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The Use of Rare Earth Glass Microspheres and Graphene Quantum Dots Glass Microspheres for Biological Applications: Cancer Insight

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ABSTRACT

Purpose: This study explores the use of glass microspheres doped with rare earth elements, specifically samarium (Sm) and neodymium (Nd), and graphene quantum dots (GQDs) in biological applications, particularly cancer therapy.
Methods: Glass microspheres were synthesized using an eco-friendly approach with recycled glass and subsequently doped with Sm, Nd, or GQDs. The samples were characterized by scanning electron microscopy (SEM) and energy-dispersive X-ray spectroscopy (EDS). In vitro cytotoxicity was assessed in MCF-7 (breast cancer) and DU-145 (prostate cancer) cell lines.
Results: In vitro assays demonstrated that these doped microspheres significantly reduced cell viability in breast (MCF-7) and prostate (DU-145) cancer cell lines. The GQD microspheres showed a marked reduction in cell proliferation, attributed to mechanisms involving apoptosis and reactive oxygen species (ROS) production. Samarium and neodymium microspheres also decreased cell survival, with Nd microspheres showing the highest efficacy.
Conclusion: The study highlights the potential of rare earth elements and graphene quantum dots in developing advanced nanotherapeutic agents for cancer treatment, emphasizing their role in disrupting cellular functions and promoting cytotoxic effects in tumor cells.

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Introduction

Glass microspheres are small, spherical particles made from glass, typically ranging from a few micrometers to several millimeters in diameter. These microspheres are characterized by their uniform size, smooth surface, and chemical inertness, making them versatile in a wide range of applications, including healthcare.[1–4]

In medical assistance, glass microspheres are utilized for both therapeutic and diagnostic purposes. They are employed as carriers for drug delivery, where their surface can be modified to attach to specific molecules, enabling targeted delivery to specific tissues or cells. This targeted approach minimizes systemic side effects and enhances the efficacy of treatments, particularly in chemotherapy and radiotherapy.[5–7]

Moreover, glass microspheres are used in medical imaging as contrast agents. Their unique optical properties allow them to enhance the contrast in imaging techniques like ultrasound, MRI, and CT scans, facilitating better visualization of tissues and organs. This is crucial for accurate diagnosis and monitoring of various medical conditions.[8–11]

Another innovative application of glass microspheres is in tissue engineering. They serve as scaffolds or support structures in the regeneration of bone and soft tissues.[12] The biocompatibility of glass microspheres ensures that they integrate well with biological tissues, supporting cell growth and tissue repair.

Rare earth microspheres (REMS) are a class of nanomaterials derived from rare earth elements (REEs), which include the fifteen lanthanides, scandium, and yttrium. These elements possess unique electronic, magnetic, and optical properties, making them highly valuable in various technological and scientific applications. REMS harness these properties at the nanoscale, offering enhanced performance and novel functionalities compared to their bulk counterparts. They are emerging as promising tools in cancer research and therapy due to their unique physicochemical properties. Their applications range from diagnostics to therapeutics, and they are leveraging their luminescent, magnetic, and catalytic characteristics to significantly improve cancer detection and treatment efficacy.[13]

Samarium (Sm) is a rare earth element that has garnered significant attention in nanotechnology and oncology due to its unique magnetic, electronic, and radiative properties. Samarium-based micro/nanoparticles (SmNPs) offer diverse applications, particularly in diagnostic imaging, targeted therapy, and radiotherapy enhancement.[14]

Neodymium (Nd), a member of the lanthanide series, is renowned for its magnetic properties and applications in various technological fields. Neodymium-based micro/nanoparticles (NdNPs) have recently gained attention in nanotechnology and oncology due to their unique optical, magnetic, and catalytic properties.[15]

Graphene quantum dots (GQDs) are a novel class of carbon-based nanomaterials characterized by their small size, typically ranging from 2 to 20 nanometers, and their unique electronic and optical properties. These properties arise from quantum confinement effects, where the electronic and optical behaviors are influenced by the size and shape of the quantum dots, leading to discrete energy levels and size-dependent fluorescence. QQDs are known for their strong and tunable fluorescence, which can be adjusted by modifying their size, shape, and surface chemistry. This property is particularly useful in bioimaging, where GQDs can be used as fluorescent markers to

visualize cells and tissues with high resolution. Unlike many conventional quantum dots, GQDs are generally considered to be biocompatible and have low cytotoxicity. This makes them suitable for in vivo applications, including imaging, drug delivery, and biosensing. Also, GQDs have a high surface area to volume ratio, allowing for extensive functionalization with various chemical groups. This property enables the conjugation of biomolecules, such as antibodies, peptides, or drugs, enhancing their specificity and functionality in biological systems. Finally, GQDs are chemically stable, resistant to photobleaching, and can maintain their properties under various physiological conditions, which is critical for reliable long-term applications in medical diagnostics and therapy.[16–19]

The strong fluorescence of GQDs makes them ideal for bioimaging applications, including fluorescence microscopy, magnetic resonance imaging (MRI), and computed tomography (CT) imaging.[20,21] They provide high-contrast images and can be used to track biological processes at the cellular and molecular levels. Also, GQDs can be engineered to carry therapeutic agents, enabling targeted drug delivery to specific cells or tissues. This targeted approach reduces systemic toxicity and enhances the therapeutic efficacy of drugs, especially in cancer therapy.

