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Review Article

Nanosponge A Novel Drug Delivery System.

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ABSTRACT

Nanosponge is a targeted drug delivery system in that active pharmaceutical agent is respectively targeted to its site of action and not to the non-targeted organs, tissues or cells. Nanosponge's modern effective drug carriers which decrease the problems of toxicity and increase bioavailability of both hydrophilic and hydrophobic drugs. Nanosponge is a modern drug delivery system, is one of the most promising approaches in the life science. Nanosponges are tiny mesh like structure, a three-dimensional network and nanometric cavity. Nanosponges are highly porous in nature and they have ability to entrap active molecules. Cyclodextrins and other appropriate crosslinking agents in a specified ratio use for preparation of nanosponge. Nanosponges fast absorb in the body until they reach the specific target site, stick on the surface and release the drug in control manner. Nanosponge has a high drug loading capacity as compare to other nanocavity. Hence, they have high stability, solubility and delayed release of actives. Especially nanosponge is use for a loading of low water-soluble drug and targeting to its specific site, it's an advantage of nanosponge. Nanosponge can deliver the drugs in different routes like oral, topical, parenteral etc. and act as vehicle t in the delivery of enzymes, proteins, vaccines and antibodies. These reviews explain the characteristic features (advantage and dis - advantage), preparation methods, factors, characterization, and applications of nanosponges in the field of drug delivery.

KEYWORDS

Nanosponges, Cyclodextrins, Cross-linking agents, controlled release.

1. INTRODUCTION

Targeting the drug to the specific place in the body has been creating a problem to the medical researchers, how to administered in right place and how to control its release and overdose. Nanotechnology is potentially the most important process in the industrial area. Nanotechnology process contains the several of formulations like nanoparticles, Nano capsules, Nano spheres, Nano suspensions, Nano crystals, nano erythosomes etc. Nano- technology contain mainly nanomaterial's are defined as materials they have dimension in the range between 1-100 nm[1-3]. Nanosponges were firstly developed for drug administered in topical drug delivery system. Nanosponges are tiny sponges with a size of about an average diameter below 1μm.[4]. Nanosponges are tiny sponges with a size of about a virus, which can be filled with a different variety of drugs. Nanosponges are insoluble in water and organic solvents, as compare to another nanoparticle. They have porous, non-toxic and stable at high temperatures up to 3000C. The nanosponges are solid in nature and can be administered by oral, parenteral, topical or inhalational dosage forms.[4]. Nanosponge is a modern dosage form of material and it is formulated through tiny particles with a narrow cavity of few nanometres. These narrow cavities are filled with different types of substances. These tiny particles are having capacity to able to carry both hydrophilic and lipophilic drug substance and they increase the stability and solubility of poorly water-soluble drug substance or molecules.[1]

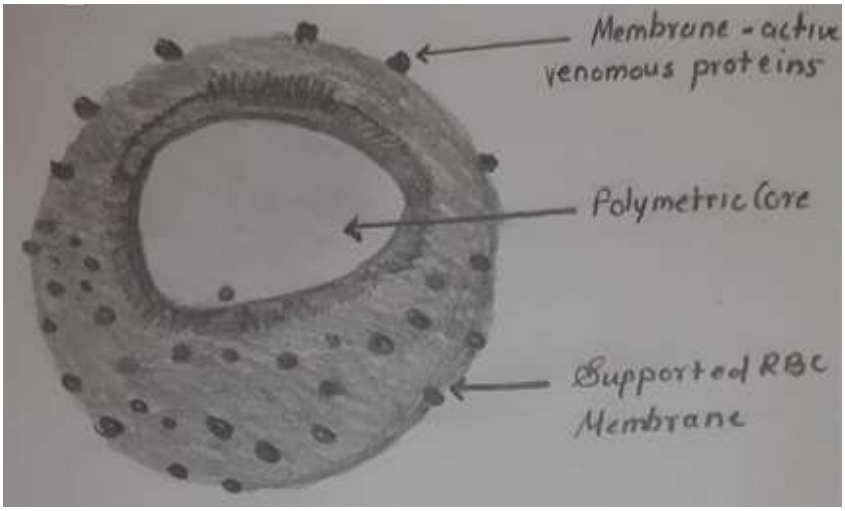

Fig. 1. Structure of nanosponge

A novel nanostructured material can be obtained by reacting polyesters (Cyclodextrins) with appropriate crosslinking agents, known as nanosponges.[1]

