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NANOSPONGES: RECENT TECHNIQUE FOR ENHANCEMENT OF SOLUBILITY

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ABSTRACT
In recent years, nanosponges (NS) have gained tremendous impetus in drug delivery through nanotechnology. Nanosponges are capable of providing solutions for several formulation related problems. Nanosponges are tiny sponges with a size of about a virus, which can be filled with a wide variety of drugs. These tiny sponges can circulate around the body until they encounter the specific target site and stick on the surface and begin 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. Another important character of these sponges is their aqueous solubility; this allows the use of these systems effectively for drugs with poor solubility. Owing to their small size and porous nature they can bind poorly-soluble drugs within their matrix and improve their bioavailability. They can be crafted for targeting drugs to specific sites, prevent drug and protein degradation and prolong drug release in a controlled manner.

KEYWORDS: Nanosponges, Cyclodextrins, Bioavailability.

INTRODUCTION
Nanosponges are a novel class of hyper cross-linked polymer based colloidal structures made of sub-microscopic particles with cavities a few nanometres wide. The renowned examples of Nanosponges are titanium based Nanosponges, silicon nanosponges, hyper cross-linked polystyrene nanosponges, cyclodextrin based nanosponges (CD-NS).

In the field of pharmaceuticals, the era of nanoporous materials comprised of cyclodextrins, started in 1992, the first studies on cyclodextrin microparticles were reported by Loftsson et al. Cyclodextrin nanosponges for pharmaceutical use were reported by Cavalli et al. and Swaminathan et al. Many drugs are hydrophobic and present a challenge for effective in vivo delivery. Shrinking materials to nano size has profoundly improved the efficacy of such drugs. A number of polymers have been investigated and used as Novel drug delivery systems (NDDS). NS when used for target specific drug delivery can improve therapeutic response resulting in minimum side-effects. “Tagging” drug-loaded NS ensures desired pharmacological response by targeting disease affected cells, while leaving the healthy ones unharmed.10 Drugs included within the NS pores are shielded from premature destruction and drug stability is enhanced.[1]

Nanosponges are tiny mesh-like structures in which a large variety of substances can be encapsulated. They have a proven spherical colloidal nature, reported to have a very high solubilization capacity for poorly soluble drugs by their inclusion and non-inclusion behavior. Nanosponges have recently been developed and proposed for drug delivery. Nanosponges can solubilize poorly water soluble drug and provide prolonged release as well as improving drugs bioavailability.[2] Nanasponges are able to load both hydrophilic and hydrophobic drug molecules because of their inner hydrophobic cavities and external hydrophilic branching, thereby offering unparalleled flexibility. Nanosponges are more like a three dimensional network or scaffold. The nanosponges are a three-dimensional scaffold (backbone) or network of polyester that are capable of degrading naturally. These polyesters are mixed with a cross linker in a solution to form Nanosponges. Here, the polyester is generally biodegradable, so it breaks down in the body moderately. Once the scaffold of nanosponges breaks down it releases the drug molecules which is loaded, in a derogatory fashion.[3]

Advantages of Nanosponges[4]
1. Increase aqueous solubility of the poorly water-soluble drug.
2. Nanosponges can release the drug molecules in a predictable fashion.

3. Because of their tiny pore size (0.25 μm), bacteria cannot penetrate the nanosponges an they act like a self-sterilizer.
4. Nanosponges drug delivery system are non-irritating, nonmutagenic and non-toxic.
5. Nanosponges help to remove the toxic and venom substance from the body.
6. Nanosponges drug delivery system minimize side effect.
7. Increase formulation stability and enhance the flexibility of the formulation.
8. Reduce dosing frequency.
9. Better patient compliance.
10. Nanosponges complexes are stable over wide range of pH (i.e. 1 and a temperature of 130 °C.

Disadvantages of Nanosponges[4]

1. Nanosponges have the capacity of encapsulating small molecules, not suitable for larger molecules.
2. Dose dumping may occur at times.

FACTORS INFLUENCE NANOSPONGE FORMATION[5]

a. Type of 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 drug molecule of particular size.

b. Type of drugs: Drug molecules to be complexed with nanosponges should have certain characteristics mentioned below.

