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NANOSPONGES A VERSATILE DRUG DELIVERY FOR THE ENHANCEMENT OF BIOAVAILABILITY: A REVIEW

M. R. Prashanth[*1], E. Gopinath[1], Farooq Sayyed[1], Vineeth Chandy[1]

[1*]Department of Pharmaceutics, T. John College of Pharmacy, Banglore-560083, Karnataka, India.

ABSTRACT

A promising technique for delivering medications to the desired spot is pharmaceutical nanotechnology. They are widely used in both illness diagnosis and treatment. A cutting-edge technology called nanosponge allows for the regulated delivery of medication for targeted sites. They are minuscule particles with nanoscale cavities that can encapsulate a wide range of medications. They are beneficial as a result of their improved bioavailability and stability. By cross linking CD (cyclodextrin) with carboxylate, nanosponges can be made (cross-linkers). They come in a variety of forms, including Polyamidoamine NS, Modified NS, CD-based carbamate NS, CD-based carbonate NS, and CD-based ester NS. Both oral and topical preparations use them. For the manufacture of Nanosponges, several techniques have been used, including the melt method, solvent method, and ultrasound-assisted synthesis, among others. Polymers, co-polymer, cross-linkers and bioactive substances are used in the manufacture of nanosponges. Proteins, enzymes, antibodies, and vaccinations can all be effectively transported using nanosponges.

KEYWORDS

Nanosponge, Polymers, Cross-linkers and Preparation.

Author for Correspondence:

Prashanth M R,
Department of Pharmaceutics,
T John College of Pharmacy,
Bangalore-560083, Karnataka, India.

Email: mrprashanth65@gmail.com

INTRODUCTION

Researchers have struggled to deliver drugs to the proper location in the body while also managing their release to avoid overdosing. As of right now, development has been heavily influenced by the intricacy of chemistry required in creating new systems. By using nanotechnology to create new, complicated molecules, this issue can be resolved[1]. Nanoparticles, nanocapsules, nanospheres, nanosuspensions, nanocrystals, nano-erythosomes, etc., have all been created so far using

nanotechnologies. Materials created at the nanoscale level to exhibit unique features make up nanotechnology. Materials with dimensions less than 100 nanometers are referred to as nanomaterials. Biocompatible materials, textile fictionalization, UV-blocking coatings, medication delivery, DNA delivery, enzyme immobilization and other uses for nanoparticles are only a few examples.

In a broad sense, the term "nanotechnology" refers to the design, production, characterization, and application of various nanoscale materials in a variety of fields, primarily the medical industry. It also refers to the development of active ingredients at the nanoscale[2].

The design, manufacture, characterization, and application of numerous nanoscale materials in a range of disciplines, primarily the medical business, are collectively referred to as "nanotechnology" in its broadest sense[3].

The mechanism that can be employed for prolonged, targeted drug administration is called a nanosponge. These are nanometric-sized particles that can have a polymeric coating around a medication or other core substance. The compound that improves the drug's solubility, dissolving rate, and stability makes this system advantageous[4].

Nanosponges are small molecules known as cross-linkers combined with a three-dimensional network-like structure. As a result, hollow sphere-shaped particles containing cavities for medication storage are created.

The main benefit of the nanosponges is that the medicine may be released in this system at a predictable rate[1].

