REVIEW ARTICLE

Nanosponges- A Versatile Approach of Drug Delivery System

Alka Singh*, Chetan S Chauhan

Bhupal Nobles' Institute of Pharmaceutical Sciences, Bhupal Nobles' University, Udaipur, Rajasthan, India.

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ABSTRACT

With the escalating number of diseases, an opportunistic target drug delivery system is needed. Nanosponges (NS) are nanosized drug delivery systems having three-dimensional (3D) configurations, fabricated by crosslinking of polymers to ensnare a wide assortment of drugs. These small particles move inside the body till they arrive at the target site and deliver the medication in a specific and controlled way. They can ensnare (entrap) both hydrophilic and hydrophobic moieties in a smarter manner and improve the solubility and bioavailability of drugs. NS have been utilized to examine the medication conveyance by oral, parenteral, and topical routes. Another significant property of NS is that they can work on the solvency of ineffectively water-soluble moieties and are utilized for the storage of gases, and proteins as well as for the removal of toxins from the systemic circulation. The present review highlights the types of nanosponges, their methods of preparation, characterization, and applications in drug delivery.

Keywords: Nanosponges, Cross-linker, Bioavailability, Polymer, Nanotechnology, Target drug delivery.

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INTRODUCTION

While designing a drug delivery system, researchers mainly focus on delivering the accurate amount of drug at the target site. In this way, many approaches are utilized by using modern nanotechnology, which proved best in its manner.[1] Nanotechnology is a branch of science that employs nanomaterials at the nanoscale for creating nanoengineered products with advanced features and improved characteristics in the size range of 1 to 100 nm. One billionth of a meter is a nanometer. Nanomaterials are physical compounds with at least one fraction in the range of 1 to 100 nm.[2] These NPs are observed in a number of diverse shapes, including polymeric nanoparticles, hard-phospholipid nanoparticles, nanoemulsions, dendrimers, nanosponges, liposomes, carbon nanotubes, micellar systems, etc.[3] In this regard, the use of nanotechnology in the medical field is transitioning from passive structures' to 'active structures' through more precise pharmacological drug therapies or "smart drugs" that are made by coupling certain ligands to nanocarriers or aptamers. A wide variety of drug substances like antifungal, antiviral, anti-cancer, volatile oils, gases, proteins and peptides can be ensnared in colloidal nanoparticulate structures known as nanosponges.

NS are 3D spongy structures, around the size of a virus containing nanometric cavities or voids. Simply they are encapsulating drug delivery systems.4,5 These sponges move all around the body until they identify the exact target, attach to the surface, and release the drug gradually. They are five times more efficient than conventional techniques at delivering drugs for breast cancer and are non-irritating, non-mutagenic, non-allergic, and non-toxic.[6] NS are solid by nature, capable of ensnaring both hydrophilic and lipophilic substances. Due to this property, they are suitable for enhancing the solubility, permeability as well as bioavailability of compromised drugs like camptothecin, paclitaxel, dexamethasone, etc. It also helps less or poor water-soluble molecules become more soluble by encapsulating them in polar cavities. They are porous, insoluble in water and other organic solvents, innocuous and stable up to 300°C.

The development of nanosponges involves the use of many polymers and cross-linkers which result in the delivery of entrapped drugs in a controlled predictable way at the target site.[7] In this way, NS is the leading frontier in drug delivery which reduces the dose and dose-related toxicities. It can be administered through oral, parenteral, and topical routes. Oral administration of NS can be done in the form of capsules, tablets, or solid dispersions by using suitable excipients and diluents that deliver the drug efficiently at the target site.[8] For the parenteral route different aqueous solutions like sterile water, and saline is used for NS dispersion while in topical delivery hydrogel is best suited. This ultimately results in improved safety, effectiveness, patient compliance, an extended drug shelf life, and ultimately lower healthcare expenditures.