Breast and prostate cancer are two of the most prevalent cancers worldwide, significantly impacting public health and healthcare systems. Both cancers have distinct epidemiological characteristics, diagnostic challenges, and treatment approaches, contributing to substantial morbidity, mortality, and economic burden.[22,23] Breast cancer is the most common cancer among women globally, accounting for approximately 24.5% of all new cancer cases in women. In 2020, there were an estimated 2.3 million new cases of breast cancer worldwide, leading to approximately 685,000 deaths in 2020.[24] The major risk factors include age, family history, genetic mutations (e.g., BRCA1 and BRCA2), hormonal factors, lifestyle factors (e.g., obesity, alcohol consumption), and reproductive history.[25] Early detection and improved treatment options have increased the 5-year survival rate for localized breast cancer to about 90%. However, survival rates drop significantly for metastatic breast cancer.[26]

In the United States alone, the annual direct medical cost of breast cancer is estimated to be over $20 billion, including costs for screening, treatment, and follow-up care. Indirect costs, such as lost productivity due to illness and premature death, add significantly to the economic burden, with estimated costs exceeding $10 billion annually.[27,28]

Prostate cancer is the second most common cancer in men worldwide, accounting for approximately 14.1% of all new cancer cases in men.[29] In 2020, there were an estimated 1.4 million new cases of prostate cancer globally, leading to approximately 375,000 deaths in 2020. The major risk factors include age, family history, genetic factors (e.g., BRCA2 mutations), race (higher incidence in African American men), and lifestyle factors. The 5-year survival rate for localized prostate cancer is nearly 100%.[30] However, for advanced or metastatic prostate cancer, the 5-year survival rate drops to about 30%. The annual direct medical cost of prostate cancer in the United States is estimated to be around $10 billion, encompassing screening, treatment, and follow-up care. Indirect costs, including lost productivity due to illness and premature death, add to the economic burden, with estimated costs exceeding $5 billion annually.[31,32]

Breast and prostate cancer together represent a significant proportion of the global cancer burden. In 2020, they accounted for approximately 14% of all new cancer cases and 10% of all cancer deaths worldwide. The combined

morbidity and mortality associated with these cancers highlight the critical need for effective screening, early detection, and advanced treatment strategies. In terms of economic impact, the combined economic burden of breast and prostate cancer is substantial, with direct healthcare costs and indirect costs related to lost productivity and premature death exceeding $35 billion annually in the United States alone.[33–35]

The development of new drugs for breast and prostate cancer is crucial for several reasons, including addressing unmet clinical needs, improving patient outcomes, and managing the evolving landscape of cancer biology.[36,37] Despite advances in early detection and treatment, significant challenges that necessitate continued pharmacotherapy innovation remain. Many patients with breast cancer, especially those with advanced or metastatic disease, eventually develop resistance to standard treatments such as hormone therapy (e.g., tamoxifen, aromatase inhibitors), HER2-targeted therapy (e.g., trastuzumab), and chemotherapy. This resistance often leads to disease progression and limited treatment options. Similarly, castration-resistant prostate cancer (CRPC) represents a significant therapeutic challenge. Patients who no longer respond to androgen deprivation therapy (ADT) require new therapeutic options to manage their disease effectively.[38–41]

Nanotechnology is revolutionizing the field of oncology, particularly in the diagnosis, treatment, and management of breast and prostate cancers. By manipulating materials at the nanoscale, researchers and clinicians can develop more precise, effective, and less toxic interventions for cancer patients.[42–45] Using nanotechnology to encapsulate chemotherapeutic drugs ensures they are delivered specifically to cancer cells while minimizing systemic toxicity.[46–48] Targeting ligands, such as antibodies or peptides, can be attached to the surface of these nanoparticles to recognize and bind to specific receptors on cancer cells.[49]

The necessity for new drugs in breast and prostate cancer is driven by the need to overcome resistance to existing treatments, address tumor heterogeneity, manage metastatic disease, and improve patient outcomes.[50,51] Advances in targeted therapies, immunotherapy, and precision medicine hold significant promise in transforming the treatment landscape for these cancers. Continued research and development efforts are essential to bring innovative and effective treatments to patients, ultimately reducing the burden of breast and prostate cancer on individuals and healthcare systems.[52–54]

In this direction, developing new nanodrugs based on rare earth metals and graphene quantum dots can represent an important achievement with good results, especially in reducing toxicological aspects related to rare earth use in biological systems. Also, the use of graphene quantum dots immobilized in a different platform for cancer therapy can also represent an important achievement. Thus, in this study, we have produced, fully characterized, and *in vitro* evaluated two nanoparticles based on rare earth metals, including samarium and neodymium and one based on graphene quantum dots.

