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Research Article

NANOSPONGE AND MICRO SPONGES: A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

Nanosponge and Microsponge delivery System was originally developed for topical delivery of drugs can also be used for controlled oral delivery of drugs using water soluble and bioerodible polymers. It holds a promising future in various pharmaceutical applications in the coming years like enhanced product performance and elegancy, extended release, reduced irritation, improved thermal, physical, and chemical stability of product. A Nanosponge and Microsponge delivery system can entrap wide range of drugs and then release them onto the skin over a time and also in response to other stimuli including rubbing, moisture, pH, friction, or ambient skin temperature. It is a unique technology for the controlled release of topical agents and consists of nano or micro porous beads loaded with active agent and also use for oral delivery of drugs using bioerodible polymers, especially for colon specific delivery and controlled release drug delivery system.

Keywords: Nanosponges, Microsponges, topical drug delivery.

INTRODUCTION

Nanosponge and Microsponge was originally developed for topical delivery of drugs. They are colloidal carriers have recently been developed and proposed for drug delivery, since their use can solubilize poorly water soluble drug and provide prolonged release as well as improving drugs bioavailability and in some case modifying it's pharmacokinetics parameters. The average diameter of a nanosponge is below 1 µm as shown in **Figure No. 1** but fractions below 500 nm can be selected, micro sponges are 10-25 microns in diameter. They can also decrease side effect and protect drug from degradation[1].

Nanosponges may be made of many different organic or inorganic materials; their structure presents a nanometric dimension or smaller. Well-known examples are titanium or other metal-oxide based nanosponges, silicon nanosponge particles, carbon coated metallic nanosponges, hyper-cross-linked polystyrene nanosponges and also cyclodextrin based nanosponges. The common characteristic of these materials is the presence of nano-scale pores that give them particular properties. Nanosponges can encapsulate various types of molecules by forming inclusion and non-inclusion complexes[1].

Cyclodextrins are capable of including compounds whose geometry and polarity are compatible with those of the cavity, but native cyclodextrins are incapable of forming inclusion compounds with hydrophilic or high-molecular-weight molecules. Since it is cheapest and most useful cyclodextrin has low water solubility (1.85 wt% at r. t.) and is toxic when injected intravenously, many chemical modifications of cyclodextrins have been studied in order to overcome their drawbacks and to improve their technological characteristics. Some cyclodextrin derivatives are well tolerated parenterally, especially hydroxyl propyl cyclodextrin. However, because individual cyclodextrins, and even individual cyclodextrin derivatives, easily dissociate from the drug on dilution, many of the advantages of cyclodextrins are limited in parenteral treatment[2].

A possible solution is to synthesize dimers or trimers that cooperate in

forming the inclusion compound with the guest molecule. But due to the presence of many reactive hydroxyl groups on cyclodextrins, complex reactions are required in order to prepare the desired monomer, generally with very low yields and high cost. On the other hand, the production of simple cross- linked cyclodextrins has long been possible. The best known network is generated using epichloridrine as cross-linking agent, and these cyclodextrins have been used for several purposes, including column packing for inclusion chromatography, elimination of bitter components from grapefruit juice, for copper analysis, and cobalt determination in foods. Glutaraldeide is also reported to give a cross-linked cyclodextrin. High cross-linked cyclodextrins have also been synthesized for molecular recognition purposes, but only after the work by DeQuan Li and Min Ma was the term **"cyclodextrin nanosponges"** introduced Cyclodextrin-based nanosponges are generally used for decontamination processes[2].

At present, cyclodextrin-based nanosponges can easily be obtain by reacting the selected cyclodextrin with a suitable cross-linking agent; these include diisocianates, diarylcarbonates and carbonyl diimidazoles, carboxylic acid dianhydrides and 2, 2-bis (acrylamido) acetic acid.

