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Nanosponges: A Novel Carrier for Targeted Drug Delivery

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Abstract: Targeted drug delivery system is a special form of drug delivery system where the pharmacologically active agent is selectively targeted only to its site of action and not to the non targeted organs, tissues or cells. Nanosponges are such type of effective drug carriers which solves the problems of toxicity and poor bioavailability as they can load both hydrophilic and hydrophobic drugs. Different categories of drugs can be loaded into nanosponges for targeted drug delivery. This type of drug delivery is one of the most promising approaches in the life science. Nanosponges are tiny in size with a three dimensional network and nanometric cavity. Nanosponges are highly porous and having unique ability to entrap active molecules and offer programmable release. These are prepared by reacting cyclodextrins with appropriate crosslinking agents in a specified ratio. Nanosponges circulate throughout the body until they reach the specific target site, stick on the surface and release the drug in a predictable manner. They possess higher drug loading capacities compared to other nanocarriers. Hence they are suitable for solving the problems related to stability, solubility and delayed release of actives. Predictable release of the loaded active molecules of poorly water soluble drugs is the major advantage of nanosponges. They can deliver the drugs through various routes like oral, topical, parentral etc. and act as biocatalyst in the delivery of enzymes, proteins, vaccines and antibodies. Current review focuses on the characteristic features, preparation methods, factors, characterization, and applications of nanosponges in the field of drug delivery.
Keywords: Nanosponges, Cyclodextrins, Cross-linking agents, Controlled release.

Introduction:

Nanotechnology is potentially the most important engineering revolution since the industrial age[1]. So far nanotechnology resulted in variants of formulations like nanoparticles, nanocapsules, nanospheres, nanosuspensions, nanocrystals, nano-erythosomes etc[2]. Nanotechnology is defined as creation and manipulation of materials at nanoscale level to create products that shows novel properties[3]. In recent years, nanomaterials are gaining a lot of attention. In 1959 Richard P. Feynman, a physicist, at Cal Tech, forecasted about nanomaterials. 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[4]. Nanomaterials are defined as materials that are having at least one dimension in the 1-100 nm range[5-7]. Nanoparticles have wide variety of applications such as biocompatible materials, textile functionalization, and coatings against UV-radiation or allowing microbial degradation, drug delivery, DNA delivery, enzyme immobilization etc[8, 9].

Nanoparticles are available in various forms like polymeric nanoparticles, solid-lipid nanoparticles, nanoemulsions, nanosponges, carbon nanotubes, micellar systems, dendrimers etc[10].

Nanosponges are a novel class of hyper-crosslinked polymer based colloidal structures consisting of solid nanoparticles with colloidal and nanosized cavities. Some of the well known nanosponges are titanium based nanosponges, silicon nanosponge particles, hyper-crosslinked polystyrene nanosponges and cyclodextrin based nanosponges[11-14]. Nanosponges solubilizes poorly water soluble drugs and provides prolong release as well as improves the drug bioavailability by modifying the pharmacokinetic parameters of active constituents[15]. Nanosponges have the ability to load both hydrophilic and hydrophobic drug molecules because of their inner hydrophobic cavity and external hydrophilic branching, thereby offering unparalleled flexibility[16]. Nanosponges possess a three-dimensional network or scaffold[17].

By reacting polyesters (cyclodextrins) with appropriate crosslinking agents, a novel nanostructured material can be obtained, known as nanosponges[15, 18, 19].

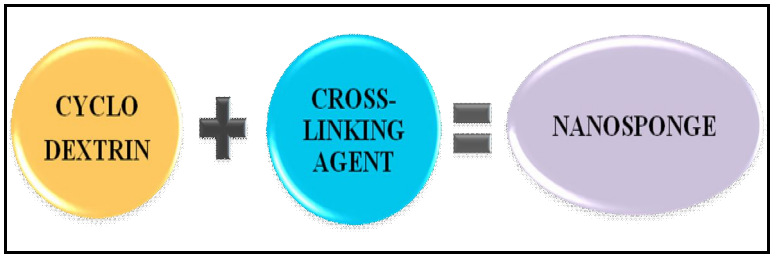

Figure 1: Formation of Nanosponges

The cyclodextrin to crosslinker ratio can be varied throughout the preparation period by improving the drug loading capacity and ultimately acquiring a tailored release profile. Highly porous nanomeric nature of nanosponges enables the drug molecules to orient themselves in inclusion as well as interact in a non-inclusion fashion, which offers higher drug loading when compared to their respective parent cyclodextrin molecules[20-22].