MATERIALS AND METHODS

Reagents

All reagents and solvents used in this study were purchased from Sigma-Aldrich (Brazil).

Graphene Quantum Dots Production

The method for producing graphene quantum dots (GQDs) dispersions was adapted from a previously published study.[55] In this procedure, a graphite rod served as the anode, and a platinum wire as the cathode. The electrolyte

solution was prepared by combining 63.5 mL of 0.2 M citric acid with 36.5 mL of 0.2 M sodium citrate, yielding a total volume of 100 mL. The electrochemical synthesis was carried out at a constant current of 190 mA for 24 hours using an ICEL PS-1500 adjustable power supply. Following electrolysis, the resulting dispersion was filtered to remove larger particles. The filtered suspension was then concentrated by drying at 60°C, reducing the volume to 10 mL. Subsequently, 50 mL of ethanol was added, and the upper phase, containing purified GQDs, was collected. The purified GQDs were further dried at 60°C until needed.

All characterization assays were conducted using a range of techniques, including Dynamic Light Scattering (DLS), Raman spectroscopy, Atomic Force Microscopy (AFM), and Powder X-ray Diffraction (PXRD). These data, which have been previously published, confirmed the successful production of graphene quantum dots (GQDs).

Glass source

The glass used was from a recycling industry in Rio de Janeiro. The glass composotion was: 75 percent silica, 10 percent lime, and 15 percent soda.

Pre-treatment of the Glass

All glasses used in this study was previously washed with a detergent solution and dried at 150ºC for 24h.

Glass Microsphere Doped with Samarium (Sm), Neodymium (Nd) and GQDs

The production process is protected by the patent BR 10 2023 023825-4. Briefly, recycled glass was used as the primary raw material. This glass was pulverized using a mortar and pestle. A total mass of 20g of the pulverized glass was weighed, and surfactant was added along with 2g of the rare earth elements, i.e., GQDs, samarium oxide and neodymium oxide, respectively. The mixture was then mixed vigorously and heated at 1200°C for 2 hours. After that, the mixture was cooled to room temperature and pulverized again using a mortar and pestle. The resulting powder was washed twice with distilled water and dried at 100°C for 24 hours.

Particle size

The powder of the synthesized samples was dispersed in acetone and after drying, they were analyzed in an optical microscope (Olen) with an attached camera. The diameter of the microspheres was measured using Gwyddion software. A sample mean and standard error were obtained from the data set (n=30).

Scanning Electron Microscopy and Energy-Dispersive X-ray Spectroscopy

The morphology of the microspheres was analyzed using Scanning Electron Microscopy (SEM). SEM measurements were carried out with a scanning electron microscope (Zeiss, Evo) on samples deposited on carbon tapes using a secondary electron detector (SE). The images were obtained with magnifications of up to 20Kx. Energy Dispersive X-ray Spectroscopy (EDS) (Bruker, XFlash 410 M) identified the distribution of chemical elements present in the samples.

Statistical analysis

The data obtained from the cell viability assay was plotted in the GraphPad Prism 8.1 program. The experiments were carried out at least three times with six experimental replicates. The data was analyzed by one-way ANOVA to determine the difference between the groups and the control. The asterisks show statistical significance. *$p < 0.05$ was considered significant, **$p < 0.01$ was considered highly significant, and ***$p < 0.001$ was considered very highly significant.

Cell Lines

Breast Cancer Cells

MCF-7 breast cancer tumor cells were selected for the study. The cells were obtained from the Rio de Janeiro Cell Bank. The cell lines were cultured in RPM1-1640 medium supplemented with 10% (v/v) fetal bovine serum, 1% (v/v) Penicillin/Streptomycin antibiotic, and 5 mM glutamine. The cells were grown in a wet oven with 5% carbon dioxide at 37ºC.

Prostate Cancer Cells

DU-145 prostate cancer cells were selected for this study and obtained from the Rio de Janeiro Cell Bank. The cells were cultured in RPMI-1640 medium, supplemented with 10% (v/v) fetal bovine serum, 1% (v/v) Penicillin/Streptomycin antibiotic, and 5 mM glutamine. They were maintained in a humidified incubator with 5% carbon dioxide at a constant temperature of 37ºC.

Cell Culture

The cells were expanded into 75cm^2 bottles (T75 Corning®). After reaching the ideal confluence of 80%, they were treated with a trypsin solution (0.1%) plus ethylenediaminetetraacetic acid (EDTA) (0.01%) for replating in flat-bottomed transparent 96-well plates. The cells were then plated at 1x10ˆ4 cells per well for subsequent cell viability experiments.

