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Nanosponges: A novel approach for targeted drug delivery system

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Abstract
The most emerging branch in pharmaceutical sciences known as "Pharmaceutical nanotechnology" presents new tools, opportunities and scope, which are expected to have significant applications in disease diagnostics and therapeutics. Pharmaceutical nanotechnology comprised of nano-sized products which can be transformed in numerous ways to improve their characteristics. A Nanosponge is a novel and emerging technology which offers targeted & controlled drug delivery for topical as well as oral use. Nanosponges are based on nano, 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. Nanosponge is the part of advance drug delivery. It is a specific aiding system for targeted drug delivery of both kind of drugs either it is lipophilic or hydrophilic in a controlled manner. These have three dimensional networks or scaffold which is filled with drug and porous insoluble nanoparticles with a crystalline or amorphous structure and have spherical shape or swelling properties. The polarity and dimension of the polymer mesh can be easily varied by varying the type of cross-linker and degree of cross-linking. This review article deals with the general introduction of nanosponges, classification of nanosponges, characteristic features of nanosponges, their advantages, disadvantages, chemicals used in their preparation, preparation methodologies, factors affecting on their preparation, mechanism of action and evaluation parameters along with some applications of nanosponges.

Keywords: nanotechnology, nanosponges, targeted delivery, cyclodextrin, solubility

Introduction
Nanotechnology is defined as the manipulation of matter on an atomic, molecular, and supramolecular scale involving the design, production, characterization and application of different nanoscale materials in different potential areas providing novel technological advances mainly in the field of medicine. Nanotechnology has created potential impact in various fields like medicine including immunology, cardiology, endocrinology, ophthalmology, oncology, pulmonology etc. In addition it's highly utilized in specialized areas like brain targeting, tumor targeting, and gene delivery. Nanotechnology also provides significant systems, devices and materials for better pharmaceutical applications [1].

Nanotechnology is potentially the most important engineering revolution since the industrial age. So far nanotechnology resulted in variants of formulations like nanoparticles, Nano capsules, Nano spheres, Nano suspensions, nanocrystals, nano-erythosomes etc. Nanotechnology is defined as creation and manipulation of materials at nanoscale level to create products that shows novel properties. In recent years, nanomaterials are gaining a lot of attention. In 1959 Richard P. Feynman, a physicist, at Cal Tech, forecasted about nanomaterial. He said that, "There is plenty of room at the bottom," and suggested that scaling down to nano level and starting from the bottom was the key to future advancement in nanotechnology. Nanomaterials are defined as materials that are having at least one dimension in the 1-100 nm range. Nanoparticles have wide variety of applications such as biocompatible materials, textile fictionalization, and coatings against UV radiation or allowing microbial degradation, drug delivery, DNA delivery, enzyme immobilization etc. Nanoparticles are available in various forms like polymeric nanoparticles, solid-lipid nanoparticles, Nano emulsions, nanosponges, carbon nanotubes, micellar system; dendrimers etc [2].

The pharmaceutical and health care industry has been creating and using nano-scale materials for solving many physical, chemical and biological problems associated with the treatment of disease. Since 1950's, nanotechnology has dominated technology [3]. Depending on the method of associating with drugs, the nanoparticles can be classified into three types.

1. **Encapsulating Nanoparticles:** This type is represented by nanosponges and nanocapsules. Nanosponges such as alginate nanosponge, which are sponge like nanoparticles containing many holes that carry the drug molecules. Nanocapsules such as poly (isobutyl cyanoacrylate) (IBCA) are also encapsulating nanoparticles. They can entrap drug molecules in their aqueous core.
2. **Complexing Nanoparticles:** This category includes complexing nanoparticles, which attracts the molecules by electrostatic charges.
3. **Conjugating Nanoparticles:** These conjugating nanoparticles link to drugs through covalent bonds [4].

Nanosponges were originally developed for topical delivery of drugs. Nanosponges are tiny sponges with a size of a virus with an average diameter below 1μm. 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. Because the drug can be released at the specific target site instead of circulating throughout the body it will be more effective for a particular given dosage [5].

Nanosponges are three dimensional network or scaffold. Scaffolds are generally composed of polymers and other materials which have been used in drug delivery system for decades. The combined efforts of medical practitioners and material scientist enable fabrication of scaffold with additional drug delivery features to which clinically important functionalities are added [6].

Nanosponges are tiny sponges with very small size of diameter below 1um. These are incorporated in specific dosage form and circulate around the body until they encounter the specific target site and bind to the surface and start to release the drug in controllable and predictable manner. The term "Nanosponge" means the nanoparticles having porous structures. It provides solution for several formulation related problems. Owing to their small size and porous nature they can bind poorly- soluble drugs within the matrix and improve their bioavailability by modifying the pharmacokinetic parameters of actives [7].

