REVIEW ARTICLE

A Review on Phytochemical Loaded Nanosponges

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ABSTRACT

Nanomaterials, particularly nanosponges, have shown significant promise in drug delivery and cancer therapy due to their excellent penetration, absorption, biocompatibility, bioavailability, and stability. Nanosponges are crystalline, crosslinked, polymer structures, nansized, porous, and have three-dimensional, hyper-reticulated, structures that are capable of encapsulating an assortment of compounds. Other examples include cyclodextrin based nanosponges, which can be used to create complexes with drugs to increase their solubility and bioavailability as can be seen with its use in delivering lapatinib anticancer drug. Although they are at a very early stage of development and only small molecules are covered, current research is concerned with creativity that innovative designs and synthesis processes have to be made in order to enhance their efficacy and safety. The phytochemical loaded nanosponges are an up and coming development in the field of drug conveyance that shows promising new solubility, controlled discharge, targeting, and upgraded stability of helpful chemicals. The nanosponges are flexible and can be used in a variety of applications, whether it is medical or cosmetic, environmental or food industry. As an example, they can complex with anticancer phytochemicals like curcumin, quercetin and resveratrol where they enhance their therapeutic benefit. Nonetheless, issues like manufacturing complexities, possible toxicity, and regulatory issues need to be surmounted. All in all, phytochemical packed nanosponges offer a new and efficient approach to utilize the therapeutic potential of natural molecules; thus, this is an interesting direction in the development of nanomedicine and cancer treatment.

Keywords: Novel Drug Delivery, Nanosponges, Phytochemicals and Nano Medicine

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INTRODUCTION

Nanomaterials have, of late, received a lot of research due to their possible uses in treating cancer and in drug delivery. However, further studies with greater details are required in order to find out prospects in developing effective delivery techniques that possess high-level biocompatibility, as well as biodegradability, a key element in targeted therapies[1,2].

The effects of nanomaterials on physiological environments and on their nanotoxicological characteristics, pharmacokinetics, pharmacodynamics, metabolism, and the drug-release mechanism e.g., diffusion, erosion, targeting, swelling, dissolution, and osmosis are yet to be studied and specifically require studies in clinics. Nanosponges may also be reported as ideal carriers of targeted cancer treatment and drug delivery due to their high biocompatibility, bioavailability, and stability. Hyper-crosslinked and 3- dimensional (3D) nanoporous polymer structures are the foundation of a different form of nanosponges in which the crosslinked, solid polymer-based pores are hydrophilic and are not water-soluble. They demonstrate superb durability at many different pHs and temperatures, which means they can have many different biomedical uses[3].

The bioavailability of drugs may be enhanced by nanosponges containing cyclodextrin or noncyclodextrin[4]. A non-inclusion complex is created when the drug is trapped by the porous structures of the nanosponges rather than an inclusion complex, in which the drug bonds to the cyclodextrin. A variety of applications have been studied for nanosponges containing cyclodextrin, including drug delivery, remediation of environmental contamination, gas detection, and catalysis. The internal cavities of nanosponges can encapsulate hydrophobic molecules, while the hydrophilic exterior polymer network can accommodate less lipophilic substances. Incorporating drugs into nanosponges can enhance their solubility and biodegradability, thereby improving their bioavailability[5]. Lapatinib is highly soluble and bioavailable in nanosponges, reducing the oral dosage by improving solubility and bioavailability.

Additionally, these nanostructures are not able to incorporate large molecules, which makes them undesirable. Nanosponges are still in their developmental phase, and further studies should aim at creating novel nanosponge-based systems, either on their own or combined with other polymers, for pharmaceutical and biomedical uses[6,7]. In addition to cyclodextrin nanosponges, hypercrosslinked polystyrene, silicon, DNAzyme, and ethylene glycol nanosponges are also available[8]. Biopharmaceuticals, phytochemicals, volatile oils, anticancer agents, genetic material, proteins, and peptides can all be encapsulated in nanosponges[9]. For instance,

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peptide nanosponges (~80 nm) have been developed for use in cell-based cancer therapies. As well, nanosponges based on cyclodextrin can be used to eliminate toxic molecules from the body, such as indole, potentially without the need for dialysis[9,10].

