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Effect of Doxorubicin-Loaded Tetraborate Nanoparticles on HUVEC Behavior for Tumor Angiogenesis

Doksorubisin Yüklü Tetraborat Nanopartiküllerin Tümör Anjiyogenezinde HUVEC Davranışı Üzerine Etkisi

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ABSTRACT

Angiogenesis supports tumor growth and facilitates metastasis to nearby tissues, making its inhibition a key target in cancer therapy. Human umbilical vein endothelial cells (HUVECs) are commonly used for in vitro angiogenesis studies due to their role in forming blood vessels. This study investigates the effects of doxorubicin (Dox)-loaded calcium tetraborate nanoparticles (CaB_4O_7-Dox) and magnesium tetraborate nanoparticles (MgB_4O_7-Dox) on HUVEC behavior, aiming to inhibit cell proliferation and enhance the cancer treatment efficiency. CaB_4O_7 and MgB_4O_7 nanoparticles have approximately 200 nm and 300 nm sizes, respectively. Cytotoxicity studies showed that the IC50 of Dox was determined to be approximately 350 ng/mL (440 nM) for HUVECs. Dox-loaded calcium and magnesium tetraborate nanoparticles significantly outperformed free Dox and control groups in inhibiting HUVEC proliferation. Additionally, these nanoparticles significantly changed cell morphology and disrupted the tendency to tube formation, indicating their anti-angiogenic effect. These findings indicate that Dox-loaded tetraborate nanoparticles effectively modulate HUVEC behavior and angiogenesis, highlighting their potential as a nanoparticle-based system to improve the efficacy of cancer therapies.

Key Words
Tetraborate nanoparticles, HUVEC, doxorubicin, angiogenesis.

ÖZ

Angiogenez, tümör büyümesini destekler ve yakın dokulara metastazı kolaylaştırır, bu nedenle inhibisyonu kanser tedavisinde ana hedeflerden biridir. İnsan göbek kordonu venöz endotel hücreleri (HUVECler), kan damarlarının oluşumundaki rolleri nedeniyle in vitro angiogenez çalışmalarında sıklıkla kullanılmaktadır. Bu çalışma, doxorubisin (Dox) ile yüklenmiş kalsiyum tetraborat nanopartikülleri (CaB_4O_7-Dox) ve magnezyum tetraborat nanopartiküllerinin (MgB_4O_7-Dox) HUVEC davranışları üzerindeki etkilerini incelemekte olup, hücre proliferasyonunu inhibe etmeyi ve kanser tedavi etkinliğini artırmayı amaçlamaktadır. CaB_4O_7 ve MgB_4O_7 nanopartiküllerinin boyutları sırasıyla yaklaşık 200 nm ve 300 nm olarak belirlenmiştir. Sitotoksisite çalışmaları, Dox'un HUVECler için yaklaşık 350 ng/mL (440 nM) IC50 değerine sahip olduğunu göstermiştir. Dox ile yüklenmiş kalsiyum ve magnezyum tetraborat nanopartikülleri, HUVEC proliferasyonunu inhibe etmede serbest Dox ve kontrol gruplarına göre belirgin derecede üstündür. Ayrıca, bu nanopartiküller hücre morfolojisini önemli ölçüde değiştirmiş ve tüp oluşum eğilimini bozmuştur, bu da anti-anjiyogenik etkilerini göstermektedir. Bu bulgular, Dox ile yüklenmiş tetraborat nanopartiküllerinin HUVEC davranışını ve anjiyogenezini etkili bir şekilde modüle ettiğini ve bu nanopartikül bazlı sistemlerin kanser tedavilerinin etkinliğini artırma potansiyelini vurgulamaktadır.

Anahtar Kelimeler
Tetraborat nanopartiküller, HUVEC, doksorubisin, anjiyogenez.

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INTRODUCTION

Cancer is a serious threat to life because it may spread to distant tissues or organs necessitating the development of innovative treatment strategies. Angiogenesis, which involves the formation of new blood vessels from pre-existing ones, is vital for tumor growth and metastasis by supplying essential nutrients and oxygen to cancer cells [1,2]. Therefore, inhibiting angiogenesis plays a vital role in improving cancer treatment. Angiogenesis involves multiple steps, including endothelial cell activation, cellular proliferation, transformation into tube-like structures, and the formation of capillary tubes [3]. Preventing angiogenesis, especially at the early stages of tumor development, is crucial and at this point targeting endothelial cell proliferation is a key strategy. Human umbilical vein endothelial cells (HUVECs) are commonly utilized as an *in vitro* model for studying angiogenesis in pharmacology and tissue engineering applications due to their role in forming blood vessels [4].

Doxorubicin (Dox) is a chemotherapeutic drug commonly used to treat various cancers. Also, it has anti-angiogenic properties by downregulating the expression of vascular endothelial growth factor (VEGF) [5]. However, its clinical application is limited due to side effects and potential toxicity, particularly its cardiotoxicity [6]. Also, the cancer cells may develop resistance to Dox, reducing its effectiveness [7]. Nanoparticle-based drug delivery systems improve the bioavailability and reduce the toxicity of chemotherapeutic agents by allowing controlled release at the tumor site [8].

