



Nanosponges: A Novel Approach of Drug Delivery System

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ABSTRACT

Targeted drug delivery to specific sites is the significant problem which is being faced by the researchers. The development of new colloidal carrier called nanosponges has the potential to solve these problems. Nanosponge is a novel and emerging technology which offers controlled drug delivery for topical use. In this review article, application of nanosponges, its preparation methods and evaluation have been discussed. Nanosponges play a vital role in targeting drug delivery in a controlled manner. A wide variety of drugs can be loaded into nanosponge for targeting drug delivery. Both lipophilic as well as hydrophilic drugs can be loaded into nanosponges. Nanosponge drug delivery system has emerged as one of the most promising fields in life science.

Keywords: Nanosponges, topical application, polymers, targeted drug delivery, controlled drug delivery, colloidal carrier.

INTRODUCTION

The drug delivery technology has certainly a new interest for drugs by providing them new life through their therapeutic targets. Nowadays, targeting drug delivery is the major problem which is being faced by the researchers. Target oriented drug administration with improvements in therapeutic efficacy, reduction in side effects and optimized dosing regimen, shall be the leading trends in the area of therapeutics. 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.¹

Nanosponge is a novel approach which offers controlled drug delivery for topical use. Nanosponge is an emerging technology for topical drug delivery. Nanosponge drug delivery system is employed for the improvement of performance of topically applied drugs. 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.² Nanosponges have emerged as one of the most promising fields of life science because of their application in controlled drug delivery.³ Nanosponge technology offers entrapment of ingredients and is believed to contribute towards reduced side effects, improved stability, increased elegance and enhanced formulation flexibility.³ Nanosponges are non-irritating, non-mutagenic, non-allergenic and non-toxic.⁴

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 breast cancer than conventional methods.⁵ Nanosponges are made up 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 molecules.⁶ Nanosponges are encapsulating type of nanoparticles which encapsulates the drug molecules within its core.² As compared to other nanoparticles, nanosponges are insoluble in water and organic solvents, porous, non toxic and stable at high temperatures up to 300°C.²

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 feature of these nanosponges is their aqueous solubility which allows the use of these systems effectively for drugs with poor solubility.

The nanosponges are solid in nature and can be formulated as oral, parenteral, topical or inhalational dosage forms. For oral administration, these may be dispersed in a matrix of excipients, diluents, lubricants and anticaking agents which is suitable for the preparation of tablets or capsules.⁷ For parenteral administration, these can be simply mixed with sterile water, saline or other aqueous solutions.⁷ For topical administration, they can be effectively incorporated into topical hydrogel.^{3,8}

The researchers at Vanderbilt University and Emory University recently reported on a controlled - release nanoparticle drug delivery system, which may be an improved delivery method for delivering anticancer therapies, including direct injection into tumour site. These nanoparticle circulate in the body until they encounter the surface of a tumour cell, where they adhere to the surface and start releasing the drug in a controlled and predictable manner.^{3,2}



Targeted drug delivery systems of this type have several basic advantages. As the drug is released at the tumor site instead of circulating widely through the body, it should be more effective for a given dosage. They also should have fewer harmful adverse effects because smaller amounts of the drug come into contact with healthy tissue. Another advantage is that the Nanosponge particles are soluble in water. Encapsulating the anticancer drug in Nanosponge allows the use of hydrophobic drugs that do not dissolve readily in water. Recently, these drugs must be mixed with adjuvant

reagents, which potentially can reduce the efficacy of the drug or cause adverse effects.^{31, 32}

Polymers Used in Nanosponge Preparation²

There are various polymers and cross linkers are used in the preparation of nanosponges, listed in table 1.

Drugs Formulated as Nanosponges

Some drugs formulated as nanosponges are given in Table 2.