Treatment with rare earth microspheres and Graphene Quantum Dots

After 24 hours of cell growth on the plates, both tumor cell lines were treated with the rare earth metal microspheres and the GQD microspheres. Each nanosystem (Samarium Oxide, Neodymium and GQD) was tested at 6 different concentrations of 3.125 ug/ml, 6.25 ug/ml, 12.5 ug/ml, 25 ug/ml, 50ug/ml, and 100ug/ml. Positive controls were incorporated into the experiment with the pure compound at the highest concentration tested of 100 ug/ml and at the lowest concentration tested of 3.12 ug/ml. A negative control was added to the experiment containing cells cultured in cell growth medium.

Viability Assay

The cells were incubated with the microspheres for 24 hours. After the end of the incubation period, the medium containing the nanosystems was removed, and a 1mg/ml MTT solution was added to each well of the plate. The solution was kept for 2 hours, and after this, a solvent (DMSO) was added to solubilize the formazan crystals for 30 minutes. After the crystals had been completely solubilized, each plate had its absorbance measured on a microplate reader (Multiskan FC; Thermo Fisher Scientific Inc., Waltham, MA, USA) at a wavelength of 450 nm.

RESULTS AND DISCUSSION

The morphology and compositional information of the microspheres obtained by SEM/EDS are presented in Figure 1. The morphology of the ME_Nd and ME_Sm samples (Figure 1a-b) are similar in that they form elongated structures, while the ME_GQD sample (Figure 1c) has greater agglomeration with globular and plate structures. By dispersing the samples in acetone, it was possible to observe the microspheres separately and calculate their diameter with values of 1.11 ± 0.03 µm for ME_Nd, 1.02 ± 0.04 µm for ME_Sm and 1.04 ± 0.02 µm for ME_GQD, according to Figure 2.

Meanwhile, the compositional analysis, through the maps and EDS spectra, showed the presence of the elements from recycled glass, silicon (Si), carbon (C), chlorine (Cl), calcium (Ca), oxygen (O), iron (Fe), aluminum (Al), and titanium (Ti), as well as the doping elements, neodymium (Nd), samarium (Sm) and carbon (C). These elements present uniform distribution, suggesting that the dopants are homogeneous in the material.

The ME_GQD sample showed morphological and compositional differences from the other samples, with greater particle agglomeration and a high concentration of Al. It is suggested that the greater agglomeration observed in this sample was mainly influenced by Al, given the already observed effect of Al ions in inducing graphene oxide agglomeration compared to Ca and Na ions.[56]