Nanoporous structures have been broadly classified into nanoporous membranes, nanoporous hydrogels and nanoporous particles. Nanosponges fall into the category of nanoporous particles. The thin line of distinction among nanoparticles and NS is the difference in porosity and size. Nanoparticles have size in nanometer whereas NS have pores in nanometers while their overall size can extend up to micrometers, and are usually smaller than 5 µm. Many times NS have been reported as Nanoporous nanoparticles/ microparticles [8].

Characteristic Features of Nanosponges [7, 9]

1. Nanosponges provide a range of dimensions (1 µm or less) with tunable polarity of the cavities.
2. Nanosponges of specific size can be synthesized by changing the crosslinker to polymer ratio.
3. They exhibit paracrystalline or crystalline forms, depending on the process conditions. Crystal structure of nanosponges plays a crucial role during complexation with drugs.
4. Drug loading capacity depends on the degree of crystallization.
5. Various drug loading capacities can be shown by paracrystalline nanosponges.
6. They are nontoxic, porous particles, insoluble in most organic solvents and stable up to 300 °C.
7. They are stable at the pH range of 1-11.
8. They form clear and opalescent suspension in water.
9. They can be reproduced by simple thermal desorption, extraction with solvents, by using microwaves and ultrasounds.
10. Their three-dimensional structure allows capture, transportation and selective release of a variety of substances.
11. They can be sited to different target sites because of their capacity to link with different functional groups.
12. Chemical linkers permit nanosponges to bind preferably to the target site.
13. By complexing with different drugs nanosponges can form inclusion and non-inclusion complexes.
14. By adding magnetic particles into the reaction mixture, magnetic properties can also be imparted to nanosponges.
15. Nanosponges are porous particles having high aqueous solubility, used mainly to encapsulate the poor soluble drugs.
16. These Nanosponges are capable of carrying both lipophilic and hydrophilic drugs.
17. They protect the drug from physicochemical degradation.
18. They are able to remove the organic impurities from water.

Advantages [9-12]

1. These formulations are stable over range of pH 1 to 11.
2. These formulations are stable at higher temperatures.
3. These formulations are compatible with most vehicles and ingredients.
4. These are self-sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate.
5. These formulations are free flowing and can be cost effective.
6. This technology offers entrapment of ingredients and reduced side effects, improved stability, increased elegance, and enhanced formulation flexibility.
7. Nanosponges are non-irritating, non-mutagenic, non-allergenic, and non-toxic.
8. Extended release action up to 12 hrs can be attained.
9. Allows incorporation of immiscible liquid, Improves material processing as liquid can be converted to powders.
10. Easy scale up for commercial production.
11. Size of the nanosponges can be varied by modifying the proportion of crosslinker to polymer.
12. Depending on the dosing requirement, the drug release profiles can be varied from fast, medium to slow release.
13. Predictable release.
14. Regeneration of nanosponges can be done by washing with eco-compatible solvents, stripping with moderately inert hot gases, mild heating, changing pH or ionic strength.
15. Less harmful side effects because of drug having less contact with healthy tissue.

Disadvantages

1. Nanosponges have ability to include only small molecules.
2. Nanosponges could be either paracrystalline or in crystalline form.
3. The loading capacity of nanosponges depends mainly on degree of crystallization.
4. Paracrystalline nanosponges can show different loading capacities

Types of nanosponges [2]

Classification of nanosponges is provided in Figure 1.

Cyclodextrin Nanosponges [11]

DeQuan Li and Min Ma in 1998 were the first who used the term cyclodextrin nanosponges (CDNS) to indicate a cross-

linked β-cyclodextrin with organic diisocyanates leading to the formation of an insoluble network which indicate high inclusion constant with various organic pollutants. CDNS are suggested as a new nanosized drug delivery system with crosslinked polymers of cyclodextrin nanostructure within a three-dimensional network. CD polymer can form porous insoluble nanoparticles with crystalline or amorphous structure and spherical shape with tunable polarity and dimension by changing the crosslinker and degree of cross-linking.

There are three types of CD: Alpha-cyclodextrin (α) Beta-cyclodextrin (β) Gamma-cyclodextrin(γ) Delta-cyclodextrin(δ), the 3 natural CDs, α-, β- and γ- CDs differ in their ring size and solubility.

Cyclodextrins have been mainly considered for pharmaceutical field because

1. They are semi-natural products, produced from renewable natural material of starch, by relatively simple enzymatic conversion.
2. They are produced in thousands of tons per year by environmental friendly techniques.
3. Any of their toxic effect is of secondary character and can be eliminated by selecting the appropriate Cyclodextrin type or derivatives or mode of application.

