International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 1588-1606 www.ijprajournal.com ISSN: 2456-4494

Nanosponges: A Comprehensive Review

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Submitted: 10-12-2022 Accepted: 23-12-2022

ABSTRACT –
A targeted drug delivery system is a method of delivery of drugs to the Target site. For this many carrier- system is used, one such carrier is nanosponges. Nanosponges have a sponge-like morphology and are of nano size. They contain hydrophilic cavities with hydrophobic branches that help them in the loading of hydrophilic as well as hydrophobic drugs. These are tiny sponges that circulate in the body to reach a specific site and release the drug in a controlled and predictable manner and help in overcoming many problems like drug toxicity and poor bioavailability. This review gives comprehensive detail on nanosponges.
KEYWORDS: Targeted drug delivery system, nanosponges, cyclodextrin

I. INTRODUCTION

Nanosponge technology is a newer and emerging technology which uses the targeted drug delivery system to release the drug in a controlled manner to the targeted site. Nano sponges are class of materials made up of tiny sponge like structure with narrow cavity of few nano meter, with an average diameter below 1µm. They cross-link the segments of polyester to form a spherical shape which has many cavities where the drug can be stored. Those narrow cavities can be filled with different type of substance.These are able to carry both hydrophilic and lipophilic drug substances and thereby increasing the solubility of poorly water-soluble drug substance. This technology is considered to be a novel approach which offers controlled drug delivery system for topical use. It efficiently offers the entrapment of ingredients with reduced side effects, improved stability, increased elegance and enhanced formulation flexibility.[5]

NSs are tiny virus shaped sponges with diameter below1µm, which can trap the drug inside their three-dimensional (3D) sponge-like structure and at target site,it releases the drug in predictable and controlledmanner12. NSs is a type of nanoformulation that is saidto be produced by the interaction of polymers andcrosslinkers at a specified temperature. NSspossesshydrophobic cavity with tunable polarity and hydrophilicbranching making them capable of encapsulating bothhydrophobic and hydrophilic moieties[24]

Nanosponges are type of encapsulating nanoparticles which encapsulate the drug molecule within the core by different method of association and it can be classified into encapsulating nanoparticle, complexing nanoparticles, conjugating nanoparticles. When comparing with other nanoparticle, Nano sponges are insoluble in water and organic solvents. Nano sponges are mostly in solid form and it can also be formulated as oral, parenteral, topical or inhalation dosage form. Proteins, peptides, genes, anti-cancer agents and biomolecules have been widely studied using the nanoparticulate system which helps to lower undesired effects and to increase the efficacy. [5]

When orally administrating, these may be dispersed within a matrix of excipients, diluents and lubricants and anticaking agents which are more suitable for the formulation of either capsule or tablet. Saline or other aqueous solution or simply mixing with sterile water can be used for parenteral administrations.[5]

Nanosponges are novel class of hyper-crosslinked polymer based colloidal structures consisting of solid nanoparticles with colloidal sizes and nanosized cavities. They enhance stability, reduce side effects and modify drug release. The outer surface is typically porous, allowing sustain release of drug. They are mostly use for topical drug delivery. Size range of nanosponge is 50nm-100nm1.3They can be used for targeting drugs to specific sites, prevent drug and protein degradation. These tiny sponges can circulate around the body until they encounter the specific target site and stick on the surface and began to release the drug in a controlled and predictable manner. It is possible to control the size of nanosponge. To varying the portion of cross-linkers and polymers, the nanosponge particles can be made larger or smaller.[14]

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 1588-1606 www.ijprajournal.com ISSN: 2456-4494

The nanoparticles can be categorized into three groups based on how they associate with medicines. [19].

1. **Encapsulating Nanoparticles**: Nanosponges and nano capsules are examples of encapsulating nanoparticles. Alginate Nanosponges, which are sponge-like nanoparticles, have multiple hollows that allow drug molecules to pass through. Nanoparticles are also encapsulated in nano capsules such as poly (isobutyl cyanoacrylate) (IBCA). Drug molecules can be located in their aqueous core. [19]
2. **Complexing nanoparticles:** Such nanoparticles bind electrostatic charges to the molecule.[6]
3. **Conjugating nanoparticles:** Such nanoparticles are connected by a tight covalent bond with drug molecules.[6]

A number of polymers and cross-linkers are used in the preparation of nanosponges. They can be used as carrier for gases like oxygen and carbon dioxide and also act as a carrier for the release and delivery of enzymes, proteins and peptides in biomedical field.[9]

Different Polymers for the Nanosponges [9]

Formulation Polymers: Hyper-cross- linked polystyrenes, CDs and its derivatives like Alkyloxycarbonyl Cyclodextrin, Methyl beta-cyclodextrin, Hydroxy Propyl betacyclodextrin. [9]

Copolymers: Poly (Valero lactone, allyl valerolactone) Ethyl cellulose, Poly vinyl alcohol. Cross Linkers: Carbonyldiimidazole, carboxylic acid dianhydride, diary carbonates, dichloromethane, diisocynate, diphenyl carbonate, epichloridine, gluteraldehyde, pyromellectic anhydride, 2,2-bis (acrylamido) Acetic acid. [9]

Advantagesof Nanosponges[5]

1. Efficient entrapment of ingredients and reduced side effects.
2. Improved stability, increased elegance and enhanced formulation flexibility.
3. These formulations are stable up to a temperature of 130°c.
4. These formulations are compatible with most vehicles and ingredients.
5. These are self-sterilizing as their average pore size is 0.25µm which makes the bacteria unable to penetrate.
6. These are free flowing and can be cost effective.
7. These formulations modify the release of the drug.
8. They increase the solubility of poorly soluble drug.
9. It can be used to mask flavours and to convert liquid substance to solids.
10. These formulations increase the bioavailability of the drug.
11. They are non-irritating. Non mutagenic, nontoxic and non-allergic.
12. It has an extended release which provide continuous action up to 12 hrs.
13. Easy scale up for commercial production
14. Biodegradable
15. The material used in this system can provide a protective barrier that shields the drug from premature destruction within the body.
16. Reduce dosing frequency. Better patient compliance. Nanosponges help to remove the toxic and venom substance from the body. [3]
17. Incorporation of immiscible liquids is possible; [13]
18. Improved material processing since liquids may be converted to powders [31]
19. These formulations are stable over range of pH 1 to 11. [4]
20. This reduces discomfort and provides goodtolerance, leading to better compliance with thepatient.[6]

DisadvantgesOf Nanosponges[5]

1. They include only small molecule.
2. They depend only upon the loading capacities.
3. Retarded release may occur.[20]
4. Both crystalline and paracrystalline nanosponges arepossible.[20]
5. Dose dumping may occur at times. [15]

Classification Of Nanosponges[8]

Nanosponges are synthesized from organic or inorganic materials.Based on nature of material used in the synthesis of nanosponges, these are classified into 4 types. They are

1. Cyclodextrin based nanosponges
2. Hyper cross -linked polystyrene nanosponges
3. Titanium or other metal oxide based nanosponges
4. Silicon based nanosponge [8]

1. Cyclodextrin (CDs) [1]

In 1998, De Quan Li and Min Ma[12] used the term cyclodextrin firstly, which indicates a cross-linked β-CD with organic diisocyanates leading to an insoluble network showed a very high inclusion constant with several organic pollutants

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 1588-1606 www.ijprajournal.com ISSN: 2456-4494

such as p-chlorophenol was almost completely removed from wastewater. However, Trotta and co-workers pioneered the syntheses of new kinds of cyclodextrin NS which revealed their full potential in other fields, particularly as drug carriers. CDs have since enjoyed widespread popularity especially due to their ability to solubilize poorly water-soluble drugs. The mechanism is rooted in their ability to form non-covalent dynamic inclusion complexes