Nanosponges are solid in nature. They are found to be safe for oral and invasive routes; hence they can serve as an inherent carrier for drug delivery[22-24]. The tiny shape of nanosponges permits the pulmonary and venous delivery of nanosponges[25]. For oral delivery, the complex may be dispersed in a matrix of excipients (diluents, lubricants and anti-caking agents). For parenteral delivery, the complex may be simply carried in sterile water, saline or other aqueous solutions. For topical delivery they can be effectively integrated into topical hydrogel[26, 27]. Nanosponges are encapsulating type of nanoparticles which encapsulates the medicament within its core[28]. A nanosponge can circulate throughout the body until they reach the specific target site, stick on the surface and release the drug in a predictable manner[29].

Advantages:[24, 30, 31]

- Improved stability, elegance and formulation flexibility.
- Non-mutagenic, non-irritating, non-toxic, biodegradable.
- Provides extended release up to 12 hrs.
- Protects the active ingredient from degradation.
- Cost effective, easy to scale up.
- Masks unpleasant flavours.
- Nanosponges being soluble in water, encapsulation can be carried out within the nanosponges, by the addition of adjuvant reagents.
- Size of the nanosponges can be varied by modifying the proportion of crosslinker to polymer.
- Depending on the dosing requirement, the drug release profiles can be varried from fast, medium to slow release.
- Predictable release.
- Immiscible liquids can be incorporated.
- 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.

Characteristic Features of Nanosponges:[32]

- Nanosponges provide a range of dimensions (1 μm or less) with tunable polarity of the cavities.
- Nanosponges of specific size can be synthesized by changing the crosslinker to polymer ratio.
- They exhibit paracrystalline or crystalline forms, depending on the process conditions. Crystal structure of nanosponges plays a crucial role during complexation with drugs.
- Drug loading capacity depends on the degree of crystallization.
- Various drug loading capacities can be shown by paracrystalline nanosponges.
- They are nontoxic, porous particles, insoluble in most organic solvents and stable up to 300 °C.
- They are stable at the pH range of 1-11.
- They form clear and opalescent suspension in water.
- They can be reproduced by simple thermal desorption, extraction with solvents, by using microwaves and ultrasounds.
- Their three-dimensional structure allows capture, transportation and selective release of a variety of substances.
- They can be sited to different target sites because of their capacity to link with different functional groups.
- Chemical linkers permit nanosponges to bind preferably to the target site.
- By complexing with different drugs nanosponges can form inclusion and non-inclusion complexes.
- By adding magnetic particles into the reaction mixture, magnetic properties can also be imparted to nanosponges.

Methods of Preparation of Nanosponges:

