

An Examination of Nanosponges

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Abstract: *Recent advancements in nanotechnology have led to the development of highly efficient targeted drug delivery systems. Achieving precise delivery of therapeutic molecules to a specific site within the body requires a specialized and sophisticated delivery mechanism. In this context, the emergence of nanosponges represents a significant breakthrough, addressing challenges such as drug toxicity, poor bioavailability, and unpredictable drug release profiles. Owing to their porous architecture, nanosponges possess the unique ability to encapsulate both hydrophilic and hydrophobic drugs, thereby enabling controlled and sustained drug release.*

Nanosponges are minute, sponge-like structures capable of circulating within the body, reaching the target site, adhering to the surface, and releasing the drug in a controlled and predictable manner. They are typically synthesized through the crosslinking of cyclodextrins with carbonyl or dicarboxylate crosslinkers. This technology has been extensively explored for oral, topical, and parenteral drug delivery. Additionally, nanosponges have shown potential as carriers for enzymes, proteins, vaccines, and antibodies. The present review provides an overview of the preparation methods, characterization techniques, and potential applications of nanosponges in drug delivery systems..

Keywords: Targeted Drug Delivery System, Nanosponges, Hydrophilic and Hydrophobic Drugs, β -Cyclodextrin

I. INTRODUCTION

Targeted delivery of therapeutic agents has long posed a significant challenge for medical researchers, particularly with respect to ensuring that drugs reach the intended site within the body and controlling their release to avoid adverse effects or overdosing. The emergence of novel and advanced nanoscale structures known as nanosponges offers promising solutions to these challenges. Nanosponges represent a modern class of materials composed of tiny particles containing narrow cavities measuring only a few nanometers. These cavities can encapsulate a wide range of substances. Due to their unique architecture, nanosponges are capable of carrying both hydrophilic and lipophilic drug molecules, thereby enhancing the stability of poorly water-soluble compounds. These microscopic, porous systems possess the capacity to encapsulate diverse materials and improve the solubility of drugs with low aqueous solubility.[1]

Nanosponges function as mesh-like, nanoscale networks that have the potential to revolutionize the treatment of numerous diseases. Early studies indicate that this technology may be up to five times more effective in delivering therapeutic agents for conditions such as breast cancer compared to conventional delivery methods. Structurally, nanosponges consist of a three-dimensional scaffold or network of polyesters capable of undergoing natural degradation. These polyesters are combined with suitable crosslinkers during formulation to create the nanosponge matrix. Because the polyesters are biodegradable, they gradually break down within the body. A major limitation associated with many newly developed chemical entities is their poor water solubility, which leads to significant formulation difficulties and reduced bioavailability. In recent years, nanosponge-based nanotechnology has gained considerable attention for its ability to address these challenges and provide effective solutions to several formulation-related problems.[2]

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NANOSPONGES

Nanosponges are nanoscale, sponge-like structures with dimensions comparable to those of certain viruses (approximately 250 nm to 1 μ m). They possess internal cavities capable of encapsulating a wide variety of therapeutic agents. Structurally, nanosponges function as a three-dimensional scaffold composed of a backbone formed from long-chain polyesters. These polyesters are combined with suitable crosslinkers in solution to form the nanosponge polymeric matrix.

Targeted drug delivery has long posed challenges for researchers, particularly in achieving site-specific delivery within the body and ensuring controlled drug release to prevent overdosing. The development of advanced nanoscale entities, such as nanosponges, offers significant potential for overcoming these limitations. Nanosponges represent an innovative and emerging technology that plays a crucial role in achieving controlled and targeted drug delivery.[5]

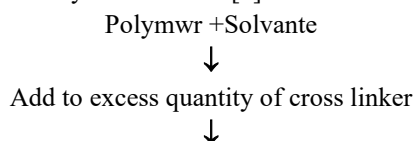
MECHANISM OF DRUG RELEASE FROM NANOSPONGES

Nanosponge particles possess an open, porous structure that allows the active drug molecules to move into and out of the sponge matrix until equilibrium is achieved. In topical delivery systems, once the formulation is applied to the skin, the active drug present in the vehicle is absorbed first, leading to the depletion of drug concentration in the vehicle.[6] This creates an unsaturated environment, disturbing the equilibrium and prompting the release of additional drug molecules from the nanosponge matrix into the vehicle, and subsequently into the skin, until the vehicle is either absorbed or dries completely.

