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Review Article

Nanosponge- A Novel Carrier System of Drug Delivery: A Review.

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ABSTRACT

Nanosponge are the novel effective advancement in the nanotechnology drug delivery system as tiny mesh like targeted class hyper cross-linked polymer based colloidal structure in which variety of drug incorporated in its nanosponge core. And their normal average diameter below 1 µm. Nanosponge are the impressive drug carrier which possess larger drug loading capacities compare to other Nano carrier Nanosponge technology has widely applicable in improving solubility, stability. Bio availability and also targeted sustain release of drug also reducing toxicity or side effect of drug .it has eligible for encapsulated both hydrophilic as well as lipophilic drug of different category. Nanosponge have 3- dimensional network (3D) or scaffold with also highly porous Nature Nanosponge delivery can delivered by various rout like orally, and topically can be given.

KEYWORDS

Nanosponge, Solubility enhancement, Encapsulation, Particle size, Carrier.

1. INTRODUCTION

Nanosponge are tiny mesh like novel effective class of hyper cross-linked polymer based colloidal structure at maximum variety of drug molecule incorporated in their core. Many drugs which are poorly water soluble as BCS class II category and also poor bioavailability to reduce these limitations of drug delivery system by nanosponge technology are most applicable [1]. Nanotechnology is the technique in which manufacturing and conversion of substance at Nano scale that prepares final product shows novel properties. Nanotechnology provides various formulations like Nano capsule, Nanosphere, Nanoparticle, Nano suspension and Naosponge. Nanosponge Have tiny mesh like effective novel class of hyper cross-linked polymer based colloidal structure at maximum variety of drug molecule incorporated in their core. they have proved spherical colloidal structure and very high solubilizing capacity for BCS class II (High permeability Low solubility) drug by its inclusion and non-inclusion behavior Nanosponge can solubilized poor water-soluble drug by provide controlling release manner, increasing drug Bioavailability and stability are improving, formulation flexibility [1,2,7]**.** Nanosponge is solid Nano size nature and administrated by safe for oral, Topical and also parenteral rout serve as potential conductor for drug delivery system [2]. For oral dosage form as Tablet, and capsule prepare by using excipients, Diluent, lubricant and anti- caking agent are included in this formulation. For Parenteral administration are prepare by using simply carried sterile water, saline and other aqueous solution. also Gel and Hydrogel are the effectively dosage form in topical administration [4]**.** Drug molecule are encapsulating in nanoparticle core size average diameter is below 1 µm [3, 6, 23]**.**

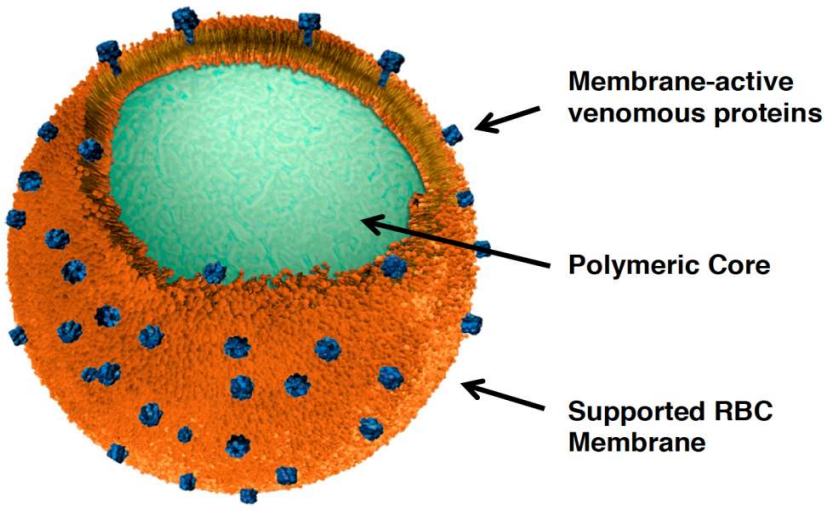

Fig. 1. Structure of Nanosponge.

***Advantages* [10, 11, 12, 13]**

- Nanosponge is the applicable for site specific and effective targeted drug delivery system in predetermined rate.
- They Have Non-toxic, Non –irritant and non- mutagenic.
- Nanosponge is protecting the active ingredient against the decomposition and degradation.
- Mask the unpleasant taste of active ingredient and other material.
- Commercial formulation is easy to scale up.
- Improve the solubility of lipophilic and hydrophilic drug substance.
- Improve stability, elegance, extended release also enhances formulation flexibility.
- Biodegradable
- Predictable release.
- Minimize the harmful side effect.