Boron-containing nanoparticles are attractive for cancer treatment due to their effectiveness in boron neutron capture therapy (BNCT). It is a specialized form of radiation therapy where the boron-10 isotope triggers a nuclear reaction that produces highly ionizing α-particles, resulting in the irreversible destruction of cancer cell DNA [9]. Also, the boron-based nanoparticles are biocompatible and their surface properties can be modified for targeting [10,11]. Combining boron nanoparticles with drug delivery and BNCT can generate a synergistic effect, substantially increasing the overall efficacy of cancer therapy.

In this study, the effects of calcium tetraborate (CaB_4O_7) and magnesium tetraborate (MgB_4O_7) nanoparticles as carriers for Dox on the behavior of HUVECs were investigated, focusing on their role in angiogenesis. Their potential impact on angiogenesis was determined by evaluating how nanoparticles influence cell viability, morphology, and tube formation *in vitro*. The findings of this study could contribute to the development of more effective cancer treatment systems and improve the life standards of patients.

MATERIALS and METHODS

Materials

All chemicals and materials used in this study and their companies are summarized in Table 1 below.

Synthesis and characterization of nanoparticles

The synthesis procedures of CaB_4O_7 and MgB_4O_7 nanoparticles were given in detail in the previous study [10]. Briefly, CaB_4O_7 and MgB_4O_7 nanoparticles were synthesized by solution-combustion and combustion synthesis methods, respectively. In this study, SEM analysis was used to assess the morphology of the nanoparticles. Before the examination, the nanoparticle suspension was pipetted onto the carbon stubs, allowed to dry, and coated with a gold-palladium. Then the nanoparticles were examined by using SEM (QUANTA 400F Field Emission, USA). ImageJ software (NIH, Bethesda, MD) was used for particle size analysis. Transmission electron microscopy (TEM, FEI Tecnai G2 Spirit BioTwin, USA) at 120 kV also assessed the morphological properties and nanoparticle sizes.

The effect of free Dox on HUVEC viability

HUVECs (passage no. 5) were used in the cell culture studies. RPMI-1640 including 1% (v/v) penicillin-streptomycin and 10% (v/v) FBS was used as a culture medium for these cells. The cells were cultured in an incubator at 37°C (Heraeus Instruments, Germany). Before seeding the cells to the wells, they were detached from the flasks with 0.05% (w/v) trypsin/EDTA, followed by centrifugation and resuspension in the fresh culture medium.

For cytotoxicity studies, varying Dox concentrations (0-1200 ng/mL) prepared in cell culture medium interacted with the HUVECs. The cells were added in 96-well plates with 10^4 cells/well concentration and kept in the incubator for 24 hours. Afterwards, the culture medium over the cells was removed and 200 µL of Dox solutions were added to each well. The mitochondrial activities of the cells were determined by MTT assay. The media

Table 1. Chemicals and biological materials used in the study.

Materials	Company	Country
Doxorubicin hydrochloride (Dox)	Sigma-Aldrich	Germany
Dimethyl sulfoxide (DMSO)	Sigma-Aldrich	Germany
Glutaraldehyde solution (GA) (25%, v/v)	Sigma-Aldrich	Germany
Paraformaldehyde (PFA)	Sigma-Aldrich	Germany
3-[4,5-dimethylthiazol-2-yl]-diphenyltetrazolium bromide (MTT)	Sigma-Aldrich	Germany
Bovine serum albumin (BSA)	Sigma-Aldrich	Germany
Triton X-100	Merck	Germany
Alexa fluor 488	Thermo Scientific	USA
4′,6-diamidino-2-phenylindole (DAPI)	Thermo Scientific	USA
Ethidium homodimer-1	Sigma-Aldrich	Germany
Calcein AM	Thermo Fisher Scientific	USA
RPMI-1640	Capricorn Scientific	Germany
Dulbecco's Phosphate Buffer Saline (DPBS)	Sigma-Aldrich	Germany
L-glutamine	Sigma-Aldrich	Germany
Fetal bovine serum (FBS)	Capricorn Scientific	Germany
Penicillin/streptomycin	Sigma-Aldrich	Germany
Trypsin-EDTA	Sigma-Aldrich	Germany

covering the cells were carefully removed and 200 µL of prewarmed RPMI-1640 and 20 µL of MTT solution (2.5 mg/mL in PBS) were added to each well. Then, the wells were incubated for three hours at 37°C and after incubation, the media on the wells were removed. Subsequently, DMSO (200 µL) was added to each well, and the absorbance was measured at 570 nm (with a reference wavelength of 690 nm) spectrophotometrically by a microplate reader (ASYS Hitech UVM 340 Plate Reader). Cell viability was determined by normalizing the absorbance of cells treated with Dox and/or nanoparticles to the absorbance of untreated control cells.

Cytotoxicity of nanoparticles against HUVECs

Cell seeding was performed as in the previous part. After 24 h, the nanoparticles were dispersed homogeneously in the cell culture medium after being sterilized under UV light for 45 minutes. Varying nanoparticle suspensions (0-1000 µg nanoparticle/mL) were prepared using cell culture medium. Before exposing the cells to the nanoparticles, the existing media were removed, and the prepared nanoparticle suspensions were homogeneously stirred and added with 200 µL onto the cells. The impact of free Dox on HUVECs was also evaluated.

Cell viability

The effect of the nanoparticles and free Dox on HUVEC viability was investigated by MTT assay as described above.

