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REVIEW ARTICLE

# SCAFFOLD BASED DRUG DELIVERY SYSTEM: A SPECIAL EMPHASIS ON NANOSPONGES

**KURHE AJINKYA[1*], KENDRE PRAKASH[2] AND PANDE VISHAL[3]**

1. Ajinkya R. Kurhe, Research Scholar, Department of Pharmaceutics
2. Prakash N. Kendre, Assistant Professor, Department of Pharmaceutics
3. Dr. Vishal V. Pande, Associate Professor and Head, Department of Pharmaceutics and Quality Assurance Techniques,
Sanjivani College of Pharmaceutical Education and Research Kopargaon.

**Email: ajinkyakurhe2414@gmail.com**

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**Abstract:**
The advent of nanotechnology lead to invention of many dosage forms. Effective targeted drug delivery systems with controlled release 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 scaffold 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 in the pores. 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 fashion. 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. Owing to their small size and porous nature they can encapsulate poorly-soluble drugs within their matrix and improve their solubility and bioavailability. This review attempts to elaborate the interesting features of nanosponges as a scaffold, method of preparation, characterization and recent updates of nanosponges in drug delivery.

**Keywords:** Nanosponges, Polymer, Scaffold, Cross Linking Agent, Encapsulation.

## Introduction

An ideal drug therapy achieves efficient concentration of drug at the targeted site for a specific period of time in order to reduce general and local side effects. To achieve a desirable therapeutic response, the appropriate amount of drug should be delivered to the site of action. The drug distribution to the other tissues rather than the targeted tissue is a potential cause of toxicity. Targeted drug delivery is the delivery of drug to organ or any part of body to which drug is to be delivered [1].

Effective targeted drug delivery systems with controlled release have been a dream for long time, but it has been largely frustrated by the complex chemistry that is involved in development of new system [2].

The invention of new porous and polymeric network nanosponges has become significant to overcome this problem. Nanosponges are tiny sponges with very small size of diameter below 1um. Nanosponges are incorporated in specific dosage form and circulate around the body until they encounter the specific target site and bind to the surface and start to release the drug in controllable and predictable manner [3]. Nanosponges are three dimensional network or scaffold. Scaffolds are generally composed of polymers and other materials which have been used in drug delivery system for decades. The combined efforts of medical practitioners and material scientist enable fabrication of scaffold with additional drug delivery features to which clinically important functionalities are added.

The backbone serves is a long length of polyester which is mixed in a solution containing small molecules called cross linkers that act as a tiny grappling hooks to fasten different parts of the polymer together.

These tiny sponges have ability to encapsulate a poorly water soluble drug and increase its solubility and also release the drug at target site in controlled manner [1]. The nanosponges occurred in paracrystalline or crystalline form. The entrapment capacity of nanosponges depends on degree of crystallization. Paracrystalline form of nanosponges can show different entrapment capacities. Nanosponges are able to encapsulate both hydrophilic and lipophilic drug substance [4].

It is possible to control the size of nanosponges by varying the concentration of polymer to cross linkers. The particle size was observed 285nm using polymethylmethymethacrylate polymer, 370 nm using ethyl cellulose as polymer and 310nmusing pluronic F-68 as polymer [5].

Nanosponges are water soluble but do not chemically break up in water. They mix up with the water and serves as a transporter fluid. Class II drug and the drugs with smaller half life are the choice for encapsulation in nanosponge for increasing the solubility and half life of the drug. Nanosponges are solid in nature and can be formulated as oral, topical, parenteral dosage form [6].

Nanosponges are classified as encapsulating nanoparticles, complexing nanoparticles and conjugating nanoparticles. Encapsulating nanoparticles consist of many holes that carry the drug molecule in their aqueous core. Complexing nanoparticles are nanoparticle that attracts the molecule by electrostatic charges and conjugating nanoparticles are the nanoparticles that link the drug through covalent bond [1, 7].