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

c. Temperature: Temperature changes can affect Drug/Nanosponge complexation. In general, increasing in the temperature decreases the magnitude of the apparent stability constant of the Drug/Nanosponge complex may be due to a result of possible reduction of drug/nanosponge interaction forces, such as van-der Waal forces and hydrophobic forces with rise of temperature.

d. Method of preparation The method of loading the drug into the nanosponge can affect Drug/Nanosponge complexation. However, the effectiveness of a method depends on the nature of the drug and polymer, in many cases freeze drying was found to be most effective for drug complexation.

e. Degree of substitution: The complexation ability of the nanosponge may be greatly affected by type, number and position of the substituent on the parent molecule.

METHODS OF PREPARATION OF NANOSPONGES

1. Solvent method: In this method the polymer was mixed with a suitable solvent, in particular in a polar aprotic solvent such as dimethylformamide, dimethylsulfoxide. This mixture was added to excess quantity of the crosslinker, preferably in crosslinker/polymer molar ratio of 4 to 16. The reaction was carried out at temperature ranging from 10 °C to the reflux temperature of the solvent, for time ranging from 1 to 48 h. Preferred cross linkers are carbonyl compounds (dimethyl carbonate and carbonyl diimidazole). After completion of the reaction, the solution was allowed to cool at room temperature, then the product was added to large excess of bidistilled water and recovered the product by filtration under vacuum and subsequently purified by prolonged Soxhlet extraction with ethanol. The product was dried under vacuum and grinded in a mechanical mill to obtain homogeneous powder.[6]

2. Ultrasound-assisted synthesis: In this method nanosponges were obtained by reacting polymers with crosslinkers in the absence of solvent and under sonication. The nanosponges obtained by this method will be spherical and uniform in size. The polymer was mixed and the crosslinker in a particular molar ratio in a flask. The flask was placed in an ultrasound bath filled with water and heated it to 90°C. The mixture was sonicated for 5 h. Then the mixture was allowed to cool and the product was broken roughly. The product was washed with water to remove the non reacted polymer and subsequently purified by prolonged Soxhlet extraction with ethanol. The obtained product was dried under vacuum and stored at 25 °C until further use.[7]

3. Loading of drug into Nanosponges: Nanosponges for drug delivery should be pretreated to obtain a mean particle size below 500nm. The Nanosponges were suspended in water and sonicated to avoid the presence of aggregates and then centrifuged the suspension to obtain the colloidal fraction. The supernatant was separated and dried the sample by freeze drying. The aqueous suspension of nanosponges was prepared and dispersed the excess amount of the drug and maintained the suspension under constant stirring for specific time required for complexation. After complexation, the uncomplexed (undissolved) drug was separated from complexed drug by centrifugation. Then the solid crystals of nanosponges was obtained by solvent evaporation or by freeze drying. Crystal structure of nanosponge plays a very important role in complexation with drug. A study revealed that paracrystalline nanosponges showed different loading capacities when compared to crystalline nanosponges. The drug loading is greater in crystalline nanosponges than paracrystalline one. In poorly crystalline nanosponges, the drug loading occurs as a mechanical mixture rather than inclusion complex.[8]

CHARACTERIZATION OF NANOSPONGES

1. Solubility studies: The most widely used approach to study inclusion complexation is the phase solubility method described by Higuchi and Connors, which examines the effect of nanosponges on the solubility of drug. Phase solubility diagrams indicate the degree of complexation. In this method the drug was added to an Erlenmeyer flask containing an aqueous solution of various percentages of nanosponges. The Erlenmeyer flask was stirred on a mechanical shaker at room temperature. When a steady state was reached, 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 obtained was analyzed to determine the drug concentration by high performance liquid chromatography.[9]

2. Microscopy studies: Scanning electron microscopy and transmission electron microscopy can be used to study the morphology and surface topography of the drug, nanosponges and the product (drug/nanosponge complex). The difference in crystallization state of the raw materials and the product observed under electron microscope indicates the formation of the inclusion complexes.[10]