**Author for Correspondence: alkasingh1790@gmail.com*

Diverse Characteristics of Nanosponges

- NS are colloidal nanocarriers able to ensnare a wide variety of drug moieties in the core.[9]
- The drug should have a molecular weight falling between 100 to 400 Dalton.[10]
- The degree of cross-linking affects the polarity and cavity size of the three-dimensional (scaffold) of NS.[11]
- Depending on the method of preparation and cross-linker used, NS are available in both crystalline and Para crystalline form.[12]
- The ability of drugs to be encapsulated depends on the degree of crystallization. The encapsulation efficiency is better in para-crystalline forms.
- NS are stable, non-toxic, biodegradable, and can withstand a higher temperature of approximately up to 300°C.[13]
- They remain firm (stable) at a wide pH range of 1 to 11.
- Due to the ability to bind a wide variety of functional groups, NS ensures target drug delivery.
- They can entrap both hydrophilic and lipophilic drugs.
- It offers tailored delivery of BCS class II and IV drugs i.e., having low solubility and low permeability.
- The three-dimensional scaffold helps in the efficient delivery of a wide range of compounds.
- NS preparations are available in oral, parenteral, topical, and inhalation formulations for target drug delivery.
- They are non-immunogenic and non-mutagenic in nature.

Types of Nanosponges[14]

NSs can be created, formulated, or fabricated into a variety of forms based on the type of polymer, cross-linker, polymer cross-linker ratio, and technique of synthesis. Due to the ease of formulation beta-cyclodextrin NSs are the most common type which is widely utilized by formulation development scientists.[15] Figure 1 represents the different types of NS.

Material used in the Preparation of Nanosponges[16]

The major components involved in the formulation of NSs are polymer, copolymer, cross-linker, and drug moiety.[17] The polymer along with the copolymer creates a backbone of a 3D scaffold which is further linked by a suitable crosslinker with the development of void space between the developed structure after the completion of the complexation reaction.[18] Table 1 gives information about the material used in NSs preparation.

Advantages of Nanosponges[19]

- Enhances the aqueous solubility of poorly water-soluble drugs.[20]

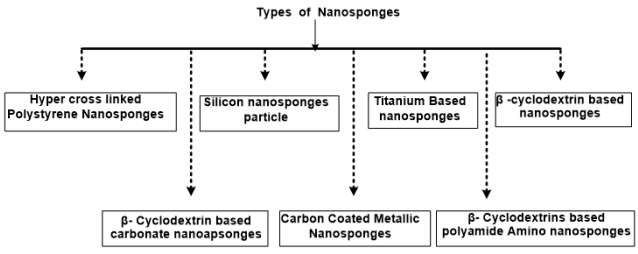

Figure 1: Different types of nanosponges based on polymer and type of cross-linker used.

Table 1: Chemicals used in the preparation of nanosponges

Polymer	*Copolymer*	*Crosslinker*
Hyper crosslinked cyclodextrin Alpha-cyclodextrin Beta-cyclodextrin and their derivatives Alkyloxy carbonyl cyclodextrin, 2-hydroxy propyl beta-cyclodextrin Eudragit RS 100	Poly-allylvalerolactone, Polyvalerolactone Poly-oxepanedione Poly-methylmethacrylate, Hydroxypropyl methylcellulose Poly-vinyl alcohol Ethylcellulose	Diphenyl carbonate 2,2-bis-acrylamido acetic acid Diaryl carbonate Pyromellitic anhydride (PMDA) Hexamethylene diisocyanate Epichlorohydrin carbonyl diimidazole (CDI) Toluene-2,4-diisocyanates Dichloromethane Polyamidoamine.

- Allows formulation of both hydrophilic and hydrophobic drug moieties.
- Enables site-specific drug delivery and predetermined release.[21]
- Stable over the pH ranges of 1–11 and temperature up to 300°C.
- Non-irritating, non-mutagenic, non-allergic and non-toxic.
- Reduces side effects by providing entrapment of active ingredients.
- Protects drug from physiological degradation.[22]
- Mask the unpleasant flavor of drug substance.
- Average pore size of 0.25 µm prevents bacterial penetration and increases formulation stability.
- Decreases the frequency of dosing.
- Improves patient compliance.

Disadvantages of Nanosponges[23]

- NS are not suitable for large molecules and can only encapsulate small molecules.[24]
- NS primarily rely on their loading capacity for drug encapsulating.[25]
- Sometimes due to premature initial dissolution of the crosslinker there may be chances of dose dumping.

Method of Preparation of Nanosponges

Solvent method

As the name indicates, in the solvent method a suitable polar aprotic solvent is used as a medium for carrying out the reaction. Generally, in a molar ratio of 1:4 polymer and crosslinker are taken and permitted to reflux for 1 to 48 hours at 10°C.[26] Once the reaction is completed the solution is allowed to cool at room temperature and washed with bi-distilled water and finally the product is recovered by the Soxhlet method and dried in a vacuum oven as shown in Figure 2.