**Boons of Nanosponges [8, 6, 2]**

1. Hydrophobic drugs can be encapsulated within the nanosponges
2. Controllable and predictable release of drug
3. Targeted drug delivery
4. Improved stability and formulation flexibility
5. Can mask the unpleasant flavours and potential to convert liquid substance to solid substance
6. Particle size vary according to proportion of cross-linker to the polymer
7. Less harmful side effects because of drug having less contact with healthy tissue
8. Nanosponges are non-irritating, non-mutagenic, non-toxic and non-allergenic Biodegradable
9. Easy scale up for commercial production.

**Chemicals Used for the Synthesis of Nanosponges**

**Polymers**

Polymer used for synthesis of nanosponges are including polyvinyl alcohol (PVA), ethyl cellulose, polymethylmethacrylate, hyper cross linked polystyrenes, cyclodextrines and its derivatives like methyl beta cyclodextrine, alkyloxycarbonylcyclodextrine [9].

**Crosslinkers**

Dichloromethane, diphenyl carbonate, diisocyanates, epichloridine, glutardehyde and pyrimelliticanhydride[9].

**Preparation of Nanosponges**

**1. Emulsiom solvent diffusion method**

Nanosponges can be prepared by using different concentration of ethyl cellulose and polyvinyl alcohol. The various ratio of drug to polymer are used to improve the drug loading and to obtain a tailored release. The dispersed phase containing drug and polymer dissolved in 20 ml of dichloromethane was added slowly to definite amount of polyvinyl alcohol in 100ml of aqueous external phase with 1000-1500 rpm stirring speed using magnetic or mechanical stirrer for 3-5 hrs. The formed nanosponges were collected by filtration and dried in oven for 40˚C for 24hrs and packed in a container [10].

**2. Ultrasound-assisted synthesis**

Nanosponges can be prepared by reacting polymers with cross-linkers in absence of solvent under sonication. In this method, the polymer is mixed with the cross-linker in a appropriate molar ratio in a flask. The flask is then placed in ultrasound bath which is filled by water and heated at 90˚C. Sonication of the above mixture is done for few hours. Then, the above mixture is to be cooled and product obtained is broken roughly. The product is washed by water to remove non-reacted polymer and purified by using soxhlet extraction using ethanol and further drying will give nanosponges[2].

**3. Hyper cross linked beta cyclodextrins**

Nanosponges can be obtained by cross linking with different types of cyclodextrins with a carbonyl as a crosslinker. They are obtained by reacting cyclodextrin with cross-linkers such as diphenyl carbonate diisocianates. The transparent block of hyper cross linked cyclodextrin was roughly ground and excess of water is added remove solvent. The product obtained is purified using soxhlet extraction with ethanol and product obtained is dried in oven at 60˚C overnight[4].

**Loading of Drug IntoNanosponges**

Nanosponges should be pre-treated to obtainan average particle size below 500nm. Nanosponges are suspended in water and sonicate to avoid the presence of aggregates and then centrifuge the suspension to obtained colloidal

fraction. Supernatant is separated and sample is dried under freeze drying. Aqueous suspension of nanosponges is prepared. The excess amount of drug is dispersed in aqueous suspension of nanosponges and maintained the suspension under constant stirring for specific time required for complexation. After complexation, separate the uncomplexed drug from complex drug bycentrifugation. Then obtained the solid crystals of nanosponges by freeze drying or solvent evaporation.

Crystal structure of nanosponges plays a very important role in complex formation with drug. A study revealed that paracrystalline nanosponges showed different loading capacities when compared to crystalline nanosponges [1, 7].

**Factors Influencing Nanosponges Formulation**

**Types of polymer**

Type of polymer used can influence the formation as well as performance of nanosponges. Uniform and small particle of nanosponges depends on polymer complex. The polymer can be used to encapsulate the drug molecule [12].

**Types of drug**

Drug molecule to be complexed with nanosponges should have certain characteristics as mentioned below [12].

a. Molecular weight between 100-400 Daltons
b. Drug molecule should contain not more than five condensed ring
c. Solubility in water is less than mg/ml
d. Melting point of the drug substance should be below 250˚C.

**Temperature**

Temperature change can affect drug/ nanospongescomplexation. Increase in temperature reduces stability of drug/ nanosponges complexation [1].

**Method of preparation**

The method of loading the drug into nanosponges can affect drug/ nanospongecomplexation. Effectiveness of a method depends on the nature of drug and type of polymer, in most cases freeze drying was found to be more effective method for drug complex formation [1].
List of BCS class II drugs which can be developed as nanosponges are given in Table 1.

