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Nanosponges: Revolution in Nanotechnology

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ABSTRACT

Nanosponges are the advancement in nano technology, which are the conspicuous answers for the various formulation challenges like low aqueous solubility, controlled release and targeted release. Nanosponges do not show the bursting release which is the main obstacle in the most of the nano particles formulations. Nanosponges are a novel class of nanoparticles with nanostructured hyper branched polymers and few nanometres wide cavities, in which a large variety of substances can be encapsulated. Nanosponges also have colloidal sizes with a mean diameter of less than 1 μm and narrow size distribution and form opalescent suspensions on dispersion in water. The formulation of nanosponges involves simple chemistry. Nanosponges could be a perfect solution for resolving the scalability issues of various nano approaches in the pharmaceutical industry, paving the way for a nano-revolution.

Keywords: nanosponges, controlled release, targeted release, colloidal sizes.

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INTRODUCTION

Nanosponges are a novel class of nanoparticles with nanostructured hyper branched polymers and few nanometres wide cavities, in which a large variety of substances can be encapsulated.

In 2006 there was a 1 in 5,000 chance of small molecule therapeutics to advance from the discovery phase to FDA approval. It has been estimated that 90% of those failed due to issues associated with efficacy or safety[1]. The Nanosponge drug delivery platform is a network of specific polymers that slowly degrades and thus releases the chosen drug. Nanosponges are in nano size with sponge like morphology. These can be formulated into different formulations in several routes like Oral, Parenteral, Topical and Transdermal. Nanosponge is like a three dimensional network or scaffold[2]. The nanosponge is produced through fairly simple chemistry. The researchers developed simple, high-yield so-called "click chemistry" methods for making the nanosponge particles and for attaching the linkers[2]. Nanosponges contain many pores which will be filled by drug molecules. These are complex structures, normally built up from long linear molecules that are folded by crosslinking into a more or less spherical structure, about the size of a protein. By adding various materials, it is possible to control pore size, porosity and surface charge density which, in turn, makes nanosponges an interesting prospect for the delivery of many different types of drugs. The surface charge plays an important role in the attachment of different dendriomers. Some molecular transporters can be attached to the nanosponges which will easily enter the cell membrane and also drags the drug molecule along with nanosponge.

Nanosponges also have colloidal sizes with a mean diameter of less than 1 μm and narrow size distribution and form opalescent suspensions on dispersion in water. The zeta potential of carbonate nanosponges is about −25 mV, which is sufficiently high to produce stable water suspensions that do not undergo aggregation over time[3].

Conventional formulations of topical drugs are intended to work on the outer layers of the skin. Typically, such products release their active ingredients upon application, producing a highly concentrated layer of active ingredient that is rapidly absorbed. The nanosponge system can prevent excessive accumulation of ingredients within the epidermis and the dermis. Potentially the nanosponge system can significantly reduce the irritation of effective drugs without reducing their efficacy[4].

Call for nanosponges:

- Many current drugs and drug candidates are hydrophobic and thus have low solubility in water. This limited solubility in aqueous solutions presents a challenge for effective in

vivo delivery of the drug and often hinders its therapeutic index.

- Creating or improving systems for targeted drug delivery is an area of ongoing research, and is an area of particular importance to delivering anticancer therapeutics.
- Many strategies are going on, in order to control the drug release in the efficient and required manner. Nanoparticulate formulations are the present solution for the controlled drug release. But the bursting release is the main obstacle; nanosponges among the other nanoparticulate formulations have the property of predictable drug release throughout the intended period of application or administration.
- 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 and can therefore be sterilised by autoclaving at 121 °C and 2 bar for 15 minutes. FTIR and NMR analyses before and after sterilisation show their stability and the absence of degradation[5]. In addition, they do not act as surfactants and can be easily dispersed in water[3].

