation and prolong the drug release in a controlled manner. This review attempts to elaborate the interesting features of nanosponges, preparation, Characterization, applications and recent updates of nanosponges in drug delivery.

Corresponding author
Shobhana. N
Al-Ameen College of Pharmacy.
nshobhana16@gmail.com

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INTRODUCTION

In recent years it has become more and more evident that the development of new drugs alone is not sufficient to ensure progress is drug therapy. A promising strategy involves the development of suitable drug carrier system. The in -vivo fate of the drug is not only determined by the properties of the drug, but it is also by the carrier system, which permits a controlled and localized release of the active drug according to the specific need of the therapy. The development of a wide spectrum of nanoscale technologies is beginning to change the foundations of disease diagnosis, treatment and prevention.1 Various nanodevices have had a significant impact on medical technology, greatly enhancing the efficacy of many existing drugs and enabling the construction of entirely new therapeutic modalities.2 In recent years, significant efforts have been devoted to use the potentials of nanotechnology in drug delivery to develop a suitable means of site-specific and/or time controlled delivery of small or large molecular weight drugs and other bioactive cargo.3 Research into the delivery and targeting of pharmaceutical and therapeutic agents with nanosized particles is at the forefront of projects in nanomedicine. Nanoparticles show tremendous promise for drug delivery, while exhibiting structural properties that are not feasible for single molecules.4 Polymeric nanoparticles, in particular, are the most widely researched therapeutic carriers due to their unique flexibility with respect to fabrication techniques.

At present these systems are generally used for existing, fully developed off-patent drugs, the so called “low-hanging fruit” of nanotechnology-based delivery. Nanotechnology is an ideal targeting system should have long circulating time, it should be present at appropriate concentrations at the target site, and it should not lose its activity or therapeutic efficacy while in circulation. Various nanosystems, as a result of their larger size, are accumulated at higher concentrations than normal drugs.

Nanotechnology-based delivery systems can also protect drugs from degradation. Improved products may be available with a change in the physical properties when their sizes are shrunk. Reduce the number of doses required. Nano-based systems allow delivery of insoluble drugs. Allowing the use of previously rejected drugs or drugs which are difficult to administer. Drug targeting can be achieved by taking advantage of the distinct pathophysiological features of diseased tissues. An ideal targeting system should have long circulating time, it should be present at appropriate concentrations at the target site. It should not lose its activity or therapeutic efficacy while in circulation. Improve the oral bioavailability of the agents that are not effectively used orally.

Effective targeted drug delivery systems have been a dream for a long time, but it has been largely frustrated by the complex chemistry that is involved in the development of new systems. The invention of nanosponges has become a significant step toward overcoming these problems. 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. 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. Another important character of these sponges is their aqueous solubility; this allows the use of these systems effectively for drugs with poor solubility[5].

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 molecules6. Nanosponges are tiny mesh-like structures that may revolutionise 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 methods7.

The nanosponge is about the size of a virus with a „backbone‟ (a scaffold structure) of naturally degradable polyester. The long length polyester strands are mixed in solution with small molecules called cross-linkers 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 schedule7.

Nanosponge technology offers entrapment of ingredients and is believed to contribute towards reduced sideneffects by controlling the release, improved stability, increased elegance, and enhanced formulation flexibility. In addition, nanosponges system are non-irritating, non-mutagenic, nonallergenic, and non-toxic8.

Nanosponge can be prepared by optimizing formulation parameters such as drug:polymer and agitation or stirring rate. Potentially the nanosponge system can significantly reduce the irritation of the effective drugs without reducing the efficacy. Nanosponge delivery system can be incorporated into conventional dosage forms such as lotions, creams, gels, ointments and powders and share a broad package of benefits.

TABLE: 1: CHEMICALS USED FOR THE SYNTHESIS OF NANOSPONGES:[9,12]

POLYMERS	Hyper cross linked Polystyrenes, Cyclodextrines and its derivatives like Methyl β-Cyclodextrin, AlkyloxycarbonylCyclodextrins, 2-Hydroxy Propyl β- Cyclodextrins and Copolymers like Poly(valerolactone-allylvalerolactone) & Poly(valerolactone-allylvalerolactoneoxepanedione) and Ethyl Cellulose & PVA
CROSSLINKERS	Diphenyl Carbonate, Diarylcarbonates, Diisocyanates, Pyromellitic anhydride, Carbonyldiimidazoles, Epichloridrine, Glutarldehyde, Carboxylic acid dianhydrides, 2,2-bis(acrylamido) Acetic acid and Dichloromethane

Because of their nanoporous structure, nanosponges can advantageously carry water insoluble drugs (Biopharmaceutical Classification System class-II drugs). These complexes can be used to increase the dissolution rate, solubility and stability of drugs, to mask unpleasant flavors and to convert liquid substances to solids. β- Cyclodextrin based nanosponges are reported to deliverthe drug to the target site three to five times more effectively than direct injection 9. Drugs which are particularly critical for formulation in terms of their solubility can be successfully delivered by loading into the nanosponges.