CDs and their derivatives have been used for a long time to prepare inclusion complexes with various drug moieties for solubility enhancement or controlled release. CDs are a family of sugar compounds that are bound together in a cyclic ring (cyclic oligosaccharides). Cyclodextrin-glycosyltransferase (CGT) produces cyclic oligomers which causes enzymatic degradation of starch. They were first discovered by a Villers which was further elucidated by Schrodinger who described two crystalline compounds, β dextrin and α dextrin. CDs are non-reducing, crystalline, water-soluble, cyclic oligosaccharides composed of 5 or more anhydrous -D-glucopyranoside units (AGU) linked together by an a-1,4-bond. Six, seven, or eight are generally present in CD and are known as α, β, and γ-CD, respectively. CDs have a cylindrical cone with a cavity of about 7.9–8 × 10 – 10 m deep and 5–10 × 10–10m in diameter, which is depending on the number of glucose units

Beta-CD (β-CD) based NS are hyper cross-linked cyclic oligomers which have nanochannels in which both hydrophilic and hydrophobic drugs can be entrapped. This porous network has a colloidal size with a diameter of less than 1 μm and is available in crystalline or amorphous forms. NS can be prepared by using various cross-linking agents' carbonyl diimidazole, triphosgene, diphenyl carbonate, etc. The complexes between drug and NS, degree of crosslinking, methods of preparation can affect the performance of NS [21]. β-CD NS carriers were found to control Camptothecin (CPT) chemical disadvantages and increase the in vitro anti-tumor efficacy in the androgen refractory models ofprostate cancer DU145 and PC-3 and the androgen-sensitive model LNCaP. CDs NS can easily be obtained by reacting the chosen CD with appropriate cross-linking agents which includes diisocyanates, diaryl carbonate, carbonyldiimidazole, carboxylic acid dianhydrides, and 2, 2-bis (acrylamide) acetic acid.CD crosslinked with epichlorohydrin as a cross-linking agent has been used for various applications, including column packing for inclusion chromatography, elimination of bitter components from grapefruit juice, for copper analysis, and cobalt determination in foods. High cross-linked CD based NS have also been synthesized for molecular recognition purposes and generally used for decontamination processes . Also, the β-CD polymer exhibits limited toxicity and a good pharmacokinetic profile resulting in a promising emerging tool in drug delivery research.

2. Polystyrene Based Ns:

NS are tiny mesh-like structures and are about the size of a virus with a backbone of naturally degradable polyester. The long chain polyesters are mixed in solution with cross linkers that have an affinity for certain portions of the polyesters. The drug is often stored within the cross-link segments of the polyester to make a spherical shape that has many pockets/cavities, where the nanoscale materials are sufficiently small to be effective in passing through or attaching to the cell membranes.

The NS are formulated to be in a specific size and to release drugs over time and not just in the burst mode, common with other delivery methods. The engineering capacity of NS is because of the relatively simple chemistry of its polyesters and linking material (peptides). The polyester is biodegradable, so that when it breaks up in the body, the drug is released on a known schedule.

Hyper cross-linked polystyrene is a low density, microporous and transparent material that has an inner surface area measuring apparently 1000 m2 /g and having high absorption capacity. For the ease of mass transfer, they are also provided with transport pores which are opaque. Hyper cross-linked polystyrene sorbents are applicable in large scale adsorption of organic compounds from aqueous gaseous media.

They are also used for solid-phase extraction of trace compounds. The formation process of this type of NS is quite different. A long polymeric chain first extends through the initial solution and remains strongly solvated over the entire period of network formation. Later the cross-linking bridges emerge throughout the volume of the reacting system with a uniform distribution. Polystyrene NS are employed in implant material, drug delivery system and diagnostic system. Polystyrene NS were developed for drugs delivery of cancer drugs like paclitaxel and temozolomide.

3. Titanium Dioxide (Tio2) NS:

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Volume 7, Issue 6 Nov-Dec 2022, pp: 1588-1606 www.ijprajournal.com ISSN: 2456-4494

Titanium dioxide (TiO2) NS can be described as a porous metal oxide nanoparticle [32]. Porous metal oxide NS are widely popular over their bulk analogs (nonporous) since they display pronounced physical and chemical properties. Their high porosity results in higher surface area, high mass transfer, and electron mobility.Different methods are reported for synthesizing TiO2 NS. A method to synthesize TiO2 NS has been reported by Guo et al. The method involves the synthesis of functional polystyrene nano dispersion which is used as a template for coating TiO2 in situ by hydrolysis of tetra-n-butyl titanate.

Another method for the synthesis of TiO2nanospheres using a carbon sphere as a template was reported by ShenWeihua et al Synthesis for bimetallic NS such as TiO2/Ag by surface sol−gel method with natural cellulose used as template and VO2/TiO2using electrostatic spray deposition technique and Pt-TiO2 by wet oxidation of multi-layered films is also reported in the literature. Metal oxide NS of TiO2 either individually or in combination with other metals have been explored for various applications. Some applications include their use for photocatalytic properties, high-performance supercapacitors, Hydrogen chemical sensors, recyclable oil absorbents.

4. Silicon Ns (Si NS):

Porous Silicon particles are unique derivatives of elemental Silicon (Si), which are sponge-like structures formed by chemical or electrochemical etching of bulk Si. Since the discovery of their room temperature photoluminescence by Canham in 1990, porous Si particles have been explored for various applications. Their use in microelectronic, as chemical and biological sensors, is well documented. The major applications of Si NS are in areas of photoluminescence and cellular patterning on account of luminescence and light emitting properties of Si.

Si porous particles are commonly prepared by electrochemical etching of Si particles under ultrasonic agitation to achieve ordered pore structure. The method reported by Tasciotti et al involves use of heavily doped p++ type silicon wafer used as substrate coated with silicon nitride. It was made into a porous Si using photolithography. The porosity of the formed particles was adjusted by changing the current density and ratio of hydrofluoric acid and ethanol. Another method reported by Chadwick et al involves use of metallurgical grade silicon powder and its chemical etching in mixture of nitric acid and hydrofluoric acid [1]

Characteristics Of Nanosponges[2]

1. Nanosponges have a range of dimensions (1 µm or less). [2]with tunable polarity of the cavities. [15]
2. They are either in Paracrystalline form or crystal form. This depends on the process conditions of the nanosponges. Crystal structure of nanosponges plays a very important role in their complexation with drugs. Para-crystalline nanosponges have shown various drug loading capacities. [2]
3. When dissolved in water, they form clear and opalescent suspension. [2]
4. They are able to capture, transport and selectively release of a vast variety of substances, all thanks to their 3D structure. [2]
5. Nanosponges of specific size can be synthesized bychanging the cross linker to polymer ratio. [15]
6. They exhibit paracrystalline or crystalline forms,depending on the process conditions.
7. They can be sited to different target sites because oftheir capacity to link with different functional groups.
8. Chemical linkers permit nanosponges to bindpreferably to the target site.
9. By complexing with different drugs nanosponges canform inclusion and non-inclusion complexes.
10. By adding magnetic particles into the reactionmixture, magnetic properties can also be imparted tonanosponges. [15]

Composition Of Nanosponges[5]

1. **Polymer:** The selection of polymer can influence the formation along with the performance of Nano sponges. The cavity size must be suitable to incorporate the particular drug molecule. The polymer selection is based upon the required release and drug to be enclosed. The selected polymer should have the property to attach with specific ligands.
2. **Cross linking agent:** The crosslinking agent selection can be carried out depending upon the structure of polymer and the drug which is to be formulated. The different examples include Diphenyl carbonate,Dichloromethane, Diaryl carbonates, Diisocyanates.
3. **Drug substance:**

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Volume 7, Issue 6 Nov-Dec 2022, pp: 1588-1606 www.ijprajournal.com ISSN: 2456-4494

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

MECHANISM OF DRUG RELEASE FROM NANOSPONGES[26]

Nanosponges constitute three-dimensional structure ofcross-linking polymer. The entrapment efficiency and solubilizing efficiency of nanosponges can be changed according to howmuch cross-linking polymer is being added to formulation. Thetoroidal shape of nanosponges allows them to have a cavity insidethe structure which can fit various types of drug molecules. Thisbecause of such type of structure they can act as carriers for various types of drugs drug carriers, as long as the active compoundis having compatibility with geometry and polarity of cavity thedrug will release at target site. To find out when these active compounds will be delivered, the structure of nanosponge plays a crucial role which can be modified to depending on requirement ofdrug release. Several ligands or carriers can also be attached on tothe surface of the nanosponge to target the molecules to varioussites in body.[26]

METHOD OF PREPARATION [5]

1. **Nano sponges made from hyper cross-linked β-cyclodextrins:** Nano sponges are made from materials that makes a non-porous- molecules that are carriers called cyclodextrins for drug release. These cyclodextrins are a hyper-cross-linking agents that forms a numerous-networks in nano networks, or can be even a spherical shaped with many networks of protein channels, pores etc. These cross linkers stabilizes the sponge with specific surface charge density, porosity and pore sizes based on the molecules contained in them. The cross linkers help to retain the Nano sponges at different acidic and even neutral pH.