**Characterization of Nanosponges**

**1. Solubility studies**

The phase solubility method described by Higuchi and Connors is most widely used approach to study degree of complexation. Nanosponges are confirmed by insolubility in water and organic solvent like DMSO (Dimethylsulfoxide), DMF (Dimethylformamide) [7].

**Entrapment efficiency**

Dispersed the nanosponges loaded with drug in solvent which solubilises drug, soak for overnight and sonicate for 10 min to break the complex, diluted suitably and then analysed by UV spectroscopy or HPLC method.
Loading Efficiency= Actual drug content/ Theoritical drug content×100 [13].

**Microscopy studies**

For morphological study of drug, nanosponges and drug loaded with nanosponges. Scaning Electron Microscopy (SEM) and Transmission Electron Microscopy(TEM) confirms the formation of inclusion complex [2].

**Particle size and polydispersibility index**

The particle size and polydispersibility index can be determined by dynamic light scattering using 90plus particle sizer equipped with mass option particle sizing soaftware. Polydispersibility index (PDI) is an index of width within the particle size distribution. PDI for monodispersed sample is lower, whereas PDI is higher for wider particle size distribution [4, 14].

**Zeta potential determination**

Zeta potential measurement, can be made by using an additional electrode in particle size instruments. Zeta potential is useful to calculatesurface charge on the particles [14].

**Infra-Red spectroscopy**

IR spectroscopy is used to estimate interaction between nanosponges and drug molecule in solid state. Nanosponge bands slightly changes upon complex formation and if the fraction of drug molecule encapsulated in the complex is less than 25%. When interaction between drug and nanosponges occurs then it causes a shift of band which can be noticed. The technique is not generally suitable to detect the inclusion complex and is less descriptive than other methods.The application of the IR spectroscopy is limited to some drugs having some characteristic bands such as sulfonyl or carbonyl groups.The appearance or disappearance of peak in nanospongescompared to drug may indicate interaction [9].

**X-ray diffractometry and single crystal X-ray structure analysis**.

X-ray diffractiometry can be used to detect inclusion complexation in the solid state. When the drug molecule is liquid it does not shown diffraction of their own, then the diffraction pattern of newly formed substance clearly differs from that of uncomplexednanosponges. The difference of diffraction pattern indicates the inclusion complex formation. When drug substance is solid in nature a comparison has to be made between