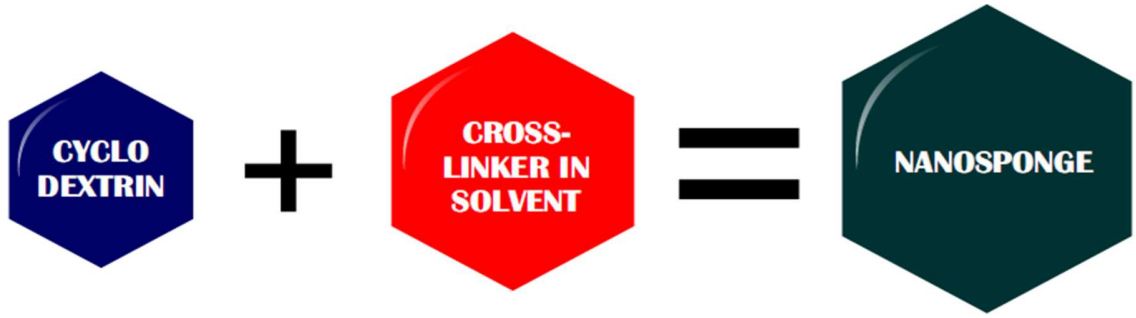

Fig. 2. Formation of Nanosponges

Nanosponges are solid in nature. They have safe for oral, topical or parenteral routes; since they have best carrier for drug delivery. The tiny shape of nanosponges useful for pulmonary and venous delivery of nanosponges. For oral delivery, the mixture may be dispersed in a matrix of excipients (diluents, lubricants and anti-caking agents). For parenteral delivery, the mixture may be simply carried a sterile water, saline or other aqueous solutions. For topical delivery they can be effectively incorporated into topical hydrogel. Nanosponges are encapsulating process of nanoparticles which encapsulates the drug particle within its core. A nanosponge can circulate in the body until they reach the specific target site, bind to the surface and release the drug in a predictable manner. [1]

Advantages of nanosponge [1,3]

- Increase aqueous solubility of the less water-soluble drug.
- Nanosponge's drug delivery system is non-irritating, no mutagenic and non-toxic.
- Nanosponges drug delivery system has less side effect.
- Increase stability, elegance and flexibility of the formulation.
- Reduce frequency of dosing.
- Provides extended release up to 12 hrs.
- Reduce the degradation of active ingredient.
- To mask the bitter taste.

Disadvantages

- Nanosponges contain only small molecules.
- Depend only upon loading capacities of drug molecules.

Characteristic Features of Nanosponges

- Nanosponge are nontoxic, porous, insoluble in most organic solvents and stable up to 300 °C.
- They are stable at the pH range of 1-11.
- Nanosponges provide a range of dimensions (1µm or less).

- They can bind to different target sites because of they have capacity to link with different functional groups.
- Nanosponges are virus size can be formulated by changing the crosslinker to polymer ratio.
- Deliver the drug molecule at the targeted site
- Nanosponge improved stability, elegance and formulation flexibility.
- Drug is protected from degradation.
- Nanosponge have less side effect since small quantities of the drug are contact with healthy tissue.
- Nanosponge have major advantage control release, they produce a control release of drug.

