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Review Article

Stimuli-Responsive and Functionalized Nanosponges: Precision Delivery to the Tumor Microenvironment

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ABSTRACT

Background: Cancer, a primary cause of mortality worldwide, is also challenging to treat because of its complexity and diverse forms. WHO has expressed the need for innovative ways to treat this serious problem. There are more than a hundred types of cancers. The hallmark of cancers is metastasis. Although oncology is evolving, a complete cure seems a distant goal. Major reasons include tumor progression, poor drug solubility, weak tumor-targeting, and off-target effects resulting in systemic toxicity which worsen survival. **Objectives:** This review aims to critically evaluate the advances in nanosponge-based drug delivery systems for cancer therapy, with emphasis on their potential to overcome the existing therapeutic barriers. The discussion centers on design strategies, mechanisms of action, and their role in tumor targeting thus improving treatment efficacy and safety. **Materials and Methods:** The review provides an overview of the structure, preparation, and characterization of nanosponges. It specifically examines the challenges posed by the Tumor Microenvironment (TME) and the attempts being made to optimize nanosponges tailored to address such complexities through passive and active targeting strategies like surface modification or stimuli responsiveness. **Results:** Nanosponges possess a unique porous nature with high loading capacity for both hydrophilic and lipophilic drugs. These carriers enhance site-specificity and bioavailability, thereby effectively reducing the required dose and minimizes adverse off-target effects. **Conclusion:** Optimized nanosponges tailored for the TME represent a promising frontier in intelligent drug delivery. They serve as a vital tool for advancing precision oncology and improving patient survival.

Keywords: Cancer, Functionalized, Nanosponges, Stimuli responsive, Surface modified.

INTRODUCTION

Cancer is a disorder characterized by uncontrolled growth of cells along with resistance to apoptosis, hence making it one of the most difficult disorders to treat.[1] According to the World Health Organization's 2024 report, cancer is the second leading cause of mortality worldwide, accounting for nearly 20 million new cases and 9.7 million deaths in 2022, while the global burden may exceed 35 million cases by 2050 according to projections.[2] This disease primarily arises due to genetic modification induced by various carcinogenic factors such as chemical agents, microbial infections, radiations, and tobacco use, many of them being closely related to day-to-day lifestyle risks.[3,4]

Although treatment modalities such as surgery, radiotherapy, hormonal therapy, immunotherapy, and chemotherapy are being widely used, their clinical effectiveness is often limited by drug resistance, poor tumor selectivity, and low solubility. Besides, commonly used agents such as paclitaxel and tamoxifen normally require very long and physically burdensome intravenous treatment.[5,6] Consequently, current researchers are now proposing nanosponges, or NS, as safer yet more targeted drug delivery systems with capabilities for improving therapeutic efficacy while minimizing systemic toxicity.

METHODOLOGY

A narrative approach has been employed in preparing this review to outline Stimuli-Responsive and Functionalized Nanosponges: Precision Delivery to the Tumor Microenvironment. Literature searches were made through PubMed, Scopus, and Google Scholar as well as standard textbooks relevant to the keywords; nanosponges, cancer, surface modified, functionalized, stimuli responsive.

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Inclusion criteria: peer-reviewed articles, WHO guidelines, and case studies published over the past 30 years (search period:1994-2025). Exclusion criteria: non-peer-reviewed sources, non-English articles language, duplicates, studies unrelated to pharmaceutical applications, grey literature or conference abstracts. The final articles were reviewed and qualitatively synthesized to highlight recent advances in precision drug delivery strategies.

REVIEW OF LITERATURE

Barriers to drug delivery in Solid Tumors and Strategies to overcome them

Growing evidence shows the critical role of the tumor microenvironment in promoting tumor growth and resistance to chemotherapy, all of which directly influence the success of drug delivery in cancer therapy. Addressing these multifaceted barriers requires a deeper understanding of cancer biology, which is essential for the development of new therapeutic strategies for improving drug penetration, targeting efficiency, and overall treatment results.[7]

Biological Barriers

Biological barriers to treatment include opsonization, selective endothelial permeability, glycocalyx barriers, and hemodynamic forces. PEGylated allows prolongation of nanoparticle circulation in the bloodstream.[8,9] The permeability and gaps within the endothelial layer of tumors are greater than those for normal tissues and result in the extravasation of even larger particles because of poor lymphatic drainage.[10]

It is important to consider the size heterogeneity of the pores in primary tumors, metastasized tumors, and even within a primary tumor. Such heterogeneity adds more difficulties to the use of the Enhanced Permeability and Retention (EPR) effect.[11]

Tumor Microenvironment

Tumor Microenvironment (TME) refers to the Extracellular Matrix (ECM) consisting of interlacing collagen, elastin, proteoglycans, and hyaluronic acid that sustain tumor integrity and extra-cellular interactions.[12] In addition, the highly compressed ECM slows down nanoparticle migration, and as a consequence, the addition of collagenase or tumor-secreting Matrix Metalloproteinases (MMPs) has been suggested as a biomarker.[13] Tumor microenvironments also include hypoxic regions (1-2%) compared to 3-6% in normal tissues, an aspect that fuels tumor cell invasion, angiogenesis, and resistance. Tumor microenvironments' acidity has been harnessed to achieve targeted release of therapeutic drugs utilizing acid-sensitive polymers.[14,15] Polymers such as polyethylenimine-Schiff base, (styrene-co-maleic anhydride) poly(beta-amino ester) poly and poly(2-(ethylmethacrylate)diisopropyl-amino)have demonstrated the ability to release drugs selectively within the tumor core.[16]