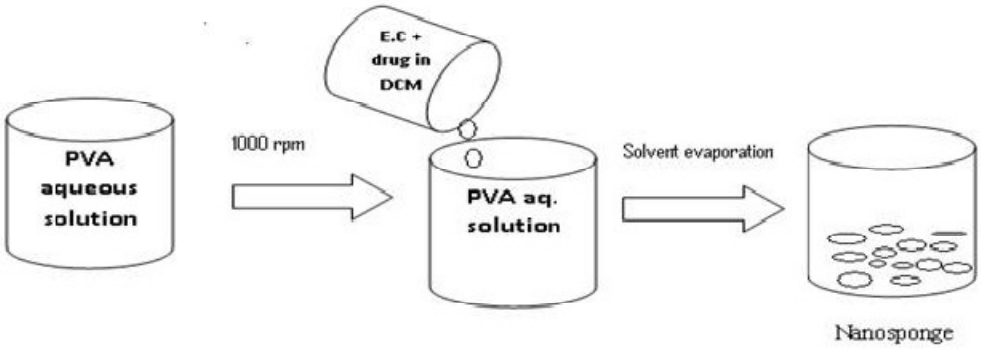


**Fig.1: Preparation of nanosponges by emulsion solvent diffusion method [11].**

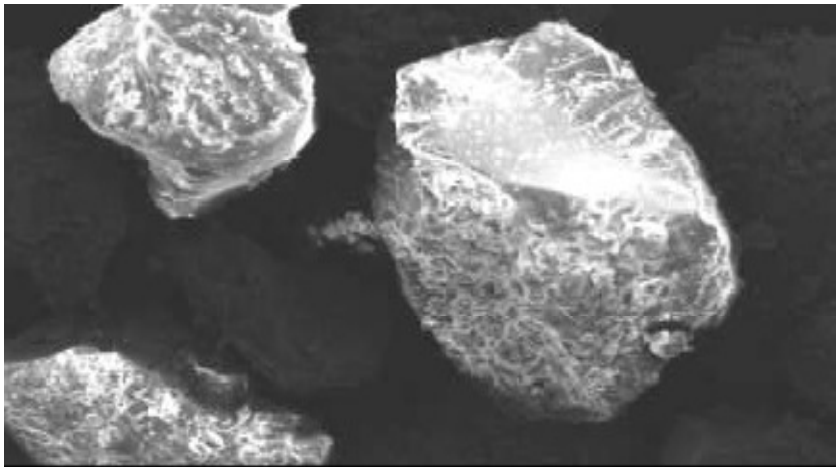

**Fig 2: SEM image of β-cyclodextrinnanosponges [14].**

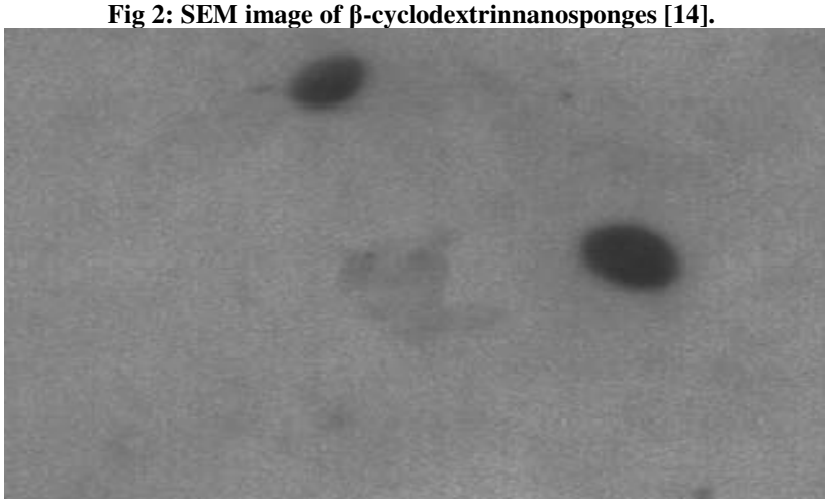

**Fig 3:TEM image of Plain nanosponges [15].**

**Table 1. Biopharmaceutical Classification System Class II drugs [3, 4].**

| | |
|---|---|
| Antianxiety drugs | Lorazepam |
| Antibiotics | Ciprofloxacin, Azitromycin, Erythromycin, Ofloxacin, Sulfamethoxazole |
| Antiarrhythmic agents | Amidarone hydrochloride |
| Anticoagulant | Warfarin |
| Antidiabetic and Antihyperlipidemic drug | Atorvastatin, Fenofibrate, Glibenclamide, Glipizide, Lovastatin, Troglitazone |
| Anticonvulsants | Carbamazepine, Clonazepam, Felbamate, Oxycarbazepine, Primidon |
| Antiepileptic drug | Phenytoin |
| Antihistamines | Terfenadine |
| Antifungal agent | Econazol nitrate, Griseofulvin, Itraconazole, Ketoconazole, Lansoprazole, Vericonazole |
| Antihypertensive drug | Felodipine, Nicardipine, Nifedipine, Nisoldipine |
| Antineoplastic agent | Camptothecin, Docetaxel, Etoposide, Exemestane, Flutamide, Irinotecan, Paclitaxel, Raloxifene, Tamoxifen, Temozolamide, Topotecan |
| Antipscychotic drugs | Chlorpromazine hydrochloride |
| Antiretrovirals | Indinavir, Nelfinavir, Ritonavir, Saquinavir |
| Antiulcer drugs | Lansoprazole, Omeprazole |
| Antioxidants | Resveratrol |
| Antihelmintics | Albendazole, Mebemdazole, Praziquantel |
| Cardiac drugs | Carvedilol, Digoxin, Talinolol |
| Diuretics | Chlorthalidone, Spironolactone |
| Gastroprokinetics agent | Cisapride |
| Immunospressants | Cyclosporine, Sirolimus, Tacolimus |
| NSAID's | Dapsone, Diclofenac, Diflunisal, Etodolac, Etoricoxib, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Mefenamic acid, Naproxen, Nimesulide, Oxaprozin, Piroxicam |
| Steroids | Danazol, Dexamethazone |
| Miscellaneous | Atovaquone, Melarsoprol, Phenazopyridine, Ziprasidone |