The natural α- CD and β- CD, unlike γ- CD are not hydrolyzed by human salivary enzyme and pancreatic amylases; though all three are subjected to fermentation by the intestinal micro flora. At moderate oral doses hydrophilic CDs are non toxic. The naturally occurring CD and its derivatives are used in oral and topical formulations, but only α-cyclodextrin and the hydrophilic derivatives of β- and γ-cyclodextrin can be used in parenteral formulations. The γ-cyclodextrin forms visible aggregates in aqueous solution and is not well suited for parenteral formulations.

CDNS are a new class of amorphous cross-linked polymers obtained by reacting CD with a suitable poly-functional agent such as carbonyldiimidazole (CDI) or pyromellitic anhydride. The reaction products turned out to be highly cross-linked, nanoporous polymers showing interesting inclusion/release properties. The presence of the lipophilic cavities of CD units and hydrophilic channels within the porous structure provides the CDNS with the capability of encapsulating a large variety of compounds. Moreover, the type and the amount of crosslinking agent may dramatically regulate the various parameters like the swelling index and hydrophilicity/hydrophobicity of the final product. These properties make CDNS highly attractive for several applications in biocatalysis, agriculture and environmental protection and drug-delivery.

CD based NS are further classified into:

1. **CD-based carbamate nanosponges**: CDs are reacted with suitable diisocyanates such as hexamethylene diisocyanate and toluene- 2, 4-diisocyanate in the presence of DMF solution at 70°C for 16 to 24 hours under a nitrogen atmosphere. Residual DMF is removed by thorough washing with acetone and powder of the crosslinked polymer is obtained. These nanosponges have an ability to bind to organic molecules and used for water purification. The loading capacity for organic molecules ranges from 20 to 40 mg per cm^3.
2. **CD-based carbonate nanosponges:** The main crosslinkers used for preparation of this type of nanosponges are active carbonyl compounds such as CDI, DPC and trifosgene. The resulting CD nanosponges exhibit carbonate bonds between two CD monomers. The reaction can be carried out at room temperature or at 80 to 100°C in the presence or absence of a solvent, i.e., employing either the solvent technique or melt technique. Some of the important characteristics of carbonate-CD-based nanosponges are adjustable polarity and changeable dimensions of their cavities. They can be obtained in different forms, like amorphous or semi-crystalline, by carrying out the reaction under different conditions. Carbonate-CD-based nanosponges have been used to encapsulate many drugs such as paclitaxel, camptothecin, dexamethasone, flurbiprofen, doxorubicin hydrochloride, itraconazole, 5-fluorouracil, cilostazol, progesterone, oxcarbamazepine, nelfinavir mesylate, resveratrol and tamoxifen. Carbonate nanosponges do not significantly affect the surface tension of water. They are non-hygroscopic in nature and they retain their crystal structure during absorption and desorption of moisture. A unique feature of CD-based carbonate nanosponges is that their ability of solubility enhancement depends significantly on their degree of crystallinity.
3. **CD-based ester nanosponges**: A suitable dianhydride such as pyromellitic anhydride is used as a crosslinking agent for fabrication of these nanosponges. The exothermic crosslinking reaction is very fast (completed within a few minutes) and is carried out at room temperature, dissolving the CD and the dianhydride in DMSO in the presence of an organic base such as pyridine or triethylamine (to accelerate the reaction in a forward direction). This type of nanosponges can host both apolar organic molecules and cations simultaneously since it contains a polar free carboxylic acid group.
4. **Polyamidoamine Nanosponges:** These types of nanosponges are prepared by carrying out the reaction in water. β- CD polymerizes with acetic acid 2, 20-bis (acrylamide) after long standing (i.e., 94 h at room temperature). They swell in water (pH dependent behavior) and have both acid and basic residues. The polymer forms a translucent gel instantly on contact with water. Time-dependent swelling studies in bio relevant media confirmed the stability of the gel for up to 72 h. The studies were carried out using albumin as a model protein exhibiting very high encapsulation efficiency, around 90%. *In vitro* drug release studies showed that protein release can be modulated up to 24 h. Sodium dodecyl sulphate (SDS PAGE) technique was used to investigate the stability of the product. Conformational stability of the protein, examined using the SDS PAGE technique, showed that the formulation was stable for as long as several months.
5. **Modified Nanosponges**: Classical carbonate based

nanosponges have been modulated by varying the reaction conditions to better fit the application selected. Fluorescent derivative has been obtained by reacting carbonate nanosponges with fluorescein isothiocyanate in DMSO at 90°C for a few hours. Fluorescent nanosponges have found their use in biological studies such as cancer therapy. In a similar manner, carboxylated nanosponges can be obtained using a cyclic organic anhydride such as succinic anhydride or maleic anhydride. These nanosponges react with biologically important carriers such as biotin, chitosan, or proteins, possibly providing a promising specific receptor targeting activity for drugs. Powder XRD studies have shown that these nanosponges are amorphous in nature. They are also nonhemolytic and non-cytotoxic. For anti-cancer drugs such as camptothecin, carboxylated nanosponges appear to be promising safe carriers for drug targeting.