METHODS OF PREPARATION OF NANOSPONGES

1) Solvent Method

In this method, the polymer is dissolved in an appropriate polar aprotic solvent, such as dimethylformamide (DMF) or dimethyl sulfoxide (DMSO). The resulting mixture is then added to an excess amount of crosslinker, typically in a crosslinker-to-polymer molar ratio of 4:1 to 16:1. The reaction mixture is maintained at a temperature ranging from 10°C to the reflux temperature of the solvent, for a period ranging from 1 to 48 hours. Preferred crosslinkers for this method include dimethyl carbonate and carbonyl diimidazole.[7]



Allow the reaction to cool



Recover the product by filtration under vacuum

In this method, the polymer is dissolved in an appropriate polar aprotic solvent such as dimethyl sulfoxide (DMSO) or dimethylformamide (DMF), followed by the addition of an excess amount of crosslinker. The reaction mixture is then refluxed for up to 48 hours at a temperature ranging from 10°C to the reflux temperature of the solvent. After completion, the reaction mixture is allowed to cool to room temperature. The resulting product is then added to an excess volume of bidistilled water and subsequently collected by filtration.[8-9]

Using the solvent method, nanosponges are prepared by dissolving the polymer in polar aprotic solvents such as DMSO or DMF. A crosslinker is then incorporated into the mixture in a typical polymer-to-crosslinker ratio of 1:4. The reaction is carried out at temperatures between 10°C and the reflux temperature of the solvent for a duration of 1 to 48 hours. After the reaction is complete, the mixture is cooled to room temperature and the resulting product is poured into bidistilled water. The nanosponges are recovered by vacuum filtration and further purified through Soxhlet extraction using ethanol, followed by drying.[10]

2) Ultrasound-Assisted Synthesis

In this method, nanosponges are synthesized by reacting the polymer with an appropriate crosslinker without the use of any solvent. The reaction mixture is subjected to sonication to facilitate polymer-crosslinker interaction. Nanosponges produced through this technique generally exhibit a uniform and spherical morphology. Polymers are made to react with crosslinkers in a flask without the solvent. The flask is placed in an ultrasound bath which is filled with water and heated to 90°C and the mixture is sonicated for 5 h.