1) Melt Method[32]**:**

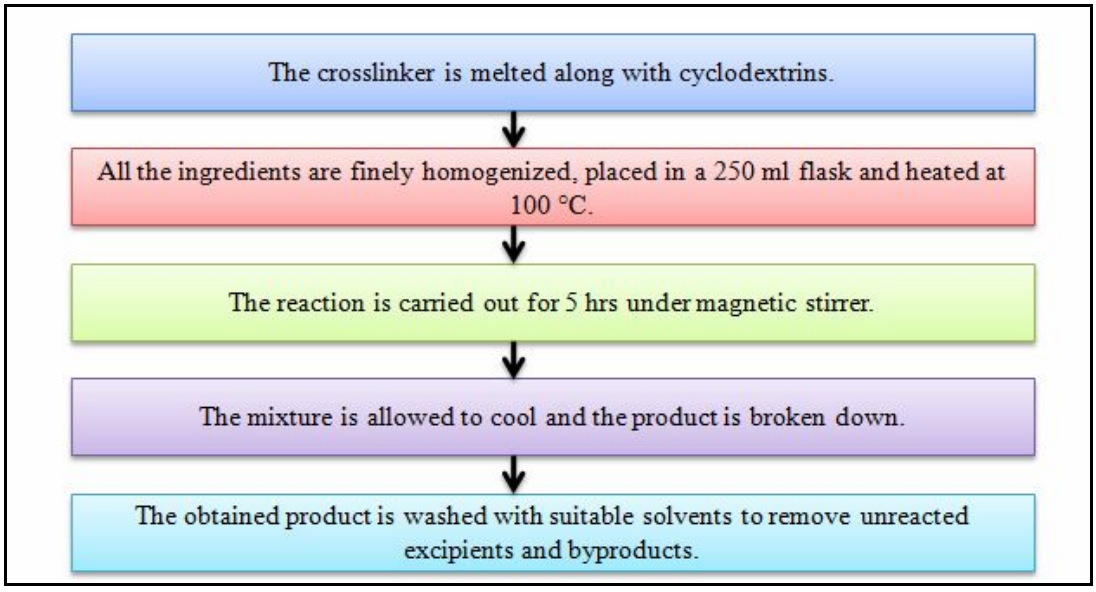

Figure 2: Schematic Representation of Melt Method

2) Solvent Method[25, 33]:

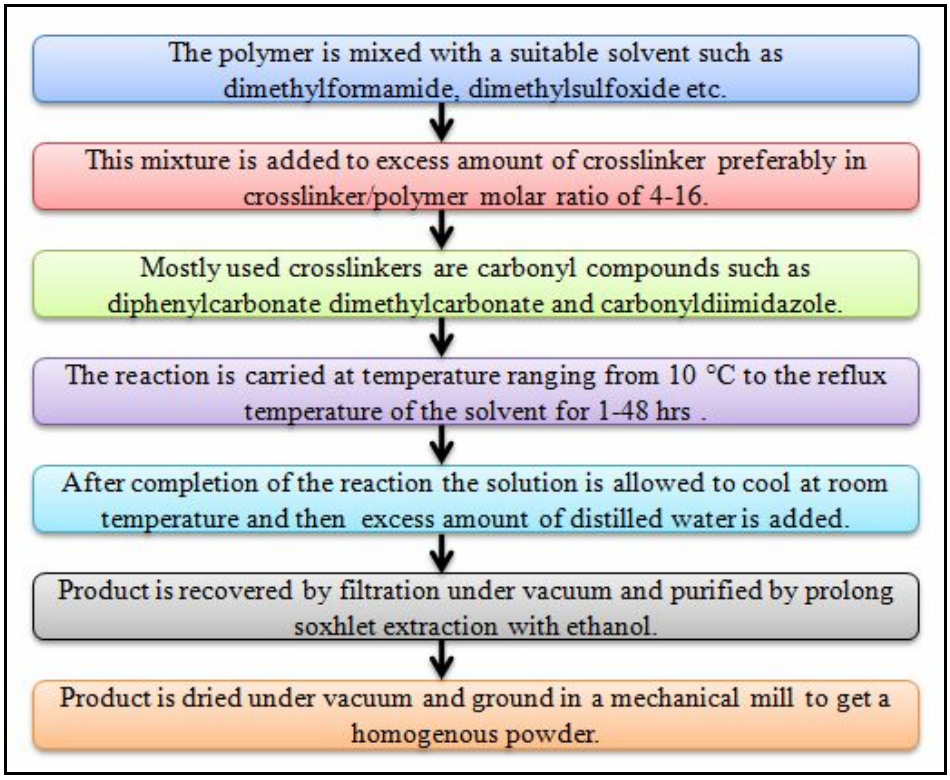

Figure 3: Schematic Representation of Solvent Method

3) Ultrasound Assisted Synthesis[23, 33]:

