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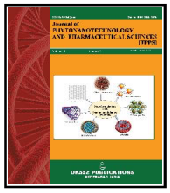

Review Article : Open Access

Nanosponge: A novel approach to cancer treatment

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Abstract

Novel or advanced nanocarriers design can help deliver anticancer drugs directly to tumour tissue, improving medical treatment and drug effectiveness. Nanosponges (NSs) have the ability to effectively deliver a broad spectrum of medications, both lipophilic and hydrophilic, thereby improving their solubility and bioavailability. These particles are designed to transport drugs through the bloodstream to the specific area of the body where they are required, such as a tumour site. Once these particles reach their intended destination, they adhere or "attach" to that site. This attachment triggers the release of the drug, depositing the medication directly where it is most needed. This targeted approach can increase the effectiveness of the drug and reduce potential side-effects since the medication is concentrated at the required site, rather than being distributed throughout the entire body. Medicinal plants offer vital compounds for medicine, including those with anticancer properties that suppress cancer cell growth and induce cell death. Nanotechnology, with its tailored nanoparticles, presents a new, promising direction in cancer combat, potentially reducing systemic toxicity and overcoming multidrug resistance. Beyond their therapeutic benefits, these particles also hold significant diagnostic value. NSs surpass traditional methods, offering improved absorption, stability, controlled release, and reduced drug toxicity. In light of the many scientific investigations, this review compiles and simplifies the most recent advancements in the medical application of NSs for cancer therapy.

1. Introduction

Nanotechnology is a scientific field that focuses on manipulating matter at the atomic, molecular, and super molecular scale, with the aim of designing, producing, characterizing, and applying various nano-scale materials in different fields, particularly medicine (Trotta *et al.*, 2014). The potential impact of nanotechnology in medicine is vast, encompassing immunology, cardiology, endocrinology, ophthalmology, oncology, pulmonology, and other specialized areas such as brain and tumour targeting, as well as gene delivery. In addition, nanotechnology offers a broad spectrum of systems, devices, and components able to improve the effectiveness of pharmaceutical applications (Lakshmi *et al.*, 2021).

Scientists are working towards achieving targeted delivery in drug delivery research. Targeted drug delivery technology has renewed interest in pharmaceuticals, by enabling them to selectively reach their therapeutic targets and improve the treatment of cancer. Future trends in therapeutics aim to improve therapeutic efficacy, reduce side effects, and optimize dosing through precise administration of drugs to cancer patients. The concept of targeted drug delivery is to deliver drugs precisely to the intended treatment area, thereby sparing healthy cells. This technique is particularly beneficial when dealing with anticancer medications, which are typically potent and can cause damage to healthy cells or tissue if not properly targeted. By focusing the drug delivery on the cancerous cells, the harmful side effects of these medications can be reduced, leading to fewer overall health complications. In addition, because the drugs are delivered directly to the cancer cells, their effectiveness in combating the disease can be significantly increased (Jilsha and Viswanad, 2013; Thakre *et al.*, 2016).

Nanosponges (NSs) represent an innovative formulation in drug delivery, especially in cancer treatment. These porous particles are made up of a biocompatible polymer network, and their small size allows them to absorb and release a wide range of medications. They have the ability to target specific body areas and can be used for dispensing chemotherapy drugs, proteins, and even nucleic acids. This method enhances drug effectiveness and reduces side effects. Moreover, NSs can be tailored to target cancer cells specifically, ensuring efficient drug delivery while protecting healthy tissues. Taking a targeted approach to cancer treatment could yield significant improvements in therapeutic outcomes while minimizing the likelihood of adverse side effects. These developments are truly encouraging and position nanosensors as an exciting new frontier in the battle against cancer (Patil *et al.*, 2017). In essence, the evolution of NSs marks a substantial advancement in the realm of drug delivery, with considerable promise for numerous medical uses, notably in cancer treatment.