Table 1: Different polymers for nanosponge formulation

Polymers	Copolymers	Cross linkers
Hyper cross linked Polystyrenes, Cyclodextrines and its derivatives like Alkyloxycarbonyl Cyclodextrins, Methyl β -Cyclodextrin, Hydroxy Propyl β -Cyclodextrins.	Poly (valerolactone allylvalerolactone), Poly (valerolactone-allylvalerolactone oxepanedione), Ethyl Cellulose, Poly vinyl alcohol.	Carbonyl diimidazoles, Carboxylic acid dianhydrides, Diarylcarbonates, Dichloromethane, Diisocyanates, Diphenyl Carbonate, Epichloridine, Gluteraldehyde, Pyromellitic anhydride, 2,2-bis (acrylamido) Acetic acid.

Table 2: drugs formulated as nanosponges

Drugs	Nanosponge vehicle	Therapeutic benefit	Ref
Antisense oligonucleotides	Sodium alginate Poly L-lysine	Cancer therapy Viral infection Pathologic disorders	9
Camptothecin	β -Cyclodextrin	Cancer	10, 11
Dexamethazone	β -Cyclodextrin	Brain tumors	12
Econazole nitrate	Ethyl Cellulose Polyvinyl alcohol	Antifungal	3, 13
Itraconazole	β -Cyclodextrin Copolyvidonum	Antifungal	14
Paclitaxel	β -Cyclodextrin	Cancer	16, 17
Resveratrol	β -Cyclodextrin	Inflammation Cardiovascular diseases Dermatitis Gonorrhoea Fever Hyperlipidemia	15
Tamoxifen	β -Cyclodextrin	Breast Cancer	7
Temozolamide	Poly (valerolactone- allylvalerolactone) Poly (valerolactone- allylvalerolactone- oxepanedione)	Brain tumors	18

APPLICATION OF NANOSPONGES

Cyclodextrin based nanosponges can bind with organic molecules and remove from water at low concentration.²⁶ The bitter components from grape fruit juice can be eliminated by combination of polymer and cross linker is based on the same concept. The three dimensional structure of nanosponges play an important role in fractionalization of peptides for proteomic application.²⁷ For the separation of inorganic electrolytes by size exclusion chromatography, microporous hyper cross linked polymers have been used. Nanosponges can

absorb specific biomarkers for diagnosis purpose. A study concluded that nanosponges can collect rare cancer marker from blood.²⁸ Nanosponges can be used as carrier for gases like oxygen and carbon dioxide. Such nanosponges could be useful for biomedical application. The oxygen-filled nanosponges could supply oxygen to hypoxic tissues present in various tissues.²⁹ Nanosponges can act as carrier for the release and delivery of enzymes, proteins and peptides in the biomedical field. Cyclodextrin based nanosponges are suitable carrier to



adsorb enzymes, proteins, antibodies and macromolecules.³⁰

The researchers developed simple and high yield Nanosponge particles for attaching the target linkers. The drug used for animal study was Paclitaxel. The researchers recorded the response of two different types of tumors: slow growing human breast cancer and fast acting mouse glioma. They gave a single injection to those tumors and recorded the response. They found that in both cases, the delivery through nanosponges increased the death rate of cancer cells and delayed tumor growth rate compared with other chemotherapy approaches.³¹

In the field of topical as well as buccal drug delivery, Nanosponge has several applications.³³ Resveratrol has been used in treatment of cancer, cardiovascular diseases, inflammation, dermatitis, hyperlipidemia, gonorrhoea and fever. In addition, resveratrol is having antibacterial and antifungal properties and can be used for human skin infections. The Nanosponge formulation of resveratrol has shown better permeation, stability and cytotoxicity against cancer cells. Thus, this type of formulation can be used for topical and buccal applications.³⁴

Nanosponges has also shown remarkable promise for stability and potential activity of molecules like camptothecin and curcumin.³⁵ Camptothecin, a potent antitumor agent, has limited therapeutic activity due to poor solubility, adverse effects and instability. When camptothecin formulated as Nanosponge, there was prolonged – release profile in its active form and resulting in increased stability. Curcumin has potential application in tumor treatment. A Nanosponge formulation of curcumin showed efficient delivery of curcumin to the tumor sites. This formulation also showed increased solubility and improved stability.