COMPOSITION AND STRUCTURE OF NANOSPONGES:

Nanosponges are complex structures, normally built up from long linear molecules that are folded by crosslinking into a more or less spherical structure, about the size of a protein. Typical nanosponges have been constructed from cyclodextrins crosslinked with organic carbonates. Nanosponges mainly consists three components.

They are,

A. Polymer
B. Crosslinking agent
C. Drug substance

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. The ability of the polymer to be crosslinked depends on the functional groups and active groups to be substituted. The selection of polymer depends on the required release and the drug to be enclosed. The polymers can be used to enclose the drug or to interact with the drug substance. For the targeted drug release the polymer should have the property to attach with the specific ligands.

The various polymers that can be used in the formulation of nanosponges are, Hyper cross linked Polystyrenes, Cyclodextrins and its derivatives like Methyl β-Cyclodextrin, Alkyloxycarbonyl Cyclodextrins, 2-Hydroxy Propyl β-Cyclodextrins and Copolymers like Poly(valerolactone-allylvalerolactone) & Poly(valerolactone-allylvalerolactoneoxepanedione) and Ethyl Cellulose & PVA[6].

Crosslinking agent:

Selection of crosslinking agent depends on the structure of polymer and the drug to be formulated. Various crosslinking agents used are,

Di phenyl Carbonate, Di aryl carbonates, Di isocyanates, Pyromellitic anhydride,

Carbonyl di imidazoles, Epichloridrine, Gluterladehyde, Carboxylic acid di anhydrides, 2,2- bis (acrylamido) Acetic acid and Dichloromethane[6].

Drug substance[6]:

Drug molecules to be formulated as 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.

Depending on the structure of nanosponges, they are classified as encapsulating type of nanoparticles which encapsulates the drug molecules within its core[6]. Nanosponges are 3D structures containing cavities of nanometric size and tunable polarity. Nanosponges will encapsulate the drug and releases the drug through its nanopores in particular medium[6].

Preparation and loading of nanosponges:

Nanosponges are prepared depending on type of delivery system. Nanosponges can be prepared by optimizing formulation parameters such as drug: polymer ratio, polymer: crosslinking agent ratio and agitation or stirring speed.

Solvent method:

Mix the polymer with a suitable solvent, in particular in a polar aprotic solvent such as di methyl formamide, di methyl sulfoxide. Then add this mixture to excess quantity of the cross-linker, preferably in crosslinker/polymer molar ratio of 4 to 16. Carry out the reaction at temperature ranging from 10°C to the reflux temperature of the solvent, for time ranging from 1 to 48h. Preferred crosslinkers are carbonyl compounds (Di methyl carbonate & Carbonyldiimidazole) [7].

After completion of the reaction, allow the solution to cool at room temperature, then add the product to large excess of bi distilled water and recover the product by filtration under vacuum and subsequently purify by prolonged soxhlet extraction with ethanol. Dry the product under vacuum and grind in a mechanical mill to obtain homogeneous powder[8].

Ultra sound-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[9].

Mix the polymer and the cross-linker in a particular molar ratio in a flask. Place the flask in an ultrasound bath filled with water and heat it to 90°C. Sonicate the mixture for 5hours. Then allow the mixture to cool and break the product roughly. Wash the product with water to remove the non reacted polymer and subsequently purify by prolonged soxhlet extraction with ethanol. Dry the obtained product under vacuum and store at 25°C until further use[8, 9].

Loading of drug into nanosponges:

Nanosponges for drug delivery should be pre treated to obtain a mean particle size below 500nm. Suspend the nanosponges in water and sonicate to avoid the presence of aggregates and then centrifuge the suspension to obtain the colloidal fraction. Separate the supernatant and dry the sample by freeze drying[8].

Prepare the aqueous suspension of Nanosponge and disperse the excess amount of the drug and maintain the suspension under constant stirring for specific time required for complexation. After complexation, separate the uncomplexed (undissolved) drug from complexed drug by centrifugation. Then obtain the solid crystals of nanosponges by solvent evaporation or by freeze drying[8, 10].