Mechanism of drug release from NS

The sponge atoms have an open arrangement and the active is free to move in and out from the particles and into the vehicle up to equilibrium is got. In case of topical delivery, once the finished product is applied to the target tissue, the active that is already in the vehicle will be absorbed into it. Depleting the vehicle, which will become unsaturated, therefore disturbs the equilibrium. This will start a flow of the active from the sponge particle into the vehicle and from it to the target tissue until the vehicle is either dried or absorbed. Even after that the sponge particles retained on the surface of tissue will continue to gradually release the active to it, providing prolonged release over time [12].

Chemicals used for the synthesis of nanosponges [4, 9, 12]

1. **Polymer:** Type of polymer used can influence the formation as well as the performance of nanosponges. For complexation, the cavity size of nanosponge should be suitable to accommodate a dug molecule of particular size. The ability of the polymer to be cross linked depends on the functional groups and active groups to be substituted. The selection of polymer depends on the required release and the drug to be enclosed.
   Ex- Hyper cross linked polystyrenes, Cyclodextrin and its derivatives like Alkyloxycarbonyl cyclodextrin, Methyl β-Cyclodextrin, 2-Hydroxy Propyl β-Cyclodextrins.
2. **Co-polymers:** Poly (Valerolactone allylvalerolactone), Poly (Valerolactone-allylvalerolactone oxepanedione), ethyl cellulose, polyvinyl alcohol.
3. **Cross-linkers:** Selection of cross linkers depends on the structure of polymer and the drug to be formulated.
   Ex: Carbonyl diimidazoles, Carboxylic acid dianhydrides. Diphenyl Carbonate, Diaryl carbonates, Diisocyanates, Pyromellitic anhydride, Carbonyl diimidazoles, Epichloridrine, Glutaraldehyde, 2, 2-bis (acrylamido) Acetic acid and Dichloromethane.
4. **Drug substances:** Drug molecule to be formulated as nanosponges should have certain characteristics-
   - Molecular weight between 100 and 400 Daltons.
   - Drug molecule consists of less than 5 condensed rings.
   - Solubility in water is less than 10mg/ml.
   - Melting point of the substance is below 250°C.

Preparation of Nanosponges

1. **Solvent method:** Mix the polymer with a suitable solvent, in particular in a polar aprotic solvent such as dimethylformamide, dimethyl sulfoxide. Then add this mixture to excess quantity of the crosslinker, preferably in crosslinker/polymer molar ratio of 4 to 16. Carry out the reaction at temperature ranging from 100C to the reflux temperature of the solvent, for time ranging from 1 to 48 hrs. Preferred crosslinkers are carbonyl compounds (Dimethyl carbonate & Carbonyldi imidazole). After completion of the reaction, allow the solution to cool at room temperature, then add the product to large excess of bidistilled water and recover the product by filtration under vacuum and subsequently purify by prolonged soxhlet [4].
2. **Emulsion solvent diffusion method:** Nanosponges can be prepared by using different concentration of ethyl cellulose and polyvinyl alcohol. The various ratio of drug to polymer are used to improve the drug loading and to obtain a tailored release. The dispersed phase containing drug and polymer dissolved in 20 ml of dichloromethane was added slowly to definite amount of polyvinyl alcohol in 100ml of aqueous external phase with 1000-1500 rpm stirring speed using magnetic or mechanical stirrer for 3-5 hrs. The formed nanosponges were collected by filtration and dried in oven for 40°C for 24hrs and packed in a container [6].
3. **Ultrasound-Assisted synthesis:** In this method, polymers react with cross- linkers in absence of solvent and under sonication. Here, mix the polymer and cross- linker in a flask. Place the flask in an ultrasound bath filled with water and heat it to 90^0c and sonicate for 5 hours. Allow it to cool and wash with water to remove the unreacted polymer. Purify by prolonged soxhlet extraction with ethanol. Dry the product under vacuum and store at 25^0C [15].
4. **Quasi-emulsion solvent diffusion:** The nanosponges can also be prepared by quasi-emulsion solvent diffusion method using the different polymer amounts. To prepare the inner phase, eudragit RS100 was dissolved in suitable solvent. Then, drug can be added to the solution and dissolved under ultrasonication at 35^0c. The inner phase was poured into the PVA solution in water (outer phase) and allowed for stirring for 1 hr, then the mixture is filtered to separate the nanosponges. The nanosponges are dried in an air-heated oven at 40˚c for 12 hrs [16].
5. **From hyper cross- linked β-cyclodextrin:** Here, β-cyclodextrin can be used as carrier for drug delivery. Nanosponges can be obtained by reacting cyclodextrin with a cross linker. Due to this 3D networks are formed which may be a roughly spherical structure about the size of a protein having channels and pores in the internal part. Reacting cyclodextrin with a cross linker such as di-isocianates, diary carbonates etc. sponges size is controlled according to porosity, surface charge density for the attachment to different molecules. Nanosponges can be synthesized in neutral or acid forms. The average diameter of a nanosponge is below 1µm but fractions below 500 nm can be selected. They are used to increased aqueous solubility of poorly-water soluble drugs. They consist of solid particles and converted in crystalline form.

