

## A comprehensive review on nanosponge drug delivery system

### Abstract-

Nanosponges are tiny sponges having size of about a virus and can be filled with variety of drugs. This sponge can circulate around the body until interact with specific target site and stick on surface and start releasing drug in a controlled manner. Important characteristic of these sponges is their solubility in aqueous form and give a effect to the drugs with poor solubility. This review is focusing on the preparation methods, applications of nanosponges in the field of drug delivery.

**Keywords-** Nanosponges, targeted site, nanodelivery.

### Introduction

The drug delivery technology has certainly a new interest for drugs by providing them new life through their therapeutic targets. Targeting drug delivery is the major problem which is being faced by the researchers. Target oriented drug improvements in therapeutic efficacy, reduction in side effects and optimized dosing regimen, shall be the leading trends in the area of therapeutics<sup>1</sup>. Targeted drug delivery implies for selective and effective localization of pharmacologically active moiety at preidentified (preselected) target in therapeutic concentration, while restricting its access to non-target normal cellular linings and thus minimizing toxic effects and maximizing therapeutic index of the drug<sup>2</sup>. They provide excellent topical delivery of drugs<sup>3</sup>. these

embraces nanotechnology which is applied to pharmacy as nano materials, diagnosing and focusing right place in the body and controlling release of the drug<sup>4</sup>. Nanosponges is about the size of virus which has been backed by naturally degradable polyster .These tiny sponges can circulate around the body they encounter the specific target site and stick on the surface and began to release the drug in a controlled and predictable manner. Owing to their small size and porous nature they can bind poorly- soluble drugs within the matrix and improve their bioavailability. These are solid in nature and it can be formulated as oral, parenteral, topical or inhalational dosage forms. For oral administration, nanosponges may be dispersed in a matrix of excipients, diluents, lubricants and anti-caking agents which is suitable for the preparation of tablets or capsules.

For parenteral administration, these can be simply mixed with sterile water, saline or other aqueous solutions. For topical administration, they can be effectively incorporated into topical hydrogel<sup>5</sup>.

### Advantages<sup>6,7,8</sup>

1. This technology offers entrapment of ingredients and reduces side effects.
2. Improved stability, increased elegance and enhanced formulation flexibility.
3. These formulations are stable over range of pH 1 to 11.
4. These formulations are stable at the temperature up to 130<sup>0</sup>C.
5. These formulations are compatible with most vehicles and ingredients.
6. These are self sterilizing as their average pore size is 0.25<sup>1</sup>/<sub>4</sub>m where bacteria cannot penetrate.
7. They increase the bioavailability of drug.
8. These modify the release of drug.
9. They increase the solubility of poorly soluble drug.

### Disadvantages<sup>9</sup>:

- 1) Nanosponges include only small molecules.

2) Depend only upon loading capacities.

### **Synthesis of nanosponges**

It is one of the important criteria for the formation of product obtained activity in  $\beta$ -cyclodextrin, titanium oxide.

#### **1. Solvent method<sup>10, 11</sup>**

The solvent required is mixed with the polymer mainly in a polar aprotic solvent, for example dimethyl formide, dimethyl sulfoxide then add this mixture to cross linker in a exceed quantity, the ratio for cross linker/ molar ratio is preferred as 4 to 16. The reaction is proceeded with a solvent reflux temperature and time ranging from 1 to 48 hr. The cross linkers which may preferred are dimethyl carbonate and carbonyl di-imidazole. The reaction is completed and solution is allow to cool at room temperature then product is added to excess of bi-distilled water and product is recovered by filtration under vaccum and simultaneously purify by prolonged soxhlet extraction with ethanol. Finally product is dried under vaccum and grinded in a mechanical mill to obtain homogeneous powder

#### **2. Ultrasound assisted synthesis<sup>12, 13</sup>**

Nanosponges are obtained by reacting polymer with cross linkers without adding or without using solvent and sonification is maintained. The polymer is mix with a cross linkers in a balanced ratio in a flask. The flask is placed in a molar ratio in an ultrasound bath field with water and temperature maintained at 90 °C, the mixture is sonicated for 5 hrs. Then the mixture is kept to cool and product is break roughly then the product is washed with water to remove non-reacted polymer and subsequently purified by soxhlet extraction with ethanol. The product is dried under vaccum at 25 °C until its further use is utilized.