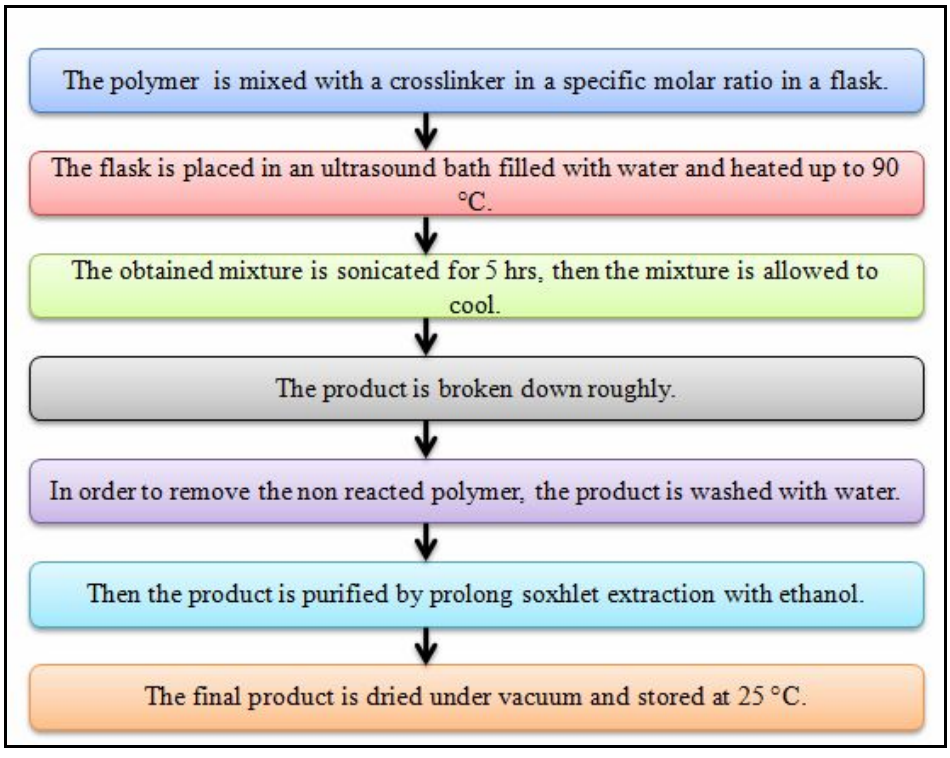

Figure 4: Schematic Representation of Ultrasound Assisted Synthesis

Loading of Drugs Into Nanosponges:[14, 25, 33]

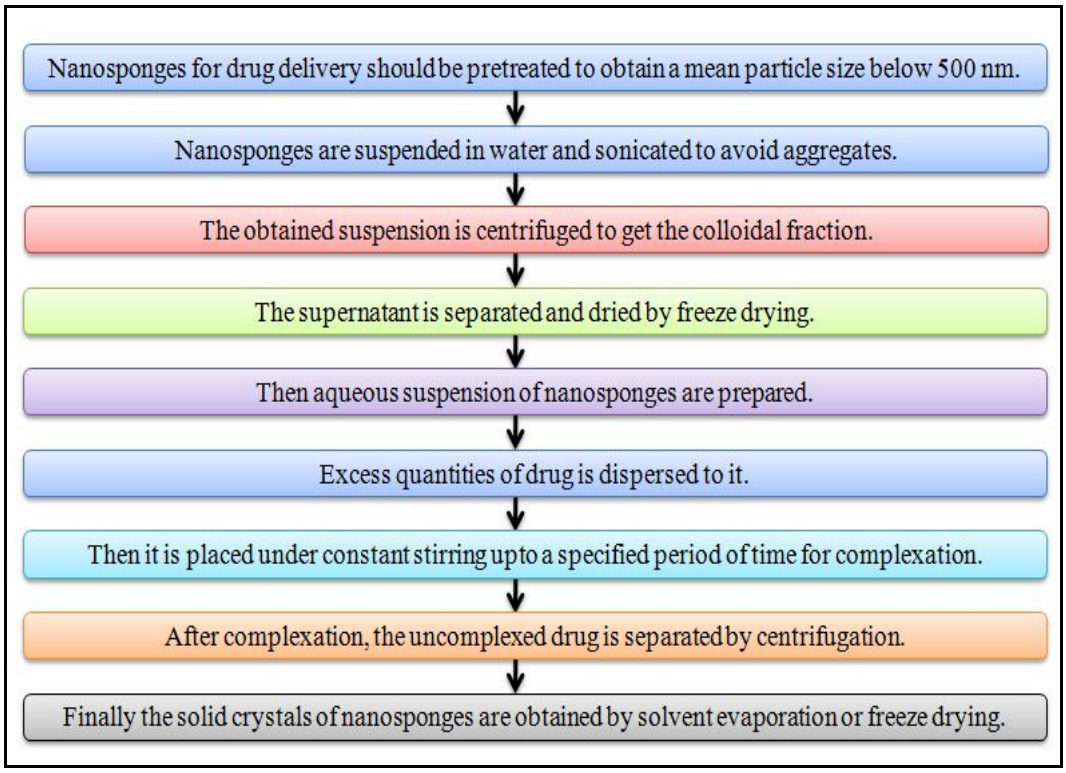

Figure 5: Schematic Representation of Loading of Drugs in to Nanosponges

Note: Crystal structure of nanosponges plays a key role in complexation with drug. Drug loading is better in crystalline nanosponges when compare to paracrystalline one.