The aim of this review is to illustrate a short summary of the recent progress made in the field of cancer therapeutics using NSs. This review is restricted to small molecule therapies in cancer research to maintain its specific focus.

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2. Methodology

Throughout the literature review, multiple search terms were employed, including "nanosponge", "antineoplastic", "cytotoxicity" and "anticancer drugs", in order to probe the potential use of various anticancer drugs in nanosponge formulations. To simplify the process of finding relevant information in electronic databases, books, and journals, search terms have been prefixed with "nanosponge". Several databases, including Google Scholar, ResearchGate, PubMed, Elsevier Scopus, and MAPA, were used to find relevant English language studies published between January 2010 and March 2022. Out of 43 publications screened, we identified 21 papers that satisfied our eligibility criteria, which included only primary studies. Only peer-reviewed articles were considered during the evaluation process, and duplicate articles and irrelevant contributions were excluded. For our review, peer-reviewed literature is preferred due to its scientific rigor and accuracy.

3. Advantages of NSs

NSs are an innovative material consisting of minuscule particles that possess small cavities for encapsulating a wide range of substances. These particles have the ability to carry both lipophilic and hydrophilic substances, thereby improving the solubility of molecules that are poorly soluble in water. NSs consist of a biodegradable three-dimensional scaffold or network made of polyester. This scaffold is created by mixing the polyester with a crosslinker in a solution (Jilsha and Viswanad, 2013; Shringirishi *et al.*, 2014). The biodegradable nature of the polyester allows it to gradually break down within the body. Once the scaffold of NSs degrades, it releases the loaded drug molecules in a controlled manner. The specific chemicals used for the synthesis of NSs can vary depending on the desired properties and applications of the NSs. However, a commonly used class of chemicals for the synthesis of NSs is crosslinking agents. These agents help in creating the three-dimensional network structure of the NSs. Examples of crosslinking agents include diphenyl carbonate, diarylcarbonates, diisocyanates, pyromellitic anhydride, carbonyldiimidazoles, epichloridrine, glutaraldehyde, carboxylic acid dianhydrides, 2,2-bis(acrylamido) acetic acid, and dichloromethane. Other chemicals, such as hyper cross-linked polystyrenes, cyclodextrin, and its derivatives like methyl α-cyclodextrin and 2-hydroxypropyl α-cyclodextrin, can be used as the main polymer components (Selvamuthukumar *et al.*, 2012; Singh *et al.*, 2021). It's important to note that the specific chemicals and their combinations can vary depending on the synthesis method and intended application of the NSs. Methods such as solvent-based techniques, ultrasound-assisted synthesis, and drug-loading processes are employed for the synthesis of NSs (Ahmed *et al.*, 2013; Bhowmik *et al.*, 2018).

NSs drug delivery offers several advantages for cancer treatment, including:

Nanosponges (NSs) offer numerous benefits in the field of targeted drug delivery, particularly for cancer treatment. The primary benefits of tailored pharmaceuticals are their ability to offer a significant advantage over traditional drugs. An incredible advantage of targeting cancer cells lies in the fact that it minimizes damage to neighbouring healthy tissues during tumour treatment. Secondly, NSs can dispense drugs in a controlled fashion, ensuring that therapeutic levels are sustained at the tumour location for extended periods, which can enhance the effectiveness of the treatment. In addition, the targeted delivery and controlled release properties of NSs can reduce systemic toxicity and minimize the side effects associated with chemotherapy. NSs can also improve the solubility and enhance the bioavailability of drugs by encapsulating both lipophilic and hydrophilic substances. Another key feature of NSs is their biocompatibility. Composed of biocompatible polymers, they are safe for use within the human body. In essence, incorporating NSs in drug delivery has the potential to revolutionize the field of cancer therapy. This is accomplished by improving the effectiveness of drugs, minimising toxicity, and reducing the side effects that are usually linked with traditional chemotherapy.

