

An Assessment on Preparations, Characterization, and Poles Apart Appliances of Nanosponge

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Abstract: Targeted drug delivery to specific sites is the significant problem which is being faced by the researchers. The development of new colloidal carrier called nanosponges has the potential to solve these problems. Nanosponge is a novel and emerging technology which offers controlled drug delivery for topical use. Site specific or targeted drug delivery is used to treat many diseases like cardiovascular disease, Osteo-diseases, hormonal deficiency diseases like Parkinson's disease, auto-immune diseases like arthritis, diabetes. Nanosponges play a vital role in targeting drug delivery in a controlled manner. A wide variety of drugs can be loaded into nanosponge for targeting drug delivery. Both lipophilic as well as hydrophilic drugs can be loaded into nanosponges. Nanosponge drug delivery system has emerged as one of the most promising fields in life science. However, the most important application of targeted drug delivery system is to treat cancer. The unregulated cell growth and non-specific nature of the treatment makes. The objective of the article is to discuss nanosponges with their method of preparation, characterization, and applications.

Keywords: Nanosponges, Cancer, Ultrasound-assisted synthesis, characterization, Polymers.

Introduction

Effective targeted drug delivery systems have been a dream for a long time, but it has been largely frustrated by the complex chemistry that is involved in the development of new systems. Targeting drug delivery has long been a problem for medical researchers i.e., how to get them to the right place in the body and how to control the release of the drug to prevent overdoses. The development of new and complex molecule called 'nanosponges' has the potential to solve this problem. The system, known as "nanosponge," uses a nanoparticle sized system to deliver the drug payload.

These nanoparticles circulate in the body until they encounter the surface of a tumor cell, where they adhere to the surface and begin releasing the drug in a controllable and predictable fashion. The controlled-release nanoparticle drug-delivery system uses a targeting peptide that can recognize a radiation-induced cell-surface receptor. The average diameter of a nanosponge is below 1 μm but fractions below 500 nm can be selected¹.

The nanosponges could be either paracrystalline or in crystalline form. The loading capacity of nanosponges depends mainly on degree of crystallization. Paracrystalline nanosponges can show different loading capacities. The sponge acts as a three-dimensional network or scaffold. The backbone is long-length polyester. It is mixed in solution with cross-linkers to form the polymer. The net effect is to form spherically shaped particles filled with cavities where drug molecules can be stored. The polyester is biodegradable, so it breaks down gradually in the body. As it breaks down, it releases its drug payload in a predictable fashion. The

nanosponges can be synthesized to be specific size and to release drugs over time by varying proportions of cross-linker to polymer. The main limitation of nanosponges is their ability to include only small molecules².

Nanosponges are a new class of materials and made of microscopic particles with few nanometers wide cavities, in which a large variety of substances can be encapsulated. These particles are capable of carrying both lipophilic and hydrophilic substances and of improving the solubility of poorly water soluble molecules. Nanosponges are tiny mesh-like structures that may revolutionise the treatment of many diseases and early trials suggest this technology is up to five times more effective at delivering drugs for breast cancer than conventional methods.

The nanosponges are encapsulating type of nanoparticles which encapsulates the drug molecules within its core. By the method of associating with drugs, the nanoparticles can be classified into encapsulating nanoparticles, complexing nanoparticles and conjugating nanoparticles. The first type is represented by nano sponges 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-cyano acrylate) (IBCA) are also encapsulating nanoparticles. They can entrap drug molecules in their aqueous core. The second category is Complexing nanoparticle, which attracts the molecules by electrostatic charges. The third type is Conjugating nanoparticle, which links to drugs through covalent bonds. These nanosponges represent a novel class of nanoparticles usually obtained by natural derivatives. As compared to the other nanoparticles, they are insoluble both in water and organic solvents, porous, non toxic and stable at high temperatures up to 300°C.³

They are able to capture, transport and selectively release a huge variety of substances because of their 3D structure containing cavities of nanometric size and tunable polarity. Furthermore, nanosponges show a remarkable advantage in comparison with the common nanoparticles: indeed, they can be easily regenerated by different treatments, such as washing with eco-compatible solvents, stripping with moderately inert hot gases, mild heating, or changing pH or ionic strength. For all these characteristics, nanosponges have been already employed in different applied fields, such as cosmetic and pharmaceutical sectors.⁴

Nanosponges can be used as a vessel for pharmaceutical principles to improve aqueous solubility of lipophilic drugs, to protect degradable molecules and to formulate drug delivery systems for various administration routes besides the oral one. The simple chemistry of polymers and cross linkers does not pose many problems in the preparation and this technology can be easily ramp up to commercial production levels. Nanosponges are water soluble but does not breakup chemically in water. They mix with water and use as a transport fluid. They can be used to mask unpleasant flavours, to convert liquid substances to solids. The chemical linkers enable the nanosponges to bind preferentially to the target site.