Factors Influencing Nanosponge Formation:

Polymers and Crosslinkers:

The formation and the performance of nanosponges depend on the type of polymers and crosslinkers used. Efficient crosslinkers transform molecular nanocavities into three-dimensional, nanoporous structures. By changing the degree of crosslinking, either hydrophilic or hydrophobic components can be formulated, which possesses ability to trap targeted compounds. Water soluble or insoluble nanosponge structures could be resulted basing on the nature of crosslinkers. By using epichlorohydrin as a crosslinker hydrophilic nanosponges can be formulated. These can modify the rate of drug release, enhance drug absorption across biological barriers, and act as a potent drug carrier even in immediate release formulations. By using diphenylcarbonate or pyromellitic anhydride, diisocyanates, carbonyldiimidazoles and other crosslinkers hydrophobic nanosponges can be formulated and act as sustained release carriers for water soluble drugs including peptides and proteins.

Types of Drugs and Medium Used for Interaction:

Drug molecules to be complexed with nanosponges should have specific characteristics for successful entrappement into nanocavities. Drug molecules having molecular mass between 100 and 400 Daltons and less than five condensed rings can be easily entrapped into the nanocavity of nanosponges. When the drug loaded into nanosponges the drug molecules should have lesser melting points. The interaction between nanosponge cavities and drug molecules strongly depends on the medium; a hydrophilic medium will carry the organic guest molecules into hydrophobic cavities, while an organic solvent tends to release the organic molecules which are trapped in nanosponges. These strong interactions between host and guest molecules depend on mutual matching of polarity, size, hydrophobic environment and structural properties.

Complexation Temperature:

Temperature changes affect the stability constant of a complex and these are inversely correlated. With a rise in temperature, the magnitude of apparent stability constant decreases due to reduction in drug/ nanosponge interaction. Hence, a proper control over the temperature should be maintained when nanosponges are prepared.

Degree of Substitution:

Complexing ability of nanosponges, are affected by the type, number and position of the substituents on the polymeric molecule. The type of substitution is important in cyclodextrin derivatives because β-cyclodextrin derivatives are available in various forms. When complexed together with the help of a crosslinking agent, different functional groups would yield different types of complexed material (β-cyclodextrin nanosponges, cyclodextrin-carbamate nanosponges, cyclodextrin-carbonate nanosponges, etc). Higher the number of substituents, higher the crosslinking ability. Increase in the degree of crosslinking leads to formation of highly porous nanosponges due to more interconnections between polymers forming a mesh type network. Production conditions effects position of the substitution. A change in the production process leads to occupy different positions by the functional group on the parent compound which yields materials with different physicochemical properties[32].

Types of Nanosponges:[11-14, 21, 34-37]