4. Limitations of NSs

The potential advantages of NSs in cancer treatment are promising, it's crucial to consider several challenges, including the limited drug-carrying capacity of these NSs. As a consequence, this can substantially impact the quantity of medication that reaches the desired area of treatment. Furthermore, while NSs are generally considered to be biocompatible, there is a potential risk of toxicity if they accumulate in high concentrations within certain organs or tissues or cells. Furthermore, the complex procedure involved in developing NSs could potentially hinder their availability for use in medical treatments. Moreover, NSs may encounter stability issues such as degradation or changes in their physical properties, which could potentially affect their ability to release drugs and deliver the desired therapeutic effect. Finally, it is worth considering that the production cost of NSs might be a limiting factor that could prevent their widespread adoption in certain healthcare settings. NSs have immense potential as a vehicle for drug delivery in cancer therapy, these limitations should be considered when evaluating their potential clinical use.

5. Role of NSs in cancer drug delivery

Over two decades ago, researchers devised the cyclodextrins-based NSs drug delivery system with the objective of confronting potential difficulties related to drug delivery and cancer management. NSs hold a pivotal role in cancer drug delivery, offering a promising treatment strategy that precisely and efficiently targets tumours, mitigates toxicity and side effects, thereby enhancing treatment efficacy and transforming cancer care.

Role of plant derived chemicals in cancer treatment

Medicinal plants, which are rich in bioactive compounds and have a long history of traditional use, could be a valuable resource for developing new cancer treatments. Only 5-15% of the 250,000 higher plant species around the world have been researched for their bioactive properties. Recent research indicates that phytochemicals in plants possess significant potential in combating cancer, potentially hindering the growth and spread of cancer cells. Dietary inclusion of plant-based foods such as fruits, vegetables, whole grains, and legumes may reduce cancer risks, promoting overall health. This implies a multitude of yet-to-be-discovered resources that could be instrumental in combating cancer. Significantly, approximately 70% of current anticancer drugs have been either directly derived from, or influenced by, natural products, including medicinal plants (Twilley *et al.*, 2020). Medicinal plants, compared to modern pharmaceuticals, offer benefits such as fewer side effects, holistic healing, affordability, historical usage, less dependency risk, and sustainability (Srinivasan,

2022). Despite the long-standing reliance on traditional cancer treatments like chemotherapy, radiation, and surgeries, their frequent ineffectiveness due to severe side effects and multidrug resistance has led to the emergence of phytochemicals, including alkaloids, flavonoids, terpenoids, and polyphenols, as powerful alternatives in the fight against cancer, offering potential to mitigate disease severity, suppress malignant cell proliferation, by neutralizing harmful free radicals, and modify cancer-related mechanisms (Choudhari *et al.*, 2020).

5.1 Camptothecin

Camptothecin (CAM, a pentacyclic alkaloid) has strong anti-cancer capabilities, but its therapeutic use is limited due to issues like low water solubility, instability of its lactone ring, and severe side effects. CAM functions by inhibiting DNA Topoisomerase-I. The use of β-cyclodextrin-NSs inhibited the growth and progression of anaplastic thyroid carcinoma (ATC) cells significantly faster and more effectively than free CAM. The NSs also inhibited tumour cell adhesion, migration, and expression of certain factors associated with angiogenesis. Animal studies revealed that β-cyclodextrin-NSs effectively inhibited the growth and metastasis of ATC tumours without causing toxicity. According to the findings of this study, β-cyclodextrin-NSs are a promising treatment option for ATC (Gigliotti *et al.*, 2017). In another study, the loading of CAM into three types of cyclodextrin NS with varying cross-linking ratios was investigated. The resulting formulations had particle sizes ranging from 450 to 600 nm and exhibited a slow and prolonged release over 24 hours. The NS formulations were found to protect the lactone ring of CAM during 24-hour incubation with HT-29 cells and showed higher cytotoxicity compared to plain CAM (Swaminathan *et al.*, 2010). In another study, delivering anticancer drugs to treat prostate cancer, β-cyclodextrin-NSs decrease the angiogenic activity in human endothelial cells and reduce the adhesion and migration of tumour cells. They also slow down the growth of PC-3 cell engraftment in SCID mice without any toxicity (Gigliotti *et al.*, 2016). CAM-loaded -Cyclodextrin NSs (CN-CPT) has a spherical shape, 38% drug loading, and a size of approximately 400 nm. HPLC analysis indicated that CN-CPT has a prolonged drug release, and it was found to be more effective than CPT in inducing DNA damage, cell cycle arrest, and inhibiting Topoisomerase I activity. CN-CPT also induced cell death at lower concentrations than CPT and inhibited androgen receptor expression in LNCaP cells (Minelli *et al.*, 2012).