6. **Polymerization:** A solution of non polar drug is made in the monomer, to which aqueous phase, usually containing surfactant and dispersant to promote suspension is added. Polymerization is effected, once suspension with the discrete droplets of the desired size is established, by activating the monomers either by catalysis or increased temperature. The polymerization process leads to the formation of a reservoir type of system, which opens at the surface through pores.

Loading of Drug into Nanosponges

Nanosponges for drug delivery should be pre-treated to obtain a mean particle size below 500 nm. Suspend the nanosponges in water and sonicate to avoid the presence of aggregates and then centrifuge the suspension to obtain the colloidal fraction. Separate the supernatant and dry the sample by freeze drying. Prepare the aqueous suspension of Nanosponge and disperse the excess amount of the drug and maintain the suspension under constant stirring for specific time required for complexation. After complexation, separate the uncomplexed (undissolved) drug from complexed drug by centrifugation. Then obtain the solid crystals of nanosponges by solvent evaporation or by freeze drying.

Factors influencing the formation of Nanosponge [6, 11, 12]

1. **Polymer and Cross-linkers:** The type of polymer used can influence the formulation as well as performance of nanosponges. Efficient cross-linker converts molecular nanocavities into 3-dimensional nanoporous structure.
   - Hydrophilic nanosponge- they are formed by using epichlorohydrin as cross linker. Hydrophilic nanosponges modify the rate of drug release and enhance drug absorption across biological barriers, serving as a potent drug carrier even in immediate release formulation.
   - Hydrophobic nanosponges can be synthesized by using diphenyl carbonate, pyromellitic anhydride, diisocynates, and carbonyldiimidazole as crosslinker. They serve as sustained release carriers for water soluble drugs including peptide and protein drugs.
2. **Types of Drug and Medium Used for Interaction:** The drug molecule used in nanosponge formulation should have following characteristics
   - Molecular weight between 100 and 400 Daltons.
   - Drug molecule consists of less than 5 condensed rings.
   - Solubility in water is less than 10mg/ml
   - Melting point of the substance is below 250°C.
3. **Complexation Temperature:** The stability constant of a complex is dependent on temperature changes. The stability constant and temperature rise are inversely correlated. At increased temperature, the magnitude of apparent stability constant decreases due to reduction in drug/nanosponge interaction forces. Hence, a thorough control over the temperature should be maintained when nanosponges are prepared.
4. **Degree of Substitution:** The number, type and position of the substituent on the polymeric molecule affect the complexation ability of nanosponges. The type of substitution is important because β-CD derivatives are available in various forms differing in functional groups present on the surface of the cyclodextrin derivative. When complexed together with the help of a crosslinker, different functional groups yield different types of complexed material (β-CD nanosponges, CD-carbamate nanosponges, CD-carbonate nanosponges, etc.) There is a direct correlation between the number of substitutions present and the degree of crosslinking, higher the number of substituent, the greater is the probability of undergoing higher crosslinking. Higher degree of crosslinking will yield highly porous nanosponges due to more interconnections between polymers forming a mesh type network. The position of substitution depends on the production conditions. A change in the production process will yield materials with different physicochemical properties due to occupancy of some different position by the functional group on the parent compound.

