



Article

In Vitro Evaluation of Cytocompatibility of B₄C-Reinforced CoCrMo, Ti, and 17-4 PH Alloys

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Abstract

Boron carbide (B₄C)-reinforced metal matrix composites (MMCs) are promising candidates for biomedical implants due to their mechanical properties and potential biological compatibility. In this study, in vitro biocompatibility and cytotoxicity of B₄C-reinforced CoCrMo, Ti, and 17-4 PH alloys were systematically evaluated using human osteoblast (HOB) cells. Composites were fabricated via powder metallurgy with varying B₄C reinforcement ratios (CoCrMo and Ti: 5–10 wt%; 17-4 PH: 3–12 wt%). Extracts prepared according to ISO 10993-12 standards were applied at different concentrations (100%, 50%, 25%, 12.5%) to assess cell viability using the MTT assay over 24, 48, and 72 h. Results demonstrated a clear dose-dependent cytotoxic effect across all composite systems. Ti composites exhibited the highest biocompatibility, with cell viability largely preserved even at higher B₄C ratios. CoCrMo composites showed moderate cytotoxicity, which decreased upon extract dilution, indicating low-concentration compatibility. In contrast, 17-4 PH composites revealed significant cytotoxicity at higher extract concentrations, exacerbated by increasing B₄C content. Literature-supported findings confirm that B₄C incorporation enhances hardness, wear resistance, and elastic modulus, yet excessive reinforcement can induce local stress and particle detachment, affecting cellular tolerance. Diluted extracts of Ti and CoCrMo composites maintained cell viability at a biocompatible level consistent with ISO 10993-5 criteria. These results highlight the promising biocompatibility of B₄C-reinforced Ti and CoCrMo alloys for biomedical applications and provide a biological basis for the design of next-generation composite implants.

Keywords: biocompatibility; biomedical alloys; boron carbide; cytotoxicity; CoCrMo; MTT assay; titanium; 17-4 PH stainless steel



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1. Introduction

CoCrMo, Ti alloys and stainless steels, which are frequently used in load-bearing orthopedic implants, have found wide application in biomedical applications due to their tissue-like mechanical properties and high structural stability [1,2]. In order to enhance the performance of implant materials, various reinforcements are incorporated into metal materials to produce composite materials. Metal matrix composites (MMC) demonstrate

considerable promise for utilization due to their optimizability in mechanical performance and biological integration [3–5].

Boron carbide (B_4C) is of particular significance in the field of materials science due to its unique properties, including its high hardness, low density, excellent wear resistance, and corrosion resistance. These properties render it one of the hardest materials utilized in the fabrication of wear-resistant materials. Their use as a ceramic reinforcement phase in the production of MMCs is particularly noteworthy [6,7]. The research conducted on the mechanical and corrosion properties of B_4C -reinforced CoCrMo, Ti, alloys, and stainless steels has yielded encouraging results, indicating a potential for significant advancements in the field [3,8–11]. However, the long-term clinical success of biomedical implants is determined not only by their high mechanical strength and corrosion resistance but also by their capacity to interact harmoniously with biological systems.

MMCs that are based on the reinforcement of CoCrMo alloy, a material frequently used in biomedical implant applications, with B_4C ceramic additives have been reported to offer an alternative for biomedical applications [7,10]. CoCrMo/ B_4C composites demonstrated an increase in brittleness due to the additive. During friction tests, the reinforcement particles exhibited an abrasive effect that adversely impacted the tribological properties when compared to the CoCrMo alloy [7]. A positive correlation has been observed between the corrosion rate and the amount of B_4C reinforcement. This observation can be associated with the development of microgalvanic cells and the enhancement of surface interactions between B_4C and the matrix [10].

Ti/ B_4C MMCs have been identified as a promising candidate for use as load-bearing orthopedic implant materials and in various automotive and aerospace applications. The load-bearing capacity of B_4C particles leads to a reduction in wear loss. This situation resulted in low corrosion tendency and low corrosion kinetics under sliding conditions against alumina balls. However, in Ti/ B_4C composites, the high reinforcement ratio has been shown to enhance corrosion kinetics under static conditions, particularly due to the bridging of B_4C particles in aggregation regions and the formation of porosity leading to localized corrosion [8].

