INTERNATIONAL JOURNAL OF ADVANCE RESEARCH AND DEVELOPMENT

(Volume2, Issue4)

Available online at www.ijarnd.com

Nanosponges: A Novel Targeted Drug Delivery for Cancer Treatment

Tukaram S. Patil*, Nishigandha A. Nalawade, Vidya K. Kakade, Sumedha N. Kale

Dept. of Pharmaceutics, Bharati Vidyapeeth college of Pharmacy,

Dept. of Pharmaceutical Chemistry, Bharati Vidyapeeth college of Pharmacy,

Near Chitranagari, Kolhapur (M.S), India

tukarampatil1991@gmail.com

ABSTRACT

Effective Drug delivery at the targeted or specific site is the significant problem which is being faced by the researchers in the anti-cancer formulation. The development of new colloidal, porous, tiny mesh-like carrier called nanosponges with the size 1μm range wich offers controlled drug delivery at a specific site in cancer treatment. Nanosponges play an important role in targeting drug delivery in a controlled manner. A wide variety of drugs, both the lipophilic as well as hydrophilic can be loaded into nanosponge for targeting drug delivery and ultimately improve solubility and bioavailability of the same drug.Nanosponge can circulate around the whole body until they interact with the specific target site and stick on the surface and begin to release the drug in a controlled manner. In this review article, application of nanosponges, its preparation methods, polymers used and characterization have been discussed.

Keywords*: *Nanosponge, Targeted Drug Delivery, Cancer, Controlled Drug Delivery, Polymers, Application.

INTRODUCTION

The targeted drug delivery is the major challenge being faced by the researchers [6]. The targeted drug delivery technology has certainly a new interest for drugs by providing them new life through their therapeutic targets in cancer treatment. Administration of drug by target oriented in cancer treatment that improves therapeutic efficacy, reduction in side effect and optimized dosing regimen will be the leading trends in the area of therapeutics. In targeted drug delivery, selective and effective localization of pharmacologically active moiety at a preidentified target in therapeutic concentration and restricting access to the non-target normal cellular lining and thus decreases toxic effects and increases the therapeutic index of the anti-cancer drug [6, 7, and 8].

The term "Nanosponge" means tiny sponges having porous structures. It offers a solution for several formulation related problems. Nanosponges are nanoparticles with a size of a virus with an average diameter below 1μm. Due to their small size and porous nature they can bind poorly- soluble drugs within the matrix and improve their bioavailability by modifying the pharmacokinetic parameters of drug molecules[2].

Nanosponge is a novel approach which offers controlled drug delivery for cancer treatment. Nanosponge is an emerging technology for cancer drug delivery. Nanosponge drug delivery system is employed for the improvement of performance of orally, parenteral and topical administered drugs in cancer treatment. Nanosponge can circulate into the whole body and release the drug at a specific site in a controlled manner. Nanosponges are beneficial for the treatment of many diseases and this technology is more effective at delivering drug for breast cancer than the conventional method [5, 13]. Nanosponges are nanoparticles in which a large number of drug substances can be encapsulated within its core. These microscopic particles are capable carrying both the lipophilic and hydrophilic substances and of improving solubility of drug molecules [9]

Characteristics of Nanosponges

1. Nanosponges are porous particles, used mainly to encapsulate the poorly soluble drugs.
2. These nanosponges have high aqueous solubility and are capable of carrying both lipophilic and hydrophilic drugs.
3. Nanosponges formulations are stable over the pH range of 1 to 11 and temperature up to 300 °C
4. Nanosponges are non-irritating and non-mutagenic, non-allergic and non-toxic and protect the drug from physiological degradation.
5. Nanosponges can encapsulate various types of drug molecules by forming inclusion and non-inclusion complexes[1, 12, 20, 14, 42, 44].