Types of Nanosponges

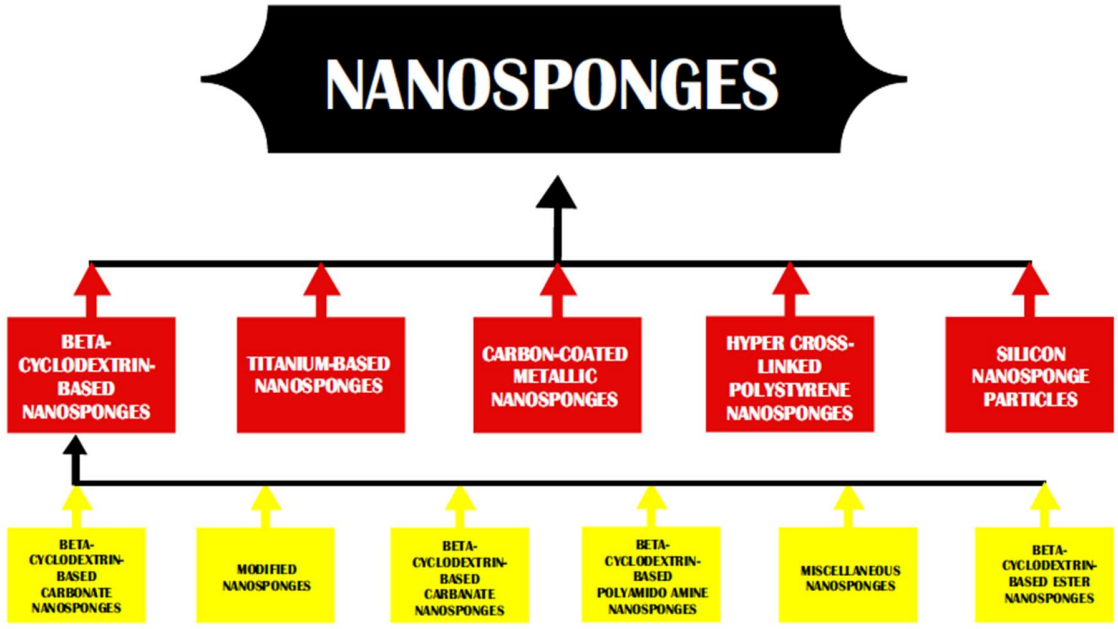

Fig. 3. Types of Nanosponges

Composition and Structure of Nanosponges[1-3]

A. Polymer

The polymer has different type and it affect the formation as well as the performance of nanosponge. Polymer have an ability to cross-link due to its functional and active group present. The selection of polymer is depending of drug release and how much quantity drug encloses.

Cyclodextrins and its derivatives like alkyloxy carbonyl cyclodextrins, hyper cross-linked polystyrenes, methyl β-cyclodextrin, hydroxy propyl β-cyclodextrins.

B. Copolymer

When two or more than two different monomers unite polymerize to together, the resultant product is called a copolymer and the process known as copolymerization. The properties of manufactured product will be change by using co-polymerization to meet specific needs, for example, to reduce crystallinity, modify glass transition temperature, and control wetting properties or to improve solubility. It is a process of improving mechanical properties. Like Poly (valerolactone allyl valerolactone) Pyromellitic anhydride, Ethyl Cellulose, PVA, 2,2-bis (acrylamide) Acetic acid, Carboxylic acid dianhydrides, Glutaraldehyde Poly (valerolactone allyl valerolactone oxepane dione), Epichloridrine.

C. Crosslinking agent

Selection of crosslinking agent depends on the structure of polymer and the drug to be encapsulate. Carbonyl Diimidazole, diarylcarbonates, dichloromethane. diisocyanates, diphenyl carbonate, gluteraldehyde, diisocyanates, diphenyl carbonate, pyromellitic anhydride, carboxylic acid dianhydrides, epichloridine, 2,2-bis (acrylamido) acetic acid.

D. Drug substance

Drug molecules to be formulated as nanosponges should have following characteristics.

- Molecular weight in range between 100 and 400 Daltons.
- Drug molecule contain less than five condensed rings.
- Drug have Solubility in water less than 10 mg/ml.
- Drug have Melting point below the 250^0C.

Table 1. Biopharmaceutical classification system class II drugs

Antiarrhythmic agents	**Amiodarone hydrochloride**
Antianxiety drugs	Lorazepam
Anticoagulant	Warfarin
Antibiotics	Azithromycin, Ciprofloxacin, Erythromycin, Ofloxacin, Sulfamethoxazole
Anticonvulsants	Carbamazepine, Clonazepam, Felbamate, Oxcarbazepine, Primidone
Antiepileptic drugs	Phenytoin
Antidiabetic and Antihyperlipidemic drugs	Atorvastatin, Fenofibrate, Glibenclamide, Glipizide, Lovastatin, Troglitazone

Antifungal agents	Econazole nitrate, Griseofulvin, Itraconazole, Ketoconazole, Lansoprazole, Voriconazole
Antihypertensive drugs	Felodipine, Nicardipine, Nifedipine, Nisoldipine
Antihistamines	Terfenadine
Antipsychotic drugs	Chlorpromazine Hydrochloride
Antineoplastic agents	Camptothecin, Docetaxel, Etoposide, Exemestane, Flutamide, Irinotecan, Paclitaxel, Raloxifene, Tamoxifen, Temozolomide, Topotecan
Antiulcer drugs	Lansoprazole, Omeprazole
Antiretrovirals	Indinavir, Nelfinavir, Ritonavir, Saquinavir
Anthelmintic	Albendazole, Mebendazole, Praziquantel
Antioxidants	Resveratrol
Cardiac drugs	Carvedilol, Digoxin, Talinolol
Diuretics	Chlorthalidone, Spironolactone
Gastroprokinetic agent	Cisapride
Immunosupressants	Cyclosporine, Sirolimus, Tacrolimus
NSAIDs	Dapsone, Diclofenac, Diflunisal, Etodolac, Etoricoxib, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Mefenamic acid, Naproxen, Nimesulide, Oxaprozin, Piroxicam
Steroids	Danazol, Dexamethasone
Miscellaneous	Atovaquone, Melarsoprol, Phenazopyridine, Ziprasidone