Stainless steels (SS) have a variety of applications in biomedical engineering and are among the biomaterials with the most extensive usage history [1,12]. Precipitation-hardened 17-4 PH SS has a variety of biomedical applications, including plates, screws, implant components, and surgical instruments. In comparison to Ti and CoCrMo matrix composites, 17-4PH/ B_4C composites demonstrate higher corrosion rates. The corrosion performance of 17-4PH/ B_4C composites was found to decrease with B_4C reinforcement. This decline has been attributed to the potential of interfacial interactions and microgalvanic effects [10].

The fundamental prerequisite for an implant material is its biocompatibility. Biocompatibility can be defined as the capacity of a given material or medical device to be both safe and functional for application in vivo. Achieving biocompatibility is imperative in order to mitigate the fundamental limitations of metallic implants [4,12]. Toxicity is defined as the degree to which a substance can harm a living organism. The toxicity of implant materials is associated with the leaching of elements from their chemical composition into the biological environment. The release of ions from the material surface of metallic implants or particles released as a result of wear can interact with surrounding tissues, potentially causing cytotoxic, inflammatory, or immunological responses [13–15].

Biocompatibility tests of biomedical implant materials are of great importance for the success of the implant. A variety of in vitro and in vivo tests are conducted to ensure the implant properties. Cytotoxicity tests, which evaluate the effectiveness of biomedical implants, are widely used as the fundamental step of biocompatibility tests. The safety of

implant materials is determined by the results of in vitro cytotoxicity tests, which evaluate their compatibility with biological systems [16–18].

A thorough review of the extant literature revealed that the mechanical properties, microstructural characterization, corrosion properties, and reliability performance of B₄C-reinforcement CoCrMo, Ti, and 17-4 PH MMCs have been thoroughly analyzed. The results obtained demonstrated that the material is structurally suitable for load-bearing implant applications [10]. However, to evaluate the biomedical clinical potential, it is necessary that the obtained data be supported by biological response. The evaluation of clinically critical CoCrMo, Ti, and 17-4 PH alloys enhanced with B₄C reinforcement in terms of biocompatibility points to an important gap in the literature.

The present study aims to determine the in vitro biocompatibility properties of B₄C-reinforced CoCrMo, Ti, and 17-4 PH MMCs. In this context, cytotoxicity of the composites was performed according to biological evaluation of medical devices in accordance with the ISO in vitro toxicity test. The findings obtained from the study are aimed to provide a scientific basis for new-generation composite implant designs and clinical applications by revealing the biological effect of B₄C reinforcement in different implant alloys.

2. Materials and Methods

2.1. Production

CoCrMo and Ti with 5 and 10 wt% B₄C reinforcement, as well as 17-4 PH composites with 3, 6, 9, and 12 wt% B₄C reinforcement, were produced by the conventional powder metallurgy method.

Cobalt powder (Alfa Aesar, Ward Hill, MA, USA) was utilized in the study, exhibiting a purity level of 99.5%, while chromium, molybdenum, and titanium powder (Nanokar Nanotechnology, Istanbul, Türkiye) were employed in the study, with purity levels ranging from 99.5% to 99.9%. Furthermore, 17-4 PH powder (Carpenter Technology, Philadelphia, PA, USA) with 99.9% purity was utilized. B₄C powder (Nanokar Nanotechnology, Istanbul, Türkiye) utilized as the ceramic reinforcement phase was 99% pure, with a density of 2.52 g/cm³ and particle size ranging from 100 to 150 µm. The metal and B₄C reinforcement powders were bonded using a 0.6% PVA binder solution (1–3 wt%).

Metal powder mixtures with added B₄C were mechanically mixed in a ball mill (MSE Technology, BM-S38003, Istanbul, Türkiye) for 20 h at 380 rpm using zirconia balls (3 mm diameter) with a ball-to-powder ratio of 10:1. The compaction of powder mixtures was conducted using a single-axis manual hydraulic press (MSE Technology, LP-M2S10, Istanbul, Türkiye) within the range of 400 to 450 MPa. This process yielded raw samples of varying dimensions, with a diameter of 10 mm, from the mixture powders. The samples were subjected to sintering in a vacuum environment for a duration of 60 min, employing a heat treatment sintering furnace (MTI, GLS-1500X, New York, NY, USA) at a temperature of 1200 °C, with a heating rate of 4 °C/min.

The MMCs were produced by determining the optimum B₄C reinforcement amount in CoCrMo, Ti, and 17-4 PH alloys, offering superior mechanical and corrosion properties [10].