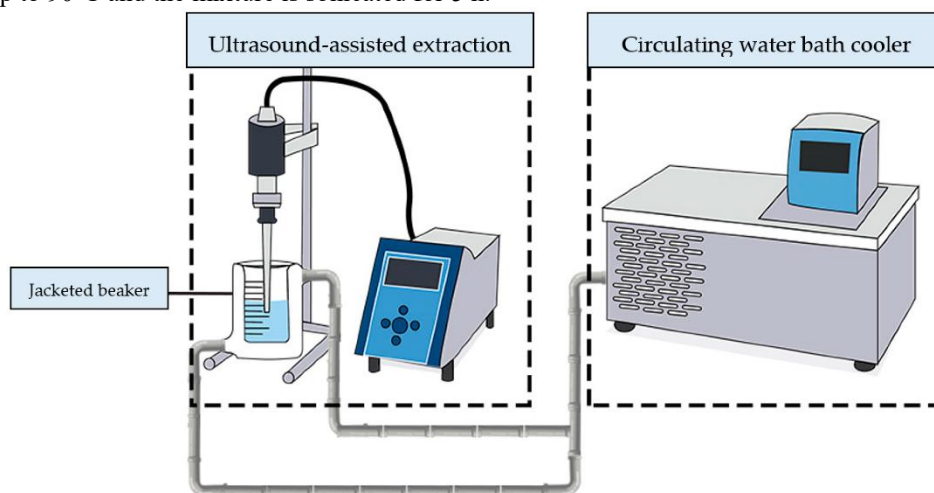


Fig 1 . Ultrasound-assisted synthesis

In ultrasound-assisted synthesis, nanosponges are prepared by reacting the polymer with a suitable crosslinker in the absence of a solvent, while subjecting the mixture to sonication. This technique typically results in uniformly spherical nanosponges.[11] The polymer and crosslinker are combined in a specific molar ratio within a reaction flask. The flask is then placed in an ultrasonic bath filled with water and heated to approximately 90°C. The mixture is sonicated for about five hours. After sonication, the reaction mixture is allowed to cool, and the solid mass is mechanically broken into smaller fragments. The material is washed with water to remove unreacted polymer and subsequently purified using prolonged Soxhlet extraction with ethanol. The final product is dried under vacuum and stored at 25°C until further use.[12-13]

3) Loading of the Drug into Nanosponges

Before drug loading, the prepared nanosponges must be processed to achieve an average particle size of less than 500 nm. The nanosponges are then dispersed in water and subjected to sonication to prevent aggregation. The resulting



suspension is centrifuged to obtain the colloidal fraction. The supernatant is collected, and the sample is dried using freeze-drying. Alternatively, an aqueous suspension of nanosponges can be prepared and continuously stirred for a specified duration to facilitate uniform dispersion and subsequent drug loading.

To achieve a particle size of less than 500 nm, the nanosponges must undergo appropriate pretreatment. For this purpose, the nanosponges are dispersed or suspended in water and subjected to vigorous sonication to prevent aggregation. The resulting suspension is then centrifuged to obtain the colloidal fraction. The supernatant is collected, and the sample is subsequently dried using a freeze dryer.[14-15] For drug loading, an aqueous suspension of nanosponges is prepared, and an excess amount of the drug is added. The mixture is continuously stirred for a specific duration to allow complexation between the drug and the nanosponge matrix. Upon completion of the complexation process, the uncomplexed drug is separated from the complexed fraction through centrifugation. The solid nanosponge crystals are then recovered either by freeze drying or by solvent evaporation. The crystalline structure of nanosponges plays a critical role in drug complexation. Crystalline nanosponges exhibit higher drug-loading capacities compared to paracrystalline forms. In weakly crystalline nanosponges, drug incorporation occurs primarily as a mechanical mixture rather than through true molecular complexation.[16]

