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RESEARCH ARTICLE

Improved Antitumor Efficacy of Liposome-Encapsulated Selenium Nanoparticles

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Abstract

Overview: This investigation chronicles the phytogenic synthesis of selenium nanoparticles (SeNPs) and their subsequent entrapment within phospholipid liposomes to construct a precision nanovector for oral-squamous-cell-carcinoma therapy. **Methods:** The plant-derived SeNPs were loaded into liposomes via a thin-film hydration approach. Dynamic light scattering (DLS) assessed their hydrodynamic diameter and zeta potential. **Results:** This nanoparticle was then sequestered via a thin-film-hydration protocol that yielded liposomes with a mean hydrodynamic diameter of 235 nm, a polydispersity index of 0.15. Dynamic-release profiling in phosphate-buffered saline (pH 7.4, 37 °C) revealed a sustained discharge of 35 % of the payload over 62 h dramatically slower than the 95 % burst exhibited by free SeNPs attesting to the kinetic moderation conferred by the bilayer matrix. Functionally, MTT assays on an oral-cancer cell line demonstrated a 72 % reduction in viability after 24 h, significantly eclipsing the 38 % inhibition achieved by unencapsulated nanoparticles ($p < 0.001$). **Conclusion:** These data indicate that liposomal sequestration furnishes SeNPs with enhanced colloidal stability, protracted release dynamics, and markedly elevated in-vitro antineoplastic potency, thereby positioning the platform as a compelling, biocompatible candidate for targeted oral-cancer therapeutics and warranting subsequent in-vivo validation.

Keywords: Anticancer activity- Oral cancer therapy- Liposomes

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Introduction

Today, a broad spectrum of scientific fields from biotechnology, nanotechnology, and materials science to machine learning, environmental engineering, and climate research are working together to solve complex challenges. This interdisciplinary convergence is delivering smart drugs and targeted delivery systems for cancer therapy, biocompatible materials for oral and bone tissue regeneration, optimized clean-energy Stirling engines, and high-resolution monitoring of natural hazards such as droughts and earthquakes. The result is better medical and dental care, higher industrial efficiency, greater environmental sustainability, and safer infrastructure evidence that the frontiers of knowledge are being harnessed to improve everyday life and drive future technologies across multiple domains [1-17]. Drawing on these studies, the deployment of cutting-edge technologies, artificial-intelligence algorithms, and advanced laboratory instrumentation has simultaneously boosted the safety and efficiency of civil infrastructure, enabled more accurate natural-hazard forecasting, and within medicine and dentistry leveraged advanced biomaterials, 3-D printing, and convolutional neural networks to improve implant design, deliver anticancer drugs with precision, and regenerate hard and soft tissues.

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In parallel, AI-driven analytics combined with temperature and pressure sensors are optimizing clean-energy systems and enhancing water-level and drought monitoring. This interdisciplinary convergence not only raises industrial efficiency and sustainability, but also provides society with more precise treatments, faster diagnoses, and safer infrastructure. Put simply, state-of-the-art techniques and devices are forging a seamless link between industry, medicine, and dentistry, charting new horizons for well-being and sustainable development [15, 18, 19-26]. The collective findings of these studies make it clear that the unprecedented pace of innovation in advanced technologies from artificial intelligence, deep learning, and bio-data analytics to nano-engineering, biotechnology, and micro-/nano-scale devices is redefining the frontiers of medical science and its allied fields. This interdisciplinary convergence is opening new horizons for faster, more accurate diagnostics, personalized therapies, and intelligent tissue-repair systems, while simultaneously charting a path toward better disease prevention, continuous health monitoring, and overall improvements in quality of life. Achieving this vision will demand deeper insight into biological mechanisms, the creation of novel computational methods, and the deployment of cutting-edge laboratory infrastructure [27-35]. Cancer is a complex, multifaceted disease that embraces many malignancies, notably colorectal cancer, esophageal cancer, and oral cancer [36-42]. For cancer treatment, liposomes and niosomes are the most widely used carriers thanks to their biocompatibility and targeting ability, whereas metallic (gold, selenium) and polymeric (PBCA) nanoparticles are also employed to optimize drug release, minimize side effects, and enhance therapeutic efficacy [43-50]. Selenium nanoparticles (SeNPs) have attracted considerable attention as antineoplastic agents due to their low inherent toxicity, antioxidative properties, and capacity to induce apoptosis selectively in cancer cells [51-53]. Moreover, green or "phytogenic" synthesis of SeNPs using plant-derived reducing extracts offers an environmentally benign and scalable route to biocompatible nanomaterials, often yielding particles with favorable stability and surface functionality [54, 55]. Nonetheless, unmodified SeNPs may still undergo premature clearance or aggregation in biological fluids, limiting their in-vivo efficacy [55, 56]. Liposomal encapsulation represents a well-established strategy to address these challenges. Phospholipid bilayers can entrap hydrophilic and hydrophobic payloads alike, provide steric stabilization, and afford tunable release profiles through bilayer composition and surface modification [57]. Liposomal formulations have been clinically validated in several oncological indications, demonstrating improved pharmacokinetics and reduced systemic toxicity [57]. By sequestering phytogenic SeNPs within liposomal carriers, it is possible to harness the cytocompatibility and antitumor activity of elemental selenium while optimizing nanoparticle stability, circulation time, and payload delivery [56, 58). we report the design, formulation, and in-vitro evaluation of a liposome-encapsulated SeNP platform tailored for OSCC treatment. We describe the green synthesis of SeNPs, their incorporation into phospholipid liposomes via thin-film hydration, and characterization of particle size, zeta potential, and release kinetics. Finally, we demonstrate the enhanced cytotoxic efficacy of the hybrid nanocarrier against an OSCC cell line, establishing a foundation for future in-vivo studies and potential translation into precision oral-cancer therapeutics.