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[11].

Quasi-emulsion solvent diffusion[4]:

The nanosponges can also be prepared by quasi-emulsion solvent diffusion method using the different polymer amounts. To prepare the inner phase, eudragit RS100 was dissolved in suitable solvent. Then, drug can be added to solution and dissolved under ultasonication at 35^0c. The inner phase was poured into the PVA solution in water (outer phase). Following 60min of

stirring, the mixture is filtered to separate the nanospnges. The naosponges are dried in an air-heated oven at 40^0c for 12 hrs.

Emulsion solvent diffusion method[4]:

In this method the two phases used are organic and aqueous. Aqueous phase consists of polyvinyl alcohol and organic phase include drug and polymer. After dissolving drug and polymer to suitable organic solvent, this phase is added slowly to the aqueous phase and stirred for two or more hours and then nanosponges are collected by filtration washed and then dried in air at room temp or in vacuum oven 40^0c for 24 hrs.

MECHANISM OF DRUG RELEASE FROM NANOSPONGES:

The active ingredient is added to vehicles in the entrapped form since nanosponges have an open structure (they do not have continuous membrane surrounding them) the active substance is free to move in or out from the particles into the vehicle until the equilibrium is reached. Once the product is applied to the skin, the active substance that is already in vehicle which will become unsaturated, therefore disturbing the equilibrium. This will start flow of active from nanosponges particle into vehicle from it, to skin until vehicle is either dried or absorbed. Even after that nanosponges particle retained on the surface of stratum corneum will continue to gradually release active substance to skin providing prolonged release over time[4].

Evaluation of nanosponges:

Inclusion complexes formed between the drug and nanosponges can be characterized by following methods.

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].

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 complexes [11, 12].

X-ray diffraction studies:

Powder X-ray diffractiometry 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, then 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[12]. 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[12]. The complex formation of drug with nanosponges 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[12].

Single crystal X-ray structure analysis:

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[12].

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 complexation[10,13].

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 not generally suitable to detect the inclusion complexes and is less clarifying than other methods[12]. 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[12].

Thin Layer Chromatography:

In Thin Layer Chromatography, the R_f values of a drug molecule diminish to considerable extent and this helps in identifying the complex formation between the drug and nanosponge[12].

Loading efficiency:

The loading efficiency (%) of Nanosponge can be determined by[13]

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

Particle size and polydispersity:

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[11].

Zeta potential:

Zeta potential is a measure of surface charge. It can be measured by using additional electrode in the particle size equipment[11].

Production Yield:

The production yield (PY) can be determined by calculating initial weight of raw materials and final weight of nanosponges[13].

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

APPLICATIONS OF NANOSPONGES:

1. **Nanosponges for solubility enhancement**

   One of the greatest limits to the development of various pharmaceuticals is the low water solubility of many drugs. About 40% of new drugs are poorly soluble in water, which hinders their clinical application. Nanosponges can improve the wetting and solubility of molecules with very poor solubility in water. The drugs can be molecularly dispersed within the nanosponge structure and then released as molecules, avoiding the dissolution step. Consequently, the apparent solubility of the drug can be increased. Drugs like Itraconazole, Tamoxifen, Paclitaxel are difficult to formulate due to their poor water solubility can be easily formulated as nanosponges by enhancing their solubility and attaining therapeutic efficacy[3].

2. **Nanosponges for modified release**

The drug release kinetics from nanosponges can be obtained with a prolonged release profile over time. Previous in vitro studies showed that flurbiprofen was released slowly from β-CD nanosponges[14], reaching a percentage of less than 10% after 130 minutes. In vitro, acyclovir-loaded carboxylated nanosponges[15] showed prolonged release of the drug without the initial burst effect, and 20% drug release was obtained after three hours. The release of Doxorubicin and Nelfinavir were found to be sustained when they formulated as nanosponges.