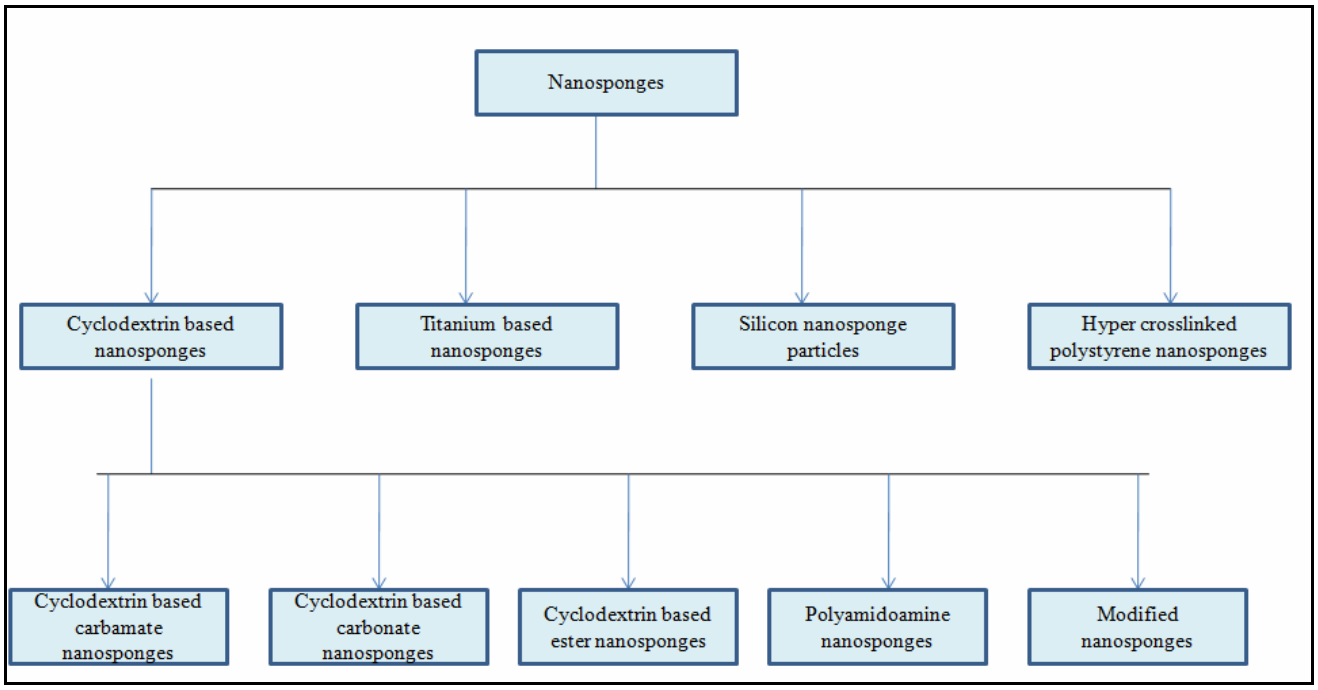

Figure 6: Types of Nanosponges

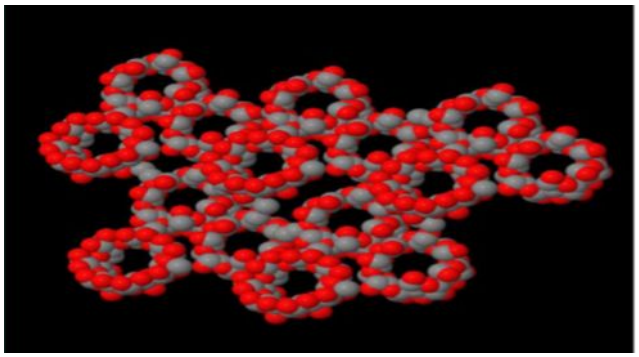

Figure 7: Molecular Structure of Cyclodextrin Carbonate Nanosponges[38]

Characterization of Nanosponges:[21, 28, 33, 39-46]

Table 1: Characterization Parameters along with their Objectives

S. No.	Charecterization parameters	Objective
1	Solubility study	Determines the drug concentration by using HPLC.
2	Porosity	Performed to check the amount of nanochannels and nanocavities formed.
3	Microscopic studies	To study the morphology and surface topography Scanning electron microscopy and Transmission electron microscopy are used.
4	Loading efficiency	Determined by the quantitative estimation of drug loaded into nanosponges.
5	Particle size and polydispersity	By dynamic light scattering using 90Plus particle size reequipped with 'MAS OPTION' particle sizing software, the particle size is determined. By using this mean diameter and polydispersity index are determined.
6	Zeta potential	Zeta potential measurement involves examination of the electric potential. Stability of the formed nanosponges is estimated by zeta potential.
7	Drug release kinetics	Drug release is calculated to determine the release pattern.
8	Swelling and water uptake	These are determined by soaking the prepared nanosponges in aqueous solvent.
9	Saturation state interaction	This study is carried out to find out the drug loading in a saturated state using UV-spectroscopy.
10	Thermo analytical methods	This method examines whether the drug substance undergoes any changes (like melting, evaporation, decomposition, oxidation or polymorphic transition) before the thermal degradation of the nanosponge.
11	X-ray diffractometry	It is used to detect inclusion complexation in the solid state.
12	Infrared spectroscopy	It is used to determine the interaction between nanosponges and the drug molecules in the solid state.
13	Thin layer chromatography	It helps in identifying the complex formation between the drug and nanosponge.
14	Raman spectroscopy	It is used to study the molecular structures.

Applications of Nanosponges:

Nanosponges have many applications in the pharmaceutical field due to their biocompatibility and versatility. Some of them are as follows.

a) Nanosponges in Solubility Enhancement:

Presence of crosslinking agent and cyclodextrin cavities in the nanosponge structure favours interaction with active molecules. These features permit several substances to be included and get solubilized in the formed cavities. Reduction in drug crystallinity occurs by preparing inclusion complexes or solid dispersions with cyclodextrins which enhances drug solubility or rate of dissolution of poorly water soluble drugs. The hydrophobic functionality of the complex hides in the interior cavity of the cyclodextrin while hydrophilic hydroxyl groups on the external surface remain exposed to the environment, the net effect is that a water soluble complex is formed[32].