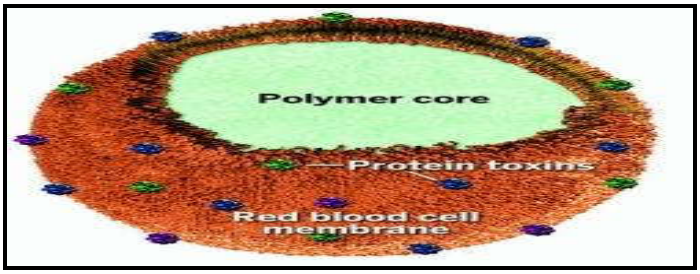


Figure No.1: Polymer-based nanospongs

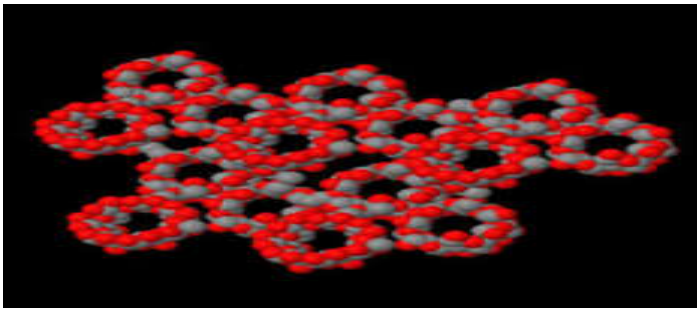


Figure No.2: Cyclodextrin based nanosponge

The backbone of nanosponges, which resemble a three-dimensional network or scaffold, is long polyester fibers. It is combined in a solution with tiny molecules known as cross-linkers that connect various polymer components by acting as teeny-tiny grappling hooks. The result is the formation of spherically shaped particles with cavities that can hold medicinal molecules. Because polyester is biodegradable, it degrades over time in the body. By adjusting the ratio of cross-linkers to polymer, it is also feasible to change the size of the nanosponge particles, allowing for either larger or smaller particles (Based on the structure of Nanosponges Figure No.1 and Figure No.2)[5].

Advantages[1-7]

This method offers ingredient entrapment and minimizes side effects.

Better formulation flexibility, increased elegance, and improve bioavailability.

They are self-sterilizing because bacteria cannot pass through their 25¼m average pore size.

Nanosponges can considerably minimize medication irritability while maintaining medicinal efficacy.

Scaling up for commercial manufacturing is simple.

Prolonged release: They have a non-collapsible structure that allows the controlled and predictable release of the active components.

The nanosponges system is biodegradable, non-toxic, non-allergic, and non-irritating.

Improved performance of the product: The therapeutic index and duration of pharmacological activity can be increased by integration into the carrier system.

Enhances the processing of materials by allowing the integration of immiscible liquids. Powders can be created from liquids.

Characteristic Features of Nanosponges[8]

Nanosponges offer a variety of diameters (1μm) with variable cavity polarity.

By altering the crosslinker-to-polymer ratio, it is possible to create nanosponges of a particular size.

Depending on the circumstances of the processing, they take on Para crystalline or crystalline forms. The nanosponge's crystal structure is essential for the complexation of drugs with them.

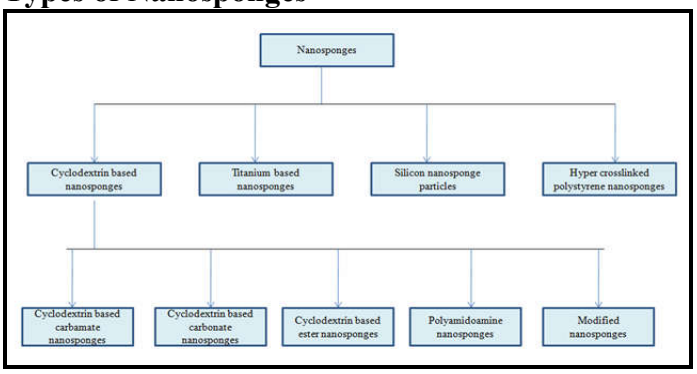
Their three-dimensional design enables the capture, transport, and controlled release of several drugs.

They can link with several functional groups, which enables them to be situated at various target places.

Nanosponges can create inclusion- and non-inclusion-containing complexes by forming complexes with pharmaceutical drugs.

Magnetic characteristics can also be added to nanosponges by including magnetic particles in the reaction mixture.

Types of Nanosponges[8]



Cyclodextrin based Nanosponges

The term "cyclodextrin nanosponges" (CDNS) was initially introduced by DeQuan Li and Min Ma in 1998 to describe a cross-linked -cyclodextrin with organic diisocyanates that results in the creation of an insoluble network and indicates a high inclusion constant with diverse organic contaminants.

In the pharmaceutical industry, cyclodextrins are predominantly used because

They are semi-natural compounds made from renewable starch through a very straight forward enzymatic conversion.

Environmentally friendly methods are used to make them in thousands of tonnes annually.

By choosing the appropriate type of cyclodextrin, its derivatives, or its method of application, any harmful effects are secondary and can be removed[8].

CD-based carbamate nanosponges

These nanosponges can bind to organic molecules and are used for water purification. The loading capacity for organic molecules ranges from 20 to 40mg per cm3[8].