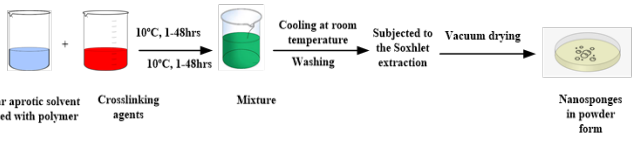

Figure 2: Nanosponges by solvent method

Ultrasound-assisted method[27]

In this method, NS are developed without using any solvent and developed by using only ultrasonic waves. In a fixed ratio, the polymer and cross-linker are placed in a suitable flask on an ultrasound bath and allowed to react for five hours at 90°C. After completion of the reaction, the mixture is allowed to cool at room temperature and washed with an excess quantity of water to remove unreacted reagents. Further, this washed material is subjected to Soxhlet extraction by using ethanol and ultimately the product is filtered, collected, and dried in a vacuum oven as depicted in Figure 3.[28]

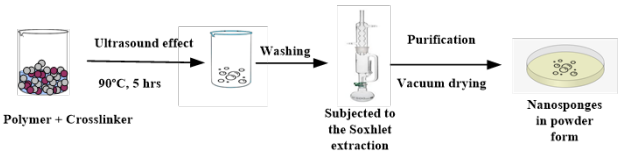

Figure 3: Ultrasound-assisted method for development of nanosponges

Melt method[29]

In this method, NS are developed by melting polymer and crosslinker together at a specific point of temperature then allowed to cool and the product is recovered by subsequent washing with appropriate solvent. The obtained product is blank NS which is further subjected to encapsulation of the drug as given in Figure 4.

Figure 4: Melt method for nanosponges

Bubble electrospinning

The main components of a traditional, common electrospinning setup are a high-voltage source, a grounded collector, a syringe pump, and a syringe. However, the main issue limiting its usage is the volume of nanofibers produced.[17] Polyvinyl alcohol is the polymer that is used in the bubble electrospinning method. A 10% aqueous solution of polymer is formed and heated up to 80 to 90°C for two hours to create a one-phase β-mixture. In the next step, the polymer mixture is permitted to cool at room temperature before being utilized to convert into nano-porous fibers as shown in Figure 5.[30]

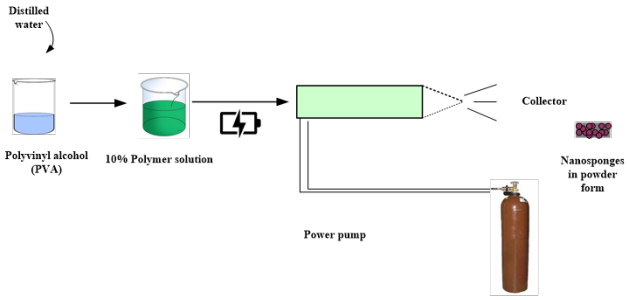

Figure 5: Nanosponges preparation by Bubble electrospinning

Micro-wave radiation assisted synthesis of nanosponges

As compared to the traditional method, the development of NS by utilizing microwave radiation is the most convenient and time-saving method.[31] In this method, NS are formulated in the presence of microwave irradiation which produces a highly crystalline nanoporous structure with improved complexation and maximum encapsulation efficiency in less time.[32] It is also advantageous to use the method since it allows for the provision of energy in a precise manner.

Nanosponges preparation from hyper crosslinked β-Cyclodextrin[33]

β-Cyclodextrin (βCD) NS acts as a drug carrier. Due to the truncated cone structure, cyclodextrins can be easily utilized for drug ensnarement.[34] NS are formed by reacting cyclodextrin and a suitable crosss linking agent like carbonyldiimidazole, diisocynates. An average diameter of developed NS is less than 1 micrometre. According to Swaminathan *et al.* (2013), various crosslinking agents modify crucial characteristics of the final nanoporus polymer such as swellability and hydrophilicity/ hydrophobicity.[35]

Emulsion solvent diffusion method[36]

Emulsion solvent diffusion is a two-step method that uses polyvinyl alcohol and ethyl cellulose. Ethyl cellulose is dissolved in dichloromethane and then the aqueous solution