Swaminathan *et al*. studied a formulation of itraconazole (BCS Class II drug that had a dissolution rate limited poor bioavailability) in nanosponges. Nanosponges improved the solubility of the drug more than 27-fold and exceeded to 55-fold when copolyvidonum was added as a supporting component of the nanosponge

formulation. Nanosponges solubilized the drug by possibly masking the hydrophobic groups of itraconazole, by increasing the wettability of the drug, and/or by decreasing the crystallinity of the drug[20].

b) Nanosponges in Drug Delivery:

Nanosponges have spherical shape and nanomeric in size making them ideal in preparing various dosage forms like topical, parenteral, aerosol, tablets and capsules[10]. Telmisartan (Telmisartan is a BCS Class II drug having dissolution rate limited bioavailability) is incorporated into the nanosponges. It is found that highest solubility and *in vitro* drug release is observed in inclusion complex[47]. Paclitaxel (BCS Class II drug having dissolution rate limited bioavailability) used for cancer chemotherapy having poor water solubility. β-cyclodextrin based nanosponges, to deliver paclitaxel is used as an alternative to cremophor EL because cremophor reduces the paclitaxel tissue penetration. The biological effect of paclitaxel *in vitro* is highly enhanced by nanosponges, not only its cytotoxicity but also the intracellular paclitaxel concentration is significantly enhanced when compared to plain paclitaxel after 72 hrs incubation[48]. Econazole nitrate which is an antifungal agent used topically to relive the symptoms of superficial candidasis, dermatophytosis and skin infections. When econazole nitrate is applied to the skin, adsorption is not significant and requires high concentration of active agents to be incorporated for effective therapy. Thus, econazole nitrate nanosponges are prepared by emulsion solvent diffusion method and these nanosponges are loaded in hydrogel as a local depot for sustained drug release[26].

c) Nanosponges for Protein Delivery:

The major obstacle in protein formulation development is the maintenance of the native protein structure both during the formulation process and upon the long term storage[49]. Swaminathan *et al*. reported that new swellable cyclodextrin based poly (amidoamine) nanosponges named nanosponges 10 and nanosponges 11, were synthesised by cross-linking β-cyclodextrins with either 2, 2-bis-acrylamido aceticacid or a short polyamido-amine chain deriving from 2, 2-bisacrylamido acetic acid and 2-methyl piperazine respectively. The prepared β-cyclodextrin based poly (amidoamine) nanosponges were found to be stable at 300 °C and high protein complexation capacity was also observed[50].

d) Nanosponges in Enzyme Immobilization:

The enzyme immobilization is particularly relevant for lipases, as it improves their stability and modifies properties like enantio selectivity and reaction rates[51]. As a consequence, the demand for new solid supports, suitable for family of enzymes is constantly growing. For this Boscolo *et al*. reported that high catalytic performances of *Pseudomonas fluorescens* lipase adsorbed on a new type of cyclodextrin based nanosponges[52].

e) Nanosponges as a Carrier for Delivery of Gases:

In diagnostic, treatment purpose gases play a key role in medicine. Hypoxia (deficiency of adequate oxygen supply) is related to various pathologies, from inflammation to cancer. Sometimes it can be difficult to deliver oxygen in appropriate form and doses in clinical practice. Cavalli *et al*. developed nanosponge formulations as oxygen delivery systems for topical application which were having the ability to store and to release oxygen slowly over time[53].

f) 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 gamma-oryzanol loaded nanosponges a gel and an O/W emulsion are formulated[54].

g) Modulating Drug Release:

The major drawback of most of the conventional, commercially available drug delivery systems is frequent administration. However, a drug loaded into the nanosponge is retained and released slowly over time. Vyas *et al*. reported that hydrophilic cyclodextrin nanosponges are employed to modify the drug release rate, to

enhance the drug absorption across biological barriers, as a potent drug carrier in immediate release formulations. Hydrophobic cyclodextrin nanosponges are utilized as sustained release carriers for water soluble drugs, including peptide and protein drugs and also used as carriers of drugs such as doxorubicin (an anticancer drug), and also they may protect the drug during its passage through the stomach. This drug is released very slowly at pH 1.1, whereas release is faster if pH is raised to 7.4[55].

h) Effective Delivery Carriers:

Antitumor drugs such as paclitaxel, camptothecin and tamoxifen shows bioavailability problem (because of poor aqueous solubility) hence cyclodextrin nanosponges can be used as vehicles inorder to improve their solubility as well as bioavailability. Torne *et al*. investigated antiproliferative effect of drugs incorporated into nanosponges and studied on various cell lines. Complexes showed high effect than that of the drug alone[15]. After loading the drug in nanosponges the mean absolute bioavailability of paclitaxel was increased and found to be 2.5-fold higher than the plain drug[56].