Femminò *et al.*, prepared oxygen-functionalized cyclodextrin NS to combat hypoxia,[17] whereas Caldera *et al.*, synthesized pH-responsive NS that expands at low pH sites to release doxorubicin.[18] Hyperthermia increases the permeability and uptake with temperature-sensitive polymers or lipids as the triggering agents at the tumor sites. The addition of moieties such as ferric oxide, peptides, albumin, avidin, cyclodextrin, and/or gelatin allows the drug delivery to take place in response to acidic pH, redox potential, and/or enzyme activity.[7]

Cellular Barriers

Barriers to cell entry include the size, charge, and hydrophobicity of the carrier. Particles with a size of less than 200 nm use clathrin-mediated endocytosis, and larger particles use clathrin-independent uptake.[19] Nanosponges (NS) take up tumor toxins, secretions, and debris. Biomimetic NS with erythrocyte membranes have good circulation and toxin clearance.[20] Negatively charged spherical NS take up various molecules. This increases the effectiveness of chemotherapeutic agents for drug-resistant cancers.[21] Erythrocyte-coated PLGA nanoparticles (<500 nm) have good circulation and liver clearance upon loading. Cancer cells overexpress numerous receptors such as transferrin, folate, EGFR, VEGF, and integrin for ligand-targeted delivery of NS.[22-24] Cholesterol-conjugated cyclodextrin NS have good interaction, uptake, and delivery of drugs.[25]

Vesicular barriers and Drug Efflux transporters

Only a fraction of the original drug dose remains effective at the target site, partly due to tumor efflux pumps like P-glycoprotein that expel drugs. To counter this, small-molecule inhibitors can be used. Arima *et al.*, developed dimethyl-β-cyclodextrin Nanosponges (NS) loaded with tacrolimus, which in rat studies showed improved bioavailability and dissolution. A pretreatment of the apical membrane with dimethyl β-cyclodextrin further caused the transporters to dislodge, functionally preventing the p-glycoprotein transport function as well as increasing drug uptake.[26,27]

Significance of Novel Drug Delivery Systems against Cancer

Nanocarriers increase therapeutic concentrations but reduce the side effects, yet the majority of anticancer compounds have poor solubility and achieve poor oral bioavailability. Lipophilic anticancer drugs require solvents. Methods like co-solvent delivery systems, surfactant-based systems, complexation-based delivery systems, and particulate delivery systems are being used to improve the solubility of poor water-soluble drugs.[28,29] Also, water-soluble nanoparticles made from polymers and lipid vesicles are easily capable of entrapment for hydrophobic drugs; however, their use has limited scope due to their inability

to produce a monodispersed particle of size <200 nm and their large polydispersity index.[30] Similarly, use of dendrimers and albumin-based proteins to make nanoparticles allows efficient drug loading; however, their release often faces initial burst release complications for administering exact drug release profiles. However, the branched structure of the dendrimer and biocompatibility of albumin-based nanoparticles are often preferred where size restriction may not play a crucial role regarding choice of drug delivery systems based on therapeutic requirements.[31]

Role of Nanosponges for Anticancer Drug Delivery

Nanosponges (NS) are a promising frontier in drug delivery due to their porous nature, nontoxicity, insolubility in water and organic solvents, and stability across wide pH ranges (1-11) and temperatures up to 300°C. These colloidal, cross-linked nanocarriers (<1 micron) can encapsulate hydrophilic or hydrophobic drugs, including anticancer agents, proteins, peptides, essential oils, and DNA.[32] A major advantage is their ability to circulate until reaching the target site, where they adhere and release drugs in a controlled manner, minimizing waste in healthy tissues. Compared to micelles, liposomes, dendrimers, and protein-based nanoparticles, NS excel in size and regulated drug release for chemotherapy.[33]

Nanosponges vs Nanoparticles

Nanoparticles release drug payloads instantly, creating unpredictable burst effects complicating dosage determination.[34] NS made from biodegradable polymers gradually release drugs in controlled manners. NS are insoluble in aqueous and organic solvents, non-toxic, heat-stable, and exceptionally versatile. Their porous structure dissolves insoluble drugs after loading. NS loading and surface modification are easier than those of other nanoparticles.[35] Unlike complex nanoparticles difficult to produce at large scale, NS composed of polymers and crosslinkers are simpler to scale for commercial manufacturing and can be easily reformulated using eco-friendly solvents.[36,37]

Composition and types of Nanosponges

Nanosponges (NS) comprise polymers, cross-linkers, and drugs. Polymers form the backbone, defining cavity size for drug loading and controlled release, while biocompatible, biodegradable polymers allow customization. Cross-linking is proportional to polymer substitution, with cross-linkers creating the porous network.[38] Dependent upon the compound type, either epichlorohydrin for hydrophilic compounds, whereas Pyromellitic anhydride for lipophilic compounds. The characteristics of the drug, which include molecular weight (100-400 Dalton), ≤5 condensed rings, and a melting point of <250°C, affect biocompatibility and embedding. NS has the ability to bind hydrophilic as well as lipophilic. NS can load hydrophilic or lipophilic drugs, modifying pharmacokinetics for targeted delivery.[29,39]

Nanosponges are nanostructured materials that are usually classified according to their chemical composition and structure. Cellulose-based, silicon-based, metal oxide-based, β-cyclodextrin-based, hyper-cross-linked polystryene, metal-organic framework (MOF), and carbon-coated metallic nanosponges are examples of nanosponges. These nanostructures are highly promising for the encapsulation of drugs and controlled release of the same due to their large surface area and porous structure.[40-42]