Light microscope analysis

Cells treated with nanoparticles or Dox for 48 hours were used for light microscope analysis. The cells were rinsed washed three times with DPBS and then observed under light microscopy (Olympus, Germany) while still in DPBS.

Assessment of cytoskeletal and nuclear structures

The morphology of the actin filaments and nuclei of the cells was examined by F-actin/DAPI staining after 48 h. Before staining, the wells were gently washed with DPBS three times. Cell fixation was performed with incubation of the cells in paraformaldehyde solution (4% (v/v)) for 30 min. Afterward, the wells were rinsed with PBS three times and 200 µL of Triton X-100 solution (0.1% (v/v)) was added for cell membrane permeability. The cells were then incubated in this solution for 10 min. After rinsing the wells with PBS three times, staining was performed. To stain cell nuclei, DAPI was diluted 1:1000, and to stain actin filaments, anti-F-actin antibody was diluted 1:100 in a PBS solution with 1% (w/v) BSA (PBS/A). Approximately 200 µL of the staining solutions were added to the wells and the cells incubated in these solutions for at dark for 1 h. The wells were rin-

sed with PBS/A several times before observing the cells under a fluorescence microscope (Olympus, Germany).

Live/dead cell staining

This staining was performed after 72 hours of interaction with the nanoparticles or free Dox. The cells were washed with Mg^{2+} and Ca^{2+} containing DPBS (DPBS+), followed by the addition of calcein AM and ethidium homodimer-1 solutions (diluted 1:1000 in DPBS+) and incubated for 30 min. Washing with DPBS was performed to remove any residual staining solutions. Finally, the living and dead cells were observed using fluorescence microscopy (Olympus, Germany).

Statistical Analysis

Statistical analysis of the experimental data was performed using GraphPad Prism version 9 (GraphPad Software Inc., CA, USA). Each experiment was conducted in triplicate, and two-way ANOVA was used to assess significant differences among the groups, with p-values below 0.05 considered statistically significant.

RESULTS and DISCUSSION

Boron-based nanoparticles are promising in cancer therapy due to their usage in BNCT. It is a kind of radiation therapy that involves concentrating boron compounds in cancer cells, which are then exposed to neutron beams [11]. The effect of different borate-based nanoparticles on brain cancer treatment was investigated in the previous study [10]. Especially CaB_4O_7-Dox and MgB_4O_7-Dox nanoparticles demonstrated toxic effects on T98G human glioblastoma cells. In this study, the impact of these systems on the behavior of HUVECs was examined to provide preliminary information for understanding whether they inhibit the vascularization of tumors. To achieve this, cell culture studies were performed with HUVECs and the cells were exposed to the nanoparticles with and without Dox. Additionally, the same concentrations of free Dox as in the nanoparticles interacted with HUVECs to determine the specific effects of the Dox-loaded nanoparticles.

Characterization of nanoparticles

The detailed characterizations of the nanoparticles were provided in the previous study [10]. Here, unlike the previous one, SEM photographs with different magnifications and TEM images are given in Figure 1. Average nanoparticle diameters are determined to be approximately 200 nm and 300 nm for CaB_4O_7 and MgB_4O_7 nanoparticles, respectively.

In the previous study, the loading capacity of the borate-based nanoparticles was found approximately 200 µg Dox/mg particle, and approximately 95% and 76% of the loaded Dox were released from CaB_4O_7-Dox and MgB_4O_7-Dox nanoparticles within 3 days, respectively [10]. The following sections describe the effect of these nanoparticles on HUVEC behavior.

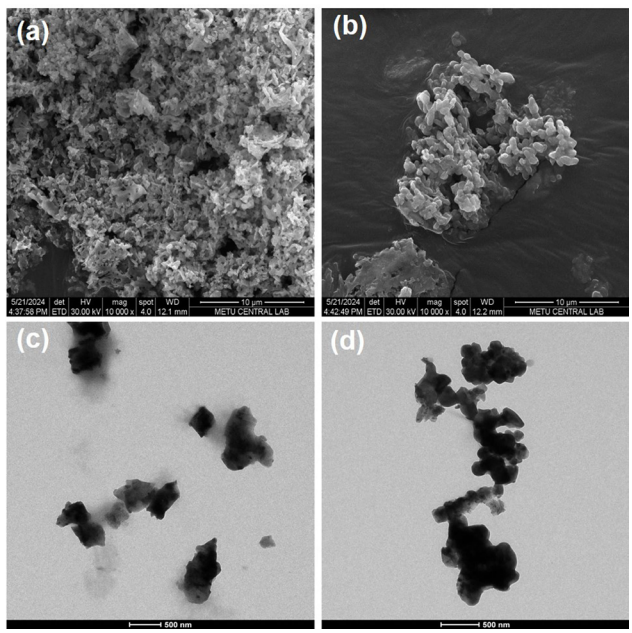

Figure 1. SEM photographs of a) CaB_4O_7 nanoparticles, and b) MgB_4O_7 nanoparticles (10,000 X magnification, scale bar: 10 µm). TEM photographs of c) CaB_4O_7 nanoparticles, and d) MgB_4O_7 nanoparticles (scale bar: 500 nm).