CD-based carbonate nanosponges

Active carbonyl compounds like CDI, DPC, and triphosgene are the primary crosslinkers used to manufacture this type of nanosponges. The resulting CD nanosponges exhibit carbonate bonds between two CD monomers. Due to their non-hygroscopic nature, they maintain their crystal structure both during moisture absorption and desorption. The ability of CD-based carbonate nanosponges to increase solubility depends heavily on their level of crystallinity, which is a distinctive characteristic[8].

CD-based ester nanosponges

These nanosponges are made by crosslinking an appropriate dianhydride, such as pyromellitic anhydride. Due to the presence of a polar free carboxylic acid group, this form of nanosponges can accommodate both cations and apolar organic molecules concurrently[8].

Polyamidoamine Nanosponges

These nanosponges are made by performing the reaction in water. They have acidic and basic residues, which causes them to swell in water (pH dependant behavior). When the polymer comes into contact with water, a translucent gel forms immediately[8].

Modified Nanosponges

Traditional carbonate-based nanosponges have been modified to better suit the application by altering the reaction conditions. These nanosponges interact with biologically significant carriers like biotin, chitosan, or proteins, perhaps resulting in a promising medication targeting action for a particular receptor[8].

Chemicals used for the synthesis of nanosponges[9]

Polymers	Hyper cross linked Polystyrenes, Cyclodextrines and its derivatives like Methyl β-Cyclodextrin, Alkyloxycarbonyl Cyclodextrins, 2-Hydroxy Propyl β-Cyclodextrins and Copolymers like Poly(valerolactone-allyl valerolactone) and Poly(valerolactone allyl valerolactone oxepane dione), Ethyl Cellulose and PVA
Cross linkers	Diphenyl Carbonate, Diarylcarbonates, Diisocyanates, Pyromellitic anhydride, Carbonyldiimidazoles, Epichloridrine, Glutaraldehyde, Carboxylic acid dianhydrides, 2, 2- bis(acrylamide) Acetic acid and Dichloromethane
Polar solvents	Ethanol, Dimethylacetamide, Dimethyl formamide

FACTORS INFLUENCE NANOSPONGE FORMATION

TYPE OF POLYMER AND CROSS LINKERS

The kind of polymers and crosslinkers utilized affects how nanosponges develop and function. Effective cross linkers create three-dimensional, nanoporous structures from molecular nanocavities. Hydrophilic or hydrophobic components that can trap desired chemicals can be created by varying the degree of crosslinking. Depending on the type of crosslinkers, water-soluble or insoluble nanosponge structures could develop. It is possible to create hydrophilic nanosponges by employing epichlorohydrin as a crosslinker. They can alter the rate of drug release, improve drug absorption via biological barriers, and serve even in formulations for immediate release as effective drug carriers[9].

Type of drug

For successful entrapment into nanocavities, drug molecules that will be complexed with nanosponges must possess several unique properties. It is simple to trap drug molecules in the nanocavity of nanosponges if their molecular weight is between 100 and 400 Daltons and they have fewer than five condensed rings. The medicinal compounds should have lower melting points when put into nanosponges. A hydrophilic medium will take the organic guest molecules into hydrophobic cavities, whereas an organic solvent tends to release the organic molecules that are trapped in nanosponges. The interaction between drug molecules and nanosponge cavities greatly depends on the medium. The polarity, size, hydrophobic environment and structural similarities of the host and guest molecules must all be compatible to produce these powerful interactions[9].

Complexation temperature

The stability constant of a complex is negatively associated with temperature variations. The apparent stability constant's magnitude decreases with temperature because there is less contact between the medication and the nanosponge. Hence, when making nanosponges, precise temperature control should be kept. Drug/nanosponge complexation may be impacted by temperature fluctuations. The magnitude of the apparent stability constant of the drug/nanosponge complex often decreases as temperature rises, which may be a result of a potential reduction in drug/nanosponge contact forces like Van-der Waal forces and hydrophobic forces[9].

Mechanism of drug release

Nanosponges constitute a three-dimensional cross-linking polymer structure. The amount of cross-linking polymer added to the formulation can alter the trapping and solubilizing efficacies of nanosponges. Nanosponges' toroidal form enables them to have cavities inside the structure that can accommodate different kinds of drug molecules. As they have this kind of structure, they can serve as drug carriers for a variety of medications. The drug will release at the target spot as long as the active ingredient is compatible with the geometry and polarity of the cavity. The structure of the nanosponge, which may be changed based on the needs of drug release, plays a critical role in determining when these active chemicals will be released. The surface of the nanosponge can also be coated with several ligands or carriers to direct the molecules to different bodily areas[10].