Materials and Methods

Materials

Lecithin, cholesterol, polyethylene glycol 400 (PEG 400), as well as organic solvents including ethanol, isopropanol, and dimethyl sulfoxide (DMSO), were procured from Sigma-Aldrich (St. Louis, MO, USA). Essential cell culture reagents such as RPMI 1640, Dulbecco's Modified Eagle Medium (DMEM), phosphate-buffered saline (PBS), fetal bovine serum (FBS), the tetrazolium-based cell viability reagent MTT, and a 100× Penicillin–Streptomycin antibiotic solution were sourced from Gibco (Thermo Fisher Scientific, USA). The human oral squamous cell carcinoma (OSCC) cell line HSC-3 was supplied by the National Cell Bank of Iran (NCBI), affiliated with the Pasteur Institute of Iran, following standard authentication and quality control protocols.

Green Biosynthesis of Selenium Nanoparticles (SeNPs)

Fresh aerial parts of Trifolium cherleri were sourced from the Iran Biological Resources Center, documented under herbarium accession code 1368, and taxonomically authenticated by a certified botanist. The collected plant material was air-dried in shaded, ventilated conditions to minimize oxidative and photolytic degradation. Once fully dried, it was ground using a laboratory-scale mechanical grinder to obtain a uniform, fine powder. For aqueous extraction, exactly 25 g of the powdered plant was infused in 120 mL of deionized water, followed by 24-hour maceration at ambient temperature to maximize the release of phytoconstituents. The mixture was subsequently filtered through Whatman filter paper (Merck, Germany) to remove insoluble residues, yielding a clear herbal extract. Selenium nanoparticles were synthesized via eco-friendly reduction using sodium selenite (Na_2SeO_3) as the precursor. A 1 mM solution of sodium selenite (250 mL) was prepared freshly under sterile laboratory conditions. To this solution, 20 mL of the clarified plant extract was added dropwise with gentle stirring at room temperature. A visible change in color ranging from pale yellow to orange-red served as a qualitative indicator of nanoparticle formation. The SeNPs were purified through repeated centrifugation at 12,000 rpm for 10 minutes, followed by triple washing with deionized water to remove residual phytochemicals and unreacted salts. Finally, the purified nanoparticles were freeze-dried and stored in moisture-free vials for further analyses and biomedical experimentation.