Disadvantages

- Encapsulating capacity of nanosponge for only small molecule not suitable in large molecule [14].
- Dose dumping can occur at time.

***Chemicals used for the preparation of nanosponge* [15]**

Polymers	Hyper crosslinked Polystyrenes, Alkyloxy-carbonyl Cyclodextrins, Cyclodextrin and its derivatives like Methyl β-Cyclodextrin, 2-Hydroxy Propyl β-Cyclodextrins and Copolymers like Ethyl Cellulose & Poly vinyl acetate.
Cross –linkers	Epi-chloridrine, Diphenyl Carbonate, Di-aryl carbonates, Glutraldehyde, Di-isocyanates, Pyromellitic anhydride, Carbonyldi-imidazoles, 2, 2- bis (acrylamido), Carboxylic acid di-anhydrides, Acetic acid and Dichloromethane

Preparation Method of Nanosponge

Nanosponge prepare by depending on the type of delivery system. They are preparing by understanding parameter such as polymer ratio, Polymer: cross-linking agent ratio and stirring speed or agitation.

1. Emulsion Solvent Diffusion Method

Nanosponge can prepare by using two phases disperse phase and continuous phase, disperse phase containing ethyl cellulose and drug at dissolve in 20 ml of Dichloromethane (cross-linker) and slowly added to continuous phase as polyvinyl alcohol with continuous stirring at 1000 rpm

for 2 Hrs.by using magnetic stirrer. After stirring nanosponge form they were collected and then filter, dried in oven at 40º C for 24 Hrs. [6, 17]

2. *QUASI – Emulsion* Solvent Diffusion [18,19]

It can also prepare by Qusi –emulsion solvent diffusion Nanosponge method by using different amount of polymer. In which Two phase containing disperse phase and continuous phase as disperse phase include polymer (Eutragit RS 100) was dissolve in suitable solvent, then drug added in that solution and dissolved by using ultrasonification at 35ºc, then these disperse phase poured in to the continuous phase containing poly vinyl alcohol solution in water for 60 min. with continues stirring, then mixture is filter and dried in Air Heated Oven at 40 ºc at 24 Hrs. nanosponge are obtained.

3. *Solvent Method* [20]

In this method mixing of polymer with polar aromatic solvent such as dimethylformamide (DMF), Dimethylsulphoxide (DMSO). Then added weighed amount of cross-linker (Dimethylcarbonate, Carbonyl diimidazole) in above mixture ratio as 1:4 and reflux for 1 Hrs. to 48 Hrs. at temperature 10ºc. After complete the reaction, solution is allowed to cool at room temperature then added bi-distilled water and filtered under vacuumed, then purified by sox let extraction with ethanol then dried under vacuum.

4. *Ultrasound Assisted Method* [18,20]

Method in which Nanosponge prepare by reaction in which polymer with cross linker by absence of solvent under the sonication. Pyromelitic anhydride or diphenyl carbonates as cross –linker, hence the mixing of polymer and cross linker in flask. Place the above flask in ultrasound bath containing water and heated up to 90º c and sonicate by 5 Hrs. After sonification process solid substance was down ground in flask remove the impurities by using soxhlet extraction with ethanol. The nanosponge is prepared and store at 25 ºc these prepare nanosponge will be spherical uniform in Nano size at below 5 microns**.**

***5. By Hyper Cross-Linked B Cyclodextrin* [19]**

Nanosponge can also obtained by using recently developed hyper cross linked β- cyclodextrin polymer that forms 3 Dimensional networks. β- cyclodextrin Nanosponge are prepare by condensation process in which Take 100 ml of Dimethyl formamide (DMF) in RBF Then added 17.42 anhydrous β- cyclodextrin to form complete dissolution then added 9.96 gm of carbonyl di- imidazole in RBF and these solution reaction for 4 Hrs. at 100 ºc. After reaction hyper cross-linked cyclodextrin down thoroughly ground then added deionized water to remove DMF. Finally, unreacted reagent removes by using soxhlet extraction with ethanol.