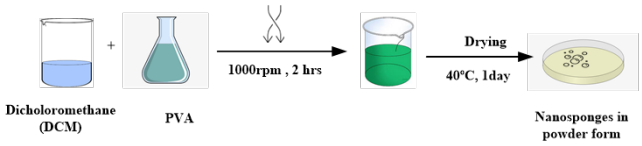

Figure 6: Formulation of nanosponges by emulsion solvent diffusion method

of polyvinyl alcohol is added to it by keeping the mixture at a magnetic stirrer at a speed of 1000 rpm for two hours.[37] After thorough stirring the reaction is completed as shown in Figure 6 and NS are collected by filtration and drying at 40°C.[38]

Quasi-emulsion solvent method[39]

In this method, different quantities of NS can be developed by using the polymer. Eudragit RS 100 is used to prepare the internal phase and added to a reasonable dissolvable.[40] The drug to be incorporated is prepared as a solution and ultrasonicated at 35°C to dissolve it. This inner phase is then added to an external phase that contains polyvinyl alcohol, which acts as an emulsifying agent.[41] The mixture is then blended at 1000–2000 rpm for three hours at room temperature before being dried for twelve hours in a hot air oven at 40°C as depicted in Figure 7.[42]

Drug Loading in Nanosponges[43-46]

NSs are pretreated to obtain a smaller particle size i.e., less than 500 nm, in this manner, NSs are first subjected to sonication to prevent aggregation followed by centrifugation and then freeze drying.[11] In the subsequent step, aqueous suspension

Figure 7: Quasi-emulsion solvent method

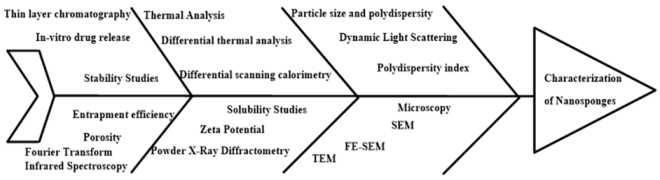

Figure 8: Different methods of characterization in the Fishbone diagram

of NSs is allowed to be stirred with an excess amount of drug for a specific period of time.[44] Once the complexation is completed the free drug is separated by centrifugation and drug-loaded NSs are retained either by solvent evaporation or freeze-drying method.[45]

Factors Affecting the Development of Nanosponges

Property of polymer and cross-linker used

Cross-linker is very important in the fabrication of NSs, it serves as a backbone in a 3D scaffold. The nature of the cross-linker and choice of polymer used identifies the hydrophilicity, lipophilicity, entrapment efficiency as well as organ-specific targeted drug delivery of developed NSs.[47]

Nature of the drug

The drug molecule requires to ensnare in NSs should have molecular weight fallen in the size range of 100–400 Dalton, less aqueous solubility (less than 10 mg/mL) and should have less than five condensed rings in its structure with a melting point less than 250°C.[48]

Temperature

A variation in temperature influences the degree and extent of the complexation of NSs and drugs. An increase in temperature leads to a decrease in the stability constant of the resultant nanocarrier and entrapped moiety which is due to a reduction in attractive forces (Van der- Walls forces and hydrogen bonding) between them.[49]

Degree of substitution and method of preparation

The complexity of NS is greatly affected by the nature, type, number of substituents of parent molecule, and the type of method adopted in the fabrication of nanocarriers.[50] Greater the number of substituents greater will be the porosity of NS. The choice of the method adopted in the development of NS depends on the nature of drug as well as the effect required from the developed NS formulation.[51]

Characterization of nanosponges

A number of methods are used to characterize the NS and to identify the degree of complexation between polymers and crosslinkers as depicted in the fishbone diagram (Figure 8).