3. Fourier transformer infrared spectroscopy: Fourier transformer infrared spectroscopy (FTIR) analysis is a primary tool for structure confirmation of NS10. Cross-linking in CD moieties can be evaluated using FTIR. The FTIR spectra of β-CD show characteristic peak of non-hydrogen-bonded O-H stretching at 3450 cm-1 due to presence of primary alcoholic groups. Absence of this peak in NS advocates that all free primary alcoholic groups of β-CD are utilized in the cross-linking process. In case of CD-NS prepared using diphenylcarbonate as cross-linking agent, the characteristic peak given by the carbonate group in DPC (1775 cm-1) shifts to 1750 cm-1 and other characteristic peaks of CD-NS are observed in the range of 1460–1600 cm-1 and 1270–1290 cm-1.[11]

4. Differential scanning Calorimetry: DSC analysis gives an explicit idea about molecular interaction of NS with the loaded drugs10. The endotherms of drug-loaded NS show decrease in enthalpy of drug due to decrease in its crystallinity. Such data is an important confirmation of interaction between the drug and NS.[11]

5. Drug loading and Entrapment efficiency: For drug loading experiment, excess of drug solution is incubated with a water dispersion of cyclodextrin nanosponges. This dispersion is shaken for approximate time at room temperature, filtered and the nanosponge aliquot is freeze dried. The product obtained after lyophillization is used to determine the amount of drug present in systems. For entrapment efficiency experiment, the drug loaded nanosponges are dispersed in solvent in which drug is soluble. It is then subjected to sonication for disruption of the complex so that the drug loaded into the nanosponges dissolves in the solvent. The amount of drug present is determined with the help of suitable analytical technique like UV-violet spectrophotometer and High Performance Liquid Chromatography (HPLC) techniques. The Entrapment efficiency can be calculated using following formula.[11]

$$\% \text{ Drug entrapment effificiency} = \text{DrugEncapsulated} / \text{DrugTotal} \times 100$$

6. Saturation state interaction: UV spectroscopy is used to find the saturated solution interaction study. To the fixed concentrations of drug, increasing concentrations of nanosponge solutions are added. Samples are then kept for overnight. Drug loading is determined by scaning of the formulation in UV range and by analyzing the shift of the absorbance maxima (λmax) in the spectra compared to pure drug.[12]

7. Phase Solubility Studies: To study inclusion complexation described by Higuchi and Connors, phase solubility study is widely used which detects the effect of a nanosponge on solubility of drug. Degree of complexation of drug to nanosponges can be studied with the help of phase solubility diagrams. Phase solubility constant can be determined by adding excess drug into suitable solvents to obtain saturated solutions. Blank nanosponges in various increasing concentration are treated with saturated drug solution. Because of increasing concentration more and more drug react with the nanosponges. Study is carried out until the equilibrium is obtained. A graph is plotted between NS concentration versus drug concentration and the type of plot is defined as per the Higuchi and Connors classification. Resulted stability constant value is the indication about the extent of interaction between nanosponges and the drug. As interaction of drug to nanosponges increase, dissolution rate and solubility of poorly water soluble drug increases.[13]

8. In vitro release studies: The release behaviour of the drug from nanosponges can be concluded by in vitro release study. Multi-compartment rotating cell in which donor compartment is filled with an aqueous dispersion of nanosponges containing the drug and receptor compartment filled with phosphate buffer at appropriate pH is used for this study. These two compartments are separated with a hydrophilic dialysis membrane. The receptor buffer is completely withdrawn at fixed time and replaced with fresh buffer. Using a suitable analytical method the amount of drug is determined and drug release is calculated.[14]

9. Porosity: Porosity gives the extent of nanochannels and nanocavities formed in the nanosponges. Helium pycnometer is used to study the porosity due to ability of helium gas to penetrate inter and intra-particular channels of material. The true volume of material can be determined from the extent of helium displacement. Percent porosity is calculated by the following formula.[14]