Advantages

1. Nanosponge provides the site-specific drug delivery and predetermined release.
2. A Smaller quantity of the drug contact with the normal tissue hence produces fewer side effects.
3. These formulations are soluble in water and capable of encapsulating hydrophobic drug.
4. Nanosponge formulation used to mask unpleasant flavors of drug substance and to convert liquid substances to solids.
5. Particles can be prepared smaller or larger by varying the proportion of cross-linker to polymer
6. Particles can be prepared smaller or larger by varying the proportion of cross-linked to the polymer.
7. Due to their average pore size, 0.25 μm bacteria cannot be penetrate
8. Improved stability, self-sterilizing, increased elegance and enhanced formulation flexibility, improve dissolution.[6, 7, 8, 12, 20]

Disadvantages

1. Nanosponge depends upon loading capacities.
2. Formulation of nanosponge includes only small molecules.[58, 7]

Chemicals used in nanosponge preparation

Formulation of nanosponge there are various types of polymer and crosslinker are used

Polymers

Hyper cross-linked Polystyrenes, Cyclodextrins and its derivatives like Methyl β- Cyclodextrin. Alkyloxycarbonyl Cyclodextrins, 2-Hydroxy Propyl β-Cyclodextrins.

Copolymer

Poly (Valero lactone-allyl Valero lactone), Poly (valerolactone-allylvalerolactone oxepanedione). Ethyl cellulose and polyvinyl alcohol.

Crosslinkers

Diphenyl Carbonate, Diarylcarbonates, Carbonyldiimidazole, Epichloridine Glutarldehyde, Carboxylic acid dianhydride, Acetic acid and Dichloromethane.[7, 9, 24, 47, 50]

FACTORS AFFECTING NANOSPONGE FORMULATION

1. Type of Drug
2. Type of Polymer used
3. Temperature
4. Method of preparation nanosponge
5. Degree of substitution

Type of Drug

The drug molecules to be incision and non-incision complexes with nanosponge should have certain characteristics given bellow:

1. Drug solubility in water is less than 10 mg/ml.
2. The molecular weight of the drug between 100 and 400 gm/mole.
3. The structure of the drug molecule should not contain more than five condensed rings.
4. The melting point of the drug should be less than 250°C.

The type of polymer used

The type of polymer used in the formulation of nanosponge that can affect the formation and performance of nanosponge. The size of the cavity of nanosponge and complexation of drug depends upon the polymer used in the formulation.

Temperature

The change in temperature can affect the drug/nanosponge complexation. Decreases the magnitude of the apparent stability by Increase in the temperature, persistent of the Drug/Nanosponge complex may be due to a result of the possible reduction of drug/Nanosponge interaction forces, with the rise of temperature.

Method of preparation of nanosponge

The method nanosponge formulation affects the loading drug into nanosponge and complexation. The effectiveness of method depends on nature of drug and polymer used in the formulation.

Degree of substitution

The type, number, and position of substituent on parent molecule can affect the nanosponge formation as well as its complexation.[8, 37, 38]

List of Drug Formulated As Nanosponge

Table 1- Drugs formulated as Nanosponges

Drug	Nanosponge vehicle	Category of drug	references
Tamoxifen	β – Cyclodextrin	Breast cancer	*13*
Paclitaxel	β – Cyclodextrin	Cancer	*50*
campothecin	β – Cyclodextrin	Cancer	*26,52*
Resveratrol	β – Cyclodextrin	Cancer, Inflammation	*55*
Temozolamide	Poly(valerolactone-allylvalerolactone)	Brain tumour	*57*
Temoxifen	β – Cyclodextrin	Cancer	*28*

Method of preparation of nanosponge

Ultrasound assisted synthesis

In ultrasound-assisted synthesis, polymers mix with cross-linkers in absence of solvent in a flask and place the flask in ultrasound bath field with water and heat it for 90oC and sonicate for 5 hours. Allow mixture to cool and break the mixture roughly. Wash the mixture with water to remove the unreacted polymer. Purify by prolonged soxhlet extraction with ethanol and dry the product under vacuum and stored at 25oC until further use.