Methods of Preparation of Nanosponges

Different methods of preparation of NS are described in the following section and the applications of these methods are enlisted in Table 1. The quality of the NS is dictated by factors such as the nature of the drug, polymers, crosslinkers, and surfactants, stabilizers, or solvents. Process variables like the speed of rotation, temperature, time period, and method of purification and collection also play a major role in the formulation of optimized NS.[43]

Solvent evaporation technique

This method exploits polymer self-assembly around drug molecules during emulsification (Figure 1(a)). Polymers and drugs are dissolved in organic solvents (dichloromethane, chloroform, ethyl acetate), reacted at specific temperatures (e.g., 100°C, 48 hr), then added dropwise to water forming o/w emulsion. Evaporation under reduced pressure with stirring forms NS, collected by centrifugation/filtration. Paclitaxel NS were formulated using this method.[50]

Polar Aprotic Solvent Method

This method employs aprotic solvents (acetone, dichloromethane, DMSO) to dissolve the crosslinker and polymer, which precipitate upon drug addition. To form NS, the polymer and crosslinker are mixed in a defined ratio and heated to the solvent's reflux temperature for 1-48 hr. After cooling the solution at room temperature it is mixed in excess double distilled water and further refined by vacuum filtration and Soxhlet extraction. The final product is homogenized and vacuum-dried.[51]

Quasi Emulsion Solvent diffusion

This process is a modification of the emulsion solvent evaporation method. Instead of traditional emulsion formation, a temporary emulsion-like environment is created by dispersing the organic phase (polymer and drug solution) dropwise into an aqueous phase containing a surfactant or stabilizer. This is done under continuous stirring or sonication for 2 hr at 1000 rpm. The nanosuspensions are then collected by centrifugation or filtration and washed to remove any residual surfactant or solvent (Figure 1(b)).[52,53]

Hyper Cross-Linking method

This method enhances the internal structure of polymers to create a highly porous material. The hyper crosslinkers like divinylbenzene and polystyrene are mixed with β-CD. Then the reaction mixture is then added to carbonyl di-imidazole and heated at 100°C for 4 hr. After the condensation of polymers is complete, excess of double distilled water is added to remove the unreacted crosslinker. Next the resultant reaction mixture undergoes Soxhlet extraction with ethanol. The product obtained is allowed to dry at 60°C in an oven overnight. The powder is then dispersed in water and lyophilized to obtain the NS.[54,55]

Green approaches for synthesis of NS

Eco-friendly methods of synthesis of NS that are simple, safe, economical and scalable are being explored.

Ultrasound Assisted Synthesis

In this method, ultrasonic waves generate cavitation bubbles in the polymer-crosslinker mixture. Their collapse under high pressure and temperature leads to Nanosponge (NS) formation (Figure 1(c)). The flask is placed in a 90°C ultrasonic water bath and sonicated for several hours. After cooling, the product is divided, washed with water to remove unreacted polymer, and purified using ethanol in a Soxhlet apparatus, yielding refined NS.[56,57]

In this method, cross-linkers (diphenyl carbonate or pyromellitic anhydride) and polymers were mixed in defined molar ratio.[58]

Melt Technique

This method (Figure (1d)) exploits polymer thermal properties to uniformly embed drugs in a molten polymer matrix. Polymers such as PLGA, chitosan, and PVA are melted above their glass transition but below degradation temperature, emulsified in aqueous surfactant, solidified, and recovered by centrifugation or filtration, yielding crystalline NS.[30,52] Amani *et al.*, (2019) prepared Ferulic acid NS using β-CD and diphenyl carbonate, homogenized at 90-100°C, purified by Soxhlet extraction, and vacuum-dried. These NS enhanced Ferulic acid solubility 15-fold, lowered IC_{50} threefold, and induced apoptosis in MCF7 and 4T1 cells.[59] Sharma *et al.*, also enhanced solubility, antioxidant activity and photostability of ellagic acid NS formulation.[60]

Microwave-Assisted Synthesis

Microwave irradiation hastening polymerization to form NS as it allows uniform heating of reaction mixtures, A blend of Cyclodextrin (CD) and crosslinker in Dimethylformamide (DMF) is exposed to microwaves at set time and temperature, with NS isolated by filtration or centrifugation. This method is about twice as fast as melting techniques.[61] Sharma *et al.*, reported microwave-assisted synthesis of CD-based NS for Ellagic acid

Table 1: Applications of different methods of synthesis of NS for treatment of cancer.

Sl. No.	Drugs	Types of NS/ Polymer used	Method of preparation	Findings	Ref.
1.	Olmesartan Medoxomil (OLM)	Ethylcellulose	Emulsion solvent evaporation method	NS enhanced drug entrapment up to three folds and higher cytotoxicity against A549 lung cell lines.	44
2.	Withaferin-A(WFA-NS)	Ethylcellulose	Ultrasonica-tion assisted emulsion, solvent evaporation	WFA-NS exhibited two-fold improved effect against MCF-7 cells with a significant stability of WFA in NS form.	45
3.	Curcumin	Eudragit L-100	Solvent evaporationmethod	Small porous nature of NS provided stable binding of Curcumin and inhibiting the metabolism and excretion thereby improved bioavailability.	46
4.	Oxyresveratrol	CD based NS	β-CD hyper crosslinking method	More robust suppression of cell viability against prostate (PC-3) and colon (HT-29 and HCT-116) cancer cell line studies.	47
5.	Doxorubicin	β-CD	hypercross-linked β-CD	Enhanced drug loading capacity, β-CD NS containing doxorubicin displayed increased ability to decrease the growth of both the ER/PR+ and the TNBC cell lines, and even of the DOX-resistant EMT6/AR10r cells.	48
6.	Quercetrin	β-CD	ultrasound-assisted synthesis method	Quercitrin loaded β-CD -NS exhibited entrapment efficiency of 94.17-99.03% and IC_{50} value improved upto1.57-5.35 fold.	49