**Table 2.Polydispersibility index**

| Polydispersity index | Type of dispersion |
|---|---|
| 0-0.05 | Monodispersed standard |
| 0.05-0.08 | Nearly monodisperse |
| 0.08-0.7 | Midrange polydispersity |
| >0.7 | Very polydisperse |

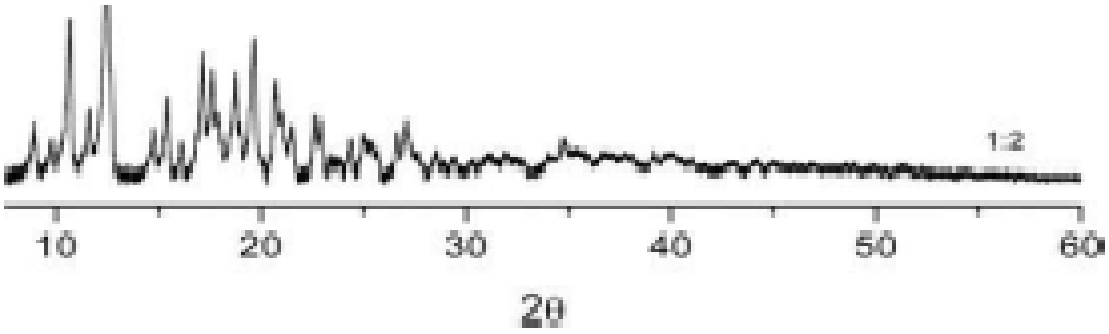


**Fig 4: X Ray Diagram of Crystalline Nanosponges at Cross-Linking Agent 1:2 Ratio [15].**

diffractograms of the assumed complex and that of mixture of drug with polymer molecules [3].
The inclusion complex formation of drug with nanosponges changes the diffraction patterns and also changes the crystalline nature of drug. Sharpening of the existing peaks and appearance of few new peaks leads to formation of inclusion complex [3].

**Single crystal X-ray structure analysis.**
It is used to determine the interaction between the host and guest molecule and precise geometrical relationship can be established [10].

**Thermo –analytical methods**
Thermo-analytical method determines whether the drug substance undergoes specific changes before the thermal degradation of nanosponges. The change of drug substance almost includes evaporation, melting, decomposition and oxidation. The change of the drug substance indicates the formation of complex. The thermo gramobtained by DSC and DTA can be observed for shifting, broadening and appearance of new few peaks or disappearance of peaks. The shift to endothermic peak is very small if their is interaction between the drug and the excipient is very weak [16].

**In-vitro drug release study**
Drug release from nanosponges can be measured across the suitable dialysis membrane by using Franz diffusion cell apparatus. The dialysis membrane soaked in receptor medium overnight which is used as barrier between donorand receptor compartment.Appropriate amount of nanosponges are placed on the donor compartment that was sealed with aluminium foil. The receptor compartment was filled by suitable medium,temperature was set to 37+_0.5˚C and stirred at 100rpm with Teflon coated magnetic stirring bars. Aliquots were collected at designated time intervals from receptor compartment and replaced by same solution to maintain the sink condition. The sample was analysed using UVspectrophotometer [13].

Drug release from nanosponges was analysed using Zero order, first order, higuchi, peppas, hixoncrowell and makoid-bankar model [1].

**Conclusion**
The nanosponges have ability to encapsulate either hydrophilic or lipophilic drug and release the drug in a controlled and predictable fashion at the target site. By controlling the ratio of polymer to cross linker and stirring rate release particle size and release rate can be modulated. Nanosponges increases the drug solubility of poorly water soluble drugs and protects the drug from physiochemical degradations. Nanosponges can be developed as different dosage forms like Parenteral, aerosol, topical, tablet and capsule. Thus, nanosponges are a boon for targeted and site specific drug delivery system.

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