Nanosponges, which typically range in size from about 200 to 300 nm, can be found in both crystalline and para-crystalline forms. The crystallization of these structures is determined by the synthesis and processing conditions, which subsequently influence their ability to load drugs[11]. Nanosponges can be synthesized using a wide range of techniques, including interfacial phenomena, hot melting, hypercrosslinked cyclodextrins, ultrasounds, etc. A complete list of techniques for synthesizing molecules includes assistant synthesis to condensate solvent, microwave assisted synthesis, interfacial condensation, mechanical synthesis, chain-growth polycondensation, and emulsion solvent evaporation. Despite these advancements, there is still a need for more environmentally friendly, safer, and cost-effective synthesis methods[12].

A microwave synthesis produces crystalline cyclodextrin nanosponges with narrow particle size distributions. It involves cyclodextrin reacting with suitable crosslinkers in polar aprotic solvent dimethyl formamide[13,14]. Another approach is ultrasound-assisted synthesis, which produces nanosponges with uniformly spherical sizes and offers environmentally friendly products and low-impact manufacturing.

The cyclodextrin-derived nanosponges have different forms, including molecularly imprinted, plain, and modified nanosponges. A molecularly imprinted nanosponge's ability to select and specific toward a specific molecule facilitates its biomedical applications[15,16]. The unique qualities of cyclodextrin nanosponges include high crosslinking density, low toxicity, sustainability, and environmental friendliness[17,18]. These features make them ideal for use in bio- and nanomedicine, where they have been explored for forming complexes with both hydrophilic and lipophilic molecules for targeted delivery, protecting these molecules from degradation.

Nanosponges can be modified with various materials, such as carbon nanotubes, silver nanowires, titanium dioxide (TiO_2). In addition to enhancing protein-cell interactions, cholesterol-functionalized cyclodextrin nanosponges facilitate protein transport[19,20]. To enhance the bioavailability of the nanosponges, doxorubicin was functionalized into them[21]. Since nanosponges have distinct pores, a substantial amount of research has demonstrated their effectiveness for encapsulating drugs and therapeutic agents. A large number of studies have demonstrated that nanosponges can reduce drug toxicity and adverse effects. The nanosponges also deliver drugs over a longer period of time, which makes them superior to conventional delivery methods. As a result of enhanced penetration, chitosan nanosponges improved trans-epidermal drug absorption compared to free drugs[22]. A substantial amount of research still needs to be conducted, however, before nanosponge-based dosage forms can be used in clinical settings. An effective product is one that is pharmacokinetically active, recyclable, bioavailable, biocompatible, cytotoxic, and histopathologically assessed. This discussion focuses on nanodextrin, DNAzyme, ethylcellulose, and cancer treatments based on these technologies.

Phytochemicals and their Importance

There are natural compounds in plants called phytochemicals and phytonutrients. These organisms play a large role in protecting plants from pests, diseases, and harsh environmental conditions. For humans, these compounds are vital due to their potential health benefits, which contribute to the prevention and management of various diseases. A summary of the phytochemicals and its significance is provided here:

Phytochemical-loaded Nanosponges

Nanosponge technology of phytochemicals hold the potential to establish a new dimension in the delivery of drugs and even therapeutic measures. Nanosponges are nanoparticles, that have the porous structure of sponge. They are made to impart the encapsulation of different goods including drugs in the body. The porous structure enables them to store active ingredientes within their body, and regulate its release[23].

Applications of Phytochemical-loaded Nanosponges

Medical Applications

Cancer Treatment: Curcumin, quercetin and resveratrol are phytochemicals that have been found to possess anticancer activity. The delivery of nanosponges can be boosted by encapsulation which leads to improved therapeutic effect because the nanosponges will be delivered in the tumor sites.

Antimicrobial Therapy: Infections may also be treated using Nanosponges and make them more than capable of beating antibiotic resistance by loading them with antimicrobial phytochemicals.

Anti-inflammatory Therapies: Anti-inflammatory phytochemicals provide a new potential to get localized delivery of anti-inflammatory therapies to the sites and aid in conditions such as arthritis and inflammatory bowel disease.

Cosmetics

Skincare: Nanosponges can enhance the delivery of antioxidants and other beneficial phytochemicals in cosmetic products, improving skin health and appearance.

Anti-aging: Encapsulation of anti-aging phytochemicals ensures better penetration and prolonged effects on the skin.

Environmental Applications

Pollutant Removal: Phytochemical-loaded nanosponges the method described above can be used to purify water and soil, leveraging the natural detoxifying properties of certain phytochemicals.

Agriculture: They can be used to deliver plant growth-promoting phytochemicals or protect plants from pests and diseases in a controlled manner[24,25].