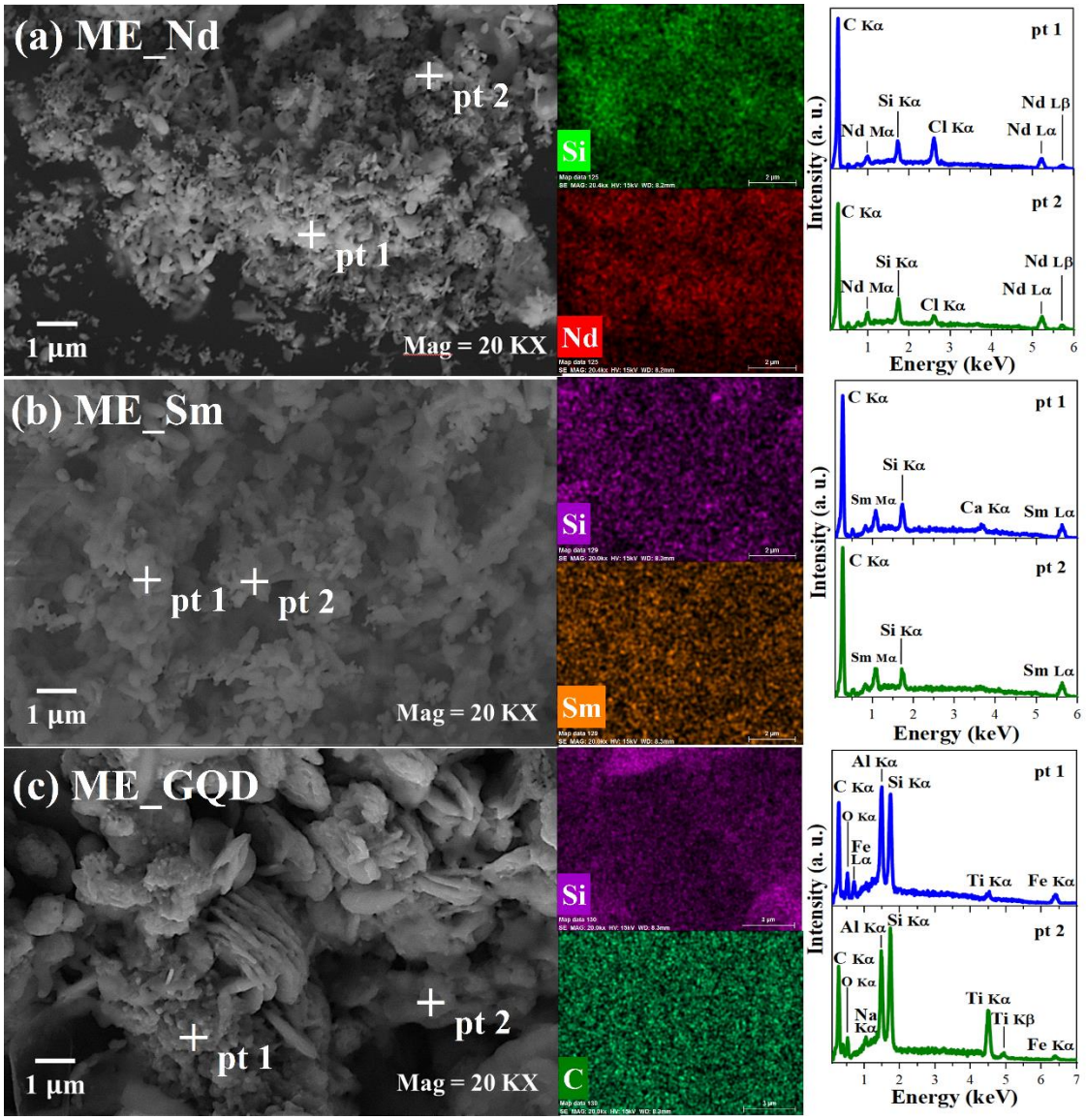

Figure 1. Micrographs, compositional maps, and EDS line spectra were obtained from the points (pt) indicated in the micrographs of the nanoparticles (a) ME_Nd, (b) ME_Sm, and (c) ME_GQD. The identified elements were silicon (Si), neodymium (Nd), samarium (Sm), carbon (C), chlorine (Cl), calcium (Ca), oxygen (O), iron (Fe), aluminum (Al) and titanium (Ti).

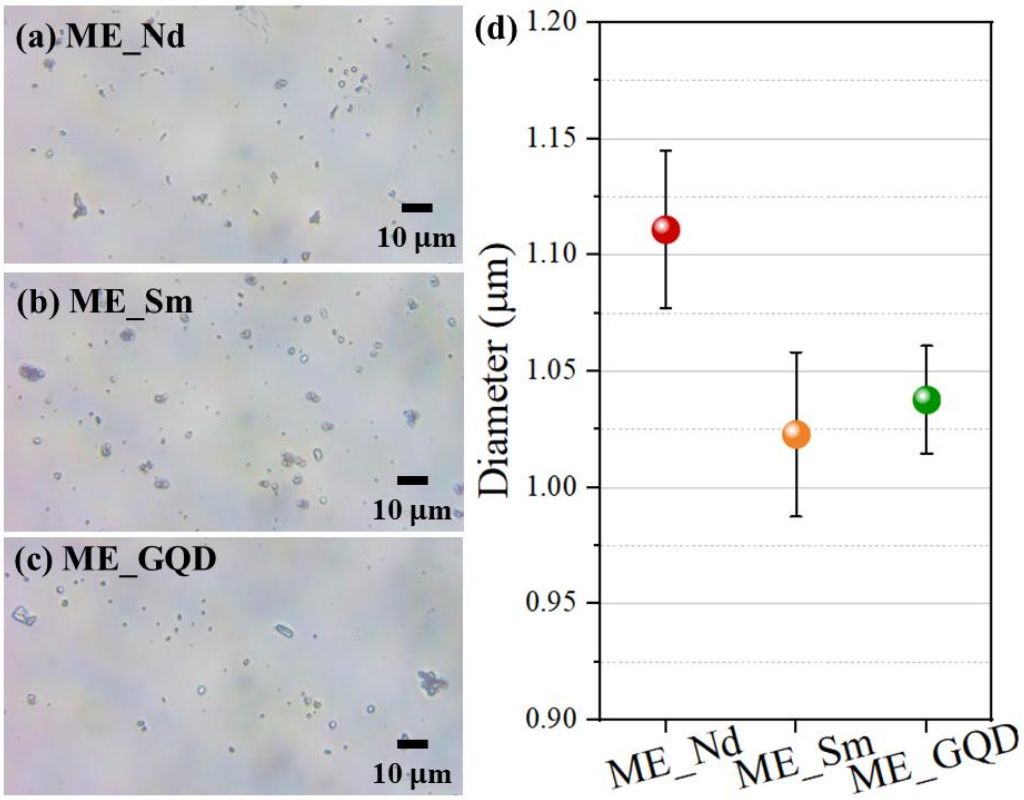

Figure 2. Optical microscopy images of (a) ME_Nd, (b) ME_Sm, and (c) ME_GQD microspheres. (d) Microsphere diameter, where data are presented as mean (sphere) ± standard error (bar) (n=30).