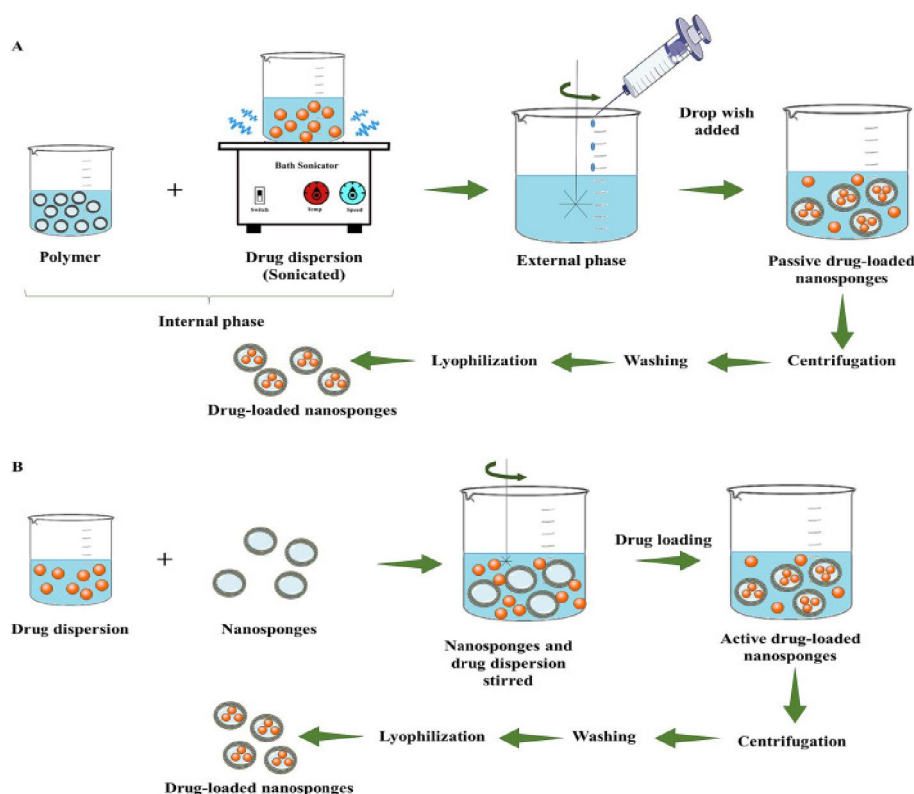


Fig 2. Loading of Drug into Nanosponges

The nanosponges obtained must be pretreated to ensure that the particle size remains below the recommended limit of 500 nm. Para-crystalline nanosponges exhibit different drug-loading capacities compared to crystalline nanosponges. In weakly crystalline nanosponges, drug loading generally occurs through mechanical mixing rather than by forming true inclusion complexes. Upon completion of the complexation process, the uncomplexed (undissolved) drug is separated from the complexed fraction by centrifugation. The solid nanosponge crystals are then obtained either through solvent evaporation or freeze-drying.[17]

ADVANTAGES OF NANOSPONGES

1. Enhance the aqueous solubility of lipophilic drugs.
2. Protect drugs that are susceptible to degradation.



3. Reduce dosing frequency.
4. Are non-irritating, non-mutagenic, and non-toxic.
5. Provide efficient entrapment of active components with reduced side effects.
6. Improve stability, aesthetic qualities, and formulation flexibility.
7. Maintain stability at temperatures up to 130°C.
8. Are compatible with most vehicles and excipients.[18]

DISADVANTAGES OF NANOSPONGES

1. Capable of encapsulating only small molecules; unsuitable for larger molecules.
2. May occasionally exhibit dose dumping.
3. Primarily incorporate small molecular entities.
4. Performance depends largely on loading capacity.
5. May exist in paracrystalline or crystalline forms, which influence drug-loading behavior.
6. Dose Dumping is a possibility[19]

Factors Influencing the Formulation of Nanosponges

1. Nature of the Polymer

The type of polymer used in the preparation of nanosponges significantly influences their formation and pre-formulation characteristics. The internal cavity size of the nanosponge must be sufficiently large to encapsulate drug molecules of specific dimensions necessary for complexation.

2. Drug Properties

For effective inclusion or non-inclusion complex formation with nanosponges, the drug should possess the following characteristics:

1. Water solubility of less than 10 mg/mL.
2. Molecular weight between 100 and 400 g/mol.
3. Molecular structure not exceeding five condensed rings.[20]
4. Melting point below 250°C.

3. Temperature

Temperature variations can influence the complexation process between the drug and the nanosponges. Elevated temperatures may reduce intermolecular interactions—such as hydrophobic interactions and Van der Waals forces—thereby affecting complexation efficiency.

Characterization of Nanosponges

1) Thermoanalytical Methods

Thermoanalytical techniques such as Differential Thermal Analysis (DTA) and Differential Scanning Calorimetry (DSC) are used to observe changes in the drug substance prior to its thermal degradation within the nanosponge matrix. Broadening, shifting, or the appearance of new peaks, as well as changes in weight loss profiles, provide evidence for the formation of inclusion complexes.