Loading of Drug into Nanosponge

Nanosponge should be perpetrated to required mean particle size below 500 nm. This nanosponge suspended in water and avoid the presence of aggregate by sonicate the nanosponge

then suspension is centrifuged to found the colloidal fraction. The supernatant is separate out and sample is a dried by freeze drying prepare aqueous suspension of nanosponge dispersed in the weighted amount of drug under continuous stirring for specific time (require for complexation) after complexation process separate out uncomplexed (undissolved) by centrifugation and again solid crystal structure of nanosponge are obtained by solvent evaporation or by freeze drying [20]. Crystal from nanosponge is play and importance role in complexation with drug. A study related that para crystalline nanosponge showed varied loading capacities as compare to crystalline nanosponge. drug loading is maximum in crystalline form than paracrystaline one. In poorly crystalline nanosponge, the loading obtained from mechanical mixture rather than inclusion complex. [18, 20]

BCS Class II Drugs

Sr. No.	Category of drug	List of drugs
1	Antianxiety drugs	Lorazepam
2	Antiarrhythmic agents	Amiodarone hydrochloride
3	Antibiotics	Azithromycin, Ciprofloxacin, Erythromycin, Ofloxacin, Sulfamethoxazole
4	Anticonvulsants	Carbamazepine, Clonazepam, Felbamate, Oxycarbazepine, Primidone
5	Anticoagulant	Warfarin
6	Antidiabetic and Antihyperlipidemic drugs	Atorvastatin, Fenofibrate, Glibenclamide, Glipizide, Lovastatin, Troglitazone
7	Antiepileptic drugs	Phenytoin
8	Antifungal agents	Econazole nitrate, Griseofulvin, Itraconazole, Ketoconazole, Lansoprazole, Vericonazole
9	Antihistamines	Terfenadine
10	Antihypertensive drugs	Felodipine, Nicardipine, Nifedipine, Nisoldipine
11	Antineoplastic agents	Camptothecin, Docetaxel, Etoposide, Exemestane, Flutamide, Irinotecan, Paclitaxel, Raloxifene, Tamoxifen, Temozolamide, Topotecan
12	Antipsychotic drugs	Chlorpromazine Hydrochloride
13	Antiretrovirals	Indinavir, Nelfinavir, Ritonavir, Saquinavir
14	Antiulcer drugs	Lansoprazole, Omeprazole
15	Anthelmintics	Albendazole, Mebendazole, Praziquantel
16	Antioxidants	Resveratrol
17	Cardiac drugs	Carvedilol, Digoxin, Talinolol
18	Steroids	Danazol, Dexamethazone
19	Gastroprokinetic agent	Cisapride

20	Immuno suppressants	Cyclosporine, Sirolimus, Tacrolimus
21	NSAIDs	Dapsone, Diclofenac, Diflunisal, Etodolac, Etoricoxib, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Mefenamic acid, Naproxen, Nimesulide, Oxaprozin, Piroxicam
22	Diuretics	Chlorthalidone, Spironolactone

Factor Affecting Nanosponge Formulation

Using polymer can affect the formulation and also performance of nanosponge for complexation (Dissolution) the cavity size of nanosponge should suitable to adapted a drug molecule of particular size[21].

1. Type of Drug

Drug molecule is complex with nanosponge should have certain properties as follow.

- Drug molecular weight should be under 100 to 400 dl
- Drug molecular structure should not be more than five condensed rings.
- Water solubility of drug should be less than 10 mg /ml.
- Melting point of drug should not more than 250ºc.

2. Temperature

In Nanosponge formulation include temperature are also effect on drug /nanosponge complexation. When increasing the temperature that decrease the magnitude of apparent stability constant of drug nanosponge complex and result reduce the interaction force of drug and nanosponge such as hydrophobic force and van-der wall force with increase of temperature. [22]

3. Method of Preparation

Drug and nanosponge complexation also affected cause due to method of loading of drug in nanosponge in which properties of drug and polymer are also important in method of preparation.in most of freeze drying was successful method for drug complexation. [22]

4. Degree of Substitution

Drug / nanosponge complexation can affect by type of molecule and also number of positions of substitution on molecule.[22]

Characterization of Nanosponges

1. **Loading Efficiency (%) of Nanosponge**

   The loading efficiency (%) of Nanosponge is calculated by using below formula [23].

$$\% \text{ LE} = \frac{\text{Actual drug content in nanosponge}}{\text{Theoretical drug content}} \times 100$$

Where,
LE is Percentage loading efficiency.