Emulsion solvent diffusion method

Nanosponges can be prepared by using ethyl cellulose (EC) and polyvinyl alcohol (PVA). Ethyl cellulose is dissolved in dichloromethane (dispersed phase). Add this mixture into an aqueous solution of polyvinyl alcohol in water. The reaction mixture was stirred at 1000 rpm for 2 hours on a magnetic stirrer. Then filter the product and dry it in an oven at 40oC for 24 hours. Dried nanosponges were stored in a vacuum desiccator to ensure the removal of residual solvent.

Solvent method

Ploymer is dissolved in in a suitable solvent like dimethylsulfoxide, dimethylformamide and to this add an excess quantity of cross- linker. Reflux the mixture for 48 hours at a temperature of 10oC to the reflux temperature. Then allow this solution to cool to 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 the mechanical mill to get homogenous powder.

From Hyper Cross- Linked B- Cyclodextrins

In this method, β- cyclodextrin (β- CD) can be used as a carrier for drug delivery which is nanoporous material. Nanosponges can be obtained by reacting cyclodextrin with a cross- linker. Nanosponges can be synthesized in both forms either neutral or acid forms. The average diameter of a Nanosponge is below 1 µm but fractions below 500 nm can be selected. Loading drug into nanosponge is carried out by the following method. Nanosponges suspended into the water and Sonicate to avoid the presence of aggregates and then centrifuge for 10 min the suspension to obtain the colloidal fractions. Separate the supernatant & dry the sample by freeze drying and then prepare the aq. suspension of Nanosponges Disperse the excess quantity of drug & maintain the suspension under constant stirring for the specific time required for complexation. Separate the uncomplexed (undissolved) drug by centrifugation and freeze dry the nanosponge to obtain solid crystals [16, 27-31, 34]

Characterization of nanosponge

1. Particle size determination

The particle size of Nanosponge is an important criterion in the optimization process of nanosponge. The particle size of the drug can affect the drug release as well as the solubility of the drug. Particle size can be determined by using the instrument, laser light diffractometry or Zeta sizer. Cumulative percentage drug release from nanosponges of different particle size can be plotted against time to study the effect of particle size on drug release. Particle size larger than 30 µm can show gritty feeling and particle size range from 10 –25 µm can be preferred for topical drug delivery[32, 54].

2. Polydispersibility index (PDI)

The poly dispersibility index (PDI) is an index of width or spread or which shows variation within the particle size distribution. Dynamic light scattering instrument is used to determine PDI. Higher PDI value indicates a wider particle size distribution and the polydispersity nature of the sample, whereas monodisperse sample has a minimum PDI. PDI can be calculated by using following equation.

$$PDI = d/d\,avg \quad \triangle$$

Where**,**

d is the width of distribution denoted by **SD,** and **d Avg** is the average particle size denoted by **MV(nm)** in particle size data sheet[59].

3. Zeta potential

Zeta potential can be measured by using instrument zeta sizer, which is the measure the surface charge of Nansponges. Zeta potential is widely used for quantification of the magnitude of the electrical surface charge at the double layer. The zeta potential value more than 30mV indicates the good stability of formulation[52].

4. Microscopy studies

Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) can be used to study the microscopic aspects of the drug and nanosponge formulation. SEM are used for the study morphology of the nanosponges. The difference in crystallization state of the raw materials used for the preparation of nanosponge and the final formulation seen under electron microscope indicates the formation of the inclusion complexes[33].

The loading efficiency (%) of Nanosponge can calculate by using following equation:

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

Loading efficiency can be also calculated by using a quantitative estimation of drug loaded into nanosponge UV spectrophotometer and HPLC method. In this, weighed the amount of drug loaded nanosponges dispersed in a suitable solvent and sonicate for a specific period of time, sonication required to break the complexes and after dilution, it is analyzed by UV spectrophotometer or HPLC method[33].