The MTT viability assay showed that in all the concentrations of GQD microspheres tested, there was a reduction in cell proliferation for prostate cancer cells, with a focus on the higher concentrations of 100ug/ml and 25 ug/ml, where this reduction was most evident (*p < 0.05 was considered significant). However, even at lower concentrations, it is possible to observe the impact of this nanosystem on cell viability (Figure 3).

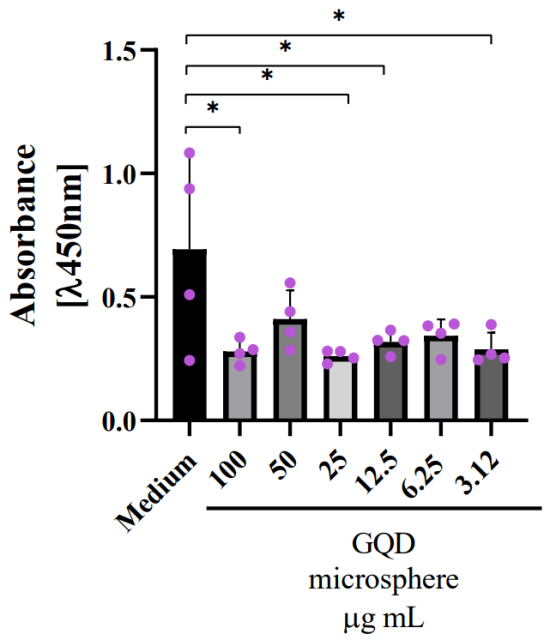

Figure 3. Cell viability assay of prostate tumor cells DU-145 with a GQD microsphere nanosystem. Cell viability was measured after 24 hours of treatment with GQD microspheres at 6 different concentrations of 3.12 ug/ml, 6.25 ug/ml, 12.5 ug/ml, 25 ug/ml, 50 ug/ml, and 100 ug/ml. The X-axis shows the absorbance measured at a wavelength of 450 nm. The Y axis shows the different concentrations tested. The negative control is equivalent to cells in medium only.

Cell viability decreased at the highest and lowest concentrations of 100 ug/ml and 3.12 ug/ml when treated with Samarium microspheres. Similarly, this drop was observed in the positive controls using Samarium in its pure form and at the same concentrations (Figure 4). Despite this, the statistical significance was greater in the controls (**p < 0.01 was considered highly significant) than in the treatment with the nanosystem (*p < 0.05 was considered significant).

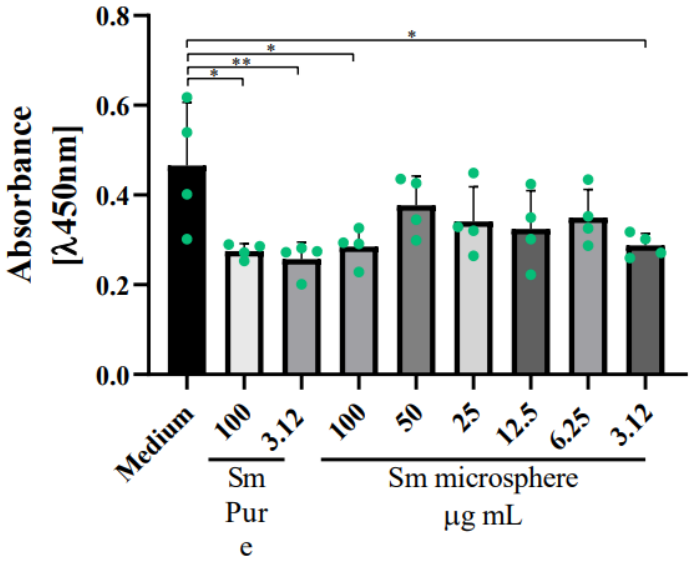

Figure 4. Cell viability assay of breast tumor cells MCF-7 with a Samarium microsphere nanosystem. Cell viability was measured after 24 hours of treatment with Samarium microspheres at 6 concentrations of 3.12 ug/ml, 6.25 ug/ml, 12.5 ug/ml, 25 ug/ml, 50 ug/ml, and 100 ug/ml. The X-axis shows the absorbance measured at a wavelength of 450 nm. The Y axis shows the different concentrations tested. The negative control is equivalent to cells in medium only, and the positive control is with the pure compound at concentrations of 100 ug/ml and 3.12 ug/ml.

As a result, we obtained a decrease in cell proliferation in breast and prostate cancer cells (Figure 5 and 6). This decrease in viability was observed when treated with the highest concentration of the nanosystem, 100 ug/ml, in both tumor cell lines (***p < 0.001 was considered highly significant). In the breast cancer cell lines, we also observed a reduction in cell viability related to treatment with the positive control, pure Neodymium, at the concentrations tested 100 ug/ml and 3.12 ug/ml.