Fabrication of Liposome-Encapsulated Selenium Nanoparticles

Encapsulation of SeNPs into liposomes was carried out using the thin-film hydration technique. Specifically, 110 mg of lecithin, 60 mg of cholesterol, and 10 mg of PEG 400 were dissolved in 8 mL of chloroform in a sterile glass vial. The lipid solution was vortexed thoroughly and subjected to rotary evaporation at 65°C and 140 rpm to evaporate the solvent and form a consistent thin lipid film on the inner wall of the evaporation flask. To hydrate the dried lipid layer, 8 mL of an aqueous SeNP dispersion (concentration: 0.8 mg/mL) prepared in sterile phosphate-buffered saline (PBS) was added. The hydration step was carried out under mild heating (60°C) with continuous rotation at 100 rpm for 25 minutes, promoting the spontaneous assembly of lipid bilayers around the nanoparticles. The resulting multilamellar vesicles were processed by probe sonication for 4 minutes at 40% amplitude to produce a homogenous suspension of nanoscale liposomes. The final formulation was stored at 4°C for subsequent characterization studies focused on physicochemical stability and therapeutic performance.

Characterization of Nanoparticles

The average particle size, zeta potential, and polydispersity index (PDI) of the prepared nanoparticles were measured using dynamic light scattering (DLS) with the aid of a Nano ZS3600 Zetasizer (Malvern Instruments Ltd., UK), providing insights into their colloidal stability and size distribution.

In Vitro Drug Release Evaluation

The release behavior of selenium nanoparticle (SeNP) formulations was investigated using a dialysis-based diffusion method designed to mimic physiological conditions. Briefly, 2 mL of liposomal SeNPs and an equal volume of non-encapsulated (free) SeNPs were transferred into separate dialysis membranes (molecular weight cutoff: 12 kDa). Each dialysis bag was submerged in 20 mL of phosphate-buffered saline (PBS, pH 7.4) and maintained at 37 °C using a thermostatically controlled water bath. To facilitate uniform diffusion, the containers were placed on a magnetic stirrer with constant agitation throughout the experiment. At predetermined intervals (2, 5, 14, 22, 38, 56, and 62 hours), 2 mL aliquots were withdrawn from the external PBS medium and replaced immediately with an equal volume of pre-warmed fresh PBS to maintain sink conditions and ensure sustained drug release. The amount of released SeNPs in each sample was quantified by measuring absorbance at 265 nm using a UV–visible spectrophotometer. The cumulative release percentages were calculated and plotted over time, enabling direct comparison between the release kinetics of the liposome-encapsulated and free SeNPs formulations under identical conditions.

Assessment of Cytotoxicity

To evaluate the cytotoxic potential of selenium nanoparticles (SeNPs) in various formulations, including liposome-encapsulated SeNPs, free SeNPs, and unloaded liposomes, an MTT-based colorimetric assay was conducted on the HSC-3 oral squamous carcinoma cell line. Cells were seeded in 96-well plates at an initial density of 1×10^4 cells per well and allowed to adhere and proliferate for 24 hours under standard culture conditions. Following this incubation, the cells were exposed to a range of concentrations (3.5 to 896 µg/mL) of both liposomal and free SeNP formulations. After another 48-hour incubation period post-treatment, MTT reagent (5 mg/mL prepared in PBS) was added to each well and allowed to incubate for an additional 3 hours to facilitate the formation of formazan crystals. Subsequently, the medium was carefully aspirated, and 100 µL of DMSO was added to solubilize the crystals formed by metabolically active cells. Absorbance was recorded at 540 nm using a microplate spectrophotometer. Cell viability was calculated as a percentage relative to the untreated control group using the formula below:

Cell viability (%) = (Absorbance of treated cells / Absorbance of control cells) × 100

Statistical Analysis

All experiments were conducted in triplicate to ensure reproducibility. Data were analyzed using GraphPad Prism (version 8), employing one-way analysis of variance (ANOVA) for comparison among groups. A p-value of less than 0.05 was considered statistically significant.

Results

Green Synthesis and Characterization of SeNPs and Liposomal Formulations

To initiate the biosynthesis process, Trifolium cherleri powder was soaked in an aqueous medium for 24 hours to enable the efficient extraction of phytochemicals. The resulting extract was subsequently clarified through filtration using Whatman-grade filter paper. Upon gradual addition of the plant extract to a pre-prepared sodium selenite (Na_2SeO_3) solution at room temperature, a visible shift in color from light yellow to reddish-orange was observed, indicating the successful bioreduction of selenium ions and the formation of selenium nanoparticles (SeNPs). The selenium nanoparticles were encapsulated using the thin-film hydration technique, resulting in liposomal formulations with an average hydrodynamic