2. **Emulsion solvent method:** The main polymers used in this method are ethyl cellulose and polyvinyl alcohol in varying proportions. The dispersed phase is formed by adding ethyl cellulose and the available drug which is dissolved in 20ml of dichloromethane. The drop wise addition of continuous phase is by prepared by dissolving polyvinyl alcohol in 150 ml of distilled water. Then the mixture is allowed to stir for 1000rpm for about 2 hrs. The obtained Nano sponges are collected, filtered and dried in oven for around 1 day and stored in desiccators.

3. **Solvent used method:** The above used polymer can be used along with some suitable polar aprotic solvent such as Dimethylformamide, dimethylsulfoxide and mix proportionally. Then to this mixture, cross-linkers available are added with a ratio of 4: 16. A temperature is maintained from 10°C for reaction of polymers for 2 days. Most of the carbonyl cross linkers (Dimethyl carbonate and Carbonyl diimidazole) are used. After the reaction is complete the product kept to cool at room temperature, then add the mixture with distilled water for recovering and filtered under air oven and purification is done by soxhchlet apparatus added with ethanol for further extraction. Again, go for drying under vacuum and powdered mechanically to get a homogeneous white powder.

4. **Ultrasound-assisted synthesis:** In this procedure Nano sponges can be obtained by using polymers with carbonyl cross linkers in the absence of solvent and kept for sonication. These developed Nano sponges will have uniform spherical dimension. Mix the polymer and the cross-linker in a sufficient quantity and is taken in a flask. The flask is filled with water and heats it to 90°C for utrasonication. The mixture is kept for 5 hours for continuous sonication. Then the mixture is cooled and washed the product with distilled water and allowed to purify it with Soxhlet extractor using ethanol. The final product obtained is dried at 25˚c and whitish powder is collected and store from humidity.

5. **Melt method:** The crosslinker and the polymer are melted together in the melting process. All the ingredients were finely homogenized. NSs were collected by washing the acquireproduct repeatedly with a suitable liquid. Cleaning the product, extracts the waste polymer and reagents which are unreacted and divides the product into the form of NSs. Such blank NSs were further exposed to the encapsulating of narcotics.[7]

6. **Bubble electrospinning:** A conventional and typical electrospinning configuration consists

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 1588-1606 www.ijprajournal.com ISSN: 2456-4494

primarily of a syringe, syringe pump, as defined in many literatures, a high-voltage power, and a grounded collector. But one of the major limitations that limits their applications is the amount of output of nanofibers. In bubble electrospinning, polyvinyl alcohol can also be used as polymer. By addition of distilled water into it, the solution of polymer (10%) was organized, which was then moved at 80–90 °C for 2 h to obtain a one-phase mixture. It was then left to achieve at room temperature with the polymer solution and then used to prepare nanoporous fibres.[7]

7. **Synthesis by the use of microwave radiation:** This is the simple technique of microwave irradiation synthesis of CD NSs that significantly decreases the reaction time. These NSs have higher crystallinity levels. Synthesis of NSs by microwave radiation showed a fourfold decrease in reaction time compared to traditional heating methods and also produced homogeneous particle size distribution with uniform crystallinity. Singireddy et al. performed an experiment to ascertain beneficial effects of microwave-assisted heating in comparison to conventional heating during the synthesis of CD-based NSs. In the research, the outcomes suggested that NSs synthesized by microwave-assisted synthesis has doubled the drug holding capacity for the model drug. The results of high resolution-transmission electron microscopy (HRTEM) displayed that the NSs obtained by microwave synthesis were highly crystalline, and showed increased degree of complexity along with narrow size distribution. The reaction time was greatly decreased for all reactions and the reaction products were improved under microwave-assisted heating conditions. The benefit by means of synthesis using microwave irradiation is that it supplies straight energy to the targeted molecules and hence energy can be provided in precise form. The energy is not lost on heating the walls of the container or the liquid adjacent the reactant molecules and hence the full effect is seen in reaction progress towards completion. Zainuddin et al., used microwave synthesizer to prepare β-CD inparacrystalline nature and used diphenyl carbonate (DPC) for crosslinking 7

8. **Quasi emulsion solvent method:** The NSs were arranged in different sums using the polymer. Using Eudragit RS 100, the inner stage is prepared and added to a fair dissolvable stage. The drug used produced a response and broke down at 35 °C under ultrasonication. As an emulsifying operator, this internal process used in the outside phase containing polyvinylalcohol goes around. At room temperature, the blend is blended at 1000–2000 rpm for 3 h and dried for 12 h in an air-warmed oven at 40 °C [7]

FACTORS INFLUENCING NANO SPONGE FORMULATION [5]

1. **Type of polymer:** The formation as well as the performance of nanosponge depend upon the selection of suitable polymer. The cavity or pore size of the nanosponge should be able to accommodate the drug molecule of suitable size.
2. **Type of drug:**Drug molecules to be complexed with nanosponges should have certain characteristics as mentioned below. [22]

- The molecular weight must be between 100 to 400 Daltons
- The drug molecule structure should contain no more than five condensed rings.
- The solubility in water should be less than 10 mg/ml
- The melting point should be less than 250 °C.

3. **Temperature**:The change in temperature can affect the drug complexation. The increase in the temperature decreases the magnitude of the apparent stability of the nanosponge complex which may occur due to possible reduction of drug nanosponge interaction forces, van der waals force and hydrophobic forces with rise of temperature.
4. **Method of preparation**:The loading of drug into the nanosponge formulation can affect the complexation. The nature of the drug and polymer can affect the complexation. In many cases freeze drying was found to be more effective method for the drug complexation.
5. **Degree of substitution:** The nanosponge formulation can be highly affected by the type, number and position of substituent on the parent molecule.

LOADING OF DRUG INTO NANOSPONGE

The nanosponges formulated for the drug delivery first of all should be pre-treated to obtain a mean particle size below 500nm. The nanosponges

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are then suspended in water for some time and subjected to sonication so as to avoid the formation of aggregates. The obtained product suspension is subjected to centrifugation to obtain a colloidal fraction. The obtained product supernatant is separated and sample is dried by freeze drying.

In other way a nanosponge aqueous suspension is prepared and dispersed it with constant stirring for a specific period of time. The nanosponge solid crystals are obtained by the solvent evaporation or either by freeze drying. The nanopsonge crystal structure plays a very important rule in the complexation with the drug. The drug loading is high in crystalline nanosponge than the paracrystalline one. In nanosponges which contain poor crystalline structure the drug loading occurs as a mechanical mixture rather than forming inclusion complex

EVALUATION OF NANOSPONGES [5]

1. **Microscopic studies:** To study the microscopic aspects of a drug, Nano sponge, or the product it can be subjected to Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM). The difference in the crystallization state indicates the formation of inclusion complexes.