Nanosponges has been used for enzyme immobilization, protein encapsulation and stabilization. The enzymes like hydrolase, isomerase, ligase, oxidoreductase and transferase has been studied. The protein, bovine serum albumin when encapsulated as nanosponges showed prolonged release of albumin.³⁶

In addition to their application in the field of drug delivery, there exist various applications in different fields like biomedicine, catalysis, cosmetics, agrochemistry and various other fields.

PREPARATION METHODS OF NANOSPONGE

Solvent Method

Dissolve the polymer in suitable solvent. Then add this to excess quantity of cross- linker. Reflux the mixture for 48 hours at a temperature of 10°C. Then allow this solution to cool at room temperature. Add this to excess quantity of bidistilled water and filter the product. Then purify by prolonged soxhlet extraction with ethanol. Dry the product and grind in mechanical mill to get homogenous powder.^{7,10}

From Hyper Cross- Linked B- Cyclodextrins

Here, β - cyclodextrin (β - 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 μ m but fractions below 500 nm can be selected.^{19,20}

Ultrasound- Assisted Synthesis

In this method, polymers react with cross- linkers in absence of solvent and under sonication. Here, mix the polymer and cross- linker in a flask. Place the flask in an ultrasound bath filled with water and heat it to 90°C and sonicate for 5 hours. Allow it to cool and wash with water to remove the unreacted polymer. Purify by prolonged soxhlet extraction with ethanol. Dry the product under vacuum and store at 25°C.^{6,10}

Emulsion Solvent Diffusion Method

Nanosponges can be prepared by using ethyl cellulose (EC) and polyvinyl alcohol (PVA). Ethyl cellulose is dissolved in dichloromethane. Add this mixture into aqueous solution of polyvinyl alcohol. Stir the mixture at 1000 rpm for 2 hours in a magnetic stirrer. Then filter the product and dry it in an oven at 40°C for 24 hours.³

EVALUATION OF NANOSPONGES

Particle Size Determination

The particle size of Nanosponge is an important criteria in the optimization process. Particle size can be determined by laser light diffractometry or Zeta sizer. Cumulative percentage drug release from nanosponges of different particle size can be plotted against time to study effect of particle size on drug release. Particle size larger than 30 m can show gritty feeling and particle size range from 10 – 25 m can be preferred for topical drug delivery.^{3,21}

Zeta Potential

Zeta potential is a measure of surface charge. The surface charge of Nanosponge can be determined by using Zeta sizer.¹⁰

Microscopy Studies

Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) can be used to study the microscopic aspects of the nanosponges.^{10,22} The morphology of nanosponges can be determined by SEM analysis.²³

Loading Efficiency

The loading efficiency (%) of Nanosponge can be determined by:²⁴

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



Loading efficiency can also be determined by quantitative estimation of drug loaded into nanosponges by UV spectrophotometry and HPLC methods.²

Production Yield

The production yield (PY) can be determined by calculating initial weight of raw materials and final weight of nanosponges.²⁴

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

Compatibility Studies

The drug should be compatible with the polymers which are used for the preparation of nanosponges. The compatibility of drug with adjuvants can be determined by Thin Layer Chromatography (TLC) and Fourier Transform Infra-red Spectroscopy (FT-IR). Crystalline characteristics can be studied by powder X-ray diffraction (XRD) and Differential Scanning Colorimetry (DSC).^{24, 25}

CONCLUSION

The nanosponges have the ability to release the drug in a controlled manner to the targeted site. They are also capable of carrying both lipophilic and hydrophilic molecules. Due to their small particle size and spherical shape these can be developed as different dosage forms like oral, parenteral and topical preparations. Nanosponge technology offers entrapment of ingredients and thus reduced side effects, improved stability, increases elegance and enhanced formulation flexibility. Thus Nanosponge technology provides site specific drug delivery and prolongs dosage intervals and thus improving patient compliance. Nanosponge formulation could be the best solution for solving various nano related issues in the pharmaceutical industry.