#### **3. Loading of drug into nanosponges<sup>14, 15</sup>**

Nanosponges obtained should be pretreated to maintain mean particle size blow 500nm. Nanosponges are suspended in water and were sonicated to avoid presence of aggregates and particles and got centrifuged to obtain colloidal fraction, then supernatant is separated and dried sample by freezing by drying. Further proceeding start with preparing aqueous suspension of nanosponges and excess amount of drug is dispensed for maintaining suspension under constant stirring for specific time period for complexation is over the undissolved drug (uncomplexed condition) is separated from complexed drug with the process of centrifugation. This process helps in evolving solid crystals of nanosponges by solvent evaporation or freeze drying. Paracrystalline nanosponges revealed different loading capacities when compared to crystalline nanosponges poorly crystalline nanosponges had act drug loading as a mechanical mixture rather than inclusion complex.

### **Factors influence nanosponge formation**

**1. Type of polymer<sup>16</sup>**- Type of polymer used can influence the formation as well as the performance of Nanosponges. For complexation, the cavity size of nanosponge should be suitable to accommodate a drug molecule of particular size.

#### **2. Type of drugs<sup>17</sup>**-

Drug molecules to be complexed with nanosponges should have certain characteristics mentioned below -

- Molecular weight between 100 and 400
- Drug molecule consists of less than five condensed rings
- Solubility in water is less than 10mg/mL
- Melting point of the substance is below 250°C

#### **3. Temperature**

Temperature changes can affect Drug/Nanosponge complexation. In general, increasing 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, such as van-der Waal forces and hydrophobic forces with rise of temperature<sup>18</sup>.

## Physicochemical characterization of nanosponge

### 1. Particle size determination

Free-flowing powders with fine aesthetic attributes will possible to obtain by controlling the size of particles during polymerization. Particle size analysis of loaded and unloaded nanosponges will be performed by laser light diffractometry or Malvern Zeta sizer. Particles larger than 30 m can impart gritty feeling and hence particles of sizes between 10 and 25 m are preferred to use in final topical formulation<sup>19</sup>.

### 2. Determination of loading efficiency and production yield<sup>20, 21</sup>

The prepared nanosponge loading efficiency is determined by subtracting the un-entrapped drug from the total amount of drug. The drug entrapment efficiency will be determined by separating un-entrapped drug estimated by any suitable method of analysis. The method used for separation of un-entrapped drug by gel filtration, dialysis and ultra centrifugation.

**3. Porosity-** Porosity study is performed to check the extent of nanochannels and nanocavities formed. Porosity of nanosponges is assessed with a helium pycnometer, since helium gas is able to penetrate inter- and intra-particle channels of materials. The true volume of material is determined by the helium displacement method. Owing to their porous nature, nanosponges exhibit

higher porosity compared to the parent polymer used to fabricate the system<sup>22</sup>.

**4. Swelling and water uptake<sup>23</sup>**- For swellable polymers like polyamidoamine nanosponges, water uptake can be determined by soaking the prepared nanosponges in aqueous solvent. Swelling and water uptake can be calculated using equations:

$$\% \text{ Swelling} = \frac{\text{Marking of cylinder at a specified time point}}{\text{Initial marking before soaking}} \times 100$$

$$\% \text{ Water uptake} = \frac{\text{Mass of hydrogel after 72 hrs}}{\text{Initial mass of dry polymer}} \times 100$$

**5. Resiliency (Viscoelastic properties)-** Resiliency of sponges can be modified to produce beadlets that is softer or firmer according to the needs of the final formulation. Increased crosslinking tends to slow down the rate of release. Hence resiliency of sponges will be studied and optimized as per the requirement by considering the release as a function of cross-linking with time<sup>24</sup>.

### 6. Zeta Potential

Zeta potential is a measure of surface charge. The surface charge of nanosponge can be determined by using Zeta sizer<sup>25</sup>.

**7. In vitro release studies-** Dissolution profile of Nanosponge can be studied by use of the dissolution apparatus usp XXIII with a modified basket consisted of 5m stainless steel mesh. Speed of the rotation is 150 rpm. The dissolution medium is selected while considering solubility of actives to ensure sink conditions. Samples from the dissolution medium can be analyzed by a suitable analytical method studied by use of the dissolution apparatus USP xxiii with a modified basket consisted of 5m stainless steel mesh. Speed of the

rotation is 150 rpm. The dissolution medium is selected while considering solubility of actives to ensure sink conditions. Samples from the dissolution medium can be analyzed by a suitable analytical method<sup>26</sup>.

**8. Permeation studies-** The diffusion studies of the prepared nanosponge can be carrying out in Franz diffusion cell for studying the dissolution release of nanospongethrough a cellophane membrane. Nanosponge sample (0.5g) can taken in cellophane membrane and the diffusion studies were carried out at  $37 \pm 1^\circ$  using 250 ml of phosphate buffer (pH 7.4) as the dissolution medium. 5ml of each sample can withdrawn periodically at 1, 2, 3, 4, 5, 6, 7 and 8 hrs and each sample will replaced with equal volume of fresh dissolution medium<sup>27</sup>.