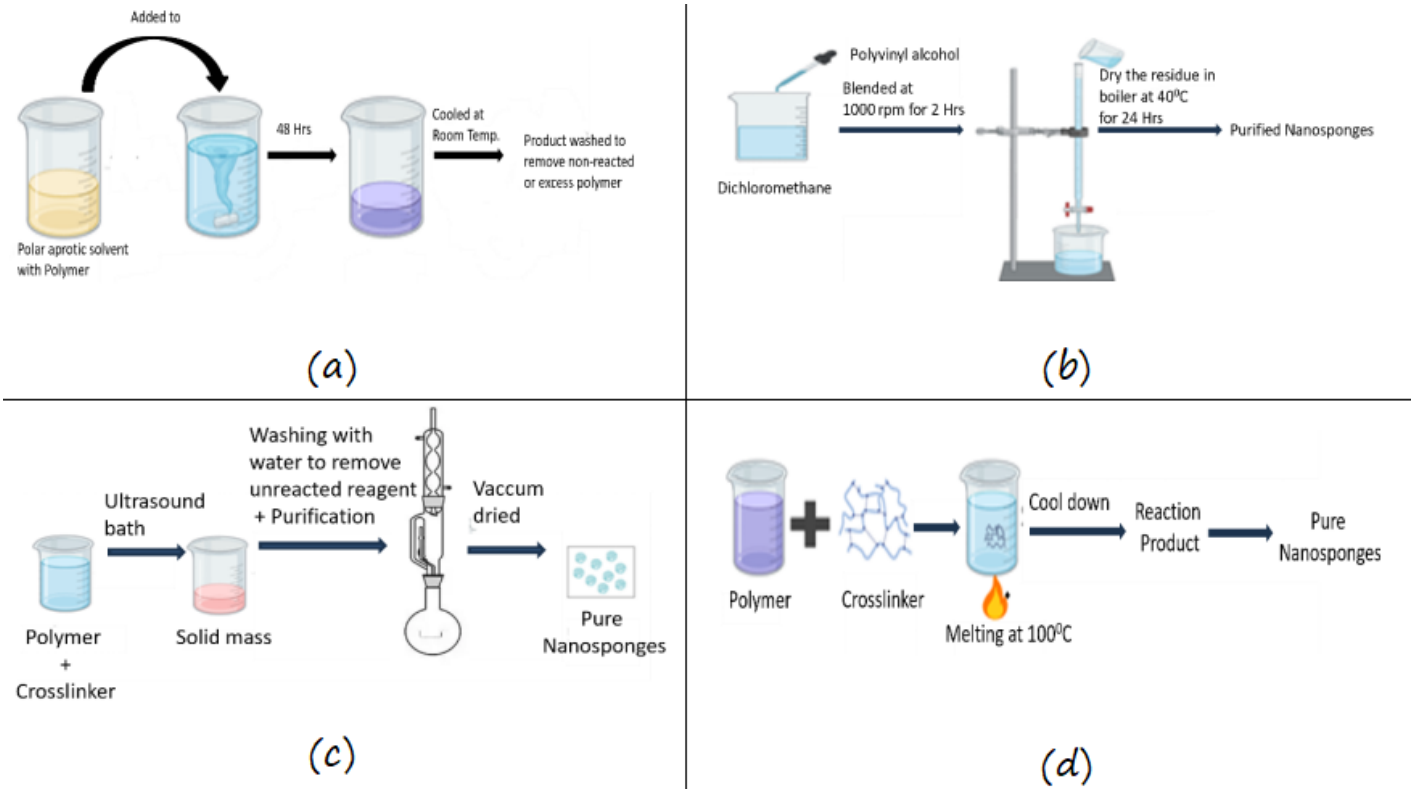

Figure 1: Different methods of formulation of NS. (a)Solvent Evaporation technique, (b) Diffusion method of emulsion solvent, (c) Ultrasonic Assisted Synthesis of NS, (d) Melt technique for synthesis of NS.

using aprotic solvents and crosslinkers. The resulting spherical NS had narrow size distribution and crystalline structure, formed rapidly in just 3.5 min at 18 W due to uniform heating.[60]

Physical Characterization and Evaluation of Nanosponges

NS are evaluated for parameters (Figure 2), that can affect drug solubility, entrapment, and stability, *in vitro* and *in vivo* release.[62,63]

Drug loading and release from Nanosponges

Drugs may be physically incorporated into NS in solution, and encapsulation and release can be affected by type of cross-linker, molar ratio, and conditions of synthesis. NS crystalline structure varies with reaction parameters, affecting drug entrapment. Swaminathan *et al.*, showed Camptothecin loading at β-CD:crosslinker ratios of 1:2, 1:4, and 1:8 achieved 21%, 37%, and 13% w/w, respectively, with 1:4 yielding optimal loading and release.[64] Polymer concentration enhances entrapment but higher drug-to-polymer ratios reduce release, likely due to NS swelling that prolongs diffusion. Abemaciclib-loaded NS release was analyzed using Higuchi-Matrix, First order, Zero order, and Korsmeyer-Peppas kinetic models, confirming controlled release behaviour.[52,65,66]