% Porosity (E) = Bulk volume- True volume/ Bulk volume X 100

10. Average diameter and polydispersity: Particle size analyser is used to determine the average diameter and polydispersity by applying the principle of dynamic light scattering (DLS) which is also known as photon correlation spectroscopy (PCS). PCS helps to correlate the variation in intensity of scattered light to particle size with auto-correlation function. DLS/ PCS considers all the particles as spherical and hence it measures the hydrodynamic diameter. By considering the effective viscosity, refractive index of the dispersing medium and temperature, DLS/PCS gives the particle size. Therefore, the measured particle size would be a parameter found after taking all factors under consideration. It is always preferable to have qualitative analysis which can be done by examining those particles with analytical technique such as scanning electron microscopy (SEM), transmission electron microscopy (TEM) or environmental scanning electron microscopy (ESEM) analysis. Particle size and morphology can be done using SEM, TEM or ESEM by dispersing sample in water or in other suitable solvents.[15]

11. Water uptake and swelling studies: Water uptake and swelling study is done for the swellable polymer-based NS. This can be done by direct soaking NS in water. Following equations are used to calculate the swelling index and water uptake respectively.[15]

Percent swelling= St/ S0 X100

Where, St = cylinder marking at specified time point after soaking and

S0 = initial cylinder arking before soaking.

Percent water uptake = Mt/ M0 X 100

Where, Mt = mass of hydrogel after specific time and M0 = initial mass of dry polymer.

12. Zeta potential: Zeta potential is a measure of surface charge. It can be measured by using additional electrode in the particle size equipment.[24] 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.[16]

13. 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.[16]

APPLICATIONS OF NANOSPONGES

a. Solubility enhancement: About 40% of novel drugs are poorly soluble in water, which obstructs their clinical application. Low water solubility of any drug is one of the great key limit for the formulation development. For oral drug administration it is necessary for the drug to be in the solution form at the site of the action to get absorbed from the GIT to the systemic circulation. Inclusion complexation of drug with the cyclodextrin is widespread option for enhancing water solubility as well as the bioavailability of lipophilic drugs. For moderately polar or hydrophilic drugs, this approach is less effective.[2] Wetting and solubility of molecules in water can be greatly improved with CD-NS. Chemical interaction of drug with CD based NS or inclusion complexation diminishes drug crystallinity concurrently leading to enhanced solubility or dissolution rate. The enhanced solubilisation can be attributed to masking of hydrophobic groups of less soluble drug inside cyclodextrin core; rendering hydrophilic groups exposed on outer side thus forming a hydrophilic complex. Amongst various CD derivatives, methylated CDs has comparatively low molar substitution and are potential solubilizers. CD based NS can also be used in enhancing drug release.[1]

b. Protein delivery: In recent years, protein and peptide delivery have received remarked attention. However, the major challenges in administration of proteins is their property to undergo denaturation, aggregation, short half-life, rapid enzymatic degradation, large molecular mass, poor bioavailability. Encapsulation of proteins and peptides into CD-NS can improve their stability and pharmacokinetic properties. Swellable cyclodextrin-based poly (amidoamine) nanosponges (PAA-NS) by cross-linking β-CD with either 2,2-bis-acrylamidoacetic acid or with poly(amidoamine) chain were synthesized for delivery of Bovine serum albumin (BSA) as a model protein.[11] The nanosponges showed extended release of BSA over a period of 24 h with remarkable swelling capacity and stability up to 250-300°C. The nanosuspensions of both PPA-NS prepared by using high pressure homogenization showed high protein encapsulation efficiency (more than 90%) and controlled release of protein. The gel formulations were stable for 72 h. A smart polymer-based formulation of lysozyme impregnated nanosponges to deliver lysozyme for antimicrobial action and calcium in hypocalcemia condition is reported to show controlled release over 24 h.[17]

c. Protection of drug from light or enzymes: Nanosponges can be used as carriers to protect drug molecules from light, chemical- and enzyme induced degradation. The photo-protection application of CD-NS using a light sensitive drug, 5-fluorouracile was studied by.[18] They reported that the protection of drug and maintenance of its cytotoxicity against MCF-7 cells can be achieved by encapsulating 5-fluorouracile in nanosponges. Another molecule camptothesin was studied by Swaminathan et al., 2010 for protection potential of CD-NS. The use of camptothesin is limited because of its poor solubility as well as high chemical instability due to susceptible of lactone ring of the molecule to hydrolysis under physiological conditions. It