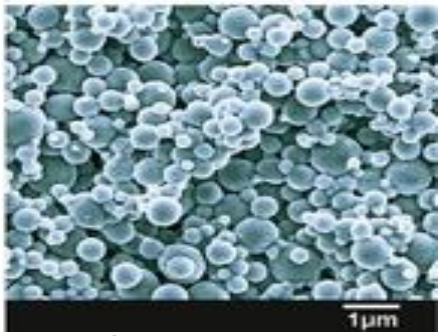

Fig.1: Porous Nanosponges

Microsponges

The microsponges are macroporous beads, typically 10-25 microns in diameter, loaded with active agent. Microsponges are porous, polymeric microspheres that are mostly used for prolonged topical administration as shown in **Figure No. 2**. Microsponges consisting of non-collapsible structures with porous surface through which active ingredients are released in a controlled manner. Microsponges are porous microsphere having interconnected voids of particle size range 5-300µm. They are uniform, spherical polymer particles. Their high degree of cross-linking results in particles that are insoluble, inert and of sufficient strength to stand up to the high shear commonly used in manufacturing. Microsponges are designed to deliver a pharmaceutically active ingredient efficiently at minimum dose and also to enhance stability, reduce side effects, and modify drug release profile[3].

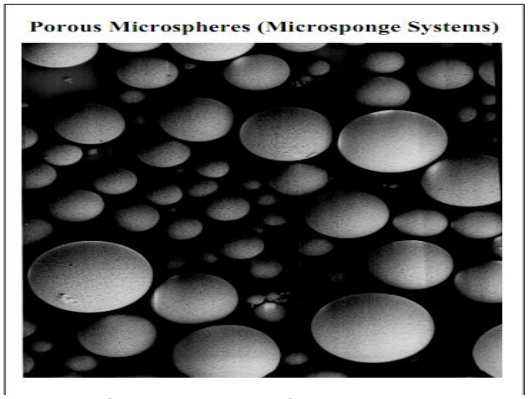

Fig. 2: Porous Microsponges

Advantages of Nanosponges and Microsponge[4]

These formulations are stable over range of pH 1 to 11

These formulations are stable at the temperature up to 130 C

These formulations are compatible with most vehicles and ingredients

These are self sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate

These formulations are free flowing and can be cost effective

Methods of Preparation of nanosponges and microsponges

Preparation of Nanosponges

1. Nanosponges prepared from hyper-cross-linked β-cyclodextrins

Nanosponges were prepared from β-cyclodextrins as nanoporous materials used as carriers for drug delivery. Nanosponges are recently developed hyper-cross-linked cyclodextrin polymers nano structured to form 3-dimensional networks; a roughly spherical structure, about the size of a protein, with channels and pores inside. They are obtained by reacting cyclodextrin with a cross-linker such as diisocianates, diarylcarbonates and carbonyl diimidazoles, carboxylic acid dianhydrides and 2, 2-bis(acrylamido)acetic acid. The surface charge density, porosity and pore sizes of sponges can be controlled to attach different molecules. Nanosponges can be synthesized in neutral or acidic forms,

depending in turn on the agent used as cross-linker. They are solid nanoparticles and can be prepared in crystalline form with spherical shape using an ultrasound-assisted preparation method. The average diameter of a Nanosponge is below 1 µm but fractions below 500 nm can be selected. Nanosponges can encapsulate various types of molecules by forming inclusion and non-inclusion complexes[5]. The capacity of the nanosponges to incorporate molecules within their structure was evaluated using drugs with different structures and solubility. The nanosponges were found capable of carrying both lipophilic and hydrophilic drugs. Nanosponges could be used to increase aqueous solubility of poorly water-soluble drugs, to remove pollutants from contaminated water, or as nano carriers for biomedical applications. Nanosponges have been used for removal of organic impurities in water[5, 6].

2. Nanosponges prepared by emulsion solvent diffusion method

Nanosponges prepared by using different proportion of ethyl cellulose and polyvinyl alcohol. The dispersed phase containing ethyl cellulose and drug was dissolved in 20ml dichloromethane and slowly added to a definite amount of polyvinyl alcohol in 150ml of aqueous continuous phase. The reaction mixture was stirred at 1000rpm for 2 hrs. The nanosponges formed were collected by filtration and dried in oven at 40^0 c for 24 hrs. The dried nanosponges were stored in vacuum desiccators to ensure the removal of residual solvent[7].