The main disadvantage of these nanosponges is their ability to include only small molecules. The nanosponges could be either paracrystalline or in crystalline form. The loading capacity of nanosponges depends mainly on degree of crystallisation. Paracrystalline nanosponges can show different loading capacities. The nanosponges can be synthesized to be of specific size and to release drugs over time by varying the proportion of cross linker to polymer. The engineering capacity of nanosponge is due to the relatively simple chemistry of its polyesters and cross-linking peptides, compared to many other nanoscale drug delivery systems. These nanosponges can be magnetized when they are prepared in the presence of compounds having magnetic properties. The tiny shape of nanosponges enables the pulmonary and venous delivery of nanosponges.⁵

Chemicals used for the Synthesis of Nanosponges

Polymers - Hyper cross linked Polystyrenes, Cyclodextrines and its derivatives like Methyl β -Cyclodextrin, Alkylloxycarbonyl Cyclodextrins, 2-Hydroxy Propyl β -Cyclodextrins and Copolymers like Poly(valerolactone-allylvalerolactone) & Poly(valerolactone-allylvalerolactone- oxepanedione) and Ethyl Cellulose & PVA

Copolymers- Poly (valerolactone allylvalerolactone), Poly (valerolactone-allylvalerolactone oxepanedione), Ethyl Cellulose, Poly vinyl alcohol.

Crosslinkers- Diphenyl Carbonate, Diarylcarbonates, Diisocyanates, Pyromellitic anhydride, Carbony - ldiimidazoles, Epichloridrine, Glutaraldehyde, Carboxylic acid dianhydrides, 2,2- bis(acrylamido) Acetic acid and Dichloromethane.

Preparation of Nanospoges

1. Solvent Method

Dissolve the polymer in suitable solvent. Then add this to excess quantity of cross- linker. Reflux the mixture for 48 hours at a temperature of 100°C. Then allow this solution to cool at room temperature. Add this to excess quantity of bidistilled water and filter the product. Then purify by prolonged soxhlet extraction with ethanol. Dry the product and grind in mechanical mill to get homogenous powder.

2. Hyper Cross Linked B- Cyclodextrins

Nanosponge has been recently developed hyper cross linked cyclodextrin polymers nano structured to form 3-dimensional networks; a roughly spherical structure, about the size of a protein, with channels and pores inside. They are obtained by reacting cyclodextrin with a cross-linker such as di isocyanates, diaryl carbonates, dimethyl carbonate, diphenyl carbonate, and carbonyl diimidazoles, carboxylic acid dianhydrides and 2, 2- bis(acrylamido)acetic acid. The surface charge density, porosity and pore sizes of sponges can be controlled to attach different molecules. Nanosponge with low cross linking gives a fast drug release.

3. Emulsion Solvent Diffusion Method

This method uses different proportion of ethyl cellulose and polyvinyl alcohol. The dispersed phase containing ethyl cellulose and drug was dissolved in 20ml dichloromethane and slowly added to a definite amount of polyvinyl alcohol in 150ml of aqueous continuous phase. The reaction mixture was stirred at 1000rpm for 2 hrs. Then Nanosponge formed were collected by filtration and dried in the oven at 40°C for 24 hrs. The dried Nanosponge was stored in vacuum desiccators to ensure the removal of residual solvent.

4. Ultrasound-Assisted Synthesis

In this method, nanosponges can be obtained by reacting polymers with cross-linkers in the absence of solvent and under sonication. The nanosponges obtained by this method will be spherical and uniform in size. In this method, the polymer is mixed with the cross-linker in a particular molar ratio in a flask. The flask is then placed in an ultrasound bath, filled with water and heated to 90°C. Sonication of the mixture is done for few hours. Then, the mixture is to be cooled and the product is broken roughly. Washing the product with water to remove the non-reacted polymer and subsequently purifying by prolonged soxhlet extraction with ethanol with further drying will give the nanosponges^{5,6}.