2. **Loading efficiency:** It can be determined by quantitative estimation of the drug which is loaded into the nanosponge using either by UV spectrophotometer or HPLC method. The loading efficiency can be calculated by.

$$Loading efficiency = \frac{Actual drug content in nanosponge}{Theoretical drug content} \times 100$$

3. **Solubility studies:** The most frequently used method include phase solubility method described by Higuchi and Connors which helps to determine the effects of nanosponge upon the solubility of the drug. The degree of complexation was indicated by phase solubility diagram.

4. **X ray diffraction studies:** For the solid state, powder X ray diffractiometry can be used to determine the inclusion complexation. When the drug molecule is liquid and liquid have 0 diffraction pattern of their own the diffraction pattern of a newly formed substance clearly differs from that of uncomplexed nanosponge. This difference in the diffraction pattern indicates the complex formation. When the drug compound is a solid substance, a comparison has to be made between the diffractogram of the complex and that of mechanical mixture of the drug and polymer molecules. A diffraction pattern of physical mixture is often the sum of those of each component, while the diffraction pattern of complexes is apparently different from each constituent and lead to a new solid phase with different diffractograms. Diffraction peaks for a mixture of compounds are useful in determining the chemical decomposition and complex formation. The complex formation of drug with nanosponge alters the diffraction pattern and also changes the crystalline nature of the drug. The complex formation leads to sharpening of the existing peaks and shifting of certain peaks.

5. **Single crystal x ray structure analysis:** Single crystal X ray structure analysis is used to determine the detailed inclusion structure and mode of interaction. The interaction between the host and guest can be identified and precise geometrical relationship can be established.

6. **Infra – red spectroscopy:**This spectroscopy method is mainly used to estimate the interaction between nanosponge and drug molecule in the solid state. Upon the complex formation nanosponge bands are tend to change often and if the fraction of guest molecules encapsulated in the complex is less than 25%, bands which could be assigned to the included part of guest molecules are easily masked by the bands of spectrum of nanosponges. The application of infra-red spectroscopy is limited to drugs having characteristic bands such as carbonyl or sulfonyl group. Infra-red spectral studies give information regarding the involvement of hydrogen in various functional group.

7. **Thin layer chromatography:**The Rf values of the drug molecule diminish to considerable extend in thin layer chromatography and this helps in identifying the complex formation between the drug and nanospsonge formulation.

8. **Particle size and polydispersity:** The particle size of a nanosponge formulation can be determined by dynamic light scattering using 90 plus particle sizer equipped with MAS

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OPTION particle sizing software. From the data obtained mean diameter and polydispersity index can be determined.

9. **Zeta potential:** Zeta potential is measured to find the surface charge. It can be measured by using additional electrode in particle size equipment .[5] For zeta potential determination, samples of the nanosponges were diluted with 0.1 mol/L KCl and placed in the electrophoretic cell, where an electric field of about 15 V/cm was applied. The mean hydrodynamic diameter and polydispersity index of the particles were calculated using the cumulated analysis after averaging of the total measurements [21]

10. **Production yield:** The production yield can be determined by calculating intitial weight of raw materials and final weight of nanosponges.
$productyield = practicalmassofnanospongeTheoretical mass \times 100$

11. **Void fraction/porosity:** Void fraction investigation makes for testing the width in the nanoholes and nanopores that are made. A helium pycnometer measures the porosity of nanosponges, since helium gas can invade associate- and intra-specific channels of fabric. The genuine amount of the fabric is measured by means of the helium uprooting cycle. Since of its permeable presence, nanosponges display more noteworthy porosity relative to guardian polymer utilized to make the gadget. %Void fraction= [((Bulk Volume-True volume))/(Bulk volume)] ×100 [10]

12. **Resiliency (Viscoelastic properties):** Resiliency of sponges can be modified to produce beadlets that is softer or firmer according to the needs of the final formulation. Increased crosslinking tends to slow down the rate of release. Hence resiliency of sponges will be studied and optimized as per the requirement by considering the release as a function of cross-linking with time [11].

13. **Saturation state interaction:**To find the saturated solution interaction study UV spectroscopy is used. To the increasing concentration of nanosponges solution, fixed amount of drug is added. Then keep the sample overnight. Drug loading is decided by analysing the shift of absorbance maxima (lambda max) within the spectra compared to pure drug and by scanning of the formulation in ultraviolet light vary[17]

14. **Swelling and water uptake**: For swellable polymers like polyamidoamine nanosponges, water uptake can be determined by soaking the prepared nanosponges in aqueous solvent. Swelling and water uptake can be calculated using equations % Swelling=Marking of cylinder at aspecified time point/Initial marking before soaking×100 % Water uptake=Mass of hydrogel after 72 hrs/Initial mass of dry polymer×100 [4]

15. **FTIR (Fourier Transform Infrared Analysis):**The FTIR analysis is used to find out the combining bonds of polymer and drug interactions. Thedrug samples and drug sponges are determined by taking IR samples at a range of 400-4000 cm-1. Helium gas is used as a purge for the detector to minimize the moisture content and high signaland IR readings are taken by the use of carbon black as references. The chemical vibrations,coupled vibrations, additional bands etc are determined.[25]

16. **Compatability studies by using DSC:** A 5 mg of drug samples are accurately weighed in aluminium pans and covered by heating at atemperature of 15 □C/min with atmospheric nitrogen at 25-430 □C.Thecompatibility of drug andpolymer can be determined.[25]

17. **Morphology and surface topography:**The morphology and surface topography of the nanosponges is determined by coating with gold–palladium which kept in room temperature with an argon gas.[25]

18. **Dissolution tests:**The dissolution of sponges can be determined from dissolution apparatus USP XXIII attached witha basket made of 5m mesh size of stainless steel, at a speed of 150 rpm. The dissolution medium ismaintained in sink conditions depending upon the solubility rate of drugs used. The correspondingis samples withdrawn from the dissolution medium are analysed by spectrometry**.** [25]

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 1588-1606 www.ijprajournal.com ISSN: 2456-4494

Table 1: Nanosponges driven research in formulation development

S. No.	Drug used	Nanosponge ingredients	Result outcomes	Ref. No.
1	Antibacterial and anti hypocalcemic drugs.	β-Cyclodextrin Nanosponges	The result was concluded as a promising anti-bacterial protein transporter and to prevent calcium depletion in the case of antibiotic hypercalcaemic.	(Singh P, etal.,2018)
2	Doxorubicin	Cyclodextrin nanosponges	Cellular uptake of nanosponges was detected and improved after the conversion of cholesterol hydrogen succinate (CHS).	(HayiyanaZ, et al.,2016)
3	Ocular drugs	Hydrophilic cyclodextrin based nanosponges	The result was studied to improve corneal penetration and drug solubility.	(Chen Y, etal.,2019)
4	Organophosphates	Cloaked oil nanosponges	Oil nanosponges serves as a prototype ofmultimodal detoxification compound has beenstudied.	(Ye H, etal.,2020)
5	Doxorubicin and indocyanine green	Exosomes	NSK (nanosponges and nanokillers) can be a promising nanomedicine for future clinical interventions for metastasis breast cancer.	(Kumar S,etal., 2018)
6	Antibacterial,anti-fungal,antioxidant, anti-inflammatory,immu nomodulory and antitumor elements.	Cyclodextrin nanosponges	The installation of Babchi oil oil in nanospongeswas bought with an active transporter frameuntil solvency, image stability, and its oil lifealongside the benefits.	(Kamble M, etal., 2019)
7	Rilpivirine	Cyclodextrin-nanosponges	The result examines uncovered conceivablemethod of capture of rilpivirine inside β-CD space.	(Rao MR, et al., 2018)
8	Anticancer drugs	Peptide nanosponge	The composition of novel nanosponges was examined clear dissolvable andsubsequent atomic(MD) re-engineering.	(Wang H, et al., 2017)