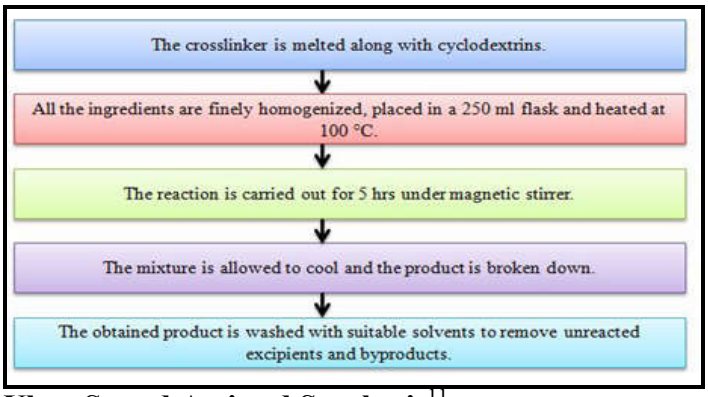
METHOD OF PREPARATION OF NANOSPONGES

Melt method

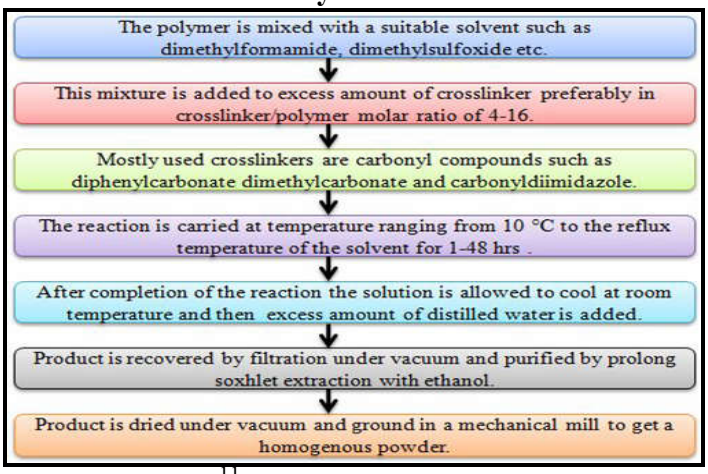
Ultrasound-assisted synthesis

Solvent method

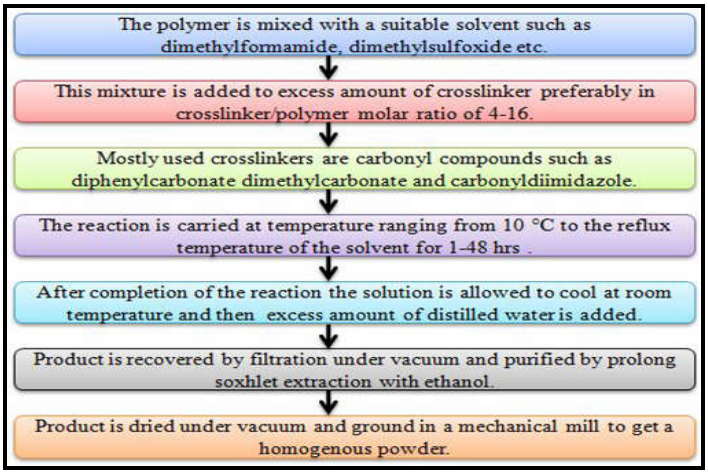
Melt Method[11]



Ultra Sound Assisted Synthesis[11]



Solvent Method[11]



LOADING OF DRUGS INTO NANOSPONGES

The nanosponges used in this procedure are first processed to produce particles with a size smaller than 500nm. To avoid the presence of aggregates, nanosponges are suspended in water and subjected to sonication. The suspension is then centrifuged to separate the colloidal fraction. Using a freeze-drying technique, the sample's liquid is separated and dried. The vast amount of the medication is manufactured and dispersed into the aqueous suspension of nanosponge, which is then kept constantly stirring for the precise period needed for complexation. After complexation, centrifugation was used to separate the undissolved drug from the dissolved drug. The solvent evaporation process or the freeze-drying procedure is then used to produce solid crystals[2].