Preparation of microsponges[8]

Drug to be entrapped in microsponges should be liquid or soluble ingredient, it should be miscible with monomer, should be water immiscible, inert to monomer and stable in presence of polymerization catalyst. Microsponges are prepared by several methods utilizing emulsion systems as well as by suspension polymerization in a liquid–liquid system. The most common emulsion system used is oil-in-water (o/w), with the microsponges being produced by the emulsion solvent diffusion (ESD) method

Microsponges are prepared by two ways

- liquid-liquid suspension polymerization and
- quasi emulsion solvent diffusion techniques

Drug loading in microsponges can take place in two ways

One-step process or by two-step process which are based on physico-chemical properties of drug to be loaded.

If the drug is typically an inert non-polar material, will create the porous structure it is called porogen. Porogen drug, which does not affect and activated by polymerization also stable to free radicals is entrapped with one-step process. Such Porogen drugs or pore forming agent can be entrapped while polymerization takes place by one-step process

When the drug is sensitive to the polymerization conditions, polymerization is performed using substitute porogen and such a process takes place by two-step process

1. Liquid-liquid suspension polymerization

The porous microspheres are prepared by suspension polymerization method in liquid-liquid systems. In their preparation, the monomers are first dissolved along with active ingredients in a suitable solvent solution of monomer and are then dispersed in the aqueous phase, which consist of additives (surfactant, suspending agents etc.). The polymerization is then initiated by adding catalyst or by increasing temperature or irradiation rate for given time period.

Monomer or combinations of monomers are selected and polymerization begins to form chain monomers as a result of cross linking ladders are formed between chains of monomer. Monomer ladder are folded to form spherical particles i.e. agglomeration of microspheres, which give rise to formation of bunches of microspheres. Binding of bunches to form microsponges, a reservoir type of system, which opens at the surface through pores[9].

Some time inert liquid immiscible with water but completely miscible with monomer is used during the polymerization to form the pore network. After the polymerization the liquid is removed leaving the porous microspheres, i.e. Microsponges, solvent may be used for faster and efficient incorporation of the drug substances. The microsponges act as carriers for topical drug delivery of variety of functional substances, e.g. Anti acne, anti inflammatory, anti purities, anti fungal, rubefacients, etc[10, 11].

2. Quasi-emulsion solvent diffusion

Microsponges were prepared by an ESD method. The organic internal phase containing drug and ethyl cellulose in dichloromethane

was gradually added into external phase, which contained PVA as emulsifying agent. The mixture was stirred at 1,000–2,000 rpm for 3 h at room temperature to remove dichloromethane from the reaction flask. The formed microsponges were filtered, washed with distilled water, and dried at room temperature. Microsponges were weighed, and production yield (PY) was determined [12, 13]. **(Shown in Figure No. 3)**