Food Industry

Food Preservation: Phytochemicals with antimicrobial and antioxidant properties can be encapsulated in nanosponges to extend the shelf life of food products.

Nutraceuticals: Delivery of health-promoting phytochemicals through food products can be enhanced using nanosponges, improving their absorption and efficacy.

Nanosponges for Drug Delivery

Nanosponges, with their tiny porous structures, are effective carriers for water-insoluble drugs. As well as being soluble, permeability-enhancing, and dissolution-enhancing, they make drug complexes more facile to dissolve. Nanosponges based on cyclodextrin deliver drugs three to five times more effectively than conventional nanosponges, according to a study. Inhalation, parenteral injection, topically applied, or oral injection can be performed with nanosponge. Various lubricants, diluents, and anti-cracking agents are added to nanosponge complexes before they are incorporated into tablets or capsules for oral administration[26].

Nanosponges for Cancer Therapy

Delivering anticancer drugs is particularly challenging due to their low solubility. A nanosponge complex reduces tumor growth three times better than direct injection. These complexes can be loaded with drugs and targeted to tumor cells using peptides that bind to receptors on the cell surface[27]. Upon encountering a tumor cell, nanosponges adhere to its surface and gradually release the drug, enhancing therapeutic effects while minimizing side effects at the same dose in Figure 1.

Nanosponges for Protein Delivery

A cyclodextrin-based nanosponge was evaluated using bovine serum albumin as a model protein. Typically stored in a lyophilized form due to instability, BSA and other proteins face the risk of denaturation during this process. Cyclodextrin-based nanosponges enhance the stability and long-term storage of such proteins, aiding in their formulation and development[28]. These nanosponges are also useful for enzyme immobilization, controlled delivery, and protein stabilization.

Nanosponges for Treating Fungal Infections

Topical therapy is preferred for skin fungal infections due to its targeted drug delivery and reduced systemic side effects. Econazole nitrate, a common antifungal, is traditionally available in various forms such as creams and lotions. However, its adsorption through the skin is minimal, requiring high concentrations for effectiveness. A conazole nitrate therapy can be enhanced by using nanosponges of emulsion solvent incorporated into hydrogels. A cyclodextrin-based nanosponge can also make itraconazole more soluble and bioavailable[29].

Nanosponges for Antiviral Applications

Nasal epithelia and lungs can be treated with nanosponges for fighting respiratory syncytial viruses, influenza viruses, and rhinovirus infections. In addition to zidovudine, saquinavir, interferon, and acyclovir in sponges (based on Eudragit), sponges can also be used to administer HIV, HBV, and HSV treatment[45].

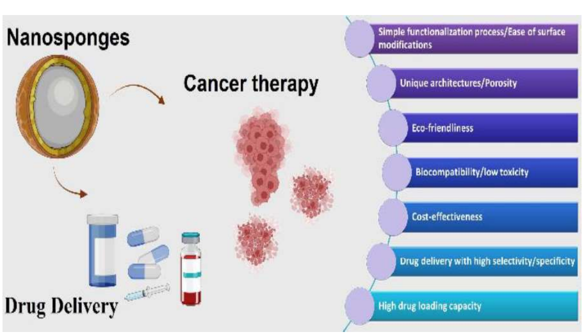

Figure 1: Nanosponges in cancer therapy

Encapsulation of Gases

As a result of the manufacturing process, nanosponges made from this material can form inclusion complexes between oxygen, carbon dioxide, and 1-methylcyclopropene. This capability is particularly useful in biomedical applications, such as delivering oxygen to hypoxic tissues. The highly porous structure of nanosponges makes them efficient gas carriers, capable of controlling the accumulation and release of gases[46,47].

Nanosponges as Absorbents for Treating Poison in Blood

Nanosponges can absorb and remove poisonous substances from the blood, offering an alternative to antidotes. When injected into the bloodstream, nanosponges mimic red blood cells, attracting and absorbing toxins. The absorption capacity of each nanosponge depends on the type of toxin.

Other Applications of Nanosponges

In these circumstances, nanosponges are highly effective in removing bitter compounds from grapefruit juice due to the fact that they bind to organic molecules in water and remove them effectively. Peptide fractionation can be accomplished with them in proteomics. It is also possible to use nanosponges to transport oxygen and carbon dioxide gases.