2) Microscopy Studies

The morphology and surface characteristics of the drug, nanosponges, and the drug–nanosponge complex can be analyzed using Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM). Differences in the crystallization states between raw materials and the resulting product, as observed under the electron microscope, indicate successful complex formation.[21]



3) Solubility Studies

Solubility analysis is one of the most widely used methods to investigate inclusion complexation. According to the phase solubility technique described by Higuchi and Connors, the effect of nanosponges on drug solubility can be quantified through phase solubility diagrams, which indicate the degree of complexation.⁴¹⁴

4) IR Spectroscopy

Infrared (IR) spectroscopy is used to evaluate interactions between the nanosponges and drug molecules in the solid state. In many cases, nanosponge bands exhibit only slight changes following complexation. If less than 25% of the guest molecule is encapsulated, the characteristic bands corresponding to the included portion may be faint or masked by the spectral bands of the nanosponge. Consequently, IR spectroscopy may not always be sufficiently sensitive for detecting inclusion complexes and is generally less informative compared to other analytical techniques.[22]

5) X-ray Diffractometry

Powder X-ray diffractometry (PXRD) is employed to detect inclusion complexes in the solid state. Liquid substances lack distinctive diffraction patterns; thus, diffractograms for nanosponge complexes differ significantly from those of uncomplexed nanosponges. For solid drugs, comparisons are made between the diffractograms of the proposed complex and a mechanical mixture of the components. Mechanical mixtures exhibit a combined diffraction pattern, whereas true complexes produce distinct diffractograms representing a new solid phase. PXRD is also useful for identifying chemical decomposition and verifying the formation of inclusion complexes. Single-crystal X-ray structure analysis further supports these evaluations.[23]

The formation of drug–nanosponge complexes alters the diffraction patterns and modifies the crystalline characteristics of the drug. Complex formation results in the sharpening of existing peaks, the appearance of new peaks, and the shifting of certain peaks.

6) Loading Efficiency

Loading efficiency refers to the proportion of drug successfully incorporated into the nanosponges. It is determined through quantitative drug estimation using UV-visible spectrophotometry and high-performance liquid chromatography (HPLC).

7) Zeta Potential

Zeta potential is a measure of the surface charge of the nanosponge particles. Using an additional electrode in particle-size analysis equipment, the zeta potential can be measured to evaluate electrophoretic mobility and the diffusion coefficient.

The surface charge plays a crucial role in determining the system's behavior in biological environments, influencing biodistribution and interactions with biological components.[24]

APPLICATIONS OF NANOSPONGES

• Nanosponges in Drug Delivery

Nanosponges are structurally robust and can be formulated into oral, parenteral, topical, and inhalation dosage forms. Their nanoporous architecture enables efficient encapsulation of hydrophobic drugs (BCS Class II), thus improving dissolution rate, solubility, and drug stability. β -Cyclodextrin-based nanosponges have been reported to deliver drugs 3–5 times more effectively than direct administration at the target site. They are suitable for incorporation into tablets, capsules, suspensions, gels, and anticancer formulations.[25]

• Cancer Therapy

Targeted drug delivery is essential in cancer treatment to minimize adverse effects and enhance therapeutic outcomes. Nanosponges have been investigated for the delivery of anticancer agents such as in breast, colon, brain, lymphatic, and lung cancers using single-dose injectable formulations.



Camptothecin (CPT), a plant-derived antitumor drug with poor water solubility, demonstrates limited clinical application and significant adverse effects. Cyclodextrin-based nanosponges (NS) have emerged as novel cross-linked derivatives used to enhance CPT solubility, protect labile functional groups, and provide controlled drug release.[26]

• Nanosponges in Enzyme Immobilization

Nanosponge systems have been explored for enzyme immobilization, particularly for lipases. Immobilization improves enzyme stability, modulates catalytic properties such as enantioselectivity, and enhances reaction rates. Thus, there is a growing demand for new solid supports suitable for this class of enzymes.[27-28]