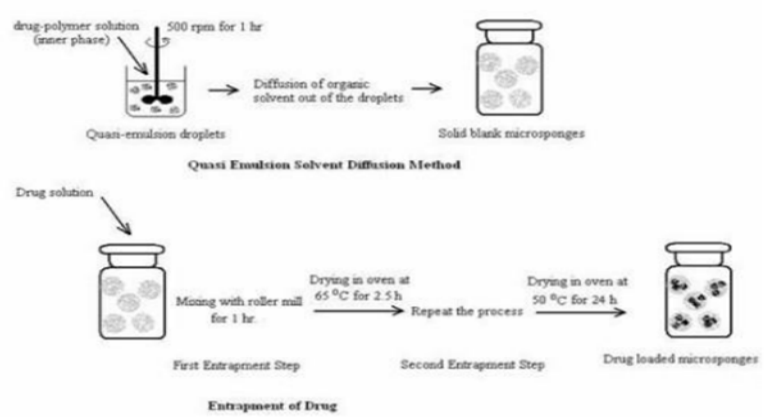

Fig. 3: Microsponge preparation by Quasi-emulsion solvent diffusion

Evaluation of Nanosponge[7] and Microsponges

1. Particle size determination

Free-flowing powders with fine aesthetic attributes are possible to obtain by controlling the size of particles during polymerization. Particle size analysis of loaded and unloaded nano and microsponges can be performed by laser light diffractometry or Malvern Zeta sizer. Cumulative percentage drug release from nano and microsponges of different particle size will be plotted against time to study effect of particle size on drug release. 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 [7,14].

2. Morphology and surface topography of microsponges

For morphology and surface topography, the prepared nano and microsponges can be coated with gold–palladium under an argon atmosphere at room temperature and then the surface morphology of the nano and microsponges can be studied by scanning electron microscopy (SEM) [15].

3. Determination of loading efficiency and production yield

The loading efficiency (%) of the nano and microsponges can be calculated according to the following equation

$$\text{Loading Efficiency} = \frac{\text{Actual drug contect in microsponge}}{\text{Theoritical drug content}} \times 100$$

The production yield of the nano and micro particles can be determined by calculating accurately the initial weight of the raw materials and the last weight of the nano and microsponge obtained [16].

$$\text{Production Yield (PY)} = \frac{\text{Practical mass of microsponges}}{\text{Theoritical mass (Polymer + drug)}} \times 100$$

4. Determination of true density

The true density of nano or microparticles and Benzoyl peroxide (BPO) using an ultra-pycnometer under helium gas and was calculated from a mean repeated determinations [17].

Polymer/ monomer composition

Selection of monomer is dictated both by ultimately to be entrapped and by the vehicle into which it will be dispersed .Polymers with varying electrical charges or degrees of hydrophobicity or lipophilicity may be prepared to provide flexibility in the release of active ingredients. Various monomer combinations will be screened for their suitability with the drugs by studying their drug release profile [18].

5. **Resiliency**

Resiliency (viscoelastic properties) of sponges can be modified to produce beadlets that is softer or firmer according to the needs of the final formulation. Increased cross-linking tends to slow down the rate of release. Hence resiliency of sponges

will be studied and optimized as per the requirement by considering release as a function of cross-linking with time[18].

6. **Compatibility studies**

Compatibility of drug with reaction adjuncts can be studied by thin layer chromatography (TLC) and Fourier Transform Infra-red spectroscopy (FT-IR). Effect of polymerization on crystallinity of the drug can be studied by powder X-ray diffraction (XRD) and Differential Scanning Colorimetry (DSC). For DSC approximately 5 mg samples can be accurately weighed into aluminum pans and sealed and can be run at a heating rate of 15 C/min over a temperature range 25–430 C in atmosphere of nitrogen [19].

7. **Dissolution tests**

Dissolution profile of microsponges can be studied by use of 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 suitable analytical method[19].

Nanosponges and Microsponge as a drug delivery system

The fundamental appeal of the Nanosponges and Microsponge technology stems from the difficulty experienced with conventional formulations in releasing active ingredients over an extended period of time. Conventional dermatological and personal care products typically provide active ingredients in relatively high concentrations but with a short duration of action. This may lead to a cycle of short-term overmedication followed by long-term under medication. Rashes or more serious side effects can occur when active ingredients penetrate the skin. In contrast, this technology allows an even and sustained rate of release, reducing irritation while maintaining efficacy[20]. This technology has many favorable characteristics which make it a versatile drug delivery vehicle. Nanosponges and Microsponge Systems are based on nano and microscopic, polymer-based spheres that can suspend or entrap a wide variety of substances, and then be incorporated into a formulated product such as a gel, lotions, cream, ointments, liquid or powder. A single Nano and Microsponge System consist of a myriad of interconnecting voids within a non-collapsible structure that can accept a wide variety of substances. The outer surface is typically porous, allowing the sustained flow of substances out of the sphere. These delivery systems are being used currently in cosmetics, over-the-counter (OTC) skin care, sunscreens products. Nanosponges and Microsponge delivery system is a unique technology for the controlled release of topical agents. When applied to the skin, the microsponge releases its active ingredient on a time mode and also in response to other stimuli like rubbing, temperature, pH, etc [21,22].