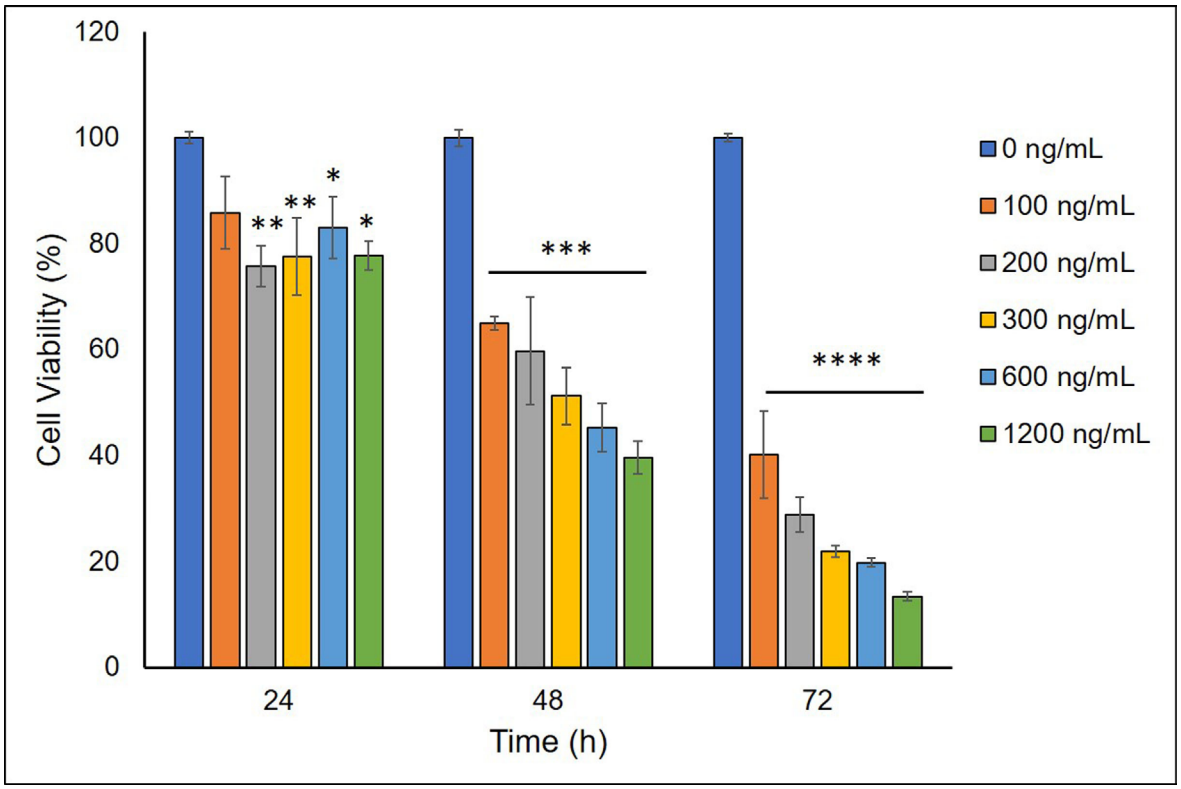

Figure 2. Cell viability of HUVECs after exposure to free Dox for 24 hours, 48 hours, and 72 hours. Values are expressed as mean ± SD (n=3). Statistical significance is indicated as *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, with the control group representing 0 ng/mL Dox.

Angiogenesis is an essential process for tumor growth; therefore, its inhibition is a critical strategy in cancer therapy [12]. Angiogenic therapies aim to inhibit the proliferation endothelial cell proliferation and HUVECs are mostly used as *in vitro* model cells for angiogenesis studies due to their ability to form tubule-like structures similar to capillaries [13]. To understand the effect of Dox on HUVEC behaviors, first, the HUVECs interacted with free Dox at varying concentrations and the half-maximal inhibitory concentration (IC_{50}) of Dox for HUVECs was determined. Then, the effect of nanoparticles with/without Dox on the viability and morphology of HUVECs was investigated.

The effect of free Dox on cell viability

Various concentrations of Dox (0-1200 ng/mL) were tested on HUVECs, and cell viability was assessed after 24, 48, and 72 hours of interaction. Cells in the culture medium without Dox (0 ng/mL) are used as the control, and the viability graph is given in Figure 2. For 24 h, statistical differences were observed at Dox concentrations higher than 200 ng/mL. However, after 48 h (p<0.001) and 72 h (p<0.0001) of interactions, the cell viability for all Dox concentrations decreased significantly. The IC_{50} value was found to be ~350 ng/mL (640 nM) after 48 h of exposure to free Dox. Hassan et al. found the IC_{50} value approximately 60 nM [14]. Our finding is ten times higher than the reported result and the appropriate nanoparticle concentrations for subsequent cell culture studies were determined according to this IC_{50} value.