Other Applications of Nanosponges:

Cyclodextrin based nanosponges strongly bind to organic molecules and remove them from water even at very low concentrations. By using selective combination of polymer and cross linker the same concept is useful for elimination of bitter components from grape fruit juice. The microporous hyper-crosslinked nanosponges can be used in selective separation of inorganic electrolytes by size exclusion chromatography. The three dimensional nanosponges plays a key role in the fractionalization of peptides for proteomic applications. Nanosponges can soak up biomarkers for diagnosis purposes. Nanosponges also can harvest rare cancer marker from blood[57].

Drugs Formulated as Nanosponges:57

Table 2: Examples of Drugs Formulated as Nanosponges

S. No.	Drug	Nanosponge vehicle	Therapeutic benefit
1	Antisense oligonucleotides	Sodium alginate Poly L-lysine	Cancer therapy Viral infection Pathologic disorders
2	Camptothecin	β-cyclodextrin	Cancer
3	Dexamethasone	β-cyclodextrin	Brain tumors
4	Econazole nitrate	Ethylcellulos Polyvinylalcohol	Antifungal
5	Itraconazole	β-cyclodextrin Copolyvidonum	Antifungal
6	Paclitaxel	β-cyclodextrin	Cancer Inflammation Cardiovascular diseases Dermatitis
7	Resveratrol	β-cyclodextrin	Gonorrhea Fever Hyper lipidemia
8	Tamoxifen	β-cyclodextrin	Breast cancer

Future Prospects:

Nanosponges are effective carriers for targeted delivery of drugs to lungs, liver and spleen. A simple approach for preparing Palladium/Silver and Palladium/Silver/Aluminium nanosponges, which contain network nanowires has been reported in a study. This strategy demonstrates for the first time preparation of alloy nanosponges with network nanowires via self regulated reduction of sodium dodecylsulfate (SDS) and adding the second or third metal salt during synthesis without additional reducing agent. Fortunately, the field of nanosponges continues to grow interest within the chemical research community with major discoveries as well as new scientific challenges. Further studies on kinetics and biochemical interactions of nanosponges within organisms are imperative. These studies must include, at least, research on nanosponges translocation pathways,

accumulation, short and long-term toxicity, their interactions with cells, the receptors and signaling pathways involved, cytotoxicity, and their surface functionalization for an effective phagocytosis. Existent knowledge on the effects of nanosponges exposure on the lymphatic and immune systems, as well as various organs, is sparse. For example it is known that nanosponges exposure is able to modulate the response of the immune system to different diseases, however much research is needed in order to better understand to what extent this occurs and the full implications of risk groups (age, genotype). In order to clarify the possible role of nanosponges in diseases recently associated with them (such as Crohn's disease, neurodegenerative diseases, autoimmune diseases, and cancer), nanoscale characterization techniques should be used to a larger extent to identify nanosponges at disease sites in affected organs or tissues, and to establish pertinent interaction mechanisms.

Conclusions:

Nanosponges are novel class of biocompatible, versatile drug carriers as they carry both hydrophilic and hydrophobic drugs by forming inclusion and non-inclusion complexes. They deliver the drugs by various routes like oral, topical, and parenteral routes. Nanosponges release the drug in a controlled and predictable manner to the target site, thus increase the bioavailability of the drug. By controlling the polymer to crosslinking agent ratio, the particle size and release rate can be modified to better fit the application. Nanosponges can be used to improve the aqueous solubility of lipophilic drugs, and protect the drugs from physicochemical degradation. They have been found to be promising materials for immediate technological use for drug entrapment and as novel drug carriers. Besides their applications in the drug delivery field, potential applications exist for cosmetics, biomedicine, bioremediation processes, agro chemistry, catalysis etc. Drugs delivered by nanosponges were proved to be safe and effective and the pharmaceutical industries will be greatly benefited if clinical studies can prove their potential for human uses.

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