3. **Nanosponges for targeted drug delivery**

These nanosponges circulate in the body until they encounter the surface of a tumour 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 used a targeting peptide that recognized a radiation-induced cell-surface receptor. This targeting agent combined a recombinant peptide with a paclitaxel-encapsulating nanoparticle that specifically targeted irradiated tumours, thereby increasing apoptosis and tumour-growth delay. When loaded with an anticancer drug, the delivery system is three to five times more effective than direct injection at reducing tumour growth[16].

4. **Nanosponges in oral drug delivery**

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[7]. Acetylsalicylic acid (ASA), a nonsteroidal anti-inflammatory drug belonging to BCS class III, was formulated into pyromellitic dianhydride cross-linked β-cyclodextrin nanosponges for oral delivery.

5. **Nanosponges in topical drug delivery**

Nanosponges can be used in gels or creams for topical application. Resveratrol-loaded nanosponges were seen to enhance drug permeation in in-vitro studies on porcine skin. The ability of nanosponges to increase the uptake of the guest molecule by the skin can be attributed to the capacity to increase solubility at the surface of the skin, as already reported for Cyclodextrins.

6. **Nanosponges as carriers for Biocatalysts**

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. The catalytic activity of enzyme depends mainly on the correct orientation of the active site[17]. These enzymes can be carried by the nanosponges towards the chemical transformations which can resist high temperatures and speeds.

7. Nanosponges for delivery & release of enzymes, proteins, vaccines and antibiotics

Proteolytic enzymes can be used to treat cancer or type I muco polysaccharidosis, while DNA and oligonucleotides are used in gene therapy. The administration of these molecules presents 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[17]. Now, it has been found that Cyclodextrin based nanosponges are particularly suitable 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[17].

8. Nanosponges for cancer treatment

Encapsulating the anticancer drug in the nanosponge allows the use of hydrophobic drugs that do not dissolve readily in water. Currently, these drugs must be mixed with adjuvant reagents, which potentially can reduce the efficacy of the drug or cause side effect[16]. The drug used for the animal studies was paclitaxel, the active ingredient in the anticancer therapy Taxol. The researchers recorded the response of two different tumour types—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 tumour growth compared with other chemotherapy approaches.

9. Nanosponges as chemical sensors

Metal oxide "nanosponges" as chemical sensors used in highly sensitive detection of hydrogen using nanosponge titania. In a nanosponge structure, however, there are no contact points. Consequently, there is much less hindrance to electron transport and results higher sensor stability. 3-dimensionally (3D) interconnected nanosponge titania (NST) is highly sensitive to H_2 gas.3D interconnected metal oxide nanostructure is a promising class of sensor material through which the ultra-high chemical sensitivity of nanostructures can be harnessed in practical devices[18].

10. Nansponges as carrier of gases

Gas storage and delivery play an important role in biology, medicine, cosmetics and pharmaceuticals. Nanosponge formulations can act as a reservoir for various types of gas. β-CD nanosponges have shown an ability to store large amounts of carbon dioxide, 1-methylcyclopropene and oxygen[19]. The nanosponges were able to release oxygen both in the presence and in the absence of ultrasound (US). All types of nanosponges were able to encapsulate, store and release oxygen for prolonged periods. Ultrasound enhanced the in vitro release and permeation of oxygen. The nanosponge/ hydrogel system produces a slower sustained release of the gas. Therefore, nanosponges could be suitable carriers for topical oxygen delivery in the presence and in the absence of US and could act as an oxygen reservoir[3].

11. Nanosponges for protection from light or degradation

Nanosponges can also be used as carriers to protect encapsulated molecules from light or from chemical and enzyme induced degradation. To evaluate the potential protection application, 5-fluorouracil was used as a light-sensitive model drug with β-CD nanosponges. Moreover, encapsulation of 5-fluorouracil in nanosponges protected the drug and maintained its cytotoxicity against MCF-7 cells. Another paradigmatic example was established with the incorporation of camptothecin in cyclodextrin nanosponges. The encapsulation of camptothecin in nanosponges was used to prolong the shelf life and release of the drug[20]. The nanosponges solubilised large amounts of the drug and protected the lactone ring from opening due to its high inclusion abilities, thereby increasing stability.