This technology offers entrapment of ingredients and is believed to contribute towards reduced side effects, improved stability, increased elegance and enhanced formulation flexibility. In addition, Nanosponges and Microsponge system are non-irritating, non allergic and non-toxic. This system is employed for the improvement of performance of topically applied drugs. Nanosponges and Microsponge can be effectively incorporated into topical drug delivery system for prolonged drug release and retention of dosage form on skin, and also use for oral delivery of drugs using bioerodible polymers, especially for colon specific delivery and controlled release drug delivery system thus reducing drug toxicity and improving patient compliance by providing site specific drug delivery system and prolonging dosage intervals[7, 23].

Advantages of Nanosponges and Microsponge drug delivery system

This technology offers entrapment of ingredients and reduced side effects,

Improved stability, increased elegance, and enhanced formulation flexibility

Nanosponges and Microsponge systems are non-irritating, non-mutagenic, non-allergenic, and non-toxic.

Extended release - continuous action up to 12 hours

Allows incorporation of immiscible liquid

Improves material processing - liquid can be converted to powders[23, 24].

Drug used in Nanosponges drug delivery

Econazole nitrate, an antifungal used topically to relive the symptoms of superficial candidasis, dermatophytosis, versicolor and skin infections available in cream, ointment, lotion and solution. Adsorption is not significant when econazole nitrate is applied to

skin and required high concentration of active of active agents to be incorporated for effective therapy. Thus Econazole nitrate nanosponges were fabricated by emulsion solvent diffusion method and these nanosponges were loaded in hydrogel as a local depot for sustained drug release[7].

Bovine serum albumin (BSA), protein in solution are not stable, they are stored in lyophilized state. However proteins can reversibly denatured on lyophilization and adopts conformation markedly different from native structure. Major drawback in protein formulation and development is to maintain its native structure during processing and long term storage. In the nanosponge based approach protein like BSA are encapsulated in swell able cyclodextrin based poly (amido-amine) nanosponges to increase the stability of proteins[25].

Itraconazole is a BCS class-II drug that has a dissolution rate limited poor bioavailability. Rational of the work was to enhance the solubility of Itraconazole so that the bioavailability problem was solved. In this nanosponge of betacyclodextrins cross linked with carbonate bonds were prepared and loaded with Itraconazole so that its solubility was increased[26].

Camptothecin (CAM), a plant alkaloid and a potent antitumor agent, has a limited therapeutic utility because of its poor aqueous solubility, lactone ring instability and serious side effects. Cyclodextrin-based nanosponges (NS) are a novel class of cross-linked derivatives of cyclodextrins. They have been used to increase the solubility of poorly soluble actives, to protect the labile groups and control the release. This study aimed at formulating complexes of Camptothecin with β-cyclodextrin based nanosponges[27].

Encapsulation of gases Cyclodextrin based carbonate nanosponges were used to form inclusion complexes with three different gases i.e. 1-methylcyclopropene, oxygen and carbon dioxide. The complexetion of oxygen or carbon dioxide could be useful for many biomedical applications. In particular the oxygen-filled nanosponges could supply oxygen to the hypoxic tissues which are present in various diseases[28].

Cyclodextrin "Nanosponges" for the Removal of Organic Pollutants from Water β-cyclodextrin Nanosponges are completely insoluble in water, have the property of encapsulating organic pollutants from water. Ceramic porous filters can be impregnated with these Nanosponges resulting in hybrid organic/inorganic filter modules. These hybrid filter modules were tested for the effective purification of water, employing a variety of water pollutants. It has been established that polycyclic aromatic hydrocarbons (PAHs) can be removed very efficiently (more than 95%). Representatives of the pollutant group of trihalogen methanes (THMs), monoaromatic hydrocarbons (BTX), and pesticides (simazine) can also be removed (>80%) [29].