Advantages

The nanosponges that have been loaded with phytochemicals are favorable in various aspects in the field of medical and pharmaceuticals. The great advantages are as shown in Figure 2:

1. Higher Solubility and Bioavailability-Phytochemicals are usually insoluble in water hence low bioavailability. By enhancing their solubility, nanosponges can help increase the body values of such compounds and make them readily absorbed by the body.
2. Controlled and Sustained Release: Nanosponges can offer a controlled and a sustained release of phytochemicals which provide consistent and a long-term effect. This aids in the sustenance of the targeted drug level in the blood.
3. Targeted Delivery: Nanosponges are capable of being programmed to target specific tissues or cells and therefore have the advantage of minimizing the side effects on the healthy tissues and improving the effectiveness of the phytochemicals.
4. Higher stability: Phytochemicals tend to become unstable. The protectability of the compounds to degradation through the environment namely light, heat and alteration of pH can be achieved through encapsulation in nanosponges.
5. Decreased Toxicity: Since the delivery and release of phytochemicals can be controlled with the use of nanosponges, toxicity caused by high doses may be reduced and make the treatment safer overall.
6. Improved Permeation: Nanosponges are known to improve the permeative capabilities of phytochemicals across the biological membranes which include the gastrointestinal tract and the blood brain barriers, making them more therapeutically effective.
7. Versatility: The nanosponges have the advantage of being able to load many different physicochemical

Table 1: Comprehensive overview of nanosponges for drug delivery

Drug	Nanosponge Vehicle	Indication	Study
Paclitaxel	Cyclodextrin-based nanosponges	Cancer Therapy	Evaluated for improved solubility and controlled release of paclitaxel in cancer treatment[30].
Curcumin	Polymeric nanosponges	Anti-inflammatory, Anticancer	Studied for enhanced bioavailability and targeted delivery in cancer therapy[31].
Doxycycline	Biodegradable nanosponges	Antimicrobial Therapy	Investigated for improved stability and targeted delivery to infected tissues[32].
5-Fluorouracil	Cyclodextrin-based nanosponges	Cancer Therapy	Explored for enhanced drug delivery in colorectal cancer treatment[33].
Ibuprofen	Polymeric nanosponges	Pain Management	Studied for controlled release in chronic pain management[34].
Tamoxifen	Cyclodextrin-based nanosponges	Breast Cancer Therapy	Investigated for improved bioavailability and reduced systemic toxicity[35].
Insulin	Biodegradable nanosponges	Diabetes Management	Explored for oral delivery of insulin to enhance bioavailability and patient compliance[36].
Rifampicin	Cyclodextrin-based nanosponges	Tuberculosis Therapy	Studied for enhanced solubility and targeted delivery to lung tissues[37].
Fluconazole	Polymeric nanosponges	Antifungal Therapy	Investigated for improved delivery and sustained release in fungal infections[38].
Vancomycin	Biodegradable nanosponges	Antibacterial Therapy	Studied for targeted delivery and enhanced efficacy in treating bacterial infections[39].
Ketoconazole	Cyclodextrin-based nanosponges	Antifungal Therapy	Explored for enhanced solubility and targeted delivery[40].
Celecoxib	Polymeric nanosponges	Anti-inflammatory, Pain Management	Investigated for controlled release and enhanced bioavailability[41].
Resveratrol	Biodegradable nanosponges	Antioxidant, Anti-inflammatory	Studied for improved solubility and bioavailability in treating chronic conditions[42].
Quercetin	Cyclodextrin-based nanosponges	Antioxidant, Anticancer	Explored for enhanced delivery and therapeutic efficacy in cancer and cardiovascular diseases[43].
Clozapine	Polymeric nanosponges	Schizophrenia Therapy	Investigated for controlled release and improved bioavailability[44].

properties phytochemicals rendering them a versatile drug delivery platform.

8. Scalability and Easy Manufacturing: Nanosponges can be produced in a relatively easy and scale-up manner and therefore become a feasible option commercially when developing drugs.

9. Shielding against Gastrointestinal Enzymatic Degradation: In the GI tract, phytochemicals are vulnerable to enzymatic breakdown, a fact that nanosponges are capable of shielding.