REFERENCES

1. S.P. Vyas, R.K. Khar. Targeted and Controlled Drug Delivery- Novel Carrier Systems. Molecular Basis of Targeted Drug Delivery. CBS Publishers and Distributors. New Delhi. 2008: 38- 40.
2. Selvamuthukumar S, Anandam S, Kannan K, Manavalan R. Nanosponges: A Novel Class of Drug Delivery System- Review. J Pharm Pharmaceut Sci. 15(1): 2012; 103-111.
3. Renuka Sharma, Roderick B. Walker, Kamla Pathak. Evaluation of Kinetics and Mechanism of Drug Release from Econazole nitrate Nanosponge Loaded Carbapol Hydrogel. Ind J Pham Edu Res. 45(1): 2011; 25-31.
4. Nacht S, Kantz M. The Microsponge: A Novel Topical Programmable Delivery System, In: Topical Drug Delivery Systems. David WO, Anfon H A editors. New York: Marcel Dekker, 42: 1992; 299-325.
5. David F. Nanosponge drug delivery system more effective than direct injection. www.physorg.com 2010.
6. Trotta F, Cavalli R, Tumiatti W, Zerbinati O, Rogero C, Vallero R. Ultrasound-assisted synthesis of Cyclodextrin-based nanosponges. EP 1 786 841 B1; 2007.
7. Jenny A, Merima P, Alberto F, Francesco T. Role of β -cyclodextrin nanosponges in propylene photooxidation. Carbohydrate Polymers. 86: 2011; 127-135.
8. Leslie Z, Benet., BCS and BDDCS. Bioavailability and Bioequivalence: Docus on Physiological Factors and Variability. Department of pharmaceutical sciences, University of California, San Francisco, USA, 2007.
9. Isabelle A, Christine V, Helene C, Elias F, Patrick C. Spongellike Alginate Nanoparticles as a new potential system for the delivery of Antisense Oligonucleotides. Antisense and Nucleic Acid Drug Development. 9(3): 1999; 301-312.
10. 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. 74: 2010; 193-201.
11. Rosalba M, Roberta C, Roberto F, Chiara D, Piergiorgio P, Leigh E, Li S, Roberto P. Antitumor activity of Nanosponge - encapsulated Camptothecin in human prostrate tumors. Cancer Res. 71: 2011; 4431.
12. Lala R, Thorat A, Gargote C. Current trends in β - cyclodextrin based drug delivery systems. Int J Res Ayur Pharm. 2(5): 2011; 1520-1526.
13. 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. 16(4): 2011; 367-376.
14. Shankar S, Vavia PR, Francesco T, Satyen T. Formulation of Betacyclodextrin based nanosponges of Itraconazole. J Incl Phenom Macrocycl Chem. 57: 2007; 89-94.
15. Khalid AA, Pradeep RV, Francesco T, Roberta C. Cyclodextrin-based nanosponges for delivery of Resveratrol: In Vitro characterisation, stability, cytotoxicity and permeation study AAPS PharmSciTech. 12(1): 2011; 279-286.
16. Torne SJ, Ansari KA, Vavia PR, Trotta F, Cavalli R. Enhanced oral Paclitaxel bioavailability after administration of Paclitaxel loaded nanosponges. Drug Delivery. 17(6): 2010; 419-425.
17. Ansari KA, Torne SJ, Vavia PR, Trotta F, Cavalli R. Paclitaxel loaded nanosponges: in-vitro characterization and cytotoxicity study on MCF-7 cell line culture. Curr Drug Deliv. 8(2): 2011; 194-202.
18. William K, Benjamin S, Eva H. Synthesis and Characterization of Nanosponges for Drug Delivery and Cancer Treatment. www.Vanderbilt.edu . 2011.
19. Eki S, Lei T, Jingquan L, Zhongfan J, Cyrille B, Thomas PD. Biodegradable Star Polymers Functionalized With β - Cyclodextrin Inclusion Complexes. Biomacromolecules. 10(9): 2009; 2699-2707.
20. Davankov VA, Ilyin MM, Tsyurupa MP, Timofeeva GI, Dubrovina LV. From a Dissolved Polystyrene Coil to Intramolecularly- Hyper – Cross- Linked "Nanosponge". Macromolecules. 29(26): 1996; 8398-8403.
21. Martin A, Swarbrick J, Cammarrata A. In: Physical Pharmacy – Physical Chemical Principles in Pharmaceutical Sciences. 3: 1991; 527.
22. Ramnik S, Nitin B, Jyotsana M, Horemat S N. Characterization of Cyclodextrin Inclusion Complexes – A Review. J Pharm Sci Tech. 2(3): 2010; 171-183.
23. Emanuele A D, Dinarvand R. Preparation, Characterization and Drug Release from Thermo responsive Microspheres. Int J Pharm. 1995; 237-242.
24. E.K. Patel, R.J. Oswal. Nanosponge and Microsponges: A Novel Drug Delivery System. IJRPC. 2(2): 2012; 237-244.
25. Wester R, Patel R, Natch S, Leyden J, Melendres J, Maibach H. Controlled release of benzoyl peroxide from a porous microsphere polymeric system can reduce topical irritancy. J Am Acad Derm. 24: 1991; 720-726.