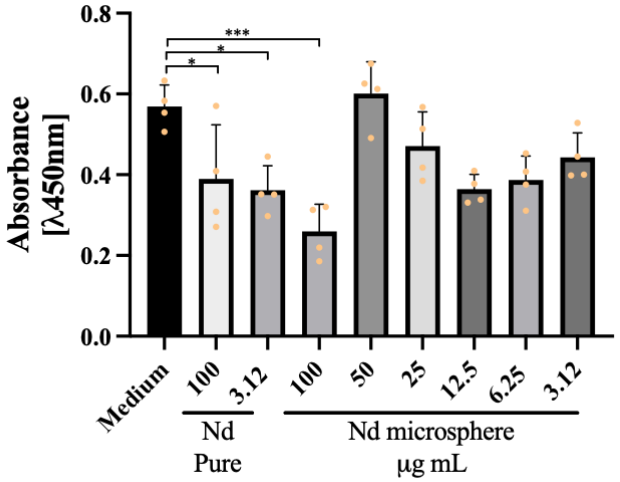

Figure 5. Cell viability assay of breast tumor cell line MCF-7 with a Neodymium microsphere nanosystem. Cell viability was measured after 24 hours of treatment with Neodymium microspheres at 6 different concentrations of 3.12 ug/ml, 6.25 ug/ml, 12.5 ug/ml, 25 ug/ml, 50 ug/ml, and 100 ug/ml. The X-axis shows the absorbance measured at a wavelength of 450 nm. The Y axis shows the different concentrations tested. The negative control is equivalent to cells in medium only, and the positive control is with the pure compound at concentrations of 100 ug/ml and 3.12 ug/ml.

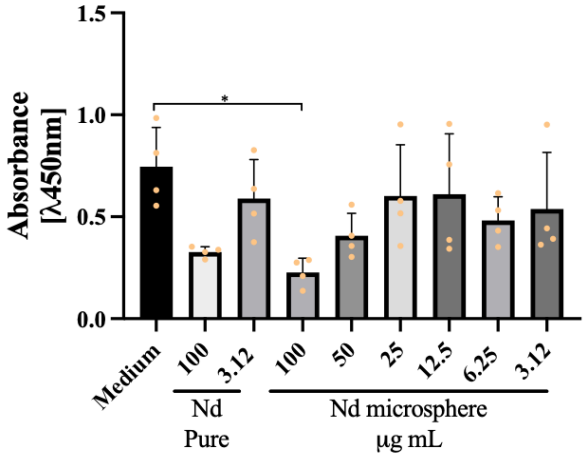

Figure 6. Cell viability assay of prostate tumor cell line DU-145 with a Neodymium microsphere nanosystem. Cell viability was measured after 24 hours of treatment with Neodymium microspheres at 6 different concentrations of 3.12 ug/ml, 6.25 ug/ml, 12.5 ug/ml, 25 ug/ml, 50 ug/ml and 100 ug/ml. The X-axis shows the absorbance measured at a wavelength of 450 nm. The Y axis shows the different concentrations tested. The negative control is equivalent to cells in medium only, and the positive control is with the pure compound at concentrations of 100 ug/ml and 3.12 ug/ml.

The production and characterization data showed that the methodology used was able to produce microspheres doped with different types of material efficiently. Also, was possible to obtain glass microspheres with an acceptable range size for biomedical application uniformly doped with the material of interest and with a spherical shape. Although the information about glass microspheres is sparse, the results is confirmed by Li et al[57] that developed hollow glass microspheres using borosilicate glass composite with different particle size. Due to their micrometer-scale dimensions, irregular morphology, high density, and elevated refractive index, the synthesized glass microspheres are incompatible with colloidal characterization techniques such as Dynamic Light Scattering (DLS) and zeta potential analysis. The determination of PDI by laser-based scattering methods is not feasible for solid glass particles of this nature, as they do not remain suspended, do not undergo Brownian motion, and exhibit excessive optical scattering. As such, characterization was instead conducted using SEM and EDS to assess morphology and elemental distribution

In vitro evaluation revealed a significant reduction in tumor cell viability following treatment with graphene quantum dots microspheres. The mechanism behind its role in protecting against cancer progression can be explained by biological pathways such as the activation of the apoptosis pathway or the production of reactive oxygen species (ROS).[58,59] It has already been shown that graphene and its derivatives can be internalized by cells and interact with various organelles and intracellular molecules, which would alter the cellular microenvironment, triggering inflammatory or apoptotic processes.[60] In addition, the production of ROS generates cytotoxic effects in cells and mitochondrial disorders, such as a reduction in membrane potential and consequent damage to the membrane.[61] Is important to notice that IC_{50} values were not determined, as the observed cytotoxicity did not follow a classic sigmoidal dose–response profile. Only partial viability reduction was observed at certain

concentrations, with an absence of a consistent monotonic trend across the tested range. Consequently, curve-fitting models for IC_{50} derivation could not be applied with sufficient statistical confidence.