Different Approaches for Targeting Cancer using Nanosponges

Several challenges must be overcome by NS to be effectively delivered in the cancerous microenvironment. These include acidic or hypoxic conditions, redox potential, hyperthermia in addition to tumor-related factors such as changes in amino acids, proteins, DNA fragments, and tumor-derived inflammatory cells.[64] Several approaches such as PEGylation, surface charge manipulation, size reduction, and CO2 generation induced by hyperthermia can be used to improve performance. Drug release from the NS can be triggered by altered pH, temperature, magnetic field, ultrasound, and laser.[60,65] The accuracy of delivering chemotherapeutic agents can be ensured by passive targeting (EPR effect) and active targeting (receptor-ligand interaction).[66-69] NS encapsulated with chemotherapeutic agents such as Paclitaxel,[50] Tamoxifen,[70] Erlotinib,[71] Oxy-Resveratrol,[47] and Camptothecin[72] are more effective and stable; however, non-specific delivery still poses a problem. Smart NS can be used for stimulus-sensitive delivery or surface-modified NS, such as those responding to redox or pH conditions can improve site specific delivery.[73] Bioavailability can be improved by cholesterol-conjugated NS, while magnetic NS composed of magnetite and maghemite provides sustained and specific delivery. All these innovations suggest the applicability and potential of NS as precise anti-cancer therapies.[74-77]

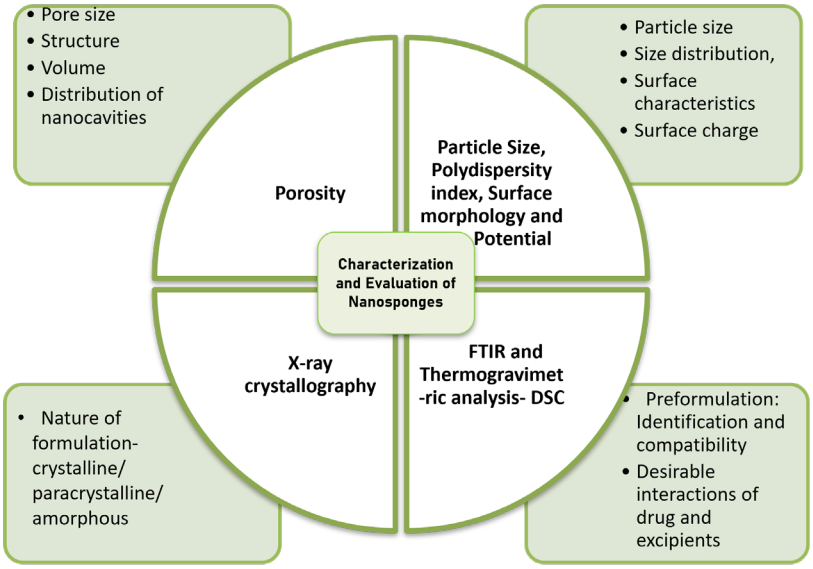

Figure 2: Physical characterization and evaluation of NS.

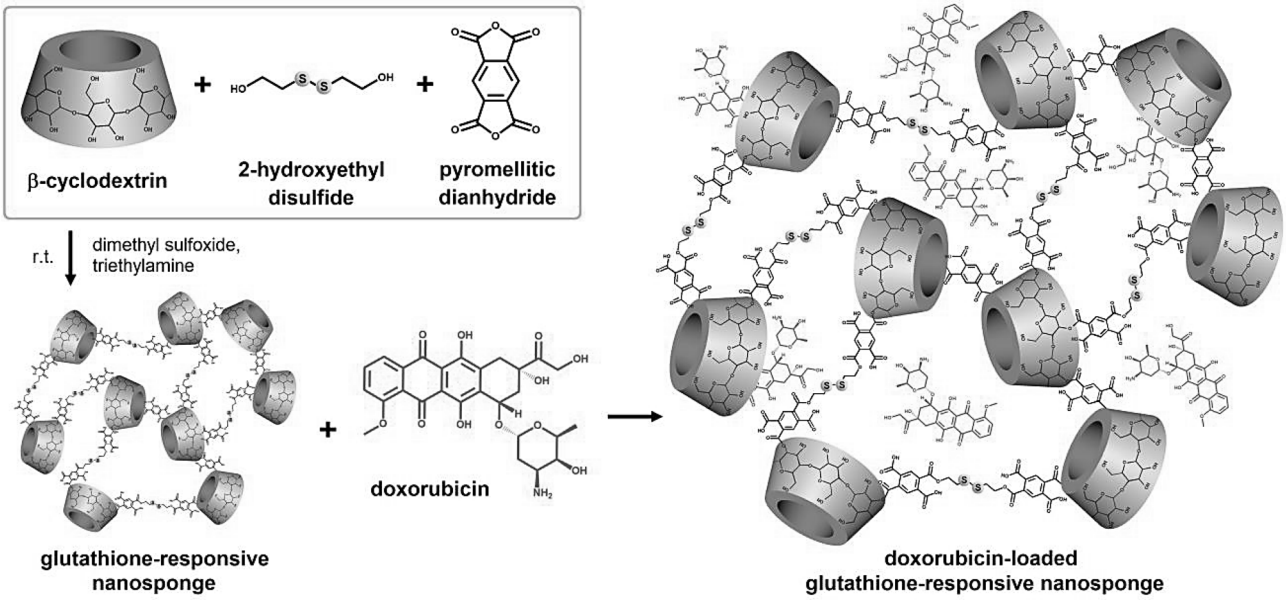

Figure 3: Doxorubicin-loaded Glutathione-Responsive Nanosponge (Dox-GSH-NSs): The one-step synthesis of GSH-Responsive Nanosponges (GSH-NS).[89]