#### **Applications of nanosponges:**

##### **1. Nanosponges for drug delivery<sup>28</sup>**

Because of their nonporous 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.

##### **2. Nanosponges as chemical sensors<sup>29</sup>**

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 initially 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<sub>2</sub> gas.

##### **3. Nanosponge for oral delivery<sup>30</sup>:**

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.

##### **4. Solubility enhancement<sup>30</sup>:**

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

##### **5. Nanosponges as a carrier for biocatalysts and release of enzymes, proteins, vaccines and Antibodies<sup>31</sup>:**

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.

##### **6. Antiviral application<sup>32</sup>:**

Nanosponges used in nasal, pulmonary route of administration. It providespecificity 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 nanocarriers are- Zidovudine, Saquinavir.

##### **7. Cancer<sup>34</sup>:**

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.

##### **8. Oxygen Delivery System<sup>33</sup>:**

Characterized by using  $\alpha$ ,  $\beta$  and  $\gamma$  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

## CONCLUSION

Nanosponges are tiny mesh-like structures that may revolutionise the treatment of many diseases and this technology is five times more effective at delivering drugs for cancer than conventional methods. Because of their small size and spherical shape nanosponges can be developed as different dosage forms like parenteral, aerosol, topical, tablets and capsules. Nanosponge are nano sized colloidal carrier so they easily penetrate through skin. The nanosponges have the ability to include either lipophilic or hydrophilic drugs and release them in a controlled and predictable manner at the target site. The nanosponges have the ability to incorporate many drugs and release them in a controlled and predictable manner at the target site. Topical nanosponge can be more patient compliant and provide sufficient patient benefits by reducing repeated doses and side effects. Nanosponge can be effectively incorporated into topical drug delivery system for retention of dosage form on skin. Hence present study concludes that nanosponges may play an important role for the treatment of different diseases.

## REFERENCES

1. Vyas SP, Khar RK. Targeted and Controlled Drug Delivery- Novel Carrier Systems. Molecular Basis of Targeted Drug Delivery. CBS Publishers and Distributors. New Delhi. 2008: 38- 40.
2. Nacht S, Kantz M, The Microsponge: A Novel Topical Programmable Delivery System. Chapter 15, In: *Topical Drug Delivery Systems*, 1992, 42, 299-325.
3. Cavalli R, Trotta F, and Tumiatti W, Cyclodextrin-based nanosponges for drug delivery. *Journal of inclusion phenomena and macro chemistry*, 2006, 56(1-2):209-213
4. Herbert AL, Martin MR, Gilbert SB, Pharmaceutical dosage forms: Disperse Systems. Marcel dekker, inc, 2005, 2(3), 88-105.
5. Selvamuthukumar Subramanian, Anandam Singiredd, Kannan Krishnamoorthy, and Manavalan Rajappan, Nanosponges: A Novel drug delivery system-Review, *J Pharm Pharmaceut Sci*, 2012, 15(1), 103 -111.
6. Liang L, De-Pei L, Chih-Chuan L, Optimizing the delivery systems of chimeric RNA DNA Oligonucleotides beyond general oligonucleotide transfer, *Eur J Biochem*, 2002; 269: 5753–5758
7. Aritomi H, Yamasaki Y, Yamada K, Honda, Khoshi M, Development of sustained release formulation of chlorpheniramine maleate using powder coated microsponges prepared by dry impact blending method. *Journal of Pharma Sci and Tech.*, 1996, 56(1):49-56
8. Yurtdas G, Demirel M, Genc L, Inclusion complexes of fluconazole with b-cyclodextrin: physicochemical characterization and in vitro evaluation of its formulation, *J. Incl. Phenom. Macrocycl. Chem*, 2011, 70, 429–435;
9. Zuruzi S, MacDonald NC, Moskovits M, Kolmakov A, Metal oxide nanosponges as chemical sensors: Highly sensitive detection of hydrogen using nanosponge titania; *Angewandte Chemie*, 2007, 46 (23): 4298-4301.
10. Swaminathan S, Vavia PR, Trotta F, Formulation of beta cyclodextrins based nanosponges of itraconazole, *J Incl Phenom Macro Chem*, 2007, 57:89-94
11. Gilardi G, Trota F, Cavalli R, Ferruti P, Ranucci IE, Di Nardo G, Roggero C, Tumiatti V, Cyclodextrin nanosponges as carrier for biocatalysts, and in the delivery and release of enzymes, proteins, vaccines and antibodies, 2009. WO2009149883 A1.
12. Wong VN, Fernando G, Wagner AR, Zhang J, Kinsel G.R, Zauscher S, Dyer D.J., Separation of peptides with polyionic nanosponges for MALDIMS. *Langmuir*, 2009, 25(3):1459-65