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9	Pazufloxacin mesylate	Ag nanosponges	Pazufloxacin mesilate (PM) were recognizedhelpfully utilizing these uniform nanospongesas SERS substrates.	(Huang Q, etal., 2018)
10	Antibacterial, anticancer, antiviral drugs	Cyclodextrin nanosponges	cyclodextrin nanosponges" (CDNSs), pull inincredible consideration from scientists fortackling significant bioavailability issues, forexample, deficientsolvency, poordisintegrationrate, and limited strength of certain specialists,just as expanding their viability and diminishing undesirable results.	(Tannous M, etal.,2021)
11	Doxycycline and Znonanoparticles	Antibacterial nanosponges	The result was showed that ZnO-NPs filled withDOX have productive UV photocatalytic actionagainst bacterial delicate decay contaminations.	(Suárez DF, etal., 2017)
12	Intraocular drugs	biomimetic erythrocyte-derived nanosponge	Biomimetic nanosponges kill pore-framingpoisons from these visual microbes and help insaving retinal capacity.	(Coburn PS, etal., 2019)
13	Antibacterial drugs	Biomimetic nanosponges	The results provide a systematic review ofRBC-NS (red blood cells nanosponges) for thetreatment of severe MRSA infections (methicillin-resistant Staphylococcus aureus) such asMRSA bacteremia and MRSA-induced sepsis.	(Chen Y, et al.,2019)
14	Antibacterial drugs	Biomimetic nanosponges	It has been shown that nanosponges coated witha membrane in combination with many proteinomic substances can also be used as effective "fishing aids" for the detection of hazardous substances specific to a particular cell type.	(Distler U and Tenzer S,2017)

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15	Anticancer drugs	Glutathione/pH-responsive nanosponges	It shows that GSH/pH-NS are a proficientinstrument for the controlled transfer of SLs to increase critical starvation and may increase thetherapeutic efficacy of thesecompounds.	(Argenziano M, et al., 2018)
16	Antibacterial drugs	Colloidal gel nanosponge	The nanosponge colloidal gel framework ispromising as an injectable application for correction applications for example,antivirulencetreatment that is close to viral infections.	(Zhang Y, et al., 2017)
17	Resveratrol and Oxyresveratrol	β-cyclodextrin nanosponges	The high solubilization of nanosponges filledwith resveratrol- and oxyresveratrol leads to ahigher cell-reinforcing action compared to drug particles alone.	(Dhakar NK, et al., 2019)
18	Polyamionazides mixtures	Calixarene basednanosponges	The ideal responsivity to pH varieties of thenanosponges acquired was confirmed by methods for ingestion tests on a bunch of naturaltoxin model particles.	(Di VincenzoA, et al.,2019)
19	Paclitaxel	Pyromellitic nanosponges	It showed that our new PTX (paclitaxel) nanoformulation can react to significant issuesidentified with paclitaxel treatment, bringingdown the counter tumour successful dosagesand expanding the adequacy in hindering melanoma development in vivo.	(Clemente N,et al., 2019)
20	Anticancer drugs	DNA zyme nanosponges	The present DNA zyme NS framework could be designed with more remedial arrangements andspecialists and was foreseen to show remarkableguarantee and adaptability for applications in biomedicine and bioengineering.	(Wang J, et al.,2019)

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21	Antibacterial drugs	Biomimetic nanosponges	It demonstrates the wide range of efficacy and high performance of hRBC nanosponges (redblood cells) as a novel anti-haemolytic drugplatform from various types of viruses.	(Chen Y, et al.,2018)
22	Paliperidone	β-cyclodextrin based nanosponges	Cyclodextrin-based nanosponges talk about anovel way of developing solvency and improving the dispersion of selected PLP (paliperidone) drugs.	(Sherje AP, etal., 2019)
23	Ibuprofen	Cyclodextrin nanosponges	It obtained from different NMR solid statemodels incorporate data from powder X-beamdiffraction profiles.	(Ferro M, et al., 2017)
24	Doxorubicin	Cyclic nig-erosyl-1-6-nigerose(CNN) nanosponges	CNN-nanosponges may promise biocompatiblenanocarriers for supported delivery of doxorubicin and anticipated inhibitory system in malignancy medicines.	(Caldera F, etal., 2018)
25	Doxorubicin	β-cyclodextrin nanosponges	The cleavage of di-sulfide bridges allows thetargeted release of cancer-fighting drugs intoglutathione-rich cells that resist cells.	(Trotta F, et al.,2016)
26	Efavirenz	β-cyclodextrin nanosponges	Nanosponge properties have been found tohave twice the oral administration of efavirenzcompared to simple drugs.	(Rao MR andShirsath C,2017)
27	Ochratoxin A	β-cyclodextrin-polyurethane polymer	These results suggest cyclodextrin nanospongematerials are suitable to reduce levels of ochratoxin A from spiked aqueous solutions and red wine samples.	(Appell M andJackson MA,2012)
28	Antimicrobial drug	Cyclodextrin nanosponges	The results described herein encourage the useof cyclodextrinnanosponges asencapsulatingagents for active food packaging applications.	(Simionato I,et al., 2019)

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29	Salvia Officinalis essential oil	β-cyclodextrin nanosponges	Salvia officinalis is a basic nanoemulsion oilbased on β-cyclodextrin-naphthalene dicarboxylic nanosponges that bring the highest potencyand promising use in the drug industry.	(Nait Bachir Y,et al., 2019)
30	L-Dopa	Cyclodextrin nanosponges	MIP-NS exhibits a prolonged released profile that is slower and longer than non-labelednanosponges. No L-DOPA-induced degradation in MIP-NS was observed after prolongedstorage at roomtemperature.	(Trotta F, et al.,2016)
31	Meloxicam	β-cyclodextrin-based nanosponges	Nanosponges based on β-cyclodextrin talkabout a novel approach to the controlled arrivalof meloxicam to detect and reduce effects.	(Shende PK, etal., 2015)
32	Atorvastatin calcium	Cyclodextrin nanosponges	It has been confirmed that AC-NS integrationwill be an effective way to improve oral availability and vivo function of AC.	(Zidan MF, etal., 2018)
33	Camptothecin	β-cyclodextrin-nanosponges.	CN-CPT significantly impaired development,vascular permeability and the use of orthotopicATC xenograftsvascularization inSCID/beigemice without significant toxic effects in vivo.	(Gigliotti CL,et al., 2017)
34	Curcumin herbal remedies	Cyclodextrin nanosponges	Cytotoxicity test results did not show celltoxicity in a healthy cell line, while it was toxiccompared to cancer cells.	(Rafati N, et al., 2019)
35	Doxorubicin	Cyclodextrin-based nanosponges	The activity of this GSH (glutathione) reactionhas been demonstrated using a few tumor cellsand doxorubicin as a model anticancer drug.The arrival of the drugs was consistent with thecontent of GSH in tumor cells.	(Mihailiasa M,et al., 2016)

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36	Melatonin	β-cyclodextrin nanosponges	The result of the union isa 3-D structureallowed, in which melatonin atoms are made harder.	(Ataee-Esfa-hani H, et al.,2011)
37	Silica particles	Pt spheres	It was shown that this technique improves theelectrocatalyticperform ance of Ptcatalysts bymaking electroactive speciesmore accessible to the entire Pt surface.	(Torne SJ, etal., 2010)
38	Doxorubicin	glutathione-responsive cyclodextrin nanosponges (GSH-NS)	It was demonstrated that GSH-NS inhibitedhuman tumour growth in xenograft studies. Itmay be a viable carrier for future drug delivery aplications.	(Alongi J, et al., 2011)

Table 2: Nanosponges based marketed formulation

Drugs	**Nanosponges vehicle**	**Indication**	**Reference**
Paclitaxel	β-cyclodextrin	Cancer	(Minelli R, et al., 2011)
Tamoxifen	β-cyclodextrin	Breast cancer	(Sharma R and Pathak K, 2011)
Camptothecin	β-cyclodextrin	Cancer	(Swaminathan S, et al., 2007)
Econazole nitrate	Ethyl cellulose, polyvinyl alcohol	Antifungal	(Aynie I, et al., 1999)
Itraconazole	β-cyclodextrin and copolyvidonum	Antifungal	(Ansari KA, et al., 2011)
Antisense	Sodium alginate	Cancer therapy	(Ansari KA, et al., 2011)
Resveratrol	β-cyclodextrin	Inflammation,cardiovascular diseases, dermatitis, gonorrhoea	(Aynie I, et al., 1999)

PHARMACEUTICAL APPLICATION OF NANOSPONGES [5] –

Due to their biocompatibility and versatility, nanosponges have many applications relating the pharmaceutical field. Nanosponges can be used as excipients in preparation of tablets, capsules, pellets, granules, suspension, solid dispersion or topical dosage forms.