5. Solubility studies

Higuchi and Connors explained the method to study the inclusion complexation known as phase solubility method. This method used to explain the effect of Nanosponge on the solubility of the drug, which indicates the degree of complexation[29].

6. IR spectroscopy

IR spectroscopy is used to estimate interaction between drug molecules and drug and nanosponge in the solid state.IR changes if there is complex formation between drug and nanosponge and if a small fraction of the drug molecule is encapsulated in complex less than 25 percent band and assigned to include part of another molecule which is marked by bands of the spectrum of nanosponges. IR has limited application to some drugs containing such as carbonyl or sulfonyl groups. IR study gives information of functional group containing drug[60].

7. X-ray diffractometry

Powder X-ray diffractometry can be used to identify inclusion complexation in the solid state. The complex formation of the drug with nanosponges changes the diffraction patterns and the crystalline nature of the drug. The diffraction pattern of a newly formed substance clearly differs from that of uncomplexed nanosponge. This difference of diffraction pattern indicates the complex formation. The formation of complex shows the sharpening of the peaks, appearance of a few new peaks[60].

Applications of nanosponge

1. Solubility Enhancement

The poorly water-soluble drugs are the major problem and can affect the performance of the formulation. Nanosponge is the carrier system, which entraps the drug into its pore and increases the solubility as well as the bioavailability of the formulation. Inclusion complex of β-cyclodextrin nanosponge approach is widely used for the improvement of solubility and bioavailability of drugs[47].

2. Antiviral application

Nanosponges used to target drug in nasal and pulmonary. It delivers the antiviral drug to lungs or nasal route through nanocarriers for targeting virus which may cause infection to RTI such as influenza virus, rhinovirus. Examples of drug used nanocarriers are Zidovudine, Saquinavir[50, 51].

3. Cancer

Targeting drug to a specific site is an important thing in cancer which reduces the side effect and increases the bioavailability. Different cancer is treated by nanosponges like breast cancer, colon cancer, brain cancer, lymph carcinoma, lung cancer, with help of single dose of injections. Camptothecin (CAM)**,** a plant alkaloid which is used as the antitumor agent. It has low aqueous solubility due that it has limited therapeutic utility and serious side effect. Cyclodextrin-based nanosponges (NS) are a novel class of cross-linked derivatives of cyclodextrins wich is used to target anti-cancer drug. This is used to increase the solubility of the poorly soluble drug, to protect the labile groups and control the release[50, 51, and 52].

CONCLUSION

Nanosponge is a novel approach which offers controlled drug delivery as well as site specific for cancer treatment. They are also capable of carrying both lipophilic and hydrophilic drug molecules. Nanosponge is small particle size and shape, this drug delivery system is employed for the improvement of performance of orally, parenteral and topical administered drugs in cancer treatment. Nanosponge technology offers entrapment of drug and thus reduced side effects, improved stability, increases elegance and enhanced formulation flexibility. Thus Nanosponge technology provides site-specific drug delivery in cancer treatment and thus improves patient compliance.

REFERENCES

1. Nacht S., and Kantz M., the Micro sponge: A Novel Topical Programmable Delivery System. Chapter 15, In Topical Drug Delivery Systems. Edited by David W. O. and Anfon H. A., 1992, Volume 42, 299-325.
2. Bezawada S., Charanjitha, Reddy V.M., Naveena, Gupta V.R., "Nanosponges: A Concise Review For Emerging Trends", International Journal of Pharmaceutical Research and Biomedical Analysis, 2014, Volume-3, 1-6.
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 A.L., Martin M.R., Gilbert S.B., Pharmaceutical dosage forms: Disperse Systems. Vol.3, Marcel Dekker, inc, 2nd. Edition, 2005, 88-105.
5. David F., Nanosponge drug delivery system more effective than direct injection, 2010, www.physorg.com, accessed on 20.12.2011.