Characterization of nanosponges

Thermoanalytical methods

It demonstrates that modifications take place in the drug substance beforethe thermal destruction of nanosponges. The medication may undergo polymeric transition, melting, evaporation, oxidation, or breakdown. Drug substance changes suggest complex formation. DTA and DSC were monitored for peak broadening, peak shifting, and peak emergence. If weight loss changes, this could be proof that inclusion complexes have formed[12].

Microscopy studies

To examine the microscopic features of drug nanosponges and products, transmission and scanning electron microscopy are used. Under an electron microscope, the raw components and the finished product have different crystallization states[12].

Solubility studies

It is the most popular method for examining inclusion complexes and is mostly explained by Higuchi and Connor's equation for phase solubility, which also aids in examining the impact of nanosponge on drug solubility[12].

IR spectroscopy

It is utilized to calculate the solid-state interaction between medicinal molecules and nanosponges. When a little portion of a molecule is encapsulated

in a complex, less than 25% of the band, it frequently changes and is assigned to contain a portion of another molecule, which is designated by bands in the spectrum of nanosponges. The use of IR is restricted to certain medications that contain bands or characteristics like carbonyl or sulfonyl groups. Information about hydrogen in different functional groups is included in IR studies. As a result of the stretching vibration of the group implicated in hydrogen bond formation, absorbance bands move to a lower frequency, intensify, and broaden[12].

X-ray diffractometry

Using powder x-ray diffractometry, inclusion complexes in the solid state are found. If we consider liquid, it completely differs from an uncomplicated nanosponge and lacks its diffraction pattern. If the drug is a solid material, a comparison between the mechanical combination of dry samples and the presumed complex diffractogram should be done to see how the latter affects diffraction patterns. A physical mixture's diffraction pattern is produced by the fusion of two elements. Yet complexes that produce "new" solid phases with distinct diffractograms have diffraction patterns that mostly depend on the constituents they include. They cause various peaks to develop in a mixture and help figure out how chemicals break down and complexes form[12].

Loading efficiency and product yield

It describes the effectiveness or assessed by quantitative estimation of drug loaded into nanosponges using UV and HPLC procedures.

$$Loading\ efficacy = \frac{\text{actual drug content in nanosponge}}{\text{theoretical drug content}} * 100$$

After accurately establishing the beginning weight of the raw material and the end weight of the produced nanosponge, the production yield of nanosponges may be estimated using the below equation[13].

$$product\ yield = \frac{practical\ mass\ of\ nanosponge}{theoretical\ yield\ (polymer + drug)} * 100$$

Zeta potential

It measures surface charge and, with the addition of an electrode, allows for the measurement of particle size[12].

Drug release kinetics

The release date was examined using models for zero order, first order, Higuchi, Korsemeyer-Peppas, Hixon Crowell, Kopcha, and Makoid-Banakar (NS). Data analysis is possible using the tool GraphPad Prism. According to which experimental findings and the non-linear function fit each other the best, the software chooses the non-linear function's parameters[13].

In the *Vito* dissolution test

To examine the dissolution profile of nanosponges, the dissolving apparatus USP XXIII with a modified basket constructed of 5m stainless steel mesh and a rotating speed of 150rpm can be utilized (NS). The dissolving media is selected while considering the actives' solubility to establish sink conditions. Samples from the dissolving media can be examined using an appropriate analytical procedure[14].

Nanosponges-based marketed formulation

S.No	Drug	Nanosponge vechicle	Indication
1	Paclitaxel	β-cyclodextrin	Cancer
2	Tamoxifen	β-cyclodextrin	Breast cancer
3	Camptothecin	β-cyclodextrin	Cancer
4	Econazole nitrate	Ethylcellulose, polyvinyl alcohol	Antifungal
5	Itraconazole	β-cyclodextrin and copolyvidonum	Antifungal
6	Resveratrol	β-cyclodextrin	Inflammation, cardiovascular diseases, dermatitis, gonorrhea
7	Antisense	Sodium Alginate	Cancer

Application of nanosponges in healthcare and environment

Cyclodextrin-based nanosponges are regarded as innovative drug delivery methods that can be exploited in pharmaceutical formulations. Insolubility, permeability, sensitivity and other issues can be resolved by molecularly encasing the drug and making other alterations with the right cyclodextrin-based nanosponges, allowing for the safe and effective delivery of medications[11].