Drug used in microsponges

Diagnostic Microsponges from Seaweed Programmable Bio-Nano-Chip (PBNCs) contains microsponges, tiny agarose beads programmed to capture biomarkers (above, right). The biomarkers help clinicians detect signs of disease in patients. Bio-Nano-Chips are programmed to detect signs of cardiac disease, cancer and HIV. PBNCs capture biomarkers -- molecules that offer information about a person's health -- found in blood, saliva and other bodily fluids. The biomarkers are sequestered in tiny sponges set into an array of inverted pyramid-shaped funnels. The agarose beads set into pyramid-shaped funnels in the PBNC are infused with antibodies to detect and capture specific biomarkers[30].

5-FU-Actinic keratoses (AK), or precancerous skin lesions, is a common condition that usually results from long-term exposure to the sun and can eventually lead to skin cancer. 5-FU is a highly effective topical drug for the treatment of AK, but its harsh side like effects irritation has presented a barrier to patient compliance. Microsponge-entrapped 5-FU provides an important breakthrough. Carac contains 0.5% fluorouracil incorporated into a patented porous Microsponge System. The particles are dispersed in a cream and hold the active ingredient until applied to the skin. Carac cream is the newest topical treatment for multiple actinic or solar keratoses to be approved by the FDA. Carac provides sufferers with options for shorter duration of therapy (1, 2 or 4 weeks), once-a-day dosing, and more rapid recovery time from irritation[31].

CONCLUSION

From the above study it is concluded that Nanosponges and Microsponge Systems are based on nano and microscopic, polymer-based spheres that can suspend or entrap a wide variety of substances, and then be incorporated into a formulated product such as a gel, lotions, cream, ointments, liquid or powder. This technology offers entrapment of ingredients and thus reduced side effects,

improved stability, increases elegance and enhanced formulation flexibility. Nanosponges and Microsponge can be effectively incorporated into topical drug delivery system for retention of dosage form on skin, and also use for oral delivery of drugs using bioerodible polymers, especially for colon specific delivery and controlled release drug delivery system thus improving patient compliance by providing site specific drug delivery system and prolonging dosage intervals