- Solubility studies- Mainly done to determine the extent of complexation and effect NS on ensnare drug. The phase solubility method devised by Higuchi and Connors is widely used to identify the impact of NS on drug solubility.[52]
- Microscopy- It is mainly done to identify the surface morphology and particle size of NS.[53] Microscopic examination is usually done by scanning electron microscopy (SEM), Field emission scanning electron microscopy (FE-SEM), and transmission electron microscopy (TEM).[54]
- Particle size and polydispersity- By using a dynamic light scattering instrument (DLS) furnished with size analyzer software, identifies the diameter as well as its polydispersity index (PDI). PDI is a measure of the particle size distribution's width, spread, or variation.[55] Higher PDI value imply a large particle size distribution and the polydisperse nature of the sample whereas monodisperse samples have a low PDI value.
- Zeta potential- It is estimated to identify the surface charge of colloidal dispersion by using the Zeta seizer instrument.[56] The greater the value of zeta potential greater the stability of dispersion.
- Thermal analysis- Thermal analysis is done by differential thermal analysis(DTA) and differential scanning calorimetry (DSC) to identify the possibility of degradation of the drug prior to heat destruction of NS.[57]
- X-ray diffractometry (XDR)- It is also known as powder X-ray diffractometry (PXRD) which produces diffractograms consisting of peaks and confirms the formation of complexation, crystalline nature and stability of fabricated NS by comparing the peaks of drug and physical mixture.[58]
- Infrared spectroscopy- It is indicative of drug-NS interaction, based on their structure elucidation obtained by spectrum produced by fourier transform infrared spectroscopy (FTIR). The method is not suitable for revealing the extent of inclusion complexation.[59]
- Entrapment efficiency- It identifies the amount of drug ensnare in NS, HPLC and ultraviolet spectroscopy methods are mainly used to calculate the entrapment efficiency of the developed formulation.[60]
- *In-vitro* drug release- Franz diffusion cell is mainly used in the study of permeation and intro release of drug from NS. A pre-treated dialysis membrane is used as a donor compartment and the drug release in the receptor compartment is analyzed by using an ultraviolet spectrometer.[61]

Application of Nanosponges

Nanosponges in drug delivery[62]

Due to the versatile ensnare capacity and small size of NS, it is a boon in nanomedicine having the ability to deliver both lipophilic and lyophobic drugs at the target site. Oral, topical, inhalation, and parenteral administration of NS can be done by using suitable excipients and diluents. As compared to other polymers NS fabricated by using beta-cyclodextrin are reported

to have five times more effective in drug delivery at a desired site in the body. Drugs like paclitaxel, tamoxifen, quercetin, curcumin, resveratrol, carboplatin, etc., have already proven their effectiveness and improved bioavailability in NS formulation.

Nanosponges in Cancer Treatment

The biggest challenge with an anticancer drug is its low solubility and permeability leading to its poor pharmacokinetic and pharmacodynamic effects.[28] But stacking such anticancer agents in nanocavities of NS, reduces such issues of bioavailability and ensures the target delivery by reducing the dose and dose-related side-effects.[63] Clemente *et al.* illustrated the therapeutic efficiency of Paclitaxel-loaded NS for inhibiting the growth and angiogenesis in Melanoma cells and reported the reduction in dose and increased effectiveness against melanoma growth.[64]

Nanosponges as biocatalysts, vaccines, protein, antibiotics[65]

There are a wide variety of drugs, vaccines, proteins, and antibiotics that require enzymes as a catalyst in the production process, and the results in low yield that are susceptible to degradation and contamination.[66] Such materials require specialized methods for retaining their activity, stability and protection from the effect of temperature, pH, and enzymatic action so that they can reach the target site without losing effectiveness.[67] By using a suitable combination of polymer and crosslinker, the nanocarrier approach transforms the enzymes and macromolecules as biocatalysts[68] which improve their yield, activity, and effectiveness as well throughout the storage and usage. Additionally, NS is also used in immobilization techniques.[69]