6. Jilsha G., Vidya Viswanand., Nanosponge A Novel Approach of Drug Delivery System International Journal of pharm. Science Review And Research 2013,19(2)
7. Balasaheb M. T., Patil P. M., Jahagirdar A. C., Khandekar D. B., Nanosponge An Emerging Drug Delivery System., International Journal of Institutional Pharmacy and Life sciences,2015,5(6)
8. Vishwakarma A., Nikam P., Mogal R., Talale S., Nanosponges A Benifiaction for Novel drug Delivery system, Int. Jour. Pharm. Tech Sciences,2014, 6(1)
9. Selvamuthukumar Subramanian, Anandam Singiredd, Kannan Krishnamoorthy, and Manavalan Rajappan, Nanosponges: A Novel drug delivery system-Review, J Pharm Pharmaceut Sci (www.cspsCanada.org) 2012, 15(1), 103 -111.
10. Gilardi G., Trota F., Cavalli R., Ferruti P., Ranucci E., Di Nardo G., Roggero C., Tumiatti V., Cyclodextrin nanosponges as a carrier for biocatalysts, and in the delivery and release of enzymes, proteins, vaccines and antibodies, 2009, WO2009149883 A1.
11. 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.
12. E. K. Patel, and R. J. Oswal, Nanosponge and Micro Sponges: A Novel Drug Delivery System, International Journal Of Research In Pharmacy And Chemistry, IJRPC 2012, 2(2) ISSN: 2231-2781, 237-244.
13. Jenny A., Merima P., Alberto F., Francesco T., Roleof β- cyclodextrin nanosponges in polypropylene photooxidation. Carbohydrate Polymers, 2011, 86, 127– 135.
14. Trotta F., Tumiatti V., Cavalli R., Rogero C., Mognetti B., Berta G., Cyclodextrin-based nanosponges as a vehicle for Anti-tumoral drugs, 2009, WO 2009/003656 A1.
15. Droz J.P., Chaladaj, A., Management of metastatic prostate cancer: the crucial role of geriatric assessment. BJU Int., 2008, 101 (Suppl 2), 23–29.
16. Trotta F., Cavalli R., Characterization, and Applications of New Hyper-Cross-Linked Cyclodextrins; Composite Interfaces 2009; 16(1):39-48.
17. Berto S., Bruzzoniti M. C., Cavalli R., Perrachon D., Prenesti E., Sarzanini C.,Trotta F., Tumiatti, W.J. Inclusion Phenom. Macrocyclic Chem. 2007, 57, 631–636. Doi: 10.1007/s10847-006-9273-0.
18. Di Nardo G., Roggero C.,Campolongo S., Valetti F., Trotta F., Gilardi G., Catalytic properties of catechol 1,2-dioxygenase from Acinetobacter radioresistens S13 immobilized on nanosponges,Dalton Trans. 2009 Sep 7;(33):6507-12. Doi: 10.1039/b903105g.
19. Thorsteinn Loftsson, Pekka Jarho, Mar Masson, Tomi Jarvinen, Cyclodextrins in drug delivery. Expert Opin. 2005; 2: 335-51.
20. NileshJ., Ruchi J., Navneet T, Braham Prakash G., Deepak Kumar J., Nanotechnology: A Safe and Effective Drug Delivery Systems, Asian Journal of Pharmaceutical and ClinicalResearch, 2010 vol.3 issue 3,159-165.
21. Nacht S, Kantz M.; (1992) the microsponge: a novel topical programmable delivery system, In: Topical Drug Delivery Systems, David W.O and Anfon H.A (ED), 42.
22. Delattre L., Delneuville I., Biopharmaceutical aspects of the formulation of dermatological vehicles. J Eur Acad Derm Vener, 1995, 5: S70.
23. http://Sciencematters, Unimelb.edu.au/ 2011/05/nanosponges for targeted- cancer-treatment/visited on 12/10/2011.
24. Lala R., Thorat A., Gargote C., Current trends in β-cyclodextrin based drug delivery systems, Int J Res Ayur Pharm, 2011, 2(5): 1520-1526, ISSN 2229-3566.
25. Jenny A., Merima P., Alberto F., Francesco T., Role of β- cyclodextrin nanosponges in polypropylene photooxidation. Carbohydrate Polymers, 2011, 86 127– 135.
26. 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.
27. Eki S., Lei T., Jingquan L., Zhongfan J., CyrilleB., and Thomas P. D., Biodegradable Star Polymers Functionalized With β-Cyclodextrin Inclusion Complexes , Biomacromolecules, 2009, 10(9):2699 2707.
28. Davankov V.A., Ilyin M. M., Tsyurupa M. P., Timofeeva G.I., and Dubrovina L.V., From a Dissolved Polystyrene Coil to Intramolecularly-Hyper-Cross Linked"Nanosponge". Macromolecules, 1996, 29(26):8398–8403.
29. Sharma R., Roderick B., and Pathak K., Evaluation of kinetics and mechanism of drug release from Econazole nitrate Nanosponges loaded carbopol Hydrogel. Indian J of Pharma Edu and research, 2011, 45(1):25-31.
30. Embil K., and Nacht S., The microsponge delivery system atopical delivery system with reduced irritancy incorporating multiple triggering mechanisms for the releaseof actives. J Microencapsule, 1996, 13:575–88.