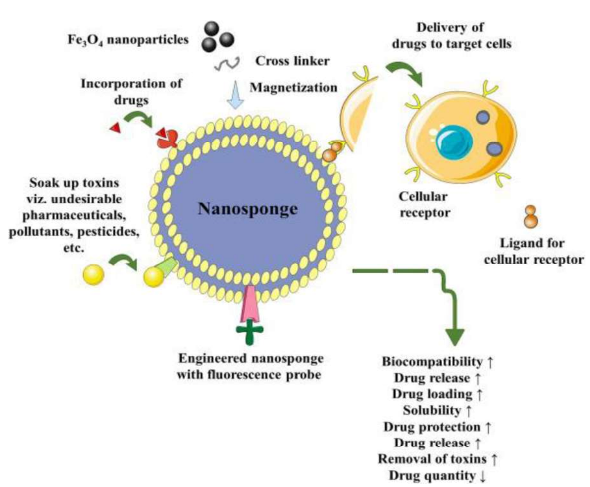

Figure 2: Applications and advantages of nanosponges

10. Lower Dose Frequency: Nanosponges controlled release formulations can offer lower dose frequency, which is more convenient and increases the patient compliance.

These are some of the reasons why phytochemical loaded nanosponges may become an effective method, alongside creating more potent and non-toxic therapeutic agents, based on naturally produced products.

Disadvantages

Although phytochemical-loaded nanosponges have a number of benefits, it is possible to realize a number of potential drawbacks related to the utilization of these nanosponges:

1. Involved Manufacturing Process: Nanosponges can have a complicated and advanced manufacturing process, which implies the need of specialised equipment and skill. This will make production more expensive and difficult.

2. Scale-up Issues: The production that is lab scale needs to be transferred to industrial scale, which can also prove challenging and may include some issues to do with uniformity, consistency and quality of the nanosponges.

3. Potential Toxicity: Nanosponges have the potential to cause the reduction of the toxic effect of phytochemicals, but the underlying material used in the formulation of nanosponges can be toxic in itself. Biocompatibility and toxicity surveys should be done in detail.

4. Regulatory Hurdles: Nanosponges are still so new that obtaining regulatory approval may be difficult; the

nanosponges may be poorly understood by the regulators. They need much documentation and testing to prove their safety and efficacy.
5. Stability Problems: Although it is quite possible to enhance the stability of phytochemicals loaded on nanosponges, the nanosponges can be subject to degradation themselves over time or under specific storage conditions, which can affect shelf life of the product.
6. Cost: Nanosponges may be costly since their production and development may be expensive thus making the end product expensive as well compared to standard formulations.
7. Low Knowledge and Studies: Nanosponges are a newer field and there might not be much information about long-term implications, the best formulations and all possible side effects.
8. Unintended Interactions: Since nanosponges are likely to bind to other molecules, it is possible that the reaction between nanosponges and the biological system will be unintended. These interactions require detailed investigations to be able to comprehend them.
9. Environmental Impact: There may be environmental implication of the production and disposal processes of nanomaterials, such as nanosponges, nanoparticles. It is imperative that such materials do not have an adverse effect on the environment.
10. Patient Acceptance: Reluctance or objection to the adoption of new technologies is perhaps felt by patients and/or healthcare providers, on the one hand, who may be reluctant when unfamiliar to new technologies or when they are regarded as, or they themselves may regard them to be, experimental.
11. Drug Loading Capacity: Drug loading capacity of nanosponges could be a limiting factor due to which it cannot be used in some applications where large amounts of phytochemicals are needed.
12. Release Kinetics: The desire release kinetics may be difficult to achieve. Excessive rate of release can cause toxicity and slower release can cause sub-therapeutic levels.
The only way to overcome these drawbacks is through continuous research and development to overcome these shortcomings, and to coordinate different scientists, regulatory and industry stakeholders so that it is apparent that phytochemical-loaded nanosponges can be used which would be safe and effective.

CONCLUSION

The phytochemical-loaded nanosponges are on the forefront of using nanotechnology and natural products. These nanocarriers can change many areas (such as healthcare and environmental management) by increasing the delivery, stability and efficacy of the phytochemicals. With the development of research, we can expect new ways of possibilities of use and better formulations taking advantage of the advantages of the given technology.
Basically, phytochemical loaded nanosponges provide a potential future in nanomedicine, especially when it comes to enhancing the delivery transport, and efficacy of natural therapeutic agents used in the management of cancer. Their planning and execution would change the way cancer is treated and have more effective as well as non-toxic cancer treatment. The technology offers a new and effective way to utilize therapeutic potential of natural combinations. It promises great potential in the drug delivery system and expansion of the level of plant derived compounds by improving phytochemical solubility, stability, and target delivery. To conclude, the concept of phytochemical-loaded nanosponges is a novel drug delivery vehicle that can be used, in particular, in cancer treatment. These nano-sized transporters enhance the solubility capacity, stability and bioavailability of plant based natural substances, the phytochemicals, which has therapeutic impacts.

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