5.2 Curcumin

Curcumin, a bioactive compound, is found in turmeric, which is derived from rhizomes of *Curcuma longa* Linn. Despite its powerful anticancer properties, curcumin (CUR) is poorly soluble in the aqueous phase and is sensitive to light. The DSC and XRD patterns revealed that curcumin became more stable and less crystalline after forming an inclusion complex with the use of pyromelitic dianhydride-crosslinked cyclodextrin NSs. It had a high encapsulation efficiency of 98% w/w and a high loading capacity. The complex did not exhibit toxicity against healthy cells but showed toxicity against cancer cells. By performing a hemolysis test on the NSs and complex, it was determined that low levels of hemolysis were observed, ranging from 0.54% to 5.09% at varying concentrations of the complex (Rafati *et al.*, 2019). In another study, a cyclodextrin NS-based hydrogel was used to deliver curcumin and resveratrol through the skin. The NSs increased the release of curcumin by 10 times and resveratrol by 2.5 times compared to plain forms. When combined as CUR-CDNS and RES-CDNS, they showed a synergistic cytotoxic effect on MCF-7 cells. A Box-Behnken design was used to optimize the hydrogel base, which significantly improved the permeation of curcumin and resveratrol (Pushpalatha *et al.*, 2019). *In vitro* drug release was significantly increased in CUR-pyromellitic dianhydride-cyclodextrin NSs compared to CUR-diphenyl carbonate-cyclodextrin NSs, and photostability of CUR was enhanced 1.7 times in pyromellitic dianhydride crosslinked NSs. The CUR pyromellitic dianhydride crosslinked NSs showed increased toxicity to MCF-7 cells at a lower concentration (Pushpalatha *et al.*, 2018).

5.3 Flutamide

Flutamide is a non-steroidal antiandrogen that is often used in combination with other treatments to manage prostate cancer. It works by blocking the action of androgens, which are hormones that promote the growth of prostate cancer cells. Low bioavailability is a common drawback associated with oral administration of Flutamide. Flutamide-loaded cyclodextrin NSs (1:4) had a higher encapsulation and faster dissolution rate of FLT compared to cyclodextrin NSs (1:2). Cyclodextrin NSs (1:4) had efficient cellular uptake and was not toxic against PC3 cells. Moreover, flutamide-loaded cyclodextrin NSs were less toxic than free flutamide. Cyclodextrin NS (1:4) can be a non-toxic and effective delivery system for flutamide with improved dissolution (Allahyari *et al.*, 2021).