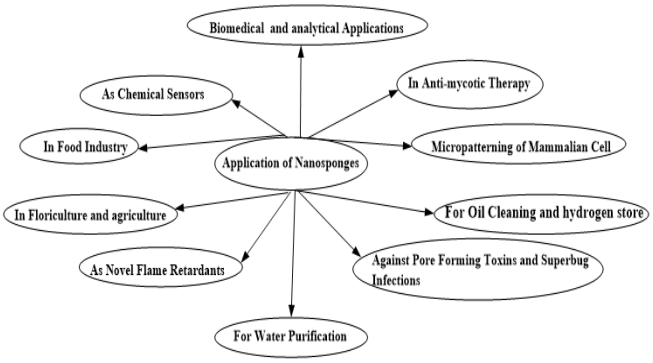

Figure 9: Other applications of nanosponges

Table 2: Recent advancements in nanosponges

Drug	*Method of preparation*	*Disease*	*Inference*	*Reference*
Hesperetin and Piperine (2023)	Ball milling technique	inflammation	Solubility and bioavailability enhancement	76
Hesperetin (2022)	Quasi-emulsion solvent diffusion	inflammation	Solubility and bioavailability enhancement	77
Curcumin (2022)	Emulsion solvent diffusion	Ulcerative colitis	Bioavailability enhancement of curcumin	78
Nisin (2022)	Freeze-drying	Colon and breast cancer	Safeguarding peptides and facilitating drug delivery to target cancer cells in colon and breast	79
Carboplatin (2021)	Double emulsion solvent evaporation	Testicular, ovarian, cervical and lung cancer	Sustained release of hydrophilic therapeutic agent	80
Olmesartan medoxomil (2021)	Emulsion solvent evaporation	Hypertension	Reduce blood pressure	81
Lapatinib (2021)	Emulsion solvent Diffusion	Breast cancer	Enhances solubility	82
Resveratrol (2021)	Freeze-drying	Breast and ovarian cancer	Target drug delivery	83
Brigatinib (2020)	Ultrasonication Assisted-emulsion solvent evaporation	Lung cancer	Target drug delivery	84
Lornaxicam (2020)	Emulsion solvent evaporation	Inflammation	Improve permeation and treatment by topical delivery	85
Luliconazole (2020)	Emulsion solvent evaporation	Fungal infection	Improve antifungal effect	86
5-fluorouracil (2019)	Emulsion solvent evaporation	Colon cancer	Target drug delivery	87
Erlotinib glutathione (2018)	Solvent method	Lung cancer	Target drug delivery	88
Dexamethasone (2017)	Solvent method	Inflammation	Improved occular anti-inflammatory affect	89
Gliclazide (2016)	Emulsion solvent diffusion	Diabetes mellitus	Bioavailability enhancement and sustained release obtained	36
Oxygen 2010	Solvent method	Hypoxia	Sustain oxygen delivery by topical application	90

Solubility enhancement

Drugs having low solubility is one of the major challenges for formulation development scientists. NS can enhance solubility by dissolution rate and improve the therapeutic efficacy of the drug.[70] Rao *et al.* investigated the effect of β-cyclodextrin NS for solubility and dissolution rate enhancement of Rilpivirine a BCS class -II drug and found upto a three-fold increment in solubility and dissolution of the drug.[71]

Encapsulation of Gases

Cyclodextrin-based carbonate NS proved their efficiency in the entrapment of three gases namely oxygen, carbon dioxide, and 1-methyl cyclopropene in their studies.[72] Trotta et al, have identified and illustrated the unambiguous gases entrapment property of NS. These entrapped gases have their biomedicinal usage, the oxygen-ensnared NS delivers the gas to hypoxic tissues, and 1-methyl cyclopropane shows greater antiethylenic capability in long-lasting cut flower.[73]

Absorbent in treating poison in the blood

Human red blood cell nanosponges are used for the detoxification process. By injecting these NS they absorb and remove the toxins or poisonous substances from the blood without using any antidote and help in the neutralization and purification of blood without producing any immunogenic or antigenic effect in the host body.[74]

Antiviral application

Nanosponges offer good target delivery of antiviral agents from different routes like oral, nasal, parenteral, etc., and overcome the limitations associated with the antiviral drugs such as dose, dosing frequency, solubility, poor pharmacokinetics, and pharmacodynamics.[45] Nanocarriers fabricated with beta-cyclodextrin have shown good entrapment and release kinetics at the target site.

Cellular nanosponges have proved their effectiveness in the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by acting and neutralizing the virulent effect of the virus.[75]

Apart from drug delivery NS has other applications which are illustrated in Figure 9 and a short summary of the recent advancement in drug delivery by using NS formulations is depicted in Table 2.

CONCLUSION

According to the study, it was concluded that NS can be formulated in different types, by using different polymers and different methods. They showed a wonderful ensnare capacity leading to the entrapment of both lipophilic and hydrophobic drugs and improving their pharmacokinetics and pharmacodynamic characteristics by releasing the drug in a controlled, predictable manner at target sites. Owing to the nanometric size they can be formulated for various routes of administration like oral, inhalation, parenteral, topical, etc., leading to a reduction in dose and dose-related side effects and improved patient compliance. Additionally, the numerous applications of nanosponges like solubility enhancement, target delivery of anticancer, antiviral, and antifungal agents, entrapment of gases, removal of toxins and pollutants and biocatalysts, etc., proved their usage as a leading frontier in modern drug delivery.

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