1. **Nanosponges as a sustained delivery system:** Acyclovir is one of the widely used antiviral agent for the treatment of herpes simplex virus infection. Its absorption in the GIT is slow and incomplete and highly variable. The in vitro release profile of the acyclovir from different types of Nano sponges showed sustained release of the drug. The percentage release of acyclovir from carb-nanosponges and nanosponges after the 3 h of administration were about 22% and 70%. The drug was not adsorbed on the nanosponge surface since no initial burst effect was not observed.

2. **Nanosponges in solubility enhancement:** Itraconazole is a BCS class II drug which has a dissolution rate limited poor bioavailability. Thus, the application of nanosponges improved the solubility of the drug more than 27- fold. The solubility was found to be exceeded to 55- fold, when copolyvidonum was added as a Supporting component. Either by masking the hydrophobic groups of itraconazole, by increasing the wetting ‘of the

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drug or by decreasing the crystallinity of the drug nanosponges improve the solubility of the drug.

3. **Nanosponges in drug delivery:** Nanosponges can be formulated by different dosage form like topical, parentral, aerosol, tablet and capsules. Telmisartan (TEL) is a class Ⅱ drug with dissolution rate limited bioavailability. TEL was incorporated in nanosponge formulation. The saturation solubility and vitro dissolution of β-CD complex of TEL was compared with plain TEL and the nanosponge complexes of TEL. The highest solubility and in vitro drug release was observed in inclusion complexes prepared from nanosponge and NaHCO3.Paclitaxel is an anticancer drug with poor water solubility. β-CD based nanosponges is an alternative to classical formulation in cremophor because cremophor reduces the paclitaxel tissue penetration. The biological effect of paclitaxel in vitro is highly enhanced by nanosponge formulation. Econazole nitrate is an antifungal agent used for skin infections and dermatophytosis. Adsorption is not significant when econazole is applied to skin. Thus, econazole nitrate nanosponges is made up by solvent diffusion method and loaded as hydrogel form.

4. **Nanosponges in enzyme immobilization:** Nanosponges have been widely used for stabilizing the enzyme. CD-NS show much higher inclusion constants as compared to CD and is suitable to support for enzyme immobilization. They help to preserve the catalytic proficiency and stability of the immobilized enzymes. Enzyme immobilization is important for enzyme recycling and facilitates the separation and recovery of the formed products along with its increased thermal and operational stability of the biocatalysts. Boscolo et al. also studied about the high catalytic performance of some pseudomonas flurescens lipases adsorbed on cyclodextrin – based nanosponge. Lipases are widely used for catalysing the hydrolysis of triacylglucerols and trans esterification reactions which are involved in a number of industrial applications.

5. **Nanosponges for protein delivery:** A major barrier in the protein formulation development is the maintenance of the original protein structure both during the formulation process and upon long term storage. Swaminathan et al studied about new swellable cyclodextrin based poly nanosponges. Through water uptake studies they observed very good swelling capacity stable for 72 hrs. Bovine serum albumin was used as a model protein and is incorporated into the prepared nanosponge. Enhanced swelling property along with increased stability of protein was observed. At physiological pH, the lactone ring opens up and develop inactive carboxylate form. The fusion of camptothecin in nanosponges lead to a prolonged release profile in an active form which hinders the hydrolysis of the lactone form and resulting enhanced stability.

6. **Nanosponges as protective agent from light or degradation:** The Gamma–oryzanol can be encapsulated in the form of nanosponge which shows a good protection from the photodegrdation. Gamma oryzanol is a ferulic acid mixture which is a natural antioxidant and mainly used to stabilize the food and pharmaceutical raw materials. Its application is limited because of its high instability and photogegradation.

7. **Nanosponges as a carrier for biocatalyst:** Nanosponges act as carrier for the delivery of enzymes, vaccines, proteins and antibodies for diagnosis purpose. proteins and other macromolecule are adsorbed and encapsulated in cyclodextrin nanosponge.

8. **Nanosponges as gas delivery system:** The deficiency of adequate oxygen supply named hypoxia, is related to various pathologies from inflammation to cancer. Cavalli et al developed a nanosponge formulation for oxygen delivery through a topical application. Safety of nanosponge was studied in vero cells. Oxygen penetration through a silicone membrane was studied using a CD –NS hydrogel combination system. Trotta et al. reported CD-NS prepared using carbonildiimidazole cross –linker for encapsulation of 1- methylcyclopropene, oxygen and carbondioxide.

9. **Harvesting of rare Cancer Marker from Blood:**It has been seen that a new type of nanoparticle, whose interiors is decorated with different types of „bait" molecules, is used to selectively trap specific families of proteins

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from blood and protect them from degradation by enzymes in blood. [16]

10. **As an absorbent in the treatment of blood poison:** Nanosponges can remove the dangerous poisonoussubstance from our blood by absorbing the poison.Instead of using antidotes, if we incorporate nanospongesby injection into the blood, nanosponges can absorbtoxins. In the bloodstream, the nanosponge resembles ared blood cell, causing toxins to attack it and thereforeabsorb it. [15]

11. **Indetoxification and reduction of superbuginfection:**The present detoxification platforms such as antisera,monoclonal antibodies, small molecule inhibitors, etc.,exhibit their action by targeting the toxins based on theirmolecular structures. Recognizing the need forpersonalized treatment for different diseases, Che-MingJ. Hu et al., came out with biomimetic toxin NSs, whichcould act as a toxin decoy in vivo. This NSs were foundto be capable of absorbing those toxins which damagedthe membranes. After absorbing, they could divert thetoxins away from the cellular targets, thereby preventingtoxin-mediated hemolysis. According to the report, thisbiologically inspired toxin NSs can be employed to nursea large number of diseases and injuries caused by pore-producing toxins, which are the most widely found protein toxins in nature till date. They even observed thatthese NSs could clearly reduce the noxious effects ofstaphylococcal α-hemolysin and reported that thisapproach could be used to battle drug-resistantcontaminations/infections such as methicillin-resistantStaphylococcus aureus infections. They claim - One redblood cells (RBC) membrane can be utilized to blanketmore than or around 3,000 of these stealthy NSs (fullyloaded with poison) which can be safely discarded vialiver.[24]

II. CONCLUSION–

Nanosponges are a carrier system that release drug in a controlled and predictable manner at a specific target site.because of their small size and spherical shape nanosponges can be developed as different dosage form like parenteral, aerosol, topical, tablets and capsules.They can hold a wide range of drugs in various size. The ratio of cyclodextrin and cross linker can be varied to improve the drug loading and to control the release of drug by nanosponge. These are self-sterilizing as their average pore size is 0.25um where bacteria cannot penetrate.

Nanosponges have a lot of potential because of their ability to hold both hydrophilic as well as hydrophobic drugs which leads to better solubility and bioavailability and increased patient compliance.

REFERENCES –

[1]. Rao M, Sonawane A, Sapate S, Paul G, Rohom S, Nanosponges: A Multifunctional Drug Delivery System,International Journal of All Research Education and Scientific Methods (IJARESM), Volume 9, Issue 5, May -2021.

[2]. Mandan S, Chavan M, Bhadane Y, Kalal C, Nanosponges: A New Drug Delivery System, Journal of Drug Delivery and Therapeutics. 2018; 8(6- A):141-143.