Methodology for preparation of the nanosponges:

Solvent diffusion methods

1. Quassi emulsion solvent diffusion

Preparation of inner phase. Consist of polymer dissolve in suitable solvent.

↓

Drug added in to solution and dissolved under ultrasonication at 35^0C.

↓

Inner phase is added into the polyvinyl alcohol solution in water.

↓

Stirred the mixture for 60 min, then the mixture is filtered.

↓

Prepared nanosponges are dried in a hot air oven at 40^0 C for 12 h

2. Emulsion solvent diffusion method

Preparation of disperse and continuous phase.

↓

Continues phase contain copolymer.

↓

Disperse phase contain drug and polymer.

↓

Disperse phase is slowly added in the continuous phase and
Stirred for 2-3 hrs at 1000 rpm.

↓

Filtered the prepared nanosponge, washed and then dried in air at room temperature or in vacuum oven to 40^0C for 24 hrs.

3. Ultrasound assisted synthesis

Polymer is added in cross linker in balanced ratio in a flask.

↓

Then flask is placed in an ultrasound bath filled with water.
The temp is maintained at range 90^0C

↓

Sonicate the mixture for 5 hrs.

↓

Non reacted polymer removed out, and then wash out the product with water

↓

Ethanol use for product purifications' by soxhlet extraction process.

↓

Allow the product to dry under vacuum at 25^0C.

4. Quasi-emulsion solvent diffusion

Disperse phase is prepared by dissolving eudragit RS100 in suitable solvent.

↓

Then, drug can be added in solution and dissolved under ultrasonication at 35^0C.

↓

The disperse phase was added into the polyvinyl alcohol solution in water as a continuous phase.

↓

The mixture is filtered after 60min of stirring to separate the nanosponge.

↓

The nanosponge are dried in an air-heated oven at 40^0C for 12 hrs.

Characterization of nanosponges

Solubility study

The phase solubility method is the most widely used approach to study inclusion complexion described by Higuchi and Connors, who studied the effect of a nanosponge on the solubility of drug. The degree of complexation indicates through Phase solubility diagrams.

Porosity

For the checking of the extent of Nano channels and Nan cavities formed the porosity study is performed. For the assess porosity study of nanosponges Helium pycnometer is used, since helium gas is able to penetrate inter- and intra-particular channels of materials. Following equation is used for to calculate percent of porosity.

Percentage of Porosity: Bulk Volume-Tab Volume/Bulk Volume 100 ---Formula 1

Particle size and polydispersity index Determination:

Particle size

Particle size is determined by laser light Diffractometry or zeta seizer. Particle size range from 10-30μm can be useful for topical drug delivery.

The polydispersity index (PDI)

Polydispersity index is measure by using dynamic light scattering Instruments. PDI is an index of width and variation with particle size distributes. Monodisperse samples they have a lower PDI value, and the higher value of PDI indicates a wider particle size distribution and the polydisperse nature of the sample. Following equation is use for calculate the PDI.

PDI=▲d/dav g where. ▲d=width of distribution ---Formula 2

Table 2. The polydispersity index.

Polydispersity index	**Type of dispersion**
0-0.05	Monodisperse standard

0.05-0.08	Nearly monodisperse
0.08-0.7	Mid-range polydispersity
> 0.7	Very polydispers

Determination of production yield

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

Production Yield = Practical mass of nanosponges / Theoretical mass × 100. ---Formula 3

Drug entrapment efficiency

Centrifugation method is used for drug entrapment efficiency, at the 1300 rpm for 20 min. After centrifugation, the supernatant layer was removed &diluted with appropriate solvent.

% DEE =Wt of initial drug added in the formulation-wt. of free into formulation / Wt of initial drug added in the formulation × 100 ---Formula 4

Loading efficiency

The loading efficiency (%) of Nanosponge can be determined by following equation.

Loading Efficiency = Actual drug content / Theoretical drug content × 100. ---Formula 5

Zeta potential

Zeta potential is use for measuring of surface charge. It can be measured by using electrode in the particle size equipment. Zeta sizer is use for the determine the surface charge of Nanosponge.