The effect of graphene and its derivatives depends on the characteristics of the particle used, which will vary in size, oxidation, and other physical characteristics. Consequently, this data will change the way in which the particle penetrates biological systems. Graphene quantum dots are a particle of reduced size which, when combined with glass microspheres, has increased penetration power.[62] Qin et. al described the use of GQDs to test cell viability in macrophages, observing a decrease in the proliferation of these cells at high concentrations of GQDs due to apoptotic events.[63] These results correlate with our characterization and viability assay findings.

In addition, it is also described that for tumor cells, including prostate cancer, graphene can alter ATP production, reducing it and subsequently causing impairment of F-actin cytoskeleton assembly. These mechanisms are responsible for preventing cell migration and invasion of these tumor cell lines.[64]

Rare earth elements (REEs) are widely known and used for their imaging applications in the biomedical field, but they are also being used for biotechnological applications, precisely because they interact with biological molecules, which can be used in anti-tumor therapies.[65] The results showed a decrease in the cell viability of tumor cell lines in all treatments with microspheres associated with REEs. These nanosystems are possibly modulating DNA damage pathways, reactive oxygen species (ROS) production and apoptosis pathways.

Wei et. al have already shown that complexes formed with the element Dysprosium, from the lanthanide family, produce high anti-cancer activity by interfering in the S phase of the cell cycle, causing DNA damage and inducing the apoptosis pathway, preventing tumor progression.[66]

Furthermore, it has been shown in previous studies with HeLa cells that REEs nanoparticles are also responsible for inhibiting the cyclin dependent kinase 4/cyclin D complex and consequently interrupting tumor cell division.[67] Nanoparticles of the element Cerium, also from the lanthanide family, induce oxidative stress in tumor cells, activating apoptotic pathways as well as protein kinase (MAPK) signaling pathways, both of which reduce cell viability.[68]

Rumbo et. al observed that Neodynium nanoparticles caused a dose-dependent production of reactive oxygen species, while Donahue et. al also demonstrated that these same particles have a cytotoxic effect, as observed in several other nanosystems associated with REEs, in correlation with the results found in this study.[69,70]

It has already been shown that the toxicity of REEs is related to their electronegativity and how these divalent metals have a greater affinity with sites in cells that are in contact with elements such as calcium, zinc and copper, which interferes with cellular homeostasis and promotes dysfunctions that are capable of altering the proliferation of tumor cells when used for this biotechnological purpose.[71]

Nanomaterials such as glass microspheres associated with REEs or GQDs have great biotechnological potential as tools in anti-tumor therapies, due to their direct actions in various biological processes at the cellular level that promote the destabilization of tumor cells through different signaling pathways. The use of more unusual REEs for this purpose, such as Samarium or Neodynium, should be further explored, given that, like Cerium or Gadolinium, they are also successful in decreasing cell viability, as can be seen in this study. Is important to notice that the hybrid glass microsphere system exhibits enhanced structural stability, limiting the premature degradation and systemic leakage often observed in polymeric and lipid-based carriers. The integration of rare earth dopants

and graphene quantum dots within the glass matrix enables localized functionalization while maintaining material integrity. This design not only enhances safety and control but also introduces potential theranostic functionality. Furthermore, the use of recycled glass substrates supports a sustainable, cost-effective production route.

Conclusion

The study concludes that glass microspheres doped with rare earth elements, samarium (Sm) and neodymium (Nd), along with graphene quantum dots (GQDs), show significant potential as therapeutic agents in cancer treatment. These nanosystems demonstrated a considerable reduction in cell viability across both breast (MCF-7) and prostate (DU-145) cancer cell lines, primarily through mechanisms involving apoptosis and reactive oxygen species (ROS) production. The efficacy of the GQD microspheres, in particular, highlights their promise for targeted cancer therapies due to their biocompatibility and low cytotoxicity. Similarly, the rare earth elements Sm and Nd proved effective in reducing cancer cell survival, with notable activity in disrupting cellular processes critical for tumor growth and proliferation. The physicochemical stability of the microspheres in biological environments is an important consideration. Given the silica-based glassy nature of the matrix, these systems are expected to exhibit low solubility and high stability under physiological conditions. While no degradation or structural alterations were observed during the 24-hour in vitro assays, future studies will assess their behavior in biological fluids over extended periods and under dynamic conditions to better simulate in vivo environments. This research underscores the importance of further exploring the unique properties of these materials in oncology, particularly for developing novel, less toxic cancer treatments. The findings suggest that these doped microspheres could play a pivotal role in advancing nanomedicine, offering a new avenue for combating resistant and metastatic cancers.

Authors Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Jessica Ingrid Faria de Souza, Natália Cristina Gomes da Silva, Filipe Ferreira Ascenção, Beatriz da Silva Batista. The first draft of the manuscript was written by Luciana Magalhães Rebelo Alencar, Pierre Basilio de Almeida Fechine, Eduardo Ricci-Junior, Ralph Santos-Oliveira and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Competing Interest

The authors state that they have no conflict of interest.

Availability of data and materials

All data will be available under request.

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