The effect of nanoparticles on cell viability

The cell viabilities of HUVECs interacted with blank and Dox-loaded nanoparticles at varying concentrations (0-1000 µg/mL) are given in Figure 3. Free Dox with the same concentrations within the nanoparticles has also interacted with the cells. After 24 h of interaction, the cell viability remained high for blank nanoparticles (CaB_4O_7 and MgB_4O_7), with no statistical difference compared to the control (p>0.05) for all nanoparticle concentrations. However, a substantial decrease in cell viability was determined for the CaB_4O_7-Dox and MgB_4O_7-Dox groups compared to the control (p<0.0001) for all nanoparticle concentrations. While cell viability in the free Dox group was similar to that in the CaB_4O_7-Dox group, it was lower in the MgB_4O_7-Dox group compared to the free Dox. Significant statistical differences were

observed where p<0.0001 for 125 µg/mL and 250 µg/mL nanoparticle concentrations; and p<0.001 for 500 µg/mL and 1000 µg/mL nanoparticle concentrations. MgB_4O_7-Dox nanoparticles demonstrate significantly greater effectiveness in inducing cell toxicity than free Dox at equivalent concentrations. The cell viabilities for CaB_4O_7-Dox and MgB_4O_7-Dox groups are significantly lower than that of control for all nanoparticle concentrations (p<0.0001) for 48 h. For MgB_4O_7-Dox nanoparticles, cell viability is lower compared to free Dox at 125 µg/mL (p<0.001) and 250 µg/mL (p<0.01) nanoparticle concentrations. Also, cell viability decreased for CaB_4O_7 and MgB_4O_7 nanoparticles at high nanoparticle concentrations. Similar results were obtained for 72 h of interaction. In conclusion, MgB_4O_7-Dox nanoparticles are effective in decreasing the cell viability of HUVECs and they cause more toxic effects than free Dox especially for lower nanoparticle concentrations.

Morphological analysis

Light microscope analysis

The morphology of HUVECs incubated with different concentrations of nanoparticles and free Dox are observed under light microscopy (Figure 4). In the control group, HUVECs were healthy and exhibited a cobblestone-like arrangement which is their specific morphology [15]. In the CaB_4O_7 and MgB_4O_7 groups, the morphology of the cells is similar to the control for 125 µg/mL and 250 µg/mL nanoparticle concentrations, however, their numbers decreased and the morphologies changed at higher concentrations. Also, the cells lost their characteristic morphology for CaB_4O_7-Dox, MgB_4O_7-Dox, and free Dox groups. Furthermore, very few cells were observed at high nanoparticle concentrations. In the free Dox group, a greater number of cells were seen compared to those treated with Dox-loaded nanoparticles at the same concentrations, particularly at 125 µg/mL and 250 µg/mL. This highlights the greater effectiveness of Dox-loaded nanoparticles especially for low concentrations.

Assessment of cytoskeletal and nuclear structures

The detailed morphology of the actin filaments and nuclei was investigated by F-actin/DAPI staining after 48 h of interaction with the nanoparticles and free Dox

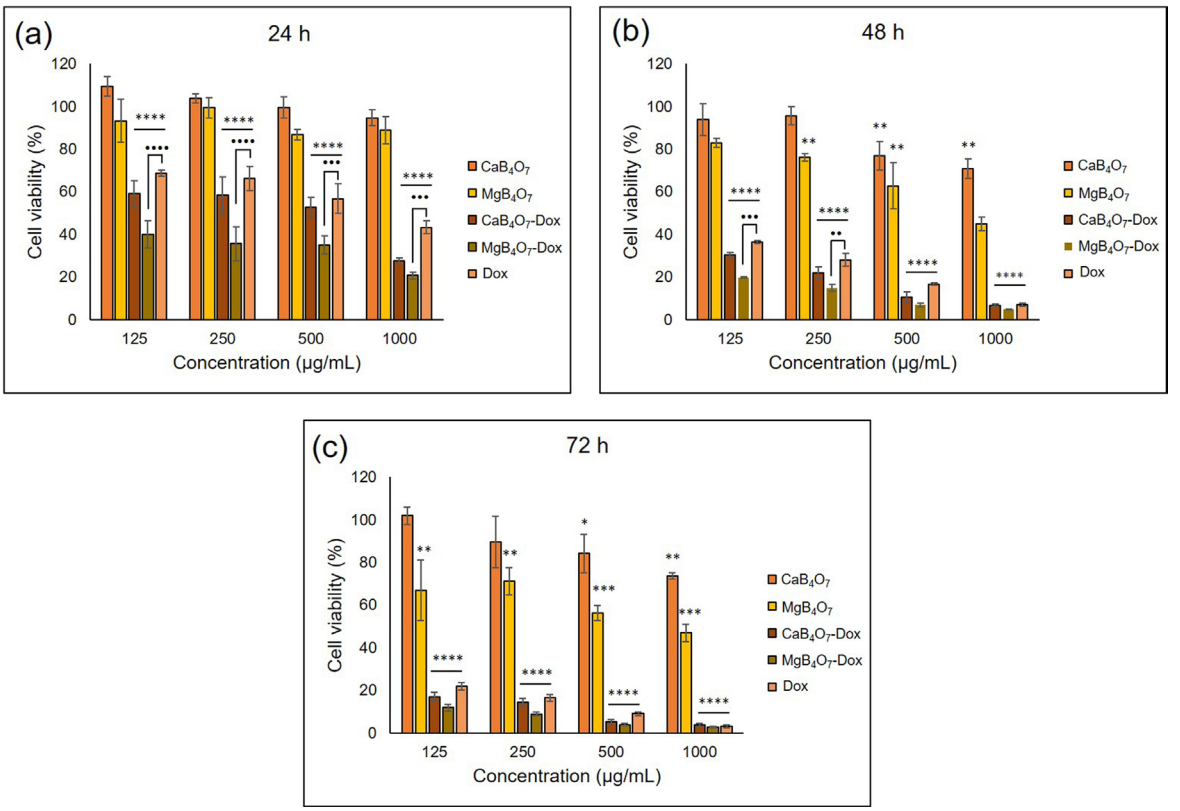

Figure 3. Cell viability of HUVECs exposed to nanoparticles with/without Dox and free Dox for a) 24 hours, b) 48 hours, and c) 72 hours of incubation. Statistical significance is indicated as follows: *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 when compared to the control group (cells not exposed to nanoparticles); •p<0.05, ••p<0.01, •••p<0.001, ••••p<0.0001 when comparing different groups.