Characterization and evaluation of Nanosponges

1. **Particle size and polydispersity index:** The particle size can be determined by dynamic light scattering using 90 Plus particle sizer equipped with MAS OPTION particle sizing software or laser light diffractometry or Malvern Zeta sizer. From this, the mean diameter and polydispersity index can be determined [4]. values of polydispersity index are given in table 2.
2. **Resiliency:** Resiliency (viscoelastic properties) of sponges can be modified to produce beadlets that are 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 release as a function of cross-linking with time [4].
3. **X-ray diffractometry and single crystal X-ray structure analysis:** X-ray diffractiometry can be used to detect inclusion complexation in the solid state. When the drug molecule is liquid it does not shown diffraction of their own, then the diffraction pattern of newly formed substance clearly differs from that of uncomplexed nanosponges. The difference of diffraction pattern indicates the inclusion complex formation. When drug substance is solid in nature a comparison has to be made between diffractograms of the assumed complex and that of mixture of drug with polymer molecules. The inclusion complex formation of drug with nanosponges changes the diffraction patterns and also changes the crystalline nature of drug. Sharpening of the existing peaks and appearance of few new peaks leads to formation of inclusion complex [6].
4. **Microscopy studies:** Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) can be used to study the microscopic aspects of the drug, nanosponges and the product (drug/nanosponge complex). The difference in crystallization state of the raw materials and the product seen under electron microscope indicates the formation of the inclusion complexes [15].
5. **Drug release kinetics:** To investigate the mechanism of drug release from the Nanosponge the release data was analysed using Zero order, First order, and Higuchi, Korsemeyer-Peppas, Hixon Crowell, Kopcha and Makoid-Banakar models. The data can be analysed using graph pad

prism software. The software estimates the parameters of a non-linear function that provides the closest fit between experimental observations and non- linear function [15].

6. **Thermoanalytical methods:** Thermo analytical methods determine whether the drug substance undergoes some changes before the thermal degradation of the nanosponge. The change of the drug substance may be melting, evaporation, decomposition, oxidation or polymorphic transition. The change of the drug substance indicates the complex formation. The thermogram obtained by differential thermal analysis and differential scanning calorimetry can be observed for broadening, shifting and appearance of new peaks or disappearance of certain peaks. Changes in the weight loss also can provide supporting evidence for the formation of inclusion complexes [17].
7. **Infra-Red spectroscopy:** The interaction between nanosponges and the drug molecules in the solid state can be detected by Infra-Red spectroscopy. Upon complex formation the nanosponges bands changes. If the fraction of the guest molecules encapsulated in the complex is less than 25% bands which could be assigned to the included part of the guest molecules are easily masked by the bands of the spectrum of nanosponges. Infra-red spectroscopy is applicable to the drugs having some characteristic bands such as carbonyl or sulfonyl groups. This spectral study reveals information regarding the involvement of hydrogen in various functional groups. This generally shifts the absorbance bands to the lower frequency, increases the intensity and widens the band caused by stretching vibration of the group involved in the formation of the hydrogen bonds. Hydrogen bond at the hydroxyl group causes the largest shift of the stretching vibration band [17].
8. **Thin Layer Chromatography:** In Thin Layer Chromatography, the Rf values of a drug molecule diminish to considerable extent and this helps in identifying the complex formation between the drug and nanosponge.
9. **Loading efficiency and production yield:** The loading efficiency (%) of the nanosponges can be calculated according to the following equation.

   Loading Efficiency =
   Actual drug content in NS÷ Theoretical drug content × 100

   The production yield of the nanosponges can be calculated by following equation after determining accurate initial weight of the raw materials and final weight of the nanosponge obtained.

   Production yield (PY) =
   Practical mass of NS ÷ Theoretical mass (polymer+Drug) × 100

10. **Solubility studies:** Higuchi and Connors have described an approach to study inclusion complexation as the phase solubility method which examines the solubility of drug in nanosponge. Phase solubility diagrams indicate the degree of complexation. In this method Erlenmeyer flask was used. The drug containing an aqueous solution of various percentages of nanosponges is added to the flask. The Erlenmeyer flask was stirred on a mechanical shaker at room temperature till it reaches a steady state, the suspension was filtered by centrifugation using a 3000 Dalton molecular filter (MICRON YN 30, Millipore Corporation, Bedford MA 1730 U.S.A).The solution was analyzed and the drug concentration is determined by high performance liquid chromatography [17].
11. **Zeta potential:** Zeta potential is used for the measurement of surface charge by using additional electrode in particle size equipment. In this process nanosponges containing samples were taken and diluted with 0.1mol/l KCl and placed in electrophoretic cell for an application of 15V/cm of electric field. From this the mean hydrodynamic diameter and poly dispersity index were determined after averaging of the total measurement [17].
12. **Dissolution test:** Dissolution profile of nanosponges 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.