31. Mishra M.K., Shikhri M., Sharma R., and Goojar M.P.,Optimization, formulation, development and characterization of Eudragit RS 100 loaded microsponges and subsequent colonic delivery. Int J of Drug Discovery And herbal Research, 2011, 1(1): 8-13.

32. Martin A., Swarbrick J., and Cammarrata A., In: Physical Pharmacy-Physical Chemical Principles in Pharmaceutical Sciences, 2003, 3rd Ed. 1991: 527.

33. Emanuele A., and Dinarvand R., Preparation, Characterization and Drug Release from Thermoresponsive Microspheres. Int JPharm.,1995, 237-42.

34. Kilicarslan M., and Baykara T., The effect of the drug/polymer ratioon the properties of Verapamil HCl loaded microspheres. Int JPharm., 2003, 252:99–109.

35. Barkai A., Pathak V., and BenitaS., Polyacrylate (Eudragit retard)microspheres for oral controlled release of nifedipine, Formulation design and process optimization. Drug Dev Ind Pharm.,1990,16:2057-2075.

36. 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.

37. Amber V., Shailendra S., Swarnalatha S., Cyclodextrin based novel drug delivery systems. J Incl Phenom Macrocycl Chem., 2008, 62:23-42.

38. Rajeswari C., Alka A., Javed A., Khar R K., Cyclodextrins in drug delivery: an update review. AAPS pharmSciTech, 2005, 6(2):E329-E357.

39. Ramnik S., Nitin B., Jyotsana M., Horemat S.,Characterization of Cyclodextrin Inclusion complexes –A Review. J Pharm Sci Tech, 2010 ,2(3):171-183.

40. Maravajhala V., Papishetty S., Bandlapalli S., Nanotechnology in the development of drug delivery system, International journal of pharmaceutical sciences & research, 2012, Vol. 3, Issue 1, 84-96.

41. Rao M. R., Bajaj A. N., Pardeshi A. A., Aghav S. S., Investigation of Nanoporous colloidal carrier for solubility enhancement of Cefpodoxime proxetil , Journal of pharmacy research, 2012, vol. 5, Issue 5, pp 2496-2499.

42. Swaminathan S., Cavalli R., Trotta F., and Vavia P.R., Invitro release modulation and conformational stabilization of a model protein using swellable polyamidoamine nanosponges of cyclodextrin. J Incl Phemon Macrocycl Chem., 2010 ,DOI10.1007/s10847-010-9765-9.