26. Trotta F, Tumiatti W. Cross-linked polymers based on cyclodextrin for removing polluting agents. WO 03/085002 A1; 2003.
27. Wong VN, Fernando G, Wagner AR, Zhang J, Kinsel GR, Zauscher S, Dyer DJ. Separation of peptides with polyionic nanosponges for MALDI-MS analysis. *Langmuir*, 25(3): 2009; 1459-65.
28. Longo C, Gambaro G, Espina V, Luchini A, Bishop B, Patanarut AS, Petricoin EF 3rd, Beretti F, Garaci E, De Pol A, Pellacani G, Liotta LA. A novel biomarker harvesting nanotechnology identifies Bak as a candidate melanoma biomarker in serum. *Exp Dermatol*. 20(1): 2011; 29-34.
29. Cavalli R, Akhter AK, Bisazza A, Giustetto P, Trotta F, Vavia P. Nanosponge formulations as oxygen delivery systems. *Int J Pharm*. 402(1-2): 2010; 254-257.
30. Gilardi G, Trota F, Cavalli R, Ferruti P, Ranucci E, Di Nardo G, Tumiatti V. Cyclodextrin nanosponges as carrier for biocatalysts and in the delivery and release of enzymes, proteins, vaccines and antibodies. WO2009149883 A1; 2009.
31. D. Salisbury, Exploration: Research News at Vanderbilt University, June 1; 2010.
32. Patricia Van Arnum. Nanosponges, a controlled – release nanoparticle system, shows promise in targeted drug delivery. *Pharmatech.com*. 35(5): 2011; 56-60.
33. Ansari KA, Vavia PR, Trotta F, Cavalli R. Cyclodextrin – based nanosponges for delivery of resveratrol: in vitro characterisation, stability, cytotoxicity and permeation study. *AAPS PharmSciTech*. 12(1): 2011; 279-286.
34. Shankar Swaminathan, Sharad Darandale, Pradeep R Vavia. Bioavailability- Nanosponge- Aided Drug Delivery. *Pharmaceutical Formulation and Quality*. 2012; 11.
35. Darandale SS, Vavia PR. Cyclodextrin – based nanosponges of curcumin: formulation and physicochemical characterization [published online ahead of print June 14, 2012]. *J Incl Phenom Macro*.
36. Swaminathan S, Pastero L, Serpe L, Trotta F, Vavia P, Aquilano D, Trotta M, Zara G, Cavalli R. In vitro release modulation and conformational stabilization of a model protein using swellable polyamidoamine nanosponges of β - cyclodextrin. *J Incl Phenom Macro*. 68(1-2): 2010; 183-191.

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