Additional Applications

- Can be used in preparing oral, topical, parenteral, and inhalation dosage forms.
- Provide protection of proteins within delivery systems, preventing degradation.
- Enhance solubility and dissolution rates of poorly water-soluble drugs while enabling controlled drug release.[29]
- Improve drug solubility by over 27-fold in some cases.
- Enhance drug wetting characteristics and reduce crystallinity.
- Serve as carriers for proteins such as bovine serum albumin.
- Demonstrate the capacity for controlled oxygen storage and release.[30]

II. CONCLUSION

Nanosponges have been identified as an advanced drug delivery platform capable of encapsulating both hydrophilic and lipophilic drugs through complex formation. They facilitate controlled drug release at specific target sites, thus improving therapeutic efficacy. Nanosponges can be incorporated into various topical formulations such as creams, lotions, and ointments, as well as prepared in liquid or powder forms.

This technology offers several advantages, including targeted drug delivery, reduced side effects, enhanced formulation stability, improved flexibility, and better patient compliance. Beyond pharmaceuticals, nanosponges hold promising applications in cosmetics, biomedicine, bioremediation, agrochemistry, and catalysis.

AUTHORS' CONTRIBUTIONS

All authors contributed equally to the preparation of this work.

REFERENCES

- [1]. HIMANGSHU BHOWMIK, D. NAGASAMY VENKATESH*, ANUTTAM KUILA, KAMMARI HARISH KUMAR. NANOSPONGES: A REVIEW, received: 29 Jan 2018, Revised and Accepted: 24 May 2018. Vol 10, Issue 4, 2018
- [2]. SELVAMUTHUKUMAR SUBRAMANIAN, ANANDA SINGIREDDY, KANNAN KRISHNAMOORTHY AND MANAVALAN RAJAPPAN. NANOSPONGES: A NOVEL CLASS OF DRUG DELIVERY SYSTEM – Review, Received, January 6, 2012; Revised, January 9, 2012; Accepted, January 11, 2012; Published, January 12, 2012, 103.
- [3]. B.SYED SALMAN AND B. THABITHA2*1. A REVIEW ON NANOSPONGES, Received, 02/01/2017; Revised, 26/02/2017; Accepted: 01/03/2017, Vol.2, No.1, 2017.
- [4]. AJAY VISHWAKARMA*, PREETAM NIKAM, RAJENDRA MOGAL, SWATI TALELE, REVIEW ON NANOSPONGES: A BENEFICIATION For Novel Drug Delivery, 13.
- [5]. NAGULAPATI SAILAJA*, MEKA ANVITHA, CHAMARTHI SUNITHA, SHAIK SABIHA BHANU, B. PRASHANTI, G. MADHAVI AND K. PADMALATHA, NANOSPONGES, Article Received: April 2021 Accepted: April 2021 Published: May 2021, 351
- [6]. SHAIKH BILAL J.*; PATIL ABHISHEK S.; BHOSALE ANKUSH S.; RAUT INDRAYANI D.; NITALIKAR MANOJKUMAR M, NANOSPONGES: AN EVOLUTIONARY TREND FOR TARGETED DRUG DELIVERY, Vol.6 Issue. 6, June- 2021, 3,5.
- [7]. Garima Verma, Anupam Kumar Sachan, Sunil Kumar, Nanosponges: A Multifunctional Targeted Drug Delivery System, October 2021, Volume 8 Issue 5, 713