43. Ajay Vishwakarma et al /Int.J.PharmTech Res.2014,6(1),pp 11-20. 20

44. Swaminathan S., Pastero L., Serpe L.,Trotta F. and Vavia P., Cyclodextrin based nanosponges encapsulating camptothecin: Physicochemical characterization, stability and cytotoxicity. Eup J of Pharmaceutics and Biopharmaceutics, 2010, 74(2):193-201.

45. Arkas M., Allabashi R., Tsiourvas D.,Mattausch E., and Perfle R.,Organic/Inorganic Hybrid Filters Based on Dendritic and Cyclodextrin “Nanosponges” for the Removal of Organic Pollutants from Water. Environ Sci Technol, 2006, 40(8):2771–2777.

46. Zuruzi S., MacDonald N.C., Moskovits M., and Kolmakov A., Metal oxide "nanosponges" as chemical sensors: Highly sensitive detection of hydrogen using nanosponge titania; Angewandte Chemie, 2007, International Edition 46 (23): 4298-4301.

47. Swaminathan S., Vavia P.R., Trotta F., Formulation of beta cyclodextrins based nanosponges of itraconazole, J Incl Phenom Macro Chem.,2007, 57:89-94.

48. Gilardi G., Trota F., Cavalli R., Ferruti P., Ranucc iE., Di Nardo G., Roggero C., Tumiatti V., Cyclodextrin nanosponges as carrier forbiocatalysts , and in the delivery and release of enzymes,proteins, vaccines and antibodies, 2009. WO2009149883 A1.

49. Wong V.N., Fernando G., Wagner A.R., Zhang J,Kinsel G.R., Zauscher S., Dyer D.J., Separation of peptides with polyionic nanosponges for MALDIM Sanalysis. Langmuir, 2009,25(3):1459-65.

50. Ansari K.A., Torne S., Vavia P.R., Trotta F., Cavalli R., Cyclodextrin - Based Nanosponges for Delivery of Resveratrol: In Vitro Characterization, Stability, Cytotoxicity and Permeation Study, AAPS Pharm Sci Tech, 2011, Vol. 12, (1), 279-86.

51. Yadav Geeta, Panchory Hiten, Nanosponges : a boon to the targeted drug delivery system, Journal of drug delivery & therapeutics, 2013, 3(4), 151-155.

52. Rosalba M, Roberta C, Roberto F, Chiara D, Piergiorgio P, Leigh E, Li S, Roberto P. Antitumor activity of nanosponge-encapsulated Camptotechin in human prostate tumors. Cancer Res,2011; 71:4431.

53. Renuka S., Roderick B.W., 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.

54. 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.

55. Khalid A.A., Pradeep R.V., Francesco T., Roberta C., Cyclodextrin-based nanosponges for delivery of Resveratrol: In Vitro characterisation, stability,cytotoxicity and permeation Study AAPS PharmSciTech,2011, 12(1): 279-286.

56. Shankar S., Vavia P.R., Francesco .T, Satyen T., Formulation of Betacyclodextrin based nanosponges of Itraconazole. J Incl Phenom Macrocycl Chem, 2007 ,57: 89–94.

57. William K, Benjamin S, Eva H. Synthesis and Characterization of Nanosponges for Drug Delivery and Cancer Treatment.www.Vanderbilt.edu accessed on 20.12.2011.

58. Kundlas J., Nautiyal U., Jassal M. Nanosponges: As Originated Form For Targeted Drug Delivery, International Journal of Recent Advances In Pharmaceutical Research, April- 2015; 5(2): 75-81.

59. Uday B.B., Manvi F.V., Kotha R., Pallax S.S., Paladugu A. and Reddy K.R., Recent Advances in Nanosponges as Drug Delivery System, International Journal of Pharmaceutical Sciences and Nanotechnology, Volume-6, April-June 2013;1934-1944.

60. Maravajhala V., Papishetty S., Bandlapalli S., Nanotechnology in the development of drug delivery system, International journal of pharmaceutical sciences & research, 2012, Vol. 3, Issue 1, 84-96.