Drug content

In 100 ml of volumetric flask 50 ml of methanol is taken and it add a formulation, allow to stand for 2hr. The volume is making up to 100 ml by using methanol. 1ml of the above solution was diluted to 10 ml with6.8 pH phosphate buffer. The drug content was determined by measuring the absorbance using UV Visible spectrophotometer.

Microscopic studies

Scanning electron microscopy and Transmission electron microscopy are used to study the morphology and surface topography.

X-ray Diffractometry

X-ray diffractometry is used for detection of inclusion complexation in the solid state.

Infrared spectroscopy

Infrared spectroscopy is used for determination of the interaction between nanosponges and the drug molecules in the solid state.

Thin layer chromatography

Identifying the complex formation between the drug and nanosponge is carried out by using thin layer chromatography.

Raman spectroscopy

Molecular structures determine by using Raman spectroscopy.

Applications of nanosponges

Nanosponges have following applications in the pharmaceutical field.

1. ***Nanosponges as Solubility Enhancer***

Nanosponge is the best carrier system for low soluble molecules, which entrap the molecule into its core and provide improved solubility as well as the bioavailability of lipophilic drugs. Nanosponges are widely used for improving the solubility and dissolution rate of poorly soluble drugs as well as providing controlled release profile.

2. ***Nanosponges in Drug Delivery***

Nanosponge have a nan porous structure, hence they perfectly carry water insoluble drugs and/or molecule (BCS Class-II drugs). Nanosponge is useful for increase the dissolution rate, solubility and stability of BCS class II drugs. Some drugs having low solubility and they are successfully delivered by loading into the nanosponges. Due to their solid nature and they can be formulated as oral, parenteral, topical or inhalation dosage forms.

3. ***Nanosponge in protein drug delivery***

Nanosponge is useful in enzyme immobilization, protein encapsulation and subsequent controlled delivery and stabilization Bovine serum albumin (BSA) protein is unstable in solution form so they are stored in lyophilized form. The stability of proteins like BSA is increase by Swellable cyclodextrin based poly (amido amino) nanosponges.

4. **Nanosponges as a Carrier for Delivery of Gases:**

The gases play a key role in medicine, they are useful to treatment purpose in diagnostic. Hypoxia (deficiency of adequate oxygen supply) through inflammation to cancer is related to various pathologies. The delivery oxygen in appropriate form and doses in clinical practice is sometimes difficult. Cavalli *et al*. developed Nanosponge formulations in that oxygen delivery system for topical application which having the ability to store and to release oxygen slowly over time.

5. Topical drug delivery system

Local anaesthetics, antifungals and antibiotics are some the category of the drug substances that can be easily formulated as topical nanosponges. In this context, nanosponges can be prepared by different methods like emulsion solvent diffusion method, etc.

6. In Antiviral Therapy

Nanosponge are useful in the ocular, nasal and pulmonary administration routes. Were the many antiviral drug are given through nanosponge in the oral, parenteral, and other drug delivery system. There are some drugs which are formulated in nano delivery systems are zidovudine, saquinavir, interferon-α, acyclovir, nelfinavir etc.

7. Modulating Drug Release

The conventional, commercially available drug have major drawback it is a frequent administration. Hence, a drug loaded into the nanosponge is retained and released slowly over time. Vyas *et al*. has been studied that the hydrophilic cyclodextrin nanosponges are to change the drug release rate, to increase the drug absorption across biological barriers, as a potent drug carrier in immediate release formulations. Hydrophobic cyclodextrin nanosponges are used as a sustained release carrier for water soluble drugs, contain peptide and protein drugs and it was best carriers for the anticancer drug such as doxorubicin, and also, they protect the drug through stomach during its passage time. At pH 1.1 this drug is released very slowly, whereas release is faster if pH is raised to 7.4([i])

2. CONCLUSION

Nanosponge have a significant advantage over other type of drug delivery system. They promote absorption feathers of the drug by increasing dissolution of the drug and increase bioavailability profile of administered drug. The goal of the nanosponge drug delivery system to provide a therapeutic amount of drug to proper absorption site in the body and to achieve and maintain desired drug concentration for sustain period of time. The nanosponge drug delivery system has approach to deliver a therapeutic substance to target site in the body. These reviews explain the characteristic features (advantage and dis -advantage), preparation methods, factors, characterization, and applications of nanosponges in the field of drug delivery.

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