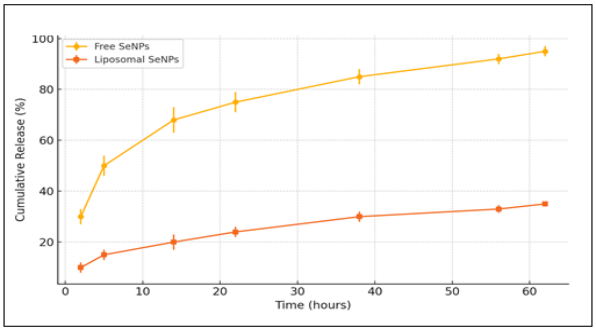

Figure 1. The Release Profile of SeNPs Encapsulated in Liposomes at 62 Hours. Data are expressed as mean ± SD from three independent experiments

Table 1. Physicochemical Properties of Liposome-Encapsulated Selenium Nanoparticles (SeNPs)

Parameter	Measured Value	Unit
Mean Hydrodynamic Diameter	235 ± 12	nm
Polydispersity Index (PDI)	0.15 ± 0.02	—
Zeta Potential	–28.6 ± 1.7	mV

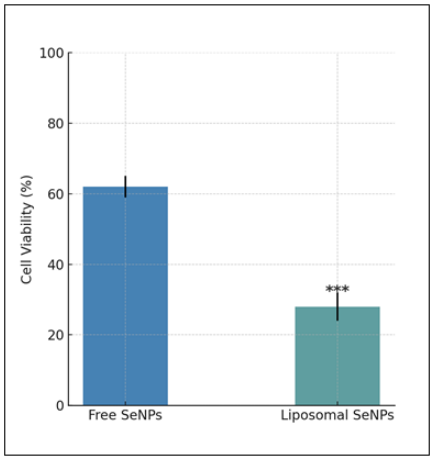

Figure 2. In vitro Cytotoxicity of Free SeNPs, Liposome Loaded SeNPs, and free liposome on HSC-3 cell line. n=3, *** $p < 0.001$

diameter of 235 ± 12 nm, a polydispersity index (PDI) of 0.15 ± 0.02, and a zeta potential of approximately –28.6 ± 1.7 mV, indicating good colloidal stability and narrow size distribution (Table 1).

Zeta Potential –28.6 ± 1.7 mV

Drug release evaluation

Figure 1 depicts the cumulative release behavior of free selenium nanoparticles (SeNPs) versus those encapsulated within liposomes over a 62-hour period in phosphate-buffered saline (PBS, pH 7.4), simulating physiological conditions. The results reveal a markedly slower release profile for liposomal SeNPs, with only approximately 35% of the payload released by the end of the experiment, in contrast to around 95% release from the free SeNPs. Notably, within the first 22 hours, 75% of free SeNPs diffused out, whereas liposomal SeNPs showed a restrained release of about 24%. The kinetic profile of the liposome-based formulation demonstrates a biphasic pattern: an initial burst release phase during the early hours (0–22 h), followed by a sustained, gradual release extending through the remainder of the study period. This sustained release behavior suggests that liposomal encapsulation effectively moderates drug diffusion, potentially enhancing the therapeutic window and reducing off-target effects.

In Vitro Cytotoxicity Evaluation

The cytotoxic effects of both free and liposome-encapsulated selenium nanoparticles (SeNPs) were evaluated on the HSC-3 oral squamous carcinoma cell line using the MTT assay. As shown in Figure 2, liposomal SeNPs exhibited significantly higher cytotoxicity compared to free SeNPs. After 24 hours of treatment, the liposome-loaded formulation reduced cell viability to 28 ± 4%, whereas the free SeNPs maintained a higher viability of 62 ± 3%. This difference was statistically significant ($p < 0.001$), indicating that liposomal encapsulation enhances the antiproliferative effect of SeNPs. These findings suggest that the liposomal formulation facilitates improved cellular uptake or prolonged intracellular retention, thereby potentiating the therapeutic impact against oral cancer cells.