(Figure 5). In the control group, arranged cells were observed to form capillary structures and indicated with white arrows. These arrangements were also observed in the CaB_4O_7 groups at 125 µg/mL and 250 µg/mL nanoparticle concentrations. However, very few arranged cells were seen in the MgB_4O_7 groups. The Dox-loaded nanoparticles demonstrated an inhibitory effect on the cells by increasing the nanoparticle concentration. Also, the morphology of the HUVECs significantly changed for CaB_4O_7-Dox, MgB_4O_7-Dox, and Dox groups with larger F-actin filaments. Furthermore, the cell nuclei were less distinct compared to those observed with blank nanoparticles. The exposure of cells to chemotherapy drugs induces a significant change in their morphology due to the genotoxic stress experienced by the cells [16,17]. This morphological alteration is an expected response of the cells as they are adapting to the cytotoxic environment.

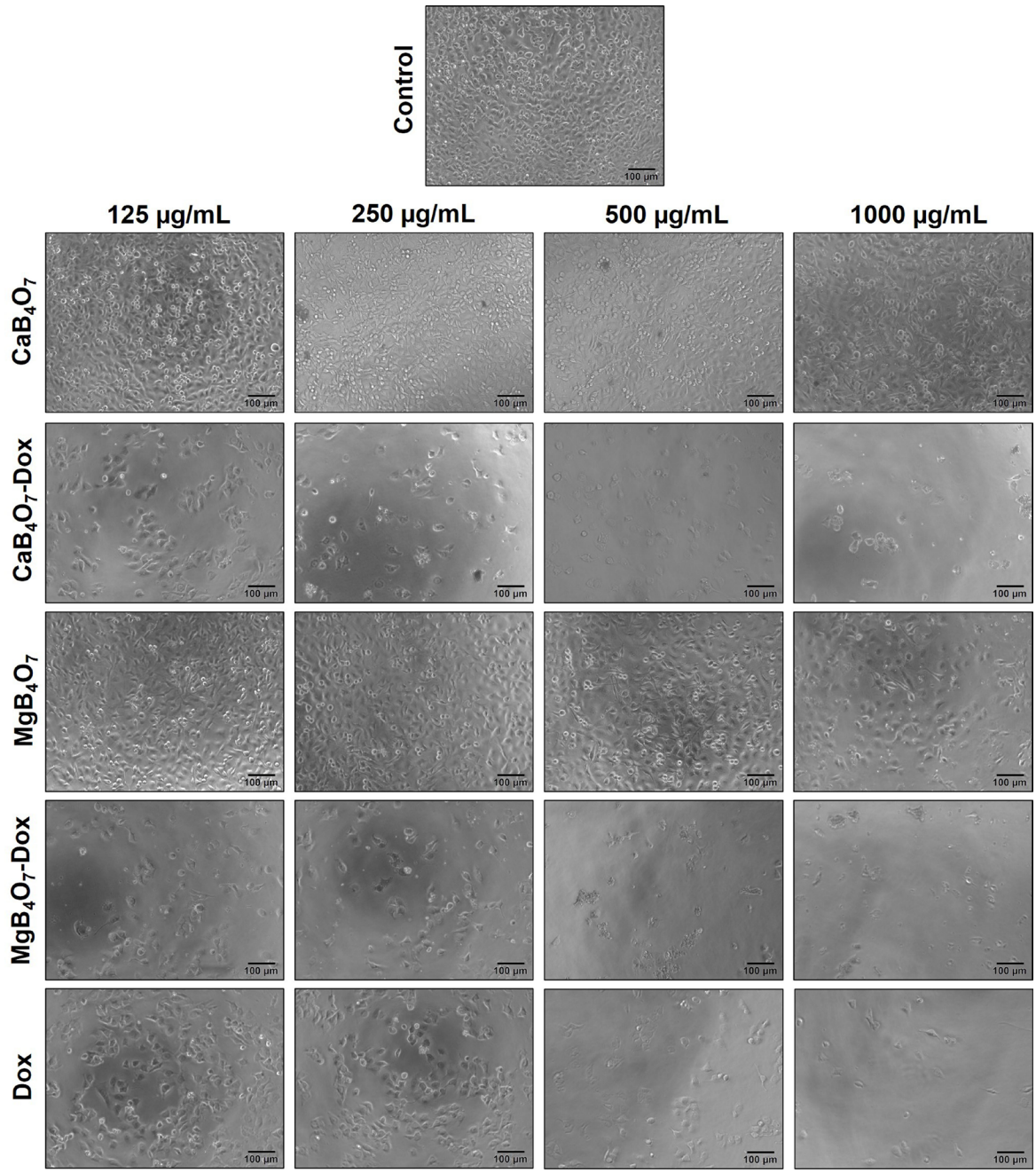

Figure 4. Light microscopy images of HUVECs incubated with nanoparticles and free Dox for 48 hours (10X magnification). Scale bar: 100 µm.