Applications of Nanosponges

1. **Solubility enhancement:** Nanosponges can improve the wetting and solubility of molecules with very poor solubility in water. The drugs can be molecularly dispersed within the nanosponge structure and then released as molecules, avoiding the dissolution step. Consequently, the apparent solubility of the drug can be increased. Many formulation and bioavailability problems can be solved by enhancing the solubility and dissolution rate of a substance, and nanosponges can greatly enhance the drug solubility [4]. Table 1 provides the BCS class II drugs which have very low solubility and these are the ideal candidates for nanosponges.
2. **Nanosponges for drug delivery:** The nanosponges are solid in nature and can be formulated as Oral, Parenteral, Topical or Inhalation dosage forms. For the oral administration, the complexes may be dispersed in a matrix of excipients, diluents, lubricants and anticaking agents suitable for the preparation of capsules or tablets. For the parenteral administration the complex may be simply carried in sterile water, saline or other aqueous solutions. For topical administration they can be effectively incorporated into topical hydrogel [13].
3. **Topical agents:** Nanosponge delivery system is a unique technology for the controlled release of topical agents of prolonged drug release and retention of drug form on skin. Local anaesthetics, antifungal and antibiotics are among the category of the drugs that can be easily formulated as topical nanosponges. 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 efficiency. A wide variety of substances can be incorporated into a formulated product such as gel, lotion, cream, ointment, liquid, or powder [16].

4. **Nanosponges as a carrier for biocatalysts and in the delivery and release of enzymes, proteins, vaccines and antibodies:** A number of systems for carrying enzymes and proteins have been developed, such as nano and microparticles, liposomes and hydrogels. Carriage in a particular system can protect proteins from breakdown, modify their pharmacokinetics and improve their stability *in-vivo*. Now, it has been found that Cyclodextrin based nanosponges are particularly suitable carrier to adsorb proteins, enzymes, antibodies and macromolecules. In particular when enzymes are used, it is possible to maintain their activity, efficiency, prolong their operation and extends the pH and temperature range of activity and allows the conduct of continuous flow processes. Moreover, proteins and other macromolecules can be carried by adsorbing or encapsulating them in cyclodextrin nanosponges [13].
5. **Nanosponges as a carrier for delivery of gases:** Gases play an important role in medicine, either for diagnostic or treatment purposes. The deficiency of adequate oxygen supply, named hypoxia, is related to various pathologies, from inflammation to cancer. It is sometime difficult to deliver oxygen in appropriate form and dosage in clinical practice. Cavalli *et al*. developed nanosponges formulations as oxygen delivery systems for topical application which have the ability to store and to release oxygen slowly over time [17].
6. **Nanosponges as protective agent against photo degradation:** Sapino *et al*. reported that gamma-oryzanol (a ferulic acid ester mixture), an anti-oxidant and usually employed to stabilize food and pharmaceutical raw materials, moreover, used as a sunscreen in the cosmetics industry. Its applications are limited due to its high instability and photodegradation. Nanosponges are prepared by encapsulating gamma-oryzanol showing a good protection from photodegradation. With the gammaoryzanol loaded nanosponges a gel and an O/W emulsion are formulated [2].
7. **Removal of Organic Pollutants from Water:** Betacyclodextrin 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. Table 3 enlist various research studies done on formulation of nanosponges of various drugs for the desirable characteristics.