Characteristics of Nanosponges [10,13]

- ✓ 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.
- ✓ 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

- ✓ 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 [10, 11,12]

TABLE: 2: Biopharmaceutical Classification System Class II drugs.

Antihypertensives	Felodipine, Nicardipine, Nifedipine, Nisoldipine
Antibiotics	Azithromycin, Ciprofloxacin, Erythromycin, Ofloxacin, Sulfamethazole
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

(10, 14).

Classification of Nanosponges

Nanosponges are encapsulating type of nanoparticles which encapsules the drug molecules within its core. By method of associating with drugs, the nanoparticles can be classified into the following:-

Encapsulating Nanoparticles

This type is represented by nanosponges and nanocapsules. Nanosponges such as alginate nanosponge, which are sponge like nanoparticles containing many holes that carry the drug molecules in their aqueous core E.g. Nanosponges such as alginate nanosponge, which are sponge like nanoparticles containing many holes that carry the drug molecules. Nanocapsules such as poly (iso-butyl-cyanoacrylate) (IBCA) are also encapsulating nanoparticles.

Complexing Nanoparticles

This type of nanoparticles attracts the molecules by electrostatic charges.

Conjugating Nanoparticles

This type of nanoparticles links to drugs through covalent bonds. As compared to the other nanoparticles, they are insoluble both in water and organic solvents, porous, non-toxic and stable at high temperature up to 300oC. They are able to capture, transport and selectively release a huge variety of substances because of their 3D structure containing cavities of Nanomeric size and tunable polarity. [15, 16]

Applications of Nanosponges:

Nanosponges as chemical sensors:

Nanosponges which are the type of "metal oxides" act as a chemical sensors which is used in highly sensitive detection of hydrogen using nanosponge titania. Nanosponge structure intially have no point of contact so there is less hinderance to electron transport and it results in higher 3D interconnect nanosponges titania which is sensitive to H_2 gas.

Nanpsponge for oral delivery:

In oral application it forms the nanosponge system consist of pores which increase the rate of solubilization of poorly water soluble drugs which get entrapped the drug in pores. The surface area is increased due to nanosize form and increase rate of solubilization.

Solubility enhancement:

β-cyclodextrin based nanosponges of itraconazole have enhance solubility of poorly soluble drug. The solubility increased by 50 folds compared to ternary dispersion system. Eg- copolyvidonum.

Nanosponges as a carrier for biocatalysts and release of enzymes, proteins, vaccines and antibodies:

It includes the process applied in industry which correlate with operational condition. Reactions which are not specific give rise to low yields and require high temperatures and pressures which consume large amount of energy and cooling water in down-stream process. This are the drawbacks can be removed by using enzymes as
biocatalysts as this operate under high reaction speed, mild condition.

Antiviral application:

Nanosponges used in nasal, pulmonary route of administration. It provide specificity to deliver antiviral drug on RNA to lungs or nasal route through nanocarriers for targeting virus which may cause infection to RTI such as influenza virus, rhinovirus. Drugs used as nanocarrriers are- Zidovudine, Saquinavir.

Cancer:

Targeting drug to specific site avoiding the obstacle created by immune system. Different cancer cells had been treated by nanosponges like breast cancer or fast acting glioma type with help of single dose of injections.

Oxygen Delivery System:

Characterized by using α, β and ϒ cyclodextrins and this are suspended in water and get saturated with water. A silicone form of membrane can also be used for oxygen permeation with the help of nanosponge/ hydrogel system. They can also applied it to hypoxic tissues caused in various type of diseases.[17,18]

Preparation of nanosponges

The following methods are used in preparation and drug loading into nanosponges

Solvent method

The following figure gives an outline of synthesis of nanosponges by solvent method

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

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.