was observed that the shelf-life and release of drug is prolonged in camptothesin loaded CD nanosponges. Alongi et al., 2011 studied the interactions between β-cyclodextrin nanosponges and two different UV stabilizers namely, 2-hydroxy-4(octyloxy)-benzophenone and triphenyl phosphite) in the photooxidation of polypropylene exposed to UV light. The combination of nanosponges with 2-hydroxy-4(octyloxy)-benzophenone showed threefold increase in oxidation induction time of polypropylene[19]

d. Diagnostic tools: Supramolecular chemistry has dual property of self- assembly and molecular recognition. β-CD is one of the most commonly used supramolecular building blocks for production of variety of materials for biomedical applications. Developed supramolecular nanoparticulate cyclodextrin/adamantine cross-linked polymer, grafted with polyamidoamine for applications in molecular diagnostics and therapeutics. Supramolecular nanostructures may be engineered to possess on-demand bio-responsibility for prevention, diagnosis, and treatment of human diseases. Prolonged accumulation problems associated with synthetic polymers could be overcome using cyclodextrin nanosponges with varying degrees of cross-linkers. The higher number of hydroxyl groups available for cross-linking could be used to produce thermosensitive nanosponges by tagging gold molecules to these hydroxyl groups. Ideal attributes of high biocompatibility, prolonged circulation in bloodstream, broad payload spectrum from small molecules to biomacromolecules, unique size characteristics for tissue permeability, excellent formulation capability, and easy tailoring/decoration for active targeting offered by cyclodextrin nanosponges make them useful as diagnostic tools.[20]

e. Prostheses and Implants: Prostheses and implants have become the medication of choice in cardiac, diabetic, and cancer treatment. They are also used for fixing broken bone, ligament, and for providing vision to the visually impaired bionic eyes. Cyclodextrin polymers are being used in these delivery systems long ago. To replace or bypass damaged arteries polyester vascular grafts are used. These polyester vascular prosthesis (Polythese) can be functionalized with CD-NS to attain the controlled release of antibiotics such as ciprofloxacin, vancomcyin, and rifampicin in order to minimize the risk of infection during and after surgical interventions.[21] CD-NS has also been studied for use in dentistry. Cyclodextrin nanosponges provide improved bonding material to restore teeth aesthetically thus, preventing formation of staining and other interfacial defects.

f. Cosmetics: The applications of Gamma-oryzanol, a ferulic acid ester mixture used in sunscreen, is limited by its high instability and photodegradation. Sapino et al., 2013 prepared a gel and an o/w emulsion of Gamma-oryzanol loaded nanosponges. The Gamma-oryzanol loaded NS showed a good protection from photodegradation. A high skin accumulation of gamma-oryzanol was observed over time in in-vitro permeability and accumulation studies carried out on porcine skin. CD-based nanosponges can trap and prolong the release of essential oil molecules such as linalool. It can also be used to eliminate or control the foul body odour formed due to sweating in toes and underarms, prevent degradation of odour producing terpenes in the perfumes. An interesting application of CD-NS in oral cosmetic is that they sustain the release of volatile ingredients, thus increasing the duration of fresh feel. NS can be used in cosmetic products such as rouge or lipsticks to give long-lasting effect.[22]

g. Gas delivery system: Gases form an important part of medical regimen either for diagnostic or therapeutic purpose. The deficiency of adequate oxygen supply, named hypoxia, is related to various pathologies, from inflammation to cancer. The amount of effective oxygen delivered has to be carefully regulated. Cavalli et al. developed a nanosponge formulation for oxygen delivery through a topical application. Safety of NS was studied in Vero cells. The NS released oxygen in presence as well as in the absence of ultrasound (US). Oxygen permeation through a silicone membrane was studied using a CD-NS hydrogel combination system. NS can be formulated as potential gas delivery systems showing the ability to store and release oxygen slowly over time.[20] Further, Trotta et al. reported CD-NS prepared using carbonildiimidazole cross-linker for encapsulation of 1-methylcyclopropene, Oxygen and Carbondioxide.