Nanosponges can be used to store and prolong the release of volatile molecules, such as essential oils, following their encapsulation. Linalool, a liquid component of many essential oils and fragrances with a boiling point of 198°C, was encapsulated in different

types of nanosponges as a liquid oil model[21].

12. Nanosponges to remove impurities or pollutants

Nanosponges based on cyclodextrins can strongly bind organic molecules and remove them from water even at very low concentrations[6]. 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.

DRUGS FORMULATED AS NANOSPONGES:

Examples of nanosponges[22]:

Drugs	Nanosponge Vehicle	Therapeutic Benefit
Antisense oligonucleotides	sodium alginate Poly L-lysine	cancer therapy, viral infection, Pathogenic disorders
Camptothecin	β- Cyclodextrin	cancer
Dexamethasone	β- Cyclodextrin	Brain tumours
Econazole nitrate	Ethyl cellulose, Polyvinyl alcohol	Anti fungal
Itraconazole	β- Cyclodextrins, Co polyvidonum	Anti fungal
Paclitaxel	β- Cyclodextrin	Cancer
Resveratrol	β- Cyclodextrin	Inflammation, Cardiovascular diseases, Dermatitis, Gonorrhoea, Fever, Hyperlipidemia
Tamoxifen	β- Cyclodextrin	Breast cancer
Temozolamide	Poly (valerolactone-allylvalerolactone),Poly (valerolactone-allylvalerolactone-oxepanedione)	Brain tumours

Molecules complexed by using nanosponges[3]:

Drug	Log p	Therapeutic administration	Route of administration
Dexamethasone	1.9	anti-inflammatory	oral, parenteral
Flurbiprofen	4.2	anti-inflammatory	oral
Doxorubicin	1.3	anti neoplastic	parenteral
Progesterone	3.9	hormonal	oral
Itraconazole	5.7	antifungal	oral, topical
5-fluorouracil	-0.9	anti neoplastic	parenteral, topical
Tamoxifen	4.0	anti estrogen	oral
Resveratrol	2.8	antioxidant	oral, topical
Paclitaxel	2.5	anti neoplastic	parenteral
Camptothecin	1	anti neoplastic	parenteral
Omeprazole	2.2	anti ulcerative	oral
Nelfinavir mesylate	4.6	anti viral	oral
Acetylsalicylic acid	1.2	analgesic	oral
Acyclovir	-1.6	anti viral	oral,topical,parenteral
Gamma-oryizanol	-	anti oxidant	topical
Telmisartan	7.7	anti hypertensive	oral

DRAWBACKS OF NANOSPONGES:

The main disadvantage of these nanosponges is their ability to include only small molecules[3].

The nanosponges could be either paracrystalline or in crystalline form. The loading capacity of nanosponges depends mainly on degree of crystallisation. Para crystalline nanosponges can show different loading capacities. So the formation of these crystalline and paracrystalline forms determines the release and encapsulation efficiency[23]. This anomalous formation depends on the various formulation and processing parameters.

CONCLUSION:

Formulations developed with NS can be considered super generics, and the pharmaceutical industries will be benefited greatly if clinical studies can prove their potential for human use. By the literature produced so far, it can be concluded that NS have versatile applications in the drug delivery field, including solubilization, stabilization, and modulation of drug release, cellular internalization, and site targeting. In addition to their application in the drug delivery field, potential applications exist for cosmetics, biomedicine, bioremediation processes, agro chemistry, and catalysis, among others. NS could be a perfect solution for resolving the scalability issues of various nano approaches in the pharmaceutical industry, paving the way for a nano-revolution. We hope that a number of NS formulations with improved physicochemical characteristics as well as efficacy will hit the market in coming years.

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