- [8]. Nanosponges: An Innovative Class of Drug Delivery System - Review Tiwadi Shreya Shrinivas¹, Jadhav Suryakant Bapurao^{1*} and Tiwari Shailee Vijay^{2,10}.
- [9]. Kaur Navdeep*, Kumar Sandeep, NANOSPONGES: NOVEL STRATEGY FOR TARGETED DRUG DELIVERY SYSTEM: A REVIEW Published: August 2020,319.
- [10]. Ravi Silpa C, Krishnakumar K and Nair Smitha K, Nano sponges: A targeted drug delivery system and its applications,Received on 31 May 2019; revised on 15 June 2019; accepted on 18 June 2019,43.
- [11]. Tukaram S. Patil*, Nishigandha A. Nalawade, Vidya K. Kakade, Sumedha N. Kale, Nanosponges: A Novel Targeted Drug Delivery for Cancer Treatment, Volume2, Issue4),56,59.
- [12]. Pooja Bhargavi Dhavala¹, V S Vinai Kumar Tenneti², An Interesting Nanosponges as a Nanocarrier for Novel drug delivery: A Review, Volume – 5 Issue – 2 April 2017Website: www.woarjournals.org/IJPMR,4,2.
- [13]. Lala R, Thorat A, Gargote C. Current trends in β -cyclodextrin based drug delivery systems. Int J ResAyur Pharm, 2011; 2(5): 1520-1526.
- [14]. Trotta F, Cavalli R, Tumiatto W, Zerbinati O, Rogero C, Vallero R. Ultrasound-assisted synthesis of Cyclodextrin-based nanosponges. EP 1 786 841 B1; 2007
- [15]. 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.
- [16]. Trotta F., Cavalli R., Characterization, and Applications of New Hyper-Cross-Linked Cyclodextrins; Composite Interfaces 2009; 16(1):39-48
- [17]. Lala R., et al. "Current trends in β -cyclodextrin based drug delivery systems". International Journal of Research in Ayurveda and Pharmacy 2.5 (2011): 1520-1526.
- [18]. Ujjwalnautiya, Meenakshi Jassal, Jyotsana Kundlas. Nanosponges: As originated form for targeted drug delivery. International journal of recent advances in pharmaceutical research.,2015;5(2):75-81.
- [19]. REFERENCES
- [20]. Yadav GV, Panchory HP. Nanosponges—a boon to the targeted drug delivery system. J Drug Delivery Ther 2013;3:151-5.
- [21]. Bolmal UB, Manvi FV, Rajkumar K, Palla SS, Paladugu A, Reddy KR. Recent advances in nanosponges as drug delivery system. Int J Pharm Sci Nanotechnol 2013;6:1934-44.
- [22]. Shivani S, Poladi KK. Nanosponges-novel emerging drug delivery system: a review. Int J Pharm Sci Res 2015;6:529.
- [23]. Thakre AR, Gholse YN, Kasliwal RH. Nanosponges: a novel approach of drug delivery system. J Med Pharm Allied Sci 2016;78:103-11.
- [24]. Rita L, Amit T, Chandrashekhar G. Current trends in β -cyclodextrin based drug delivery systems. Int J Res Ayurveda Pharm 2011;2:1520-6.
- [25]. Ahmed RZ, Patil G, Zaheer Z. Nanosponges—a completely new nano-horizon: pharmaceutical applications and recent advances. Drug Dev Ind Pharm 2013;39:1263-72.
- [26]. Singh D, Soni GC, Prajapati SK. Recent advances in nanosponges as drug delivery system: a review. Eur J Pharm Med Res 2016;3:364-71.
- [27]. Jilsha G, Viswanad V. Nanosponges: a novel approach of drug delivery system. Int J Pharm Sci Rev Res 2013;19:119-23.
- [28]. Shringirishi M, Prajapati SK, Mahor A, Alok S, Yadav P, Verma A. Nanosponges: a potential nanocarrier for novel drug delivery-a review. Asian Pacific J Trop Disease 2014;4:19-26.
- [29]. Nanosponges: A New Approach for Drug Targetting K. Arshad Ahmed, Khan. Int J Pharm Pharm Res 2016;7:381-96.
- [30]. Sharma R, Pathak K. Nanosponges: Emerging drug delivery system. Pharma Stud; 2010. p. 33-5.
- [31]. Indira B, Bolisetti SS. Nanosponges: a new era in drug delivery. J Pharm Res 2012;5:5293-6.