h. Blood purification: Kidney failure is marked by accumulation of many middle molecular weight toxins (MMW 10–20 kDa) such as uraemic toxins β2-microglobulins (MW 11.8 kDa). Blood purification has been long done using haemodialysis. Dialysis Membranes allow permeation of low molecular weight solutes but the removal of potent MMW toxins remains incomplete. Therefore, in one of the studies it was sought to investigate better techniques for blood purification. An alternative to haemodialysis was to bring the blood extracorporeally in contact with a biocompatible adsorbent packed in a column. Such a column was available in Japan but it allowed non-specific hydrophobic interactions and the therapy was also expensive. Malik et al. investigated a more specific technique for selectively allowing the MMW toxins to diffuse into the porous matrix while size-excluding serum albumins and hence avoid column flooding. They synthesized and characterized the size-selective nanoporous polymeric adsorbents of cross-linked polystyrene co-divinylbenzene with median diameters between 40 and 300 μm, with an enhanced proportion of mesopores in the range of 4–10 nm. They used a membrane emulsification technique having the ability of adsorption of MMW uraemic toxins (size range 0.5–20 kDa), 2-microglobulin (11.8 kDa), whilst size-excluding larger blood proteins like serum albumin (MW 69 kDa).[19]

i. Nanosponges for drug delivery: Because of their nanoporous structure, nanosponges can advantageously carry water insoluble drugs (Biopharmaceutical Classification System class-II drugs). These complexes can be used to increase the dissolution rate, solubility and stability of drugs, to mask unpleasant flavors and to convert liquid substances to solids. β-Cyclodextrin based nanosponges are reported to deliver the drug to the target site three to five times more effectively than direct injection.[23] 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.[24]

j. Nanosponges as a carrier for biocatalysts and in the delivery and release of enzymes, proteins, vaccines and antibodies: Many industrial processes involving chemical transformation are associated with operational disadvantages. Non-specific reactions lead to low yields, and the frequent need to operate at high temperatures and pressures requires consumption of large amounts of energy, and very large amounts of cooling water in the down-stream process. All these drawbacks can be eliminated or significantly reduced by using enzymes as biocatalysts. These enzymes operate under mild reaction conditions, have high reaction speed, and are highly specific. They have a beneficial effect on the environment because they reduce energy consumption and reduce production of pollutants.[3] The catalytic activity of enzyme depends mainly on the correct orientation of the active site. Proteins, peptides, enzymes and derivatives thereof also can be used in the biomedical and therapeutic field. Proteolytic enzymes can be used to treat cancer or type I mucopolysaccharidosis, while DNA and oligonucleotides are used in gene therapy. The administration of these molecules present various problems and limitations. Most protein drugs are poorly absorbed through the biological membranes due to the some factors such as large molecular size, hydrophilic nature, degree of ionization, high surface charge, chemical and enzymatic instability and low permeability through mucous membranes. Following intravenous administration, protein molecules may be rapidly cleared from blood, bind to plasma proteins, and sensitive towards proteolytic enzymes. With oral administration bioavailability is the problem. Various approaches exist for therapeutic use, such as increasing the dose or using absorption promoters, which can cause toxicity problems.[25]

k. Other applications of Nanosponges: Nanosponges based on cyclodextrins can strongly bind organic molecules and remove them from water even at very low concentrations. The same concept can be useful for elimination of bitter components from grape fruit juice by selective combination of polymer and crosslinker. The microporous hyper cross linked nanosponges have been used in selective separation of inorganic electrolytes by size exclusion chromatography. The three dimensional nanosponges will play important role in the fractionalization of peptides for proteomic applications. Nanosponges can be used as carrier for gases like oxygen and carbon dioxide. These nanosponges could be useful for many biomedical applications. In particular the oxygen-filled nanosponges could supply oxygen to the hypoxic tissues which are present in various deseases. Nanosponges can selectively soak up biomarkers for the diagnosis. One study concluded that Nanosponges could harvest rare cancer marker from blood.[23]