Loading of Drug into Nanosponges

Nanosponges for drug delivery should be pretreated to obtain a mean particle size below 500nm. For this, nanosponges is suspended in water and then sonicated to avoid the presence of aggregates. Further, the suspension is centrifuged to obtain the colloidal fraction. The supernatant is separated and the sample is to be dried by freeze drying. Aqueous suspension of nanosponge is prepared and dispersed in the excess amount of the drug and the suspension is maintained under constant stirring for specific time (required for complexation). After complexation, the uncomplexed (undissolved) drug from complexed drug is separated by centrifugation. Then, the solid crystals of nanosponges are obtained by solvent evaporation or by freeze drying⁷.

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 complex⁸.

Factors Influence Nanosponge Formation

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.

Type of Drugs

Drug molecules to be complexed with nanosponges should have certain characteristics mentioned below⁹.

- 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
- 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.

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.

Degree of Substitution

The complexation ability of the nanosponge may be greatly affected by type, number and position of the substituent on the parent molecule¹⁰.

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 a nanosponge, on the solubility of drug. Phase solubility diagrams indicate the degree of complexation¹¹.

2. Loading Efficiency / Entrapment Efficiency

Weighed amount of loaded nanosponge complexes is to be dissolved in suitable solvent, sonicated to break the complex, diluted suitably and then analyzed by UV spectrophotometer or HPLC methods¹².

$$\text{Loading Efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

3. 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 complexes¹³.

4. Polydispersity Index & Particle Size

The particle size can be determined by dynamic light scattering using 90 Plus particle sizer equipped with MAS OPTION particle sizing software. From this, the mean diameter and polydispersity index can be determined. The particle size can be determined by scanning electron microscopy (SEM), transmission electron microscopy (TEM), atomic force microscopy (AFM), and freeze fracture electron microscopy (FFEM)¹³.

5. Zeta Potential Determination

Zeta potential measurements can be made by using an additional electrode in particle size instruments². Also, Laser Doppler anemometry, zeta potential meter can be used¹³.

6. Infra-Red Spectroscopy

Infra-Red spectroscopy is used to estimate the interaction between nanosponges and the drug molecules in the solid state. Nanosponge bands often change only slightly upon complex formation and 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. The technique is generally not suitable to detect the inclusion complexes and is less clarifying than other methods.

The application of the Infra-red spectroscopy is limited to the drugs having some characteristic bands, such as carbonyl or sulfonyl groups. Infrared spectral studies give 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.

7. X-Ray Diffractometry

Powder X-ray diffractometry can be used to detect inclusion complexation in the solid state. When the drug molecule is liquid (since liquid have no diffraction pattern of their own), the diffraction pattern of a newly formed substance clearly differs from that of uncomplexed nanosponge. This difference of diffraction pattern indicates the complex formation. When the drug compound is a solid substance, a comparison has to be made between the diffractogram of the assumed complex and that of the mechanical mixture of the drug and polymer molecules. A diffraction pattern of a physical mixture is often the sum of those of each component, while the diffraction pattern of complexes are apparently different from each constituent and lead to a —new|| solid phase with different diffractograms. Diffraction peaks for a mixture of compounds are useful in determining the chemical decomposition and complex formation. The complex formation of drug with nano sponges alters the diffraction patterns and also changes the crystalline nature of the drug. The complex formation leads to the sharpening of the existing peaks, appearance of a few new peaks and shifting of certain peaks.

8. Single Crystal X-Ray Structure Analysis

It may be used to determine the detailed inclusion structure and mode of interaction. The interaction between the host and guest molecules can be identified and the precise geometrical relationship can be established.

9. In Vitro Release Studies

The release of the drug from the optimized nanosponge formulation can be studied using multi-compartment rotating cell with dialysis membrane (cut-off 12,000 Da). The donor phase consists of drug-loaded nanosponge complex in distilled water. The receptor phase also contains the same medium. The receptor phase is withdrawn completely after fixed time intervals, suitably diluted with distilled water and then analyzed by UV spectrophotometer¹². Also, USP II can be used in many cases depending upon the formulation¹³.

10. Photo-Degradation Study

The photo-degradation of drug loaded nanosponge complex is performed under UV lamp. The samples are kept at distance of 10 cm from the lamp for 1 hr. stirring under dark; simultaneously the samples are quantitatively analyzed by HPLC.

11. Thermo-Analytical Methods

Thermo-analytical methods determine whether the drug substance undergoes some change 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 DTA and DSC 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.

12. Thin Layer Chromatography

In Thin Layer Chromatography, the R_f values of a drug molecule diminishes to considerable extent and this helps in identifying the complex formation between the drug and nanosponge.