[3]. Bhowmik H, Venkatesh, D.N, Kuila A, Kumar Kh, Nanosponges: A Review, International Journal of Applied Pharmaceutics, Vol 10, Issue 4, 2018.

[4]. ThakreA.R., Gholse Y.N., Kasliwal R.H., Nanosponges: A Novel Approach of Drug Delivery System, Journal of Medical Pharmaceutical and Allied Sciences, (June_2016); 78-92.

[5]. Ravi Silpa C, Krishnakumar K and Nair Smitha K, Nano sponges: A targeted drug delivery system and its applications, GSC Biological and Pharmaceutical Sciences, 2019, 07(03), 040–047.

[6]. Nitish, S. Jeganath, Khilifa Fathelrahman Khalifa Abdelmagid, A Review on Nanosponges – A Promising Novel Drug Delivery System, Research J. Pharm. and Tech. 14(1): January 2021.

[7]. Tiwari K, Bhattacharya S, The ascension of nanosponges as a drug delivery carrier: preparation, characterization, and applications, Journal of Materials Science: Materials in Medicine (2022) 33:28.

[8]. Reddy R (2021) Nanosponges in Drug Delivery. Trends Green Chem. Vol.7 No.1.

[9]. Singh A, Nanosponges - An Efficient and Effective Drug Delivery System, European Journal of Biomedical and Pharmaceutical sciences, 2018, Volume 5, Issue 5 993-996.

[10]. Kaur N et al, Nanosponges: Novel Strategy for Targeted Drug Delivery System: A Review,Indo Am. J. P. Sci, 2020; 07(08).

[11]. Rahi N, Kumar K, Nanosponges: a new era of versatile drug delivery system. Universal Journal of Pharmaceutical Research 2017; 2(3): 31-35.
[12]. Krabicova. I, Appleton.S. L, Tannous. M, et.al,History of cyclodextrinnanosponges,Polymers, 2020, 12(5):1122.
[13]. G. Tejashri et al., Cyclodextrin based nanosponges for pharmaceutical use: A review, Acta Pharm. 63 (2013) 335–358.
[14]. M.Sudhir, S.Swathi, U. Pavani, The Development And Evalutionof Nanosponges Drug Delivery System Of Ketoprofin By Using Solvent Evaporation Method, Journal of Cardiovascular Disease Research ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021.
[15]. S.Shameem, N.Nithish Kumar Reddy, M.Bhavitha, M.Suman Kumar, M.Balaji Ramaiah, K.Sahithya, Nanosponges: A Miracle Nanocarrier for Targeted Drug Delivery, Int. J. Pharm. Sci. Rev. Res., 63(2), July - August 2020; Article No. 13, Pages: 82-89.
[16]. B. Syed salman and B. Thabitha. A review on Nanosponges. Global J Pharm Bio Sci. 2017; 2(1); 01-08.
[17]. Bapurao.J.S., et al., "Nanosponges: An Innovative Class of Drug Delivery System - Review", Acta Scientific Pharmaceutical Sciences 5.11 (2021): 09-18.
[18]. Iravani S, Varma R.S., Nanosponges for Drug Delivery and Cancer Therapy: Recent Advances. Nanomaterials 2022, 12, 2440.
[19]. Shaikh Bilal J, Patil Abhishek S, Bhosale Ankush S, Raut Indrayani D, Nitalikar Manojkumar M, Nanosponges: An Evolutionary Trend for Targeted Drug Delivery, Int. Journal of Pharmaceutical Sciences and Medicine (IJPSM), Vol.6 Issue. 6, June- 2021, pg. 1-14.
[20]. Ahad HA, Chintaginjala H, Rahamathulla S, Rupasree A, Anegondithimmappa SK, Barji Prasanna P, Pathfinder Nanosponges for Drug Targeting by Factorial Design: A Glance Review, Research Journal of Pharmaceutical Dosage Forms and Technology. 13(4): October - December, 2021.
[21]. Shringirishi M, Prajapati SK, Mahor A, Alok S, Yadav P, Verma A, Nanosponges: a potential nanocarrier for novel drug delivery-a review, Asian Pac J Trop Dis 2014; 4(Suppl 2): S519-S526.
[22]. Salunkhe A, Kadam S, Magar S and Dangare K, Nanosponges: A Modern Formulation Approach in Drug Delivery System, World Journal of Pharmacy and Pharmaceutical Sciences, Volume 7, Issue 2, 575-592.
[23]. Yadav G, Panchory H, Nanosponges: A Boon to The Targeted Drug Delivery System, Journal of Drug Delivery & Therapeutics; 2013, 3(4), 151-155.
[24]. Prabhu PP, Mehta CH, Nayak UY, Nanosponges-Revolutionary Approach: A Review, Research J. Pharm. and Tech. 13(7): July 2020.
[25]. Rashee N et al., A Very Instantaneous & Novel Delivery of Nanosponges, American Journal of PharmTech Research 2018.
[26]. Singh S, Monika K, Nanosponges as Emerging Carriers for Drug Delivery, Sys Rev Pharm 2022; 13(1): 55-62.
[27]. Singh P, Ren X, Guo T, Wu L, Shakya S, He, Y, et al. Biofunctionalization of β-cyclodextrin nanosponges using cholesterol. CarbohydrPolym. 2018; 190: 23-30.
[28]. Hayiyana Z, Choonara Y, Makgotloe A, du Toit L, Kumar P, Pillay V. Ester-based hydrophilic cyclodextrin nanosponges for topical ocular drug delivery. Curr Pharm Des. 2016; 22(46): 6988-6997.
[29]. Chen Y, Zhang Y, Zhuang J, Lee JH, Wang L, Feng RH, et al. Cell-membrane-cloaked oil nanosponges enable dual-modal detoxification. ACS Nano. 2019; 13(6): 7209-7215.
[30]. Ye H, Wang K, Lu Q, Zhao J, Wang M, Kan Q, et al. Nanosponges of circulating tumor-derived exosomes for breast cancer metastasis inhibition. Biomaterials. 2020; 242: 119932.
[31]. Kumar S, Trotta F, Rao R. Encapsulation of babchi oil in cyclodextrin-based nanosponges: Physicochemical characterization, photo-degradation, and in vitro cytotoxicity studies. Pharmaceutics. 2018; 10(4): 169.
[32]. Kamble M, Zaheer Z, Mokale S, Zainuddin R. Formulation optimization and biopharmaceutical evaluation of imatinib mesylate loaded β-cyclodextrin nanosponges. Pharm Nanotechnol. 2019; 7(5): 343-361.
[33]. Rao MR, Chaudhari J, Trotta F, Caldera F. Investigation of cyclodextrin-based nanosponges for solubility and bioavailability enhancement of rilpivirine.

AAPS Pharm Sci Tech. 2018; 19(5): 2358-2369.

[34]. [34]. Wang H, Yapa AS, Kariyawasam NL, Shrestha TB, Kalubowilage M, Wendel SO, et al. Rationally designed peptide nanosponges for cell based cancer therapy. Nanomed: Nanotechnol Biol Med. 2017; 13(8):2555-2564.

[35]. Huang Q, Wei W, Wang L, Chen H, Li T, Zhu X, et al. Synthesis ofuniform Ag nanosponges and its SERS application. SpectrochimActa A Mol Biomol. 2018; 201: 300-305.

[36]. Tannous M, Caldera F, Hoti G, Dianzani U, Cavalli R, Trotta F.Drug-encapsulated cyclodextrin nanosponges: Supramolecules indrug discovery and drug delivery. Springer. 2021: 247-283.

[37]. Suárez DF, Monteiro AP, Ferreira DC, Brandão FD, Krambrock K, et al. Efficient antibacterial nanosponges based on ZnO nanoparticlesand doxycycline. J Photochem Photobiol. 2017; 177: 85-94.