Strategies for using Nano sponges for Improving Solubility and Dissolution Characteristics

To build a nano sponge structure that improves the solubility of hydrophobic medications, select appropriate polymers (such as cyclodextrins) and cross-linking agents (such as diphenyl carbonate).[26]

Due to their increased surface area, smaller nano sponges can interact with the dissolving media more effectively, increasing the solubility and dissolution rates of the medication.[27]

By encasing hydrophobic medications within their porous structure, nano sponges efficiently increase the solubility of these medications and increase their bioavailability.[20]

Improvements in drug wettability and enhanced dissolving properties result from surface modification of nano sponges with hydrophilic groups.[28]

Therapeutic efficacy can be increased by controlling the cross-linking density of nano sponges to enable either immediate or prolonged medication release.[29]

To ensure regular drug release and improved stability, stabilisers and co-polymers are essential for preserving the structural integrity of nano sponges.[28]

In order to maximise absorption and therapeutic results, pH-sensitive micro sponges are made to release the medication in certain gastrointestinal tract regions.[29]

The synergistic increases in drug solubility and dissolving characteristics are provided by hybrid systems that combine nano sponges with other nanocarriers.[29]

Recent Advancement in Nanosponges for increasing solubility and Dissolution

1. **Cyclodextrin-Based Nanosponges (CDNS)**: The solubility of hydrophobic medicines is being enhanced by the use of cyclodextrin nanosponges. They greatly increase the drug molecules' water

solubility and dissolution rates by forming inclusion complexes with them. This is especially helpful for medications that have low water solubility.[30]

2. **Polymeric Nanosponges in Tablet Form**: Improved solubility and dissolution have been demonstrated when nanosponges are formulated into polymeric tablet shapes. By encapsulating pharmaceuticals within a nanosponge structure, these tablets—which frequently use polymers like β-cyclodextrin—offer a regulated and enhanced drug release mechanism.[31]
3. **Ultrasound-Assisted Synthesis**: By using no solvents, this sophisticated synthesis technique yields spherical, very uniform nanosponges. The drug release profile is more predictable and efficient due to the homogenous size and structure of these nanosponges, which also improve drug loading and dissolution rates.[32]
4. **Hyper-Cross-Linked Nanosponges**: The efficiency and stability of nanosponges are increased by hyper-cross-linking. A regulated release mechanism and improved solubility of the pharmaceuticals are provided by the interconnected gaps in these nanosponges, which can store different drug molecules.[18]
5. **Multi-Component Nanosponges**: Multi-component nanosponges, which entail packing several medications into a single nanosponge, have been the subject of recent research. The overall efficacy of treatment has been demonstrated to be improved by this strategy, which also improves the solubility and dissolution of combined medicines.[31]

These advancements have significant implications for improving the bioavailability and therapeutic effectiveness of poorly soluble drugs.

CONCLUSION

Nanosponges are versatile drug carrier system as they carry both hydrophilic and hydrophobic drugs by forming inclusion and non inclusion complexes. Nanosponges have been recognized as drug delivery system to encapsulate or accumulate for both hydrophilic and lipophilic drug by forming a complex. They can effectively deliver the drug in a controlled manner at a target site. They can deliver drugs by various routes like oral, topical and parenteral in a predictable manner to the target site. Besides their application in the drug delivery field, potential applications exist for cosmetics, biomedicine, bioremediation processes, agro chemistry, and catalysis, among others. The nanosponges have the ability to include either lipophilic or hydrophilic drugs and release them in a controlled and predictable manner at the target site. By controlling the ratio of polymer to the cross-linker the particle size and release rate can be modulated. Nanosponges enable the insoluble drugs and protect the active moieties from physicochemical degradation and controlled release. Nanosponges offer application in other areas such as cosmetics, biomedicine, bioremediation process, agrochemistry, and catalysis etc. Because of their small size and spherical shape nanosponges can be developed as different dosage forms like parenteral, aerosol, topical, tablets and capsules. The advantage of this technology offers targeting the drug to specific site reduces side effects, improve stability, and improve formulation flexibility and better patient compliance.

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