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

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

Suspend the Nanosponges in water
↓
Sonicate to avoid the presence of aggregates
↓
Centrifuge the suspension to obtain the colloidal fractions (10min)
↓
Separate the supernatant & dry the sample by freeze drying
↓
Prepare the aq. suspension of Nanosponges
↓
Disperse excess of drug & maintain the suspension under constant stirring For specific time required for complexation
↓
Separate the uncomplexed (undissolved) drug by centrifugation
↓
Obtained the solid crystals of Nanosponges by solvent evaporation or freeze drying.[19,20,21]

CHARACTERIZATION OF NANOSPONGES:

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

Loading efficiency / Entrapment efficiency:

Weighed amount of loaded nanosponge complexes is to be dissolved in suitable solvent, sonicated to break the complex, diluted suitably and then analyzed by UV spectrophotometer or HPLC methodsLoading Efficiency
The loading efficiency (%) of Nanosponge can be determined by:

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

Production Yield

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

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

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

Polydispersity index& particle size:

The particle size can be determined by dynamic light scattering using 90 Plus particle sizer equipped with MAS OPTION particle sizing software. From this, the mean diameter and polydispersity index can be determined2. The particle size can be determined by scanning electron microscopy (SEM), transmission electron microscopy (TEM), atomic force microscopy (AFM), and freeze fracture electron microscopy (FFEM)

Zeta potential determination:

Zeta potential measurements can be made by using an additional electrode in particle size instruments2. Also, Laser Doppler anemometry, zeta potential meter can be used

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 isless 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 nano sponges. The technique is generally not suitable to detect the inclusion complexes and is less clarifying than other methods

X-ray diffractometry:

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), 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 madebetween the diffractogram of the assumed complex and that of the mechanical mixture of the drug and polymer molecules.

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 differentdiffractograms. Diffraction peaks for a mixture of compounds are useful in determining the chemical decomposition and complex formation. The complex formation of drug withnanosponges 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.

Single crystal X-ray structure analysis:

Itmaybe 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.

In Vitro release studies:

The release of the drug from the optimized nanosponge formulation can be studied using multi-compartment rotating cell with dialysis membrane (cut-off 12,000 Da). The donor phase consists of drug-loaded nanosponge complex in distilled water. The receptor phase also contains the same medium. The receptor phase is withdrawn completely after fixed time intervals, suitably diluted with distilled water and then analyzed by UV spectrophotometer12. Also, USP II can be used in many cases depending upon the formulation. [22,23,24]

TABLE: 3 Examples of nanosponges [25]

Drug	Nanosponge vehicle	Indication	Study	In vitro / Invivo/ Mathematical model
Paclitaxel	β-cyclodextrin	Cancer	Bio- availability Cytotoxicty	Sprague Dawley rats MCF7 cell line
Camptothecin	β-cyclodextrin	Cancer	Haemolytic activity Cytotoxicty	Diluted blood HT-29 cell line
Tamoxifen	β-cyclodextrin	Breast cancer	Cytotoxicty	MCF-7 cell line
Resveratrol	β-cyclodextrin	Inflammation, Cardiovascular diseases, Dermatitis, Gonorrhea, Fever and Hyperlipidemia	Cytotoxicty Accumulation of drug in the buccal mucosa of rabbit Ex-Vivo Study Permeation study	HCPC-I cell line Rabbit buccal mucosa
Temozolamide	Poly (valerolactoneallylvalerolactone) And poly (valerolactoneallylvalerolactone – oxepanedione)	Brain tumors	Drug release study	In vitro and in vivo studies
Econazole nitrate	Ethyl cellulose Polyvinyl alcohol	Antifungal	Irritation study	Rat
Itraconazole	β-Cyclodextrin & copolyvidonum	Antifungal	Saturation solubility study	Higuchi Model
Dexamethasone	β-Cyclodextrin	Brain tumors	Drug release experiment	Dialysis bag technique in vitro
Antisense oligonucleotides	Sodium alginate Poly L-lysine	Cancer therapy Viral infections Pathologic disorders	Pharmacokinetic studies	Mice

CONCLUSION

Nanosponges are versatile drug carrier system as they carry both hydrophilic and hydrophobic drugs by forming inclusion and non inclusion complexes. They can deliver drugs by various routes like oral, topical and parenteral in a predictable manner to the target site. Besides their application in the drug delivery field, potential applications exist for cosmetics, biomedicine, bioremediation processes, agro chemistry, and catalysis, among others. Drugs delivered by nanosponges can be proved safe and effective and the pharmaceutical industries will benefit greatly if clinical studies can prove their potential for human use.

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