Live/dead cell staining

The effect of varying concentrations of nanoparticles and free Dox on HUVECs was investigated by staining living and dead cells after 72 h of interaction. The cell images are given in Figure 6, where dead and living are stained with red and green, respectively. Cell numbers decreased by increasing nanoparticle concentrations, especially for Dox-loaded nanoparticles and free Dox. Notably, more cells were present in the Dox group compared to the CaB_4O_7-Dox and MgB_4O_7-Dox groups, which supports the efficiency of these nanoparticles for vascularization.

In vitro cell culture studies showed that Dox-loaded CaB_4O_7 and MgB_4O_7 nanoparticles significantly decreased HUVEC viability in a dose-dependent manner. As the concentration of these nanoparticles increased, there was a marked decline in cell viability, indicating their potent inhibitory effects. Additionally, the treatment

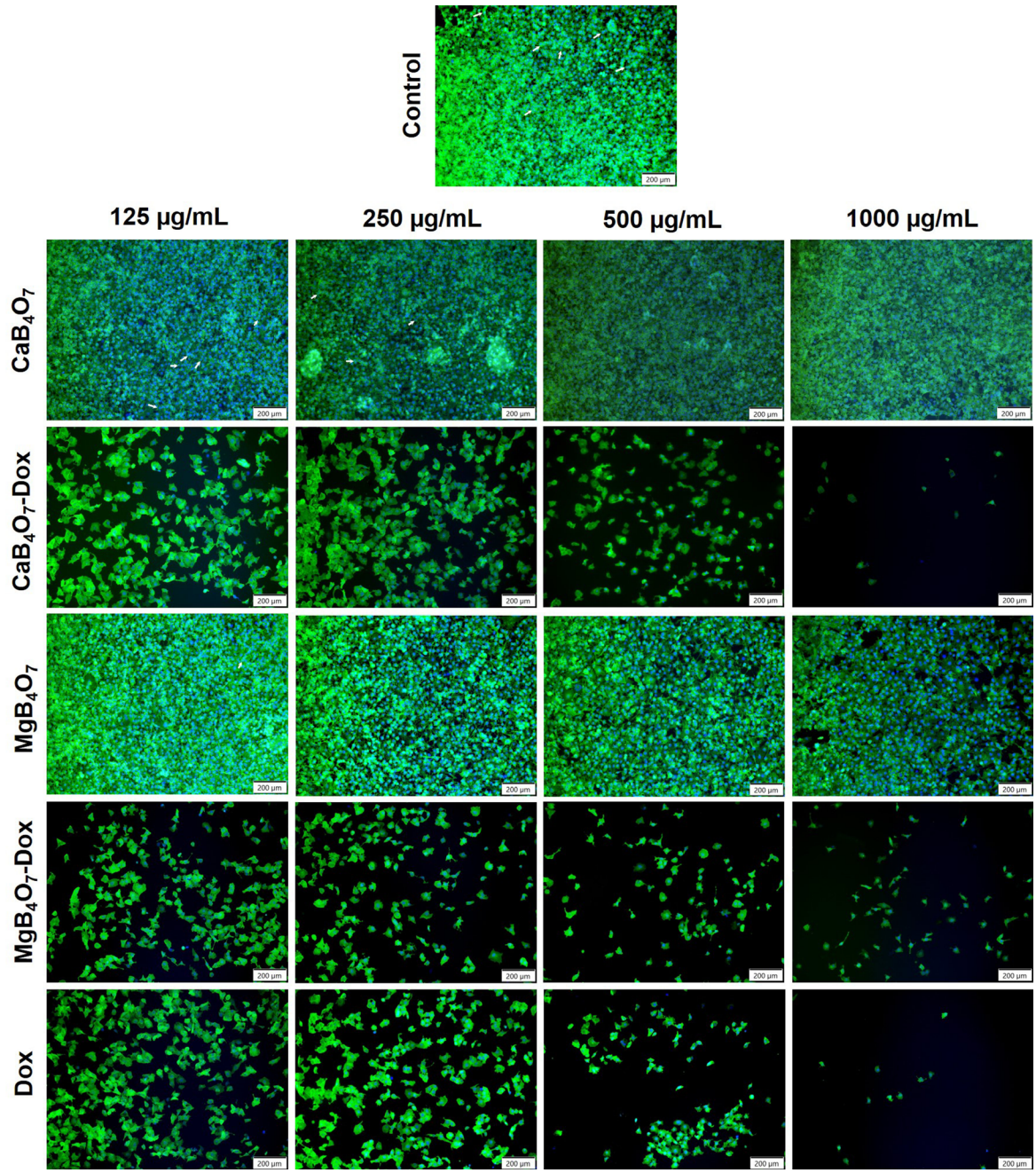

Figure 5. Fluorescence microscopy images of HUVEC cells cultured for 48 hours (10X magnification). Actin filaments are shown in green, and cell nuclei are depicted in blue. Scale bar: 200 µm. White arrows highlight the cells organized for vascularization.