13. Production Yield

The production yield (PY) can be determined by calculating initial weight of raw materials and final weight of nanosponges.

$$\text{Production Yield} = \frac{\text{Practical mass of Nanosponge}}{\text{Theoretical mass (polymer + drug)}} \times 100$$

Advantages of Nanosponges

- ✓ Targeted site specific drug delivery.
- ✓ Can be used to mask unpleasant flavours and to convert liquid substances to solids.
- ✓ Less harmful side effects (since smaller quantities of the drug have contact with healthy tissue).
- ✓ Nanosponge particles are soluble in water, so the hydrophobic drugs can be encapsulated within the nanosponge, after mixing with a chemical called an adjuvant reagent.
- ✓ Particles can be made smaller or larger by varying the proportion of cross-linker to polymer.
- ✓ Production through fairly simple chemistry called "click chemistry" (methods for making the nanosponge particles and for attaching the linkers).
- ✓ Easy scale-up for commercial production.
- ✓ The drug profiles can be tailored from fast, medium to slow release, preventing over- or under-dosing of the therapy.
- ✓ Predictable release.
- ✓ Biodegradable.
- ✓ These formulations are stable over range of pH 1 to 11.
- ✓ These formulations are stable at the temperature up to 130°C
- ✓ These formulations are compatible with most vehicles and ingredients.
- ✓ These are self sterilizing as their average pore size is 0.25µm where bacteria cannot penetrate.
- ✓ These formulations are free flowing and can be cost effective.
- ✓ This technology offers entrapment of ingredients and reduces side effects.
- ✓ Improved stability, increased elegance and enhanced formulation flexibility.
- ✓ Extended release with continuous action up to 12–24 hours.
- ✓ Incorporation of immiscible liquids is possible.
- ✓ Improved material processing since liquids may be converted to powders.¹⁴

Application:^{15,16,17}

1. Cancer

Oftentimes, the drugs injected by doctors in cancer patients are rendered inefficient. This happens mainly for two reasons – either they can't get to the tumor site, or they are attacked and dismembered by the immune system. This obstacle has now been solved by the use of nanosponge to certain extent. Experts proposed that fixing drugs into nanosponge ensures that the chemicals reach their destination in large amounts. One of the important drug formulated as nanosponge is paclitaxel, the active ingredient in the anti-cancer therapy Taxol.

The researchers have recorded the response of two different tumor types in animal studies — slow-growing human breast cancer and fast-acting mouse glioma - to single injections. In both cases, they found that the delivery through nanosponges increased the death of cancer cells and delayed tumor growth compared with other chemotherapy approaches.

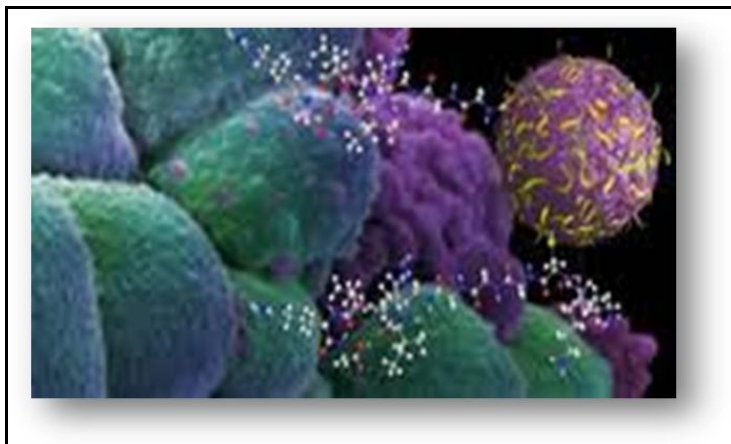


Figure 1: The illustration shows a nanosponge particle attaching to human breast cancer cells.

(The particle holds an anticancer drug that it releases gradually as the particle decomposes. Peptide linkers are shown with the ball and stick representation. Although only two are shown in the illustration, about three dozen are attached to the surface of actual particles. The linkers are specially configured to bind to the surface of irradiated cancer cells.)

2. Oxygen Delivery Systems

Cyclodextrin nanosponges have also been developed as oxygen delivery system. For this purpose, the three types of nanosponges made up of α , β and γ – cyclodextrin is suspended in water, saturated with oxygen and in vitro characterized. Oxygen permeation through a silicone membrane can also be obtained using a β -cyclodextrin nanosponge/hydrogel combination system⁶. Nanosponge has the ability to store and to release oxygen slowly over time. Oxygen-filled nanosponges could supply oxygen to the hypoxic tissues which are present in various diseases.