[38]. Coburn PS, Miller FC, LaGrow AL, Land C, Mursalin H, Livingston E, et al. Disarming pore-forming toxins with biomimetic nanospong es in intraocular infections. Msphere. 2019; 4(3).

[39]. Chen Y, Zhang Y, Chen M, Zhuang J, Fang RH, Gao W, et al. Biomi- metic nanosponges suppress in vivo lethality induced by the whole secreted proteins of pathogenic bacteria. Small. 2019; 15(6): 1804994.

[40]. Distler U, Tenzer S. Tools for pathogen proteomics: Fishing with bio mimetic nanosponges. ACS Nano. 2017; 11(12): 11768-11772.

[41]. Argenziano M, Lombardi C, Ferrara B, Trotta F, Caldera F, Blangetti M, et al. Glutathione/pH-responsive nanosponges enhance strigola tone delivery to prostate cancer cells. Oncotarget. 2018; 9(88): 35813

[42]. Zhang Y, Gao W, Chen Y, Escajadillo T, Ungerleider J. Self-assembled colloidal gel using cell membrane-coated nanosponges as building blocks. ACS Nano. 2017; 11(12): 11923-11930.

[43]. Dhakar NK, Matencio A, Caldera F, Argenziano M, Cavalli R, Di-anzari C, et al. Comparative evaluation of solubility, cytotoxicity andphotostability studies of resveratrol and oxyresveratrol loaded nano-sponges. Pharmaceutics. 2019; 11(10): 545.

[44]. Vincenzo A, Piccionello AP, Spinella A, Martino DC, Russo M. Polyaminoazide mixtures for the synthesis of pH-responsive calix-arene nanosponges. Beilstein J Org Chem. 2019; 15(1): 633-641.

[45]. Clemente N, Argenziano M, Gigliotti CL, Ferrara B, Boggio E, Chi-ochetti A, et al. Paclitaxel-loaded nanosponges inhibit growth and angiogenesis in melanoma cell models. Frontiers in Pharmacology.2019; 10: 776.

[46]. Wang J, Wang H, Wang H, He S, Li R, Deng Z, et al. Nonviolent self-catabolic DNAzyme nanosponges for smart anticancer drug de-livery. ACS Nano. 2019; 13(5): 5852-5863.

[47]. Chen Y, Chen M, Zhang Y, Lee JH, Escajadillo T, Gong H, et al. Broad-spectrum neutralization of pore-forming toxins with human erythrocyte membrane-coated nanosponges. Advanced Healthcare Materials. 2018; 7(13): 1701366.

[48]. Sherje AP, Surve A, Shende P. CDI cross-linked β-cyclodextrin nano-sponges of paliperidone: synthesis and physicochemical characteri-zation. J Mater Sci Mater Med. 2019; 30(6): 1-7.

[49]. Ferro M, Castiglione F, Pastori N, Punta C, Melone L, Panzeri W, et al. Dynamics and interactions of ibuprofen in cyclodextrin nanospong-es by solid-state NMR spectroscopy. Beilstein J Org Chem. 2017;13(1): 182-194.

[50]. Caldera F, Argenziano M, Trotta F, Dianzani C, Gigliotti L, Tannous M, et al. Cyclic nigerosyl-1, 6-nigerose-based nanosponges: An in-novative pH and time-controlled nanocarrier for improving cancer treatment. Carbohydr Polym. 2018; 194: 111-121.

[51]. Trotta F, Caldera F, Dianzani C, Argenziano M, Barrera G, Cavalli R. Glutathione bioresponsive cyclodextrin nanosponges. Chem Plus Chem. 2016; 81(5): 439-443.

[52]. Rao MR, Shirsath C. Enhancement of bioavailability of non-nucleoside reverse transciptase inhibitor using nanosponges. AAPS Pharm Sci Tech. 2017; 18(5): 1728-38.

[53]. Appell M, Jackson MA. Sorption of ochratoxin A from aqueous solutions using β-cyclodextrin-polyurethane polymer. Toxins. 2012; 4(2): 98-109.

[54]. Simionato I, Domingues FC, Nerín C, Silva F. Encapsulation of cinnamon oil in

cyclodextrin nanosponges and their potential use for antimicrobial food packaging. Food Chem Toxicol. 2019; 132: 110647.

[55]. Nait Bachir Y, Nait Bachir R, Hadj-Ziane-Zafour A. Nanodispersions stabilized by β-cyclodextrin nanosponges: Application for simultaneous enhancement of bioactivity and stability of sage essential oil. Drug Dev Ind Pharm. 2019; 45(2): 333-347.

[56]. Trotta F, Caldera F, Cavalli R, Soster M, Riedo C, Biasizzo M, et al. Molecularly imprinted cyclodextrin nanosponges for the controlled delivery of L-DOPA: Perspectives for the treatment of Parkinson's disease. Expert Opin Drug Deliv. 2016; 13(12): 1671-1680.

[57]. Shende PK, Gaud RS, Bakal R, Patil D. Effect of inclusion complexation of meloxicam with β-cyclodextrin-and β-cyclodextrin-based nanosponges on solubility, in vitro release and stability studies. Colloids Surf B. 2015; 136: 105-110.

[58]. Zidan MF, Ibrahim HM, Afouna MI, Ibrahim EA. In vitro and in vivo evaluation of cyclodextrin-based nanosponges for enhancing oral bioavailability of atorvastatin calcium. Drug Dev Ind Pharm. 2018; 44(8): 1243-1253.

[59]. Gigliotti CL, Ferrara B, Occhipinti S, Boggio E, Barrera G, Pizzimenti S, et al. Enhanced cytotoxic effect of camptothecin nanosponges in anaplastic thyroid cancer cells in vitro and in vivo on orthotopic xenograft tumors. Drug Deliv. 2017; 24(1): 670-680.

[60]. Rafati N, Zarrabi A, Caldera F, Trotta F, Ghias N. Pyromellitic dianhydride crosslinked cyclodextrin nanosponges for curcumin-controlled release; formulation, physicochemical characterization and cytotoxicity investigations. J Microencapsul. 2019; 36(8): 715-727.

[61]. Mihailiasa M, Caldera F, Li J, Peila R, Ferri A, Trotta F. Preparation of functionalized cotton fabrics by means of melatonin loaded β-cyclodextrin nanosponges. Carbohydr Polym. 2016; 142: 24-30.

[62]. Ataee-Esfahani H, Nemoto Y, Wang L, Yamauchi Y. Rational synthesis of Pt spheres with hollow interior and nanosponge shell using silica particles as template. Chem Comm. 2011; 47(13): 3885-3387.

[63]. Torne SJ, Ansari KA, Vavia PR, Trotta F, Cavalli R. Enhanced oralpaclitaxel bioavailability after administration of paclitaxel-loadednanosponges. Drug Deliv. 2010; 17(6): 419-425.

[64]. Alongi J, Poskovic M, Frache A, Trotta F. Role of β-cyclodextrinnanosponges in polypropylene photooxidation. Carbohydr Polym.2011; 86(1): 127-135.

[65]. [Minelli R, Cavalli R, Fantozzi R, Dianzani C, Pettazzoni P, Ellis L, etal. Antitumor activity of nanosponge-encapsulated camptotechin inhuman prostate tumors. Am Assoc Cancer Res. 2011.

[66]. Sharma R, Pathak K. Polymeric nanosponges as an alternative carrier for improved retention of econazole nitrate onto the skin throughtopical hydrogel formulation. Pharm Dev Technol. 2011; 16(4): 367-376.

[67]. [Swaminathan S, Vavia PR, Trotta F, Torne S. Formulation of betacyclodextrin based nanosponges of itraconazole. J Incl Phenom Macrocycl Chem. 2007; 57(1): 89-94.

[68]. Aynie I, Vauthier C, Chacun H, Fattal E, Couvreur P. Spongelike alginate nanoparticles as a new potential system for the delivery of antisense oligonucleotides. Antisense Nucleic Acid Drug Dev. 1999; 9(3): 301-312.