5.4 Paclitaxel

Paclitaxel, a alkaloidal compound derived from the bark of the Pacific yew tree (*Taxus brevifolia* Nutt.), is extensively employed as an anticancer agent in chemotherapy for various forms of cancer. It functions by binding to microtubules in cancer cells, inhibiting cell division and ultimately causing cell death. Despite its effectiveness, Paclitaxel is associated with several side effects, such as bone marrow suppression, peripheral neuropathy, and hypersensitivity. Intravenous administration is the usual route of administration. However, to enhance its solubility and efficacy, researchers have developed several nano-formulations of paclitaxel, including liposomal and nanoparticle-based formulations. In the MCF-7 cell line culture, α-cyclodextrin NSs loaded with paclitaxel showed promising cytotoxic effects (Ansari *et al.*, 2011). In order to investigate an alternative formulation to cremophor EL's conventional paclitaxel formulation, fluorescent NSs were synthesized and tested *in vitro* on cancer cells. This enhanced anticancer activity of paclitaxel may be attributed to the NSs adhering to or interfering with the cell membrane, which facilitates the release of the drug (Mognetti *et al.*, 2012). In another study, α-cyclodextrin cross-linked NSs was utilized for chemotherapy in lung cancer to achieve a synergistic delivery of camptothecin and paclitaxel (Hariri *et al.*, 2014). By comparing paclitaxel-loaded pyromellitic NSs to paclitaxel alone, there was a significant reduction in the growth of melanoma cells, an improvement in cell division, and a decrease in tumour weight and size (Clemente *et al.*, 2019).

5.5 Resveratrol

Resveratrol is a type of polyphenol that occurs naturally in some foods and plants. Several clinical studies have shown that it can help prevent and treat various types of cancer. The main challenges for utilizing resveratrol in cancer therapy are its poor aqueous solubility and lack of selectivity. The smart drug delivery system delivers

resveratrol to cancer cells through glutathione-mediated delivery, based on cyclodextrin NSs. The cyclodextrin NSs to deliver resveratrol, achieving an 80.64% entrapment efficiency and 16.12% loading efficiency. GSH-responsive, NSs are effective in targeting cancer cells while limiting side effects on normal cells by utilizing the tumour's differential redox status (Palminteri *et al.*, 2021). The resistance to light degradation (photostability) of resveratrol and oxy-resveratrol encapsulated in β-CD-NSs was examined using a UV lamp technique, revealing that these substances in their nanoparticle states demonstrated twice the photostability compared to their original forms. β-CD-NSs encapsulating resveratrol and oxyresveratrol showed improved activity against DU-145 prostate cancer cell lines with no significant toxicity of blank NSs (Dhakar *et al.*, 2019).

5.6 Tamoxifen

Tamoxifen is a non-steroidal compound with anti-estrogenic properties that is employed for the treatment and prevention of breast cancer. It is a selective oestrogen receptor modulator, which means it binds to oestrogen receptors in breast tissue and prevents the hormone from binding to these receptors. This reduces the growth and spread of breast cancer cells. β-cyclodextrin NSs were synthesised by the solvent evaporation method (particle size of 400–600 nm) and proved to be an effective nanocarrier for oral tamoxifen delivery. Promising cytotoxic activity against the MCF-7 cell line was observed upon oral administration of the β-cyclodextrin NSs. The use of NSs based on β-cyclodextrin has been shown to be an effective method for delivering Tamoxifen in the treatment of cancer (Torne *et al.*, 2013).

6. Conclusion

NS-based systems show promise for targeted drug delivery and cancer therapy. They have many advantages, including high porosity, easy modification, unique structures, environmental friendliness, and cost-effectiveness. The integration of nanotechnology in medicine shows promise in addressing the limitations of current cancer therapies. NSs have been specifically designed to tackle the various challenges posed by physical, chemical, and biological factors in disease treatments. NSs represent a drug delivery system capable of carrying both hydrophilic and hydrophobic drugs. They can be formulated for various administration routes, including oral, parenteral, and topical systems. NSs offer several advantages for delivering anticancer drugs, including the protection of drug molecules, controlled and sustained release, ensuring drug stability, reducing the dose and bitterness of drugs, overcoming biological barriers, targeted tissue localization, and improved bioavailability. Their ability to adapt makes them exceptionally well-suited for use as diagnostic agents, fulfilling a vital function in cancer imaging and other associated applications. In addition to drug delivery, NSs have potential applications in various fields, including cosmeceuticals, nutraceuticals, food industry, industrial waste management, and agrochemicals, *etc*. The technology behind NSs finds wide application in the pharmaceutical industry, allowing for the development of drugs that provide safe, effective, and sustained release.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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