Metal and Metal Oxide Nanosponges

NS, made of metal and metal oxide, usually based on gold, silver, or iron, interact with biomolecules, holding a great promise for targeted tumor treatments.[78] The porosity in their architecture imparts high surface areas to the sponges, facilitating effective binding and catalysis. NS can be mono-, bi-, or polymetallic; the multi-metallic forms impart synergism and are advantageous.[79,80] They are typically synthesized by reducing metal salts with surfactants controlling growth. Methods include dealloying, chemical reduction, solvothermal, sol-gel, and electrochemical deposition, each with distinct benefits.[81,82] For instance, silver NS form via borane reduction of silver nitrate, while Zheng *et al.*, created chemo-photoresponsive gold NS through alloying/dealloying of Au-Cu_2O nanoparticles, later functionalized with doxorubicin, demonstrating enhanced tumor targeting via dual-stimuli responsiveness.[83]

Chemo-Photoresponsive Nanosponges

Chemo-photothermal therapy combination provides greater effectiveness compared to individual therapies owing to the improvement of cytotoxicity under higher temperatures, better control of drug release, and overcome resistance to chemotherapy.[82] Nanoporous Au-based Doxorubicin NS with improved drug loading capacity, targeted delivery, multi-stimuli response, and Near-Infrared (NIR) plasmonic resonances for hyperthermia and photothermally triggered drug release were reported by Zheng

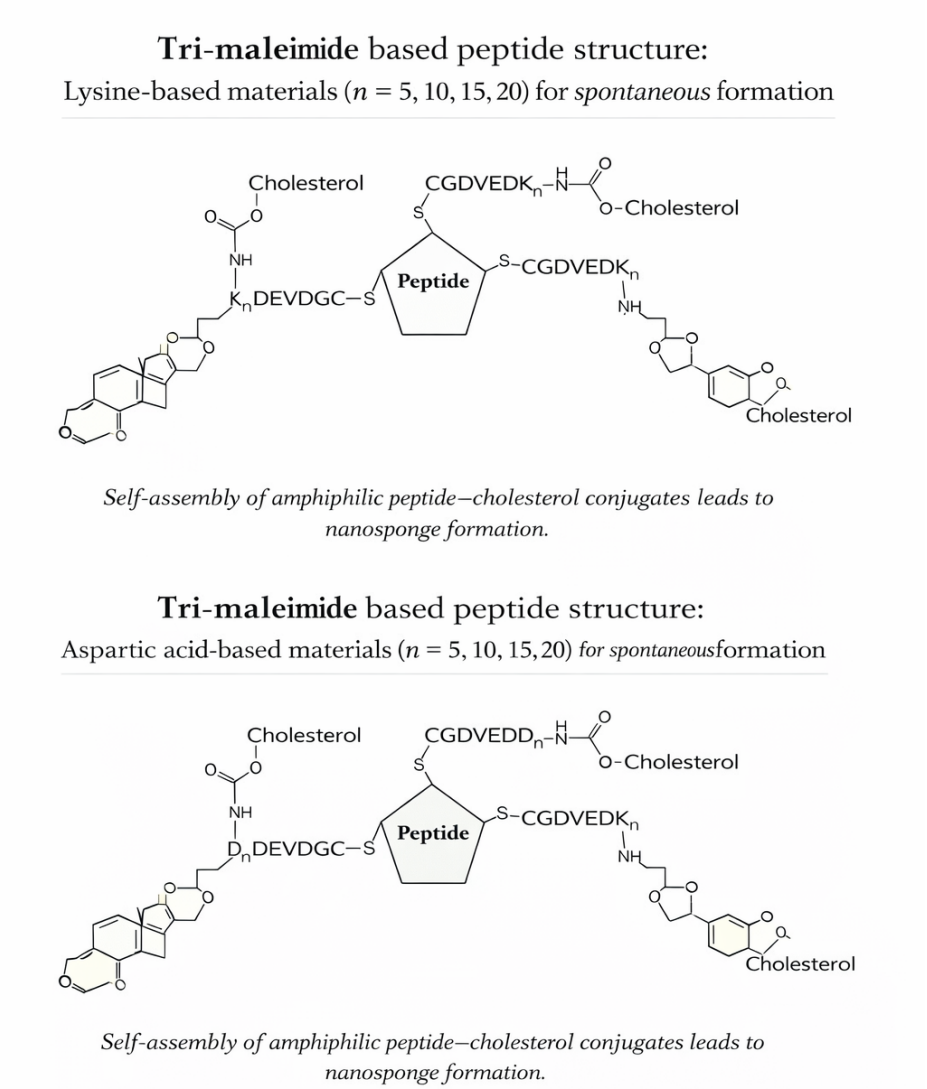

Figure 4: Tri-maleimide based peptide structures for the spontaneous development of Nanosponges.[93]

et al., These nanosponges, created *via* percolation dealloying of Au-Cu alloy nanoparticles, feature 3D porous architectures with large surface areas and controlled release. Coating with pH- and thermal-responsive copolymer-liposomes provided smart gatekeeping, while RNA aptamer functionalization targeting EpCAM enhanced tumor cell uptake, reducing systemic distribution and side effects.[83]

Polystyrene Nanosponges

Polystyrene NS, derived from styrene monomers, differ from conventional rigid nanoparticles by their porous, spongy structure, offering enhanced functionality.[84] The linear polystyrene NS were prepared by the intramolecular hyper-cross-linking method proposed by Davankov *et al.*, which involves chloromethylation, heating with zinc chloride, treating with tin chloride, followed by purification procedures to obtain stable NS.[85] This nanostructure has applications, especially for localizing the drug in the tumor environment. The polystyrene NS have synergistic delivery capabilities for chemotherapeutic drugs as well as immunomodulators. The experiments have confirmed their capacity to cause apoptosis, inhibit the cell-cycle, as well as cause oxidative stress, making it an effective candidate for the treatment of cancer with reduced side effects.[86,87]

Glutathione Responsive NS (GRNS)