3. 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. The administration of these molecules presents various problems. 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 as 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.

4. Harvesting of Rare Cancer Marker from Blood

It has been seen that a new type of nanoparticle, whose interiors is decorated with different types of 'bait' molecules, is used to selectively trap specific families of proteins from blood and protect them from degradation by enzymes in blood.

5. In the Removal of Organic Matter to Produce Ultrapure Water for Power Regeneration

The presence of organic pollutants in raw water is a major concern for a number of power plants and industries requiring ultrapure water such as pharmaceutical and electronics sectors. The effectiveness of water-insoluble cyclodextrin (CD) polymers in the removal of natural organics (volatile component), dissolved organic carbon (DOC) and total organic carbon (TOC) from water collected at a specific power plant has been

reported in the literature. The CD - polymers also has demonstrated the ability to remove dissolved organic carbon (DOC) from raw water by as much as 84%, whilst total organic carbon (TOC) removal was relatively low.

6. Solubility Enhancement

Nanosponges have been also used for improving the solubility and dissolution rate of poorly soluble drugs as well as providing controlled release profile. However the molecular dimensions and conformation are critical parameters influencing inclusion complexation within nanosponges and thus may not be universally applicable to all molecules. Nanosponges of Cefpodoxime proxetil (CP) have been prepared to improve dissolution rate of CP.

7. Novel Flame Retardants Containing Cyclodextrin Nanosponges and Phosphorus Compounds to Enhance EVA Combustion Properties

A novel flame retardant in tumescent system, aimed to improve the fire stability of ethylene vinyl acetate copolymer (EVA), has been prepared by melt blending of the copolymer and a complex of cyclodextrin nanosponge- phosphorus compounds. As compared to traditional systems, this complex which is stable in processing conditions, has the advantage that nanosponges act as both carbon sources and foam forming agents while the phosphorus compounds are able to directly generate phosphoric acid in situ. In this context, cyclodextrin nanosponges undergo dehydration in presence of the acid source, generating water vapour and char, and thus protecting the copolymer against combustion.

8. Topical Drug Delivery System

Local anesthetics, antifungals and antibiotics are among the category of the drugs that can be easily formulated as topical nanosponges. In this context, nanosponges can be prepared by various methods like emulsion solvent diffusion method, etc. The nanosponges of econazole nitrate were prepared, which are discrete free flowing nanosized particles with perforated orange peel like morphology as visualized by SEM in the literature.

9. Antiviral Application

Nanosponges can be useful in the ocular, nasal, pulmonary administration routes. The selective delivery of antiviral drugs or small interfering RNA (siRNA) to the nasal epithelia & lungs can be accomplished by nanocarriers in order to target viruses that infect the RTI such as respiratory syncytial virus, influenza virus & rhinovirus. They can also be used for HIV, HBV, and HSV. The drugs which are currently in use as nano delivery system are zidovudine, saquinavir, interferon- α , acyclovir (Eudragit based).

10. More Effectiveness than Direct Injection

Recent research suggests that nanosponge could be up to five times more effective at reducing tumor growth than direct injection. The drug delivery system is likened to be filling virus-sized sponges with an anti-cancer drug, attaching chemical linkers that bond to a receptor on the surface of tumor cells, then injecting the sponges into the body. When the sponges come into contact with a tumor cell, they either attach to the surface or are sucked into the cell, where they off-load their deadly contents in a predictable and controlled manner.

11. Floriculture

Nanosponges have been recently developed and proposed for delivering preservative and anti - ethylene compounds in order to improve cut flower vase life.

Classification of Nanosponges

Nanosponges are encapsulating type of nanoparticles which encapsules the drug molecules within its core. By method of associating with drugs, the nanoparticles can be classified into the following:-

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 in their aqueous core.

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2. Complexing Nanoparticles

This type of nanoparticles attracts the molecules by electrostatic charges.

3. Conjugating Nanoparticles

This type of nanoparticles links to drugs through covalent bonds. As compared to the other nanoparticles, they are insoluble both in water and organic solvents, porous, non-toxic and stable at high temperature up to 300°C. They are able to capture, transport and selectively release a huge variety of substances because of their 3D structure containing cavities of Nanomeric size and tunable polarity.¹⁸

Conclusion

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. Because of their small size and spherical shape nanosponges can be developed as different dosage forms like parenteral, aerosol, topical, tablets and capsules.

Thus, the nanosponge drug delivery system is a boon in the area of targeted and site specific drug delivery system. Although, more developmental studies are required to make this drug delivery useful to mankind.

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