Cancer treatment

As Nanosponges products are three to five times more effective at reducing tumor development than direct injection of pharmaceuticals, they play a significant role in drug delivery, notably in the treatment of cancer. The ultrafine nanosponges are packaged in such a way that the medications are loaded and exposed to the specified site where the peptides are bound to the Nanosponges for discharging their cargo and the cell surface receptors that are radiated. A plant alkaloid recognized for its anticancer activity, camptothecin, was isolated from the stem and bark of *Camptotheca acuminata* and is a potent antitumor agent. Camptothecin displayed a regulated release of medication, was able to protect the labile groups and displayed increased solubility when it was entrapped in cyclodextrin-based NSs.

The first Nanosponges that contained Paclitaxel was created using the cross-linker diphenyl carbonate and administered orally to increase bioavailability. Paclitaxel-loaded Nanosponge had an encapsulation efficiency of more than 99%, and after 24 hours at 72°C, only around 1.7% of the drug crystallised[15].

Nanosponges for solubility enhancement

The solubility in water is a crucial component that is required for the formulation of pharmaceuticals since it is a significant issue that has an impact on how well the drug formulations work. This can be fixed by using NS as a carrier system, which helps to entrap the medication into a specific pore and increases the bioavailability and solubility of drug formulations in controlled release profiles[15].

Removal of organic pollutants from water

Through entrapment into cyclodextrin-based NS, the medication resveratrol's solubility was also improved. To increase solubility, cyclodextrin-based NS was also employed to entrap the HIV medication rilpivirine. For the creation of a Nanosponge, carbonyldiimidazole, and pyromellitic dianhydride were utilized as cross-linking agents together with beta-cyclodextrin. A threefold improvement in dissolution with the benefit of trapping the heavy metals was observed after the medicine was loaded into the produced Nanosponges using the solvent evaporation method[15].

In enzyme immobilization

Because it enhances their stability and controls qualities like enantioselectivity and reaction speeds, enzyme immobilization is particularly beneficial for lipases. As a result, the market for new solid supports that are appropriate for this family of enzymes is continually expanding. Pseudomonas fluorescens lipase adsorbed on a brand-new kind of cyclodextrin-based NSs showed remarkable catalytic capabilities, according to Boscolo *et al*[16].

Nanosponges as a carrier for biocatalysts and in the delivery and release of enzymes, proteins, vaccines and antibodies

There are numerous mechanisms for transporting enzymes and proteins, including hydrogels, nano- and microparticles, and liposomes. Carriage in a certain system can alter the pharmacokinetics of proteins, prevent them from degrading, and increase they're *in vivo* stability. Cyclodextrin-based nanosponges have now been discovered to be an especially effective carrier for the adsorption of proteins, enzymes, antibodies, and macromolecules.

It is possible to maintain enzyme activity and efficiency, prolong operation, increase the pH and temperature range of activity and conduct continuous flow processes, in particular when enzymes are used. Moreover, by adsorbing or encapsulating proteins and other macromolecules in cyclodextrin nanosponges, they can be transported[3].

Carrier for calcium delivery

Enteric-coated calcium carbonate-based Nanosponges were created by Pravin Shende *et al*. They effectively bind to free phosphate ions and release calcium in a controlled manner. This crosslinking enhanced stability and aids in calcium regulation without having any negative side effects[17].

Biomedical application

In hospitals and the medical field, where the storage of oxygen can occasionally be challenging, the nanosponge system is used. For various gases, such as carbon dioxide, methyl cyclopropane and oxygen-carrying Nanosponges that are utilized to give oxygen during hypoxic circumstances, the formulation of carbonate Nanosponges based on cyclodextrin produces inclusion complexes[17].

CONCLUSION

For controlled and predictable topical medication administration, nanosponges have been produced. Drugs that are hydrophilic or lipophilic can be encapsulated. Increased bioavailability and improved drug solubility are both provided by NS. These colloidal particles are nanoscale and easily pass through the skin. Drugs can be entrapped using NS, which also offers benefits like improved stability, elegance, formulation flexibility and a decrease in side effects. Several dosage forms, including topical, parenteral, oral, aerosol, tablet and capsule, can be created for modifying nanosponges. Potential uses for nanosponges include biomedicine, cosmetics, agrochemistry, solubility improvement, and catalysis.

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CONFLICT OF INTEREST

We declare that we have no conflict of Interest.

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