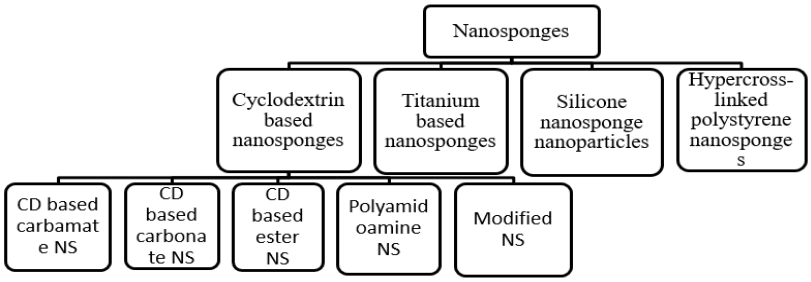

Fig 1: Types of Nanosponges

Table 1: Biopharmaceutical Classification System Class II drugs

Sr. No.	Category	Drugs
1	Antihypertensive	Felodipine, Nicardipine, Nifedipine, Nisoldipine
2	Antibiotics	Azithromycin, Ciprofloxacin, Erythromycin, Ofloxacin,
3	Antiarrhythmic agents	Amiodarone hydrochloride
4	Antifungal agents	Econazole nitrate, Griseofulvin, Itraconazole, Ketoconazole
5	Antidiabetic and Antihyperlipidemic	Atorvastatin, Fenofibrate, Glibenclamide, Glipizide, Lovastatin, Troglitazone
6	NSAIDs	Dapsone, Diclofenac, Diflunisal, Etodolac, Etoricoxib, Flurbiprofen, buprofen, Indomethacin, Ketoprofen, Mefenamic acid, Naproxen, Nimesulide, Oxaprozin, Piroxicam
7	Cardiac drugs	Carvedilol, Digoxin, Talinolol
8	Anticoagulant	Warfarin
9	Anticonvulsants	Carbamazepine, Clonazepam, Felbamate, Oxycarbazepine, Primidone.
10	Antipsychotic drugs	Chlorpromazine Hydrochloride Antiretrovirals Indinavir, Nelfinavir, Ritonavir, Saquinavir
11	Antianxiety drugs	Lorazepam
12	Antiepileptic drugs and Steroids	Phenytoin, Danazol, Dexamethazone
13	Immunosupressants	Cyclosporine, Sirolimus, Tacrolimus
14	Antiulcer drugs	Lansoprazole, Omeprazole
15	Antioxidants	Resveratrol
16	Diuretics	Chlorthalidone, Spironolactone
17	Antineoplastic agents	Camptothecin, Docetaxel, Etoposide, Exemestane, Flutamide, Irinotecan, Paclitaxel, Raloxifene, Tamoxifen, Temozolamide
18	Miscellaneous	Atovaquone, Melarsoprol, Phenazopyridine, Ziprasidone

Table 2: Polydispersity Index

Polydispersity index	Type of dispersion
0-0.05	Monodispersed standard
0.05-0.08	Nearly monodisperse
0.08-0.7	Midrange polydispersity
>0.7	Very polydisperse

Table 3: Examples of Nanosponges [19-36]

Drug	Nanosponge Vehicle	Category of drug	Study
Itraconazole	Betacyclodextrin, and copolyvidonum	Antifungal	Solubility
Voriconazole	Ethyl cellulose, Polymethyl methacrylate (PMMA), Pluronic F-68.	Antifungal	Drug release
Miconazole Nitrate	Beracyclodextrin, Di-phenyl carbonate	Antifungal	Drug release
Celecoxib	Betacyclodextrin, N, N- methylene bisacrylamide	NSAID	Solubility
Erlotinib	Betacyclodextrin	Tyrosine kinase inhibitor (Anticancer)	Solubility, bioavailability and In-vitro cytotoxicity.
Econazole Nitrate	Ethyl cellulose, PVA	Antifungal	Irritation study, Adsorption
Isoniazid	Ethyl cellulose, PVA	Anti-tubercular	Drug release
Cephalexin	Ethyl cellulose, PVA	Antibiotic	Drug release and Stability
Norfloxacin	Betacyclodextrin and Diphenylcarbonate	Antibiotic	Bioavailability
L-Dopa	Betacyclodextrin	Parkinson's Disease	Drug release
Fenofibrate	Maize starch, SDS	Fibrate	Solubility and Bioavailability
Nifedipine	Betacyclodextrin	Calcium channel blocker	Solubility
Glypizide	Betacyclodextrin	Sulfonylurea	Drug release
Ibuprofen	Ethyl cellulose and PVA	NSAID	Drug release
Resveratrol	Cyclodextrin	Antioxidant	Stability, cytotoxicity and permeation
Paclitaxel	Betacyclodextrin	Antineoplastic	Bioavailability
Camptothecin	Betacyclodextrin	Antineoplastic	Stability and solubility
Tamoxifen	Betacyclodextrin	Antiestrogen	Solubility
Temozolamie	Poly(valerolactineallylvalero lactone) and poly (valerolactoneallylvalero lactone oxepanedione)	Antitumour	Drug release
Dexamethosane	Betacyclodextrin	Antitumour	Drug release
Gamma-Oryzanol	Betacyclodextrin	Antioxidant	Stability
Telmisartan	Carbonated crosslinkers	Antihypertensive	Dissolution rate
Lysozyme	Cyclodextrin-based poly(amidoamine)	Enzyme	Solubility and drug release
Nelfinavir Mesylate	Betacyclodextrin	Antiviral	Solubility and drug release

Conclusion

Nanosponge 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 its pharmacokinetics parameters. The average diameter of a nanosponge is below 1μm but fractions below 500 nm can be selected.

Nanosponge technology involve encapsulation of medicament in a polymeric material in an innovative way and thus provide controlled site specific drug release, increased formulation efficacy, improved stability, drug dosing and patient compliance. By controlling the ratio of polymer to cross linker and stirring rate release particle size and release rate can be modulated. Nanosponges can be developed as different dosage forms like Parenteral, aerosol, topical, tablet and capsule. Besides their application in the drug delivery field, potential applications exist for cosmetics, biomedicine, bioremediation processes, agro chemistry, and catalysis, among others. Drugs delivered by nanosponges can be proved safe and effective and the pharmaceutical industries will benefit greatly if clinical studies can prove their potential for human use. Thus, nanosponges are a boon for targeted and site specific drug delivery System

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