GRNS serve as stimuli-responsive carriers that can modulate drug release from NS. The presence of glutathione in chemoresistant cancer cells makes it feasible to achieve target-specific drug release within cells.[88] β-Cyclodextrin-based GRNS, prepared with 2-hydroxyethyl disulfide and pyromellitic dianhydride can embed Doxorubicin effectively, as shown in Figure 3.[89] Disulfide bond cleavage by glutathione leads to selective release, exhibiting enhanced antiproliferative properties against HCT15, HepG-2, and A2780 cells compared to the free drug.[90]

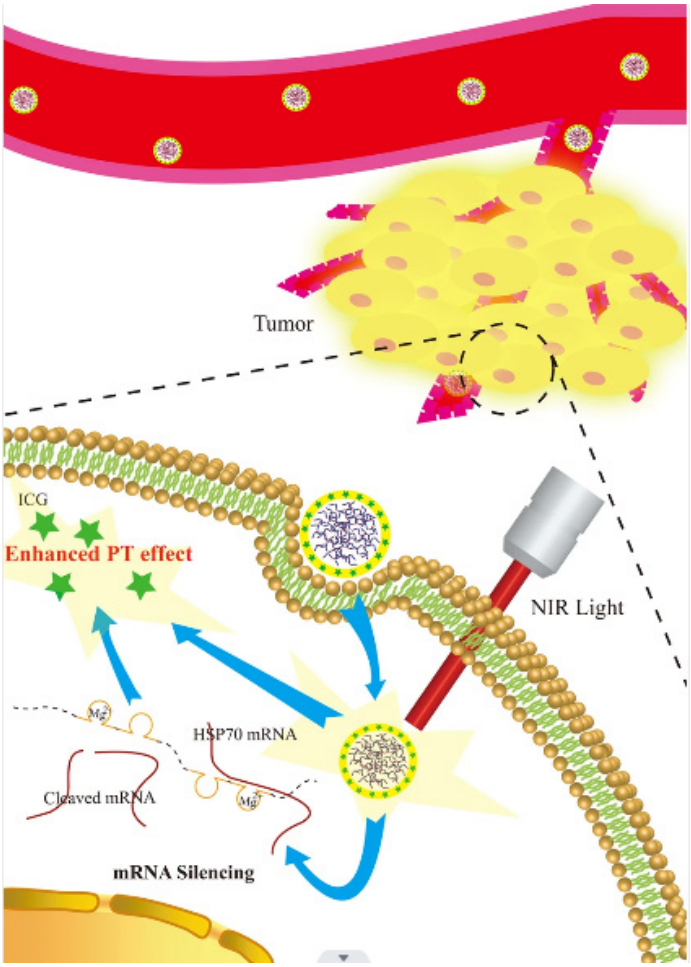

Figure 5: DNAzyme-based nanosponges for photothermal therapy.[101]

GRNS can rapidly enter cells, retain high drug concentrations, and minimize systemic toxicity. The varying concentrations of glutathione in different cancers limit its efficiency and has led to the development of pH-responsive GRNS to target acidic tumor microenvironments with improved precision.[91]

Peptide NS

Peptide-NS with HVGGSSV peptide targeting the TIP-1 receptor were successfully surface functionalized and used for effective delivery of Paclitaxel and Camptothecin inducing G2/M cell cycle arrest, apoptosis, and retention of the drug for 23 days in the target lung tissue.[92] Tri-maleimide based peptide structure for the spontaneous development of nanosponges is shown in Figure 4.[93] Combination therapy delayed tumor growth significantly compared to monotherapy and untargeted controls, while protecting unstable Camptothecin.[94,95] Peptide NS, formed from oligopeptides and hydrophobic components, improved Perillyl alcohol delivery for glioblastoma and were non-toxic in macrophage-like cells, suitable for cytotherapy.NS are biocompatible and can be adjusted in size (~80 nm) and are stable due to the formation of well-defined supramolecular structures. Synergistic activity against multidrug-resistant cancerous colorectal cells was obtained using multifunctional NS co-loaded with doxorubicin, paclitaxel, and tetrandrine.[96,97]

DNAzyme Nanosponges (DNS)

DNS represent a novel approach in nucleic acid therapy that takes advantage of molecular recognition and versatility for gene regulation.[98] DNAzymes are catalytic single-stranded DNAs first reported by Breaker and Joyce in 1994, with capabilities of silencing, adding, substituting, and modifying target genes, and are very important in cancer gene therapy based on suppression of viability, proliferation, adhesion, and enhancement of chemosensitivity and apoptosis.[99] The limitations of traditional DNAzyme delivery are lack of control and replicability, degradation, poor specificity of gene silencing in cancer cells, and insufficiency of intracellular cofactors. The nanosponge approach has solved these problems with a 3D porous scaffold that encapsulates DNAzymes and promotes efficient recognition and catalysis upon biomolecular stimulation.[97]

Recent Advances in DNS Platforms

Rolling Circle Replication (RCR) is a rapid method for assembling DNA nanosponges, though early designs had limited bioavailability and targeting. C. Wang *et al.*, developed enzyme-mediated RCR nanosponges with CpG sequences to encapsulate anti-PD-1 antibodies, releasing them via tumor-associated Metalloproteinases (MMPs). Building further, Wang introduced a "mask-cleave-release" strategy using tandem self-catabolic DNAzymes (rDNAzyme) and therapeutic DNAzymes (tDNAzyme targeting survivin mRNA) encoded in RCR templates, co-encapsulating zinc oxide nanoparticles and cytochrome. MUC-1 aptamer modification enabled tumor-specific targeting. The acidic environments brought about the dissociation of ZnO, giving rise to Zn^{2+} ions, which activated the DNAzymes. There was a substantial release of cytochrome C (64.9% vs 15.7%) due to the activation of DNAzymes.[100]