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REFERENCES

1. Cavalli R, Trotta F and Tumiatti W. Cyclodextrin-based Nanosponges for Drug Delivery. J of Inclusion Phenomena and Macro Chemistry 2006;56(1-2):209-213.
2. Trotta F and Cavalli R. Characterization and Applications of New Hyper-Cross-Linked Cyclodextrins. Composite Interfaces 2009;16(1):39-48.
3. Patel SB, Patel HJ and Seth AK. Microsponge Drug Delivery System: An Overview, Journal of Global Pharma Tech. 2010; 2(8):1-9.
4. Aritomi H, Yamasaki Y, Yamada K, Honda H and Khoshi M. Development of sustained release formulation of chlorpheniramine maleate using powder coated microsponges prepared by dry impact blending method. Journal of Pharma Scie and Tech. 1996;56(1):49-56.
5. Eki S, Lei T, Jingquan L, Zhongfan J, Cyrille B and Thomas PD. Biodegradable Star Polymers Functionalized With β-Cyclodextrin Inclusion Complexes. Biomacromolecules 2009;10(9):2699–2707.
6. Davankov VA, Ilyin MM, Tsyurupa MP, Timofeeva GI and Dubrovina LV. From a Dissolved Polystyrene Coil to Intramolecularly-Hyper-Cross-Linked "Nanosponge". Macromolecules 1996;29(26):8398–8403.
7. Sharma R, Roderick B and 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.
8. Shaha V, Jain H, Krishna J and Patel P. Microsponge drug delivery: A Review. Int J Res Pharm Sci 2010; 1(2):212-218.
9. Tansel C¸ omoglu, Nurs¸in Gonu and Tamer Baykara. The effects of pressure and direct compression on tabletting of microsponges. Int J of Pharmaceutics 2002;242:191–195.
10. Tansel C¸ omog˘lu, Nurs Gonu and Baykara T. Preparation and in vitro evaluation of modified release ketoprofen Microsponges. International Journal of Pharmaceutics. 2003;58:101-106.
11. Vyas SP and Khar RK. Targeted and Controlled Drug Delivery-Novel Carrier System: New Delhi, CBS Publication; 2002: 453.
12. Embil K and Nacht S. The microsponge delivery system a topical delivery system with reduced irritancy incorporating multiple triggering mechanisms for the release of actives. J Microencapsule 1996;13:575–88.
13. Mishra MK, Shikhri M, Sharma R and Goojar MP. 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.
14. Martin A, Swarbrick J and Cammarrata A. In: Physical Pharmacy-Physical Chemical Principles in Pharmaceutical Sciences. 3rd Ed. 1991: 527.
15. Emanuele AD and Dinarvand R. Preparation, Characterization and Drug Release from Thermo responsive Microspheres. Int J Pharm.1995;237-42.
16. Kilicarslan M and Baykara T. The effect of the drug/polymer ratio on the properties of Verapamil HCl loaded microspheres. Int J Pharm. 2003;252:99–109.
17. Barkai A, Pathak V and Benita S. Polyacrylate (Eudragit retard) microspheres for oral controlled release of nifedipine. Formulation design and process optimization. Drug Dev Ind Pharm. 1990; 16:2057-2075.
18. D'souza JI. The Microsponge Drug Delivery System: For Delivering an Active Ingredient by Controlled Time Release. Pharma info.net 2008;6(3): 62.

19. 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.
20. Melani F, Mura P, Adamo M, Maestrelli F, Gratteri P and Bonaccini C. New docking CFF91 parameters specific for cyclodextrin inclusion complexes. Chemical Physics Letters 2003;370(1-2): 280-292.
21. Ali N and Siahi M. Factors affecting the morphology of benzoyl peroxide microsponges. Microscopy in Nano biotechnology 2007;38(8):834-840.
22. Orlu M , Cevher E and Ahmet A. Design and evaluation of colon specific drug delivery system containing flurbiprofen microsponges. Int J of pharmaceutics. 2006; 318 (1-2):103-117.
23. Patel G and Patel JK. Use of a Microsponge in Drug Delivery Systems. Pharmaceutical processing 2008; 158.
24. Khopade AJ, Jain S and Jain NK. "The Microsponge". Eastern Pharmacist 1996;49-53.
25. Swaminathan S, Cavalli R, Trotta F and Vavia PR. Invitro release modulation and conformational stabilization of a model protein using swellable polyamidoamine nanosponges of cyclodextrin. J Incl Phemon Macrocycl Chem. 2010; DOI 10.1007/s10847-010-9765-9.
26. Swaminathan S, Cavalli R, Trotta F and Vavia PR. Formulation of betacyclodextrin based nanosponges of itraconazole. J. Incl. Phemon. Macrocycl. Chem 2007;57:89-94.
27. 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.
28. Trotta, F, Cavalli, R, Vavia PR andKhalid A. Cyclodextrin nanosponges as effective gas carriers. J of Inclusion Phenomena and Macrocyclic Chemistry, online first [TM], 22nd Feb 2011. DOI: 10.1007/s10847-011-9926-5.
29. 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.
30. Devitt JM. Microsponges from Seaweed May Save Lives. Science News, *Science Daily (Feb. 9, 2011).*
31. Nasdaque NM; Microsponge technology a topical technology for treatment of AK; www.appharma.com.
32. Gu H, Zheng R., Liu H, Zhang X and Xu B. Direct Synthesis of a Bimodal Nanosponge Based on FePt and ZnS. Small 2005;1: 402–406. DOI: 10.1002/smll.200400106.