2. Microscopy Study

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) are used to determine the microscopic properties of drug and formulation (drug / nanosponge complex) [15, 24].

3. Thermo Analytical Method

Thermo analytical method is used to study thermal analysis of nanosponge the change of drug substance such as melting, evaporation, decomposition, oxidation and they have affected on complex formation. The thermogram provided by DTA and DSC can observe for brooding, smipting and appearance of new peak or disappearance of peak. Losses of weight can also support evidence of formation of complex [24].

4. Particle Size and Polydispersity

Particle size in which diameter and polydispersity index can be determine by dynamic light scattering particle sizing software. [15]

5. Zeta Potential

Zeta potential means the measurement of surface charge and it can be measure by additional electrode as particle size apparatus. [15]

6. Fourier Transform Infrared* (FTIR) *Analysis

Interaction of chemical bond between drug and polymer are identifying by the FTIR. Sample has scanned in range from 400-4000cm^{-1} and detector purged carefully by clean dry helium gas to content increase signal level and decrease moisture. [24]

Application of Nanosponge

Nanosponge technique mostly useful in pharmaceutical field. Because of their biocompatibility and versality. Are applicable in excipient that use in formulation of tablet, capsule, granule, pallets. Suspension, solid dispersion and also topical dosage form. Nanosponge can encapsulated both hydrophilic and lipophilic drug substance mostly which drug belong BCS class –II such that is high permeability and low solubility. [3, 7, 22]

Nanosponge For Drug Delivery

Nanosponge technique include it can carry the poorly water-soluble drug because of their nonporous structure that improve the dissolution rate. solubility has important role in nanosponge. β-cyclodextrin based nanosponge are the most effective drug delivery for targeted site. Nanosponge obtained in solid form and can administer through the oral, parenteral, topical and also inhalation dosage form. [13, 25]

Nanosponge For Cancer Therapy

The most difficult task nowadays in pharmaceutical field is the delivery of anticancer drug. Cause of poor solubility of drug. Tumor growth are reducing by most effective nanosponge therapy than the direct injection of the drug is encapsulated into the tiny nanosponge and diffuse to targeting peptide and bind to radiation –induced cell surface receptor on tumor then they have stick in surface of tumor cell and release their carrier. The more effective treatment at same dose with fewer side effects is main benefit of this targeted delivery system. [27]

Oxygen Delivery System

Nanosponge tech. also mainly applicable for oxygen delivery system Nanosponge have prepare by using cyclodextrin as α, β, ϒ cyclodextrin is suspended in water. Saturated with water and in vitro characterized. It is also applicable for obtaining oxygen permeation through silicon membrane by using β - cyclodextrin Nanosponge. Nanosponge also able to store and to release oxygen for longer period of time [12]. Oxygen nanosponge are also useful in provide oxygen to hypoxic tissue which is present in various disorder. [28, 29]

Solubility Enhancement

Nanosponge are also applicable for enhancing the dissolution rate and solubility of poorly soluble drug and also for delivered controlled release profile however molecular dimension and affirmation critical parameter affecting the complexity of incorporation in nanosponge and this does not apply universally to all molecule.[30]

Anti-Viral Application

Nanosponges are useful in ocular, nasal, pulmonary administration pathway. An anti –viral drug or small interfering RNA can be targeted by the Nano carrier and selective delivery to the lung to targeted viruses that infect the RTI, such as respiratory infection, influenza, virus and rhinovirus. [23, 28]

Topical Drug Delivery System

In topical nanosponge can formulate the various category of drug can formulate such as local anesthetic, antifungal and antibiotic etc. with different method like emulsion solvent diffusion method. In topical nanosponge are incorporated with various dosage forms as gel, ointment, cream, hydrogel for topical application. [28, 31]

Other Application of Nanosponge

Nanosponge technology is very important role in fractionalization of peptides by proteomic application. Nanosponge can selectively applicable in biomarker for diagnosis. nanosponge tech. are supply of oxygen and carbon dioxide gases. [27, 31]

2. CONCLUSION

From the above study as concluded that Nanosponge Technology is widely applicable for targeted and site-specific drug delivery system in which they are in small size and spherical shape in which different dosage form such as parenteral, aerosol, topical and oral include tablet and capsule. The nanosponge has able to incorporate either lipophilic or hydrophilic drug in controlled release manner at targeted site.

3. CONFLICT OF INTEREST

There is no conflict of interest in this review.

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