Overcoming Thermoresistance in Photothermal Therapy

Cancer cells often develop thermoresistance via Heat Shock Proteins (HSPs), particularly HSP70, reducing photothermal therapy efficacy. Jin *et al.*, engineered DNAzyme nanosponges (DNS) combining FDA-approved NIR dye Indocyanine Green (ICG) with multivalent DNAzyme sequences targeting HSP70. Constructed through RCA with polyetherimide and DNAzyme-encoded strands, these platforms achieved dual functionality: efficient photothermal conversion and HSP70 gene silencing. By cleaving HSP70 mRNAs, they sensitized MCF-7 cells to hyperthermia as shown in Figure 5.[101] *In vitro* studies along with *in vivo* studies conducted on MCF-7 tumor-bearing mice confirmed the enhanced therapeutic efficiency, while the system facilitated multimodal imaging of tumor accumulation.[102] These developments emphasize the importance of DNS as a

programmable, multimodal system possessing considerable future for clinical application in targeted controlled tumor therapy.

Challenges in Nanosponges Based DDS

The process of forming NS is further complicated while combining synthetic and natural moieties. Aqueous instability and low solubility pose the structural challenge.[103] The nanoscale features of NS also hamper the removal of synthetic parts from the body or environment, leaving potential residues. The nature of the cross-linker, polymer, and drug affects the process of forming NS because the drug should have adequate properties to be encapsulated. A melting point of the compound can hinder in the stability during encapsulation, making it difficult to prepare the drug-NS complex. Lower stability constants are obtained with higher temperatures, making it necessary to maintain temperature controls during the NS formulation.[104]

CONCLUSION

Nanosponges stand at the intersection of material science and precision oncology, offering a robust solution to the challenges of poor drug solubility and off-target systemic toxicity. By providing a stable, biocompatible, and high-capacity vehicle, nanosponges significantly enhance the bioavailability of potent chemotherapeutics while minimizing the required dosage.

The review confirms that the ability to "tune" the nanosponge surface for specific ligands makes them particularly adept at navigating the hostile conditions of the TME, such as hypoxia and acidic pH. While conventional oncology often struggles with the "all-or-nothing" approach to toxicity, nanosponges provide a nuanced delivery mechanism that prioritizes patient survival and quality of life.

FUTURE DIRECTIONS

The transition of nanosponges from "bench to bedside" represents the next critical frontier in nanomedicine, necessitating a strategic shift toward standardized manufacturing processes to ensure scalability, establishing quality control parameters and regulatory compliance.

Developing multifunctional NS which can offer an attractive tool for chemotherapy, immunotherapy as well as, gene therapy is indeed a promising avenue. Similarly, exploring various green synthetic methods which employ biodegradable as well as, environmentally sustainable materials to ward off all concerns regarding the accumulation synthetic residues are equally challenging but attractive tasks.

Efforts should also concentrate on developing combination strategies that simultaneously address multiple cancer hallmarks including thermoresistance, multidrug resistance, and immune evasion, ultimately advancing NS toward becoming life-saving tools in precision oncology.

Ultimately, leveraging artificial intelligence and machine learning to optimize nanosponge architecture and ligand density for specific cancer genotypes will likely be the catalyst for realizing truly personalized, next-generation oncology.

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ABBREVIATIONS

NS: Nanosponges; **EPR:** Enhanced Permeability and Retention; **TME:** Tumor Microenvironment; **ECM:** Extracellular Matrix; **MMPs:** Matrix Metalloproteinases; **PLGA:** Poly(lactide-co-glycolide); **CD:** Cyclodextrins; **DPC:** Diphenyl Carbonate; **DMSO:** Dimethyl Sulfoxide; **DMF:** Dimethylformamide; **ICG:** Indocyanine Green; **NIR:** Near-Infrared; **GRNS:** Glutathione-Responsive Nanosponges; **PT:** Photothermal Therapy; **tDNAzyme:** Therapeutic DNAzymes; **rDNAzyme:** Tandem Self-Catabolic DNAzymes; **HSP:** Heat Shock Protein; **RCR:** Rolling Circle Replication; **RCA:** Rolling Circle Amplification; **AI:** Artificial Intelligence; **ML:** Machine Learning.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Priyanka S Deorankar and Neha M Munot conceptualized, structured and writing the review; Rahul B Shirsath, Nikhil P Hinge, Tejas P Bochare, Akash B Landage literature review, formatting, drawing. Kishor S Jain for critical checking, and suggestions, redrafting and proof reading and all authors contributed to the final editing of the manuscript.

SUMMARY

This review systematically discusses the merit of Nanosponges (NS) as advanced drug delivery systems for targeted cancer therapy in details. These systems are comprised of porous, cross-linked nanocarriers (<1 micron) capable of enveloping both hydrophilic or lipophilic drugs. They show very good thermal stability, pH tolerance, and biocompatibility. Various synthetic methods are detailed which include, solvent evaporation, ultrasound-assisted and microwave assisted syntheses. Various characterization approaches for optimizing drug loading and release kinetics are also detailed. Also discussed are strategies to overcome tumor microenvironment barriers using designs responsive to stimuli. These include, design of pH-sensitive, glutathione-responsive, and photothermal-responsive NS. Also,

the surface functionalization strategies using peptides, aptamers, and cholesterol conjugation for active targeting are discussed. Recent innovations in metal-based, polystyrene, and DNAzyme NS's are highlighted. These platforms combine therapeutic and diagnostic capabilities, and demonstrate superior efficacy against drug-resistant cancers while minimizing systemic toxicity compared to conventional chemotherapy.

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