13. Ansari KA, Torne S., Vavia PR, Trotta F., Cavalli R., Cyclodextrin - Based Nanosponges for Delivery of Resveratrol: In vitro characterization, stability, cytotoxicity and permeation study, *AAPS Pharm Sci Tech*, 2011, 12, (1), 279-86.
14. Yadav Geeta, Panchory Hiten, Nanosponges : a boon to the targeted drug delivery system, *Journal of drug delivery and therapeutics*, 2013, 3(4), 151-155
15. Rosalba M, Roberta C, Roberto F, Chiara D, Piergiorgio P, Leigh E, Li S, Roberto P. Antitumor activity of nanosponge-encapsulated Camptothecin in human prostate tumors. *Cancer Res*, 2011; 71:4431
16. Renuka S, Roderick BW, Kamla P. Evaluation of the kinetics and mechanism of drug release from Econazole Nitrate nanosponge loaded carbapol hydrogel. *Ind J Parm Edu.*, 2011, 45(1): 25-31.
17. Renuka S., Kamla P., Polymeric nanosponges as an alternative carrier for improved retention of econazole nitrate onto the skin through topical hydrogel formulation *Pharm Dev Technol.*2011, 16(4):367-376.
18. Mamotra R, Bharti N, Bhandari N, *World journal of pharmacy and pharmaceutical sciences*, Nanosponges as a potential carrier in novel drug delivery system, 2016, 5 (6), 415-424.
19. Wong VN, Fernando G, Wagner AR, Zhang J, Kinsel GR, Zauscher S, Dyer DJ. Separation of peptides with polyionic nanosponges for MALDIMS analysis. *Langmuir*, 2009;25(3) :1459-65
20. Cavalli R, Akhter AK, Bisazza A, Giustetto P, Trotta F, Vavia P. Nanosponge formulations as oxygen delivery systems. *Int J Pharm*, 2010; 402(1-2): 254-257
21. Sharma R, Roderick B, Pathak K, Evaluation of kinetics and mechanism of drug release from Econazole nitrate Nanosponges loaded carbopol Hydrogel, *Indian Jof Pharma Edu and research.*, 2011, 45(1) :25-31.
22. Lala R, Thorat A, Gargote C, Current trends in  $\beta$ - cyclodextrin based drug delivery systems, *Int J Res Ayur Pharm*, 2011; 2(5): 1520-1526.
23. Patil B S, Mohite SK, *European journal o f pharmaceutical and medical research*, Formulation design and development of artesunate nanosponge, 2016,3(5), 206-211.
24. Wester R, Patel R, Natch S, Leyden J, Melendres J, and Maibach H. Controlled release of benzoyl peroxide from a porous microsphere polymeric system can reduce topical irritancy, *J Am Acad Derm*; 1991, 24:720-726.
25. Renuka S, Roderick BW, Kamala P, Evaluation of the kinetics and mechanism of drug release from econazole nitrate nanosponge loaded carbapol hydrogel, *Ind J ParmEduRes*, 2011, 45:25-31.
26. Rajeswari C, Alka A, Javed A, Khar RK. Cyclodextrins in drug delivery: an update review. *AAPS pharmSciTech*, 2005; 6(2):E329-E357
27. Amber V, Shailendra S, Swarnalatha S. Cyclodextrin based novel drug delivery systems. *J Incl Phenom Macrocycl Chem*, 2008 ; 62:23-42
28. Shankar S, Linda P, Loredana S, Francesco T, Pradeep V, Dino A, Michele T, Gianpaolo Z, Roberta C. Cyclodextrin-based nanosponges encapsulating camptothecin: Physicochemical characterization, stability and cytotoxicity, *Eur J Pharm Biopharm*, 2010; 74: 193-201.
29. Jenny A, Merima P, Alberto F, Francesco T. Role of  $\beta$ - cyclodextrin nanosponges in polypropylene photooxidation, *Carbohydrate Polymers*, 2011; 86: 127– 135.
30. Ramnik S, Nitin B, Jyotsana M, Horemats SN. Characterization of Cyclodextrin Inclusion complexes – A Review. *J Pharm Sci Tech*, 2010; 2(3): 171-183.
31. Amber V, Shailendra S, Swarnalatha S, Cyclodextrin based novel drug delivery systems. *J Incl Phenom Macrocycl Chem.*, 2008; 62: 23-42
32. Martin A, Swarbrick J, Cammarrata A. In: *Physical Pharmacy–Physical Chemical Principles in Pharmaceutical Sciences*. 3: 1991; 527
33. Emanuele AD, Dinarvand R. Preparation, Characterization and Drug Release from Thermo responsive Microspheres. *Int J Pharm.*1995; 237-242.