Discussion

Oral squamous cell carcinoma (OSCC) remains one of the most prevalent and aggressive malignancies of the head and neck region, accounting for over 90% of oral cancers [59, 60]. Despite advances in surgery, chemotherapy, and radiotherapy, OSCC continues to pose significant therapeutic challenges due to late diagnosis, local recurrence, metastasis, and treatment-related toxicity [61-63]. Conventional chemotherapeutic agents such as cisplatin, 5-fluorouracil, and paclitaxel, though widely used, often suffer from limited selectivity, poor bioavailability, and severe systemic side effects that compromise patient outcomes and quality of life [60, 64, 65]. In recent years, nanotechnology-based drug delivery systems particularly liposomal carriers have gained considerable attention for their ability to overcome many of these limitations [66]. Liposomes are biocompatible, phospholipid-based vesicles capable of encapsulating both hydrophilic and hydrophobic agents. Their ability to prolong circulation time, enhance tumor-specific accumulation via the enhanced permeability and retention (EPR) effect, and reduce nonspecific toxicity makes them ideal candidates for oral cancer therapeutics. Several studies have demonstrated that liposomal formulations of conventional anticancer agents can significantly enhance antitumor efficacy while minimizing damage to healthy tissues [67-69]. In this context, the present study introduces a novel formulation: green-synthesized selenium nanoparticles (SeNPs) encapsulated within liposomes, aimed at improving OSCC treatment. The findings validate the hypothesis that encapsulating SeNPs in phospholipid liposomes not only improves their physicochemical stability but also significantly boosts their therapeutic performance [66, 70]. The green synthesis approach using Trifolium cherleri extract provided an eco-friendly and cost-effective route to produce biocompatible SeNPs [71]. The observed color change from pale yellow to orange-red upon mixing the extract with sodium selenite confirms successful bioreduction, consistent with previous phytogenic synthesis studies [72]. This method offers an

alternative to conventional chemical synthesis, reducing the risk of toxic byproducts and supporting scalability for biomedical applications [73]. The thin-film hydration method yielded liposomal SeNPs with a uniform particle size of approximately 235 nm and a narrow PDI (~0.15), indicative of monodisperse nanoscale vesicles. A zeta potential of –28.6 mV suggests sufficient electrostatic repulsion to prevent aggregation, in line with colloidal stability requirements for drug delivery systems [74, 75]. A critical advantage of the liposomal formulation was the significantly slower release kinetics observed in the in vitro drug release study. While ~95% of free SeNPs diffused within 62 hours, the encapsulated formulation released only ~35% of the payload in the same duration. This biphasic release initial burst followed by sustained release demonstrates the controlled-release capabilities of the liposomal bilayer, potentially reducing systemic toxicity and maintaining therapeutic levels over time [76, 77]. Functionally, the cytotoxicity assessment confirmed that liposomal SeNPs exhibited markedly enhanced anticancer activity against the HSC-3 OSCC cell line, reducing cell viability to 28% after 24 hours. This is significantly superior to the 62% viability seen with free SeNPs ($p < 0.001$). Such improved potency may be attributed to enhanced cellular uptake via endocytosis of the liposomes, as well as prolonged intracellular retention compared to non-encapsulated nanoparticles. Moreover, the lack of significant cytotoxicity in unloaded liposomes reinforces the biocompatibility of the delivery vehicle [78-80]. These results are in strong agreement with prior reports demonstrating the utility of liposomal carriers for elemental selenium delivery. Similar studies using folic acid-modified liposomes or polysaccharide-coated SeNPs have also shown enhanced tumor selectivity and reduced off-target effects, underscoring the potential of surface-engineered systems in precision oncology [81]. Despite these promising in vitro outcomes, further research is necessary. The mechanism of cellular uptake, possible endosomal escape, and the role of phytoconstituents in mediating cytotoxicity remain unexplored. Moreover, in vivo validation in animal models is crucial to assess pharmacokinetics, biodistribution, tumor-targeting efficiency, and long-term toxicity. These data are essential prerequisites for clinical translation [82].

In summary, this study provides a compelling proof-of-concept that phytogenically synthesized SeNPs, when encapsulated in liposomes, exhibit enhanced colloidal stability, controlled release, and superior antitumor efficacy in vitro. These findings contribute to the growing body of evidence supporting nanotechnology-based drug delivery as a potent strategy for oral cancer treatment and lay the groundwork for future in vivo and clinical investigations.

Statements and Declarations

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The authors have no relevant financial or non-financial interests to disclose.

Conflict of interests

The authors have no competing interests to declare that are relevant to the content of this article.

Ethics approval

This study did not involve any original data collection or human subjects, and therefore, ethical approval was not required.

Consent

All authors have provided consent for publication.

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