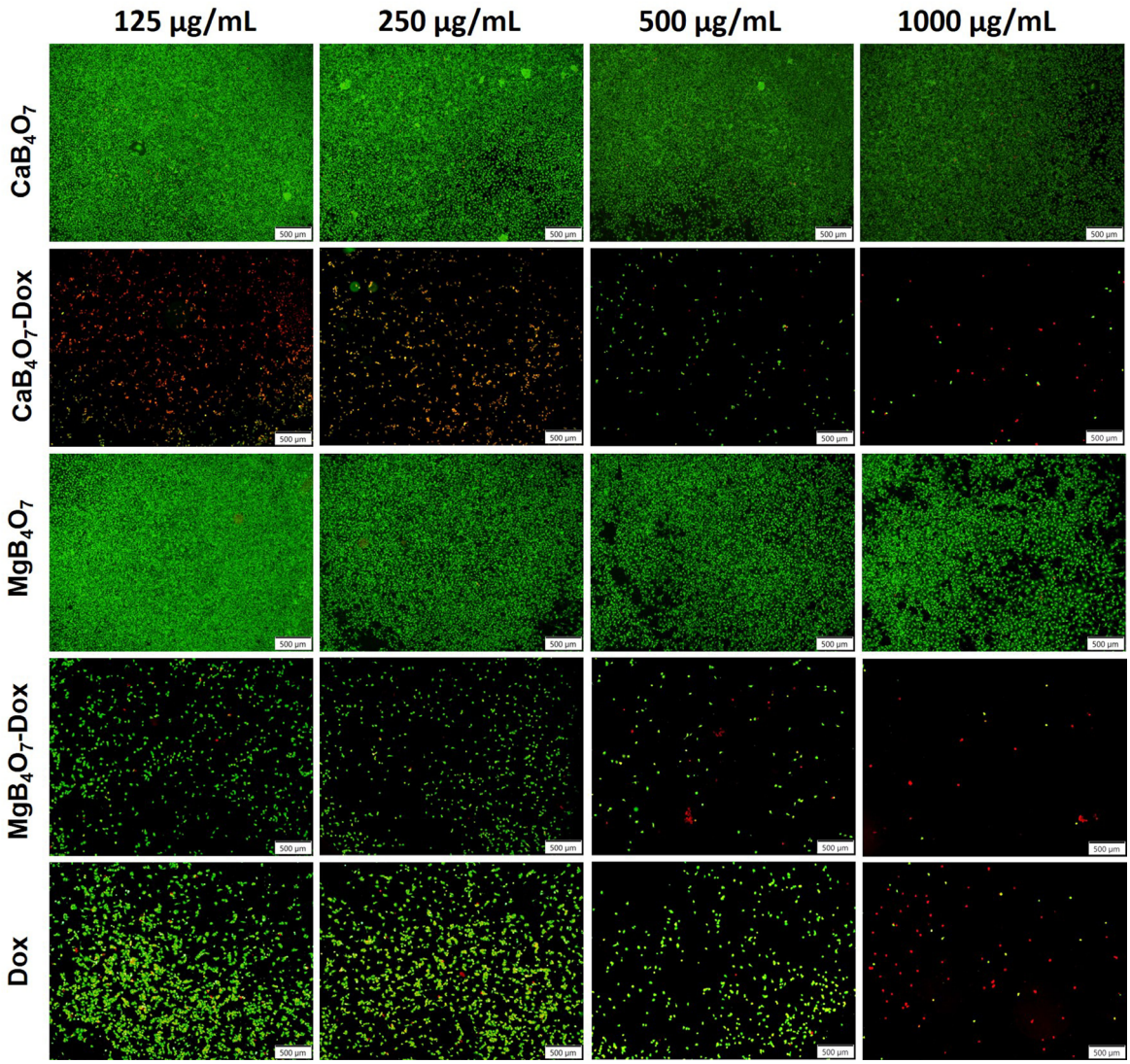

Figure 6. Fluorescence microscopy images of HUVECs cultured for 72 hours (4X magnification). Live cells are shown in green, while dead cells are shown in red. Scale bar: 500 µm.

induced notable changes in cell morphology with larger actin filaments and unclear nuclei, indicating cytotoxic stress. Moreover, these nanoparticles disrupted the organization of HUVECs, effectively inhibiting their ability to form tubular structures, which is a critical process in angiogenesis. This inhibition of tube formation further emphasizes the potential of these nanoparticles as therapeutic agents targeting angiogenesis in cancer treatment.

CONCLUSION

This study demonstrates that Dox-loaded calcium tetraborate and magnesium tetraborate nanoparticles significantly influence the morphology and inhibit the proliferation of HUVECs, playing a critical role in tumor angiogenesis at the initial stage. By disrupting the initial stages of angiogenesis, these nanoparticles enhance the anti-cancer efficacy of Dox, offering a dual approach to impair both tumor growth and vascular development. The results suggest that tetraborate nanoparticles can effectively modulate cellular behaviors essential for angiogenic processes, making them a promising system for targeted cancer therapies. Future research should focus on evaluating the therapeutic potential of these nanoparticles in complex 3D systems and advancing their application in clinical settings.

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