2.2. Characterization Studies

The materials and characterization methods for B₄C-reinforced MMCs utilized in this study are summarized in Table 1. The characterization studies were initiated with a microstructural examination of the produced samples, employing scanning electron microscopy (SEM) (JEOL, NeoScope JCM-5000, Tokyo, Japan). A microstructural analysis of B₄C-reinforced composites was conducted to observe the distribution of B₄C particles and the porosity.

Table 1. Overview of materials and characterization methods for B₄C-reinforced MMCs.

Parameter	Details
Matrix Material	CoCrMo alloy, Ti, 17-4 PH SS
Reinforcement	Boron Carbide (B ₄ C)
Production Method	Powder Metallurgy (PM)
Microstructural Analysis	Scanning Electron Microscopy (SEM)
Hardness Test	Vickers Microhardness (HV3)
Wear Test	Pin-on-disk (SiC disk, 20 m wear length)
Elastic Modulus	Ultrasonic Pulse-Echo Method
Electrical Conductivity	Eddy Current Instrument (in %IACS units)
Corrosion Tests	Potentiodynamic Polarization and Electrochemical Impedance Spectroscopy (EIS) (in SBF with a pH of 6.6)
Cytotoxicity Test	In vitro MTT Test

The hardness of the composites was determined using the Vickers hardness method (Zwick/Roell, ZHU 187.5, Kennesaw, GA, USA). Wear behavior of the composites was determined using the pin-on-disk tribometer (Devotrans, DVT DA 6, Istanbul, Türkiye) with a 20 m wear length and SiC wear surface.

The elastic modulus of MMCs is a critical parameter in the field of engineering design. The elastic modulus of composites can also be assessed non-destructively using an ultrasonic technique that measures the velocities of longitudinal and transverse waves. The accuracy of the pulse-echo method for MMCs is of significance due to the inherent microstructural complexity and the impact of interphase interactions on mechanical behavior. The accuracy of wave propagation data depends on the representativeness of the heterogeneous structure. When supported by appropriate calibration and testing methods, the pulse-echo method is a valuable way to quickly and non-destructively assess the elastic modulus of MMCs.

Non-destructive ultrasonic testing uses velocity measurement via direct probe-sample contact. A thin liquid film between the probe and the sample reduces air resistance, facilitating sound passage between them. The elastic modulus of the composites was measured using non-destructive ultrasonic testing with the ultrasonic velocity pulse-echo method at a frequency of 4 MHz (GE, USM Go+, Boston, MA, USA) with a dual-crystal normal probe. In the equation below, V_T is the transverse wave ultrasonic velocity, V_L is the longitudinal wave ultrasonic velocity, and (ρ) is the intensity [19].

$$E = \rho V_T^2 \frac{3V_L^2 - 4V_T^2}{V_L^2 - V_T^2} \quad (1)$$

The International Annealed Copper Standard (IACS) is a method for calculating the electrical conductivity of a material based on the electrical conductivity of 100% pure annealed copper at room temperature. The conductivity is accepted as 5.8×10^7 S/m at 100% IACS. The electrical conductivity of the composites was determined using an eddy current (EtherCheck, Ether NDE, St. Albans, UK) device in %IACS units.

Electrochemical corrosion tests were conducted at ambient temperature in an artificial body fluid (SBF) medium with a pH of 6.6 using a potentiostat (Gamry, Interface 1000, Philadelphia, PA, USA). The three-electrode cell configuration was used. The open-circuit potential (OCP) was initially monitored until stabilization was achieved. Potentiodynamic polarization scans were then conducted from -500 mV to $+1500$ mV at 1 mV/s. The corrosion tests were conducted using potentiodynamic polarization (Tafel extrapolation) and electrochemical impedance spectroscopy (EIS) analyses. Electrochemical impedance spectroscopy (EIS) at OCP used an AC signal of 5 mV over a range of 10^5 to 10^{-1} Hz.

2.3. In Vitro Cell Culture Studies

2.3.1. Cell Seeding for the Experiment

After cell counting was finished, the cells were planted at a density of 10×10^4 cells per well in sterile 96-well plates. Using sterile DMEM culture media supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin, the final volume in each well was adjusted to 150 μ L. After that, the plates were placed in an incubator with 5% CO₂ for a whole day at 37 °C to let the cells adhere to the plate surface. Following the first 24 h incubation, the cells seeded in the plates were subjected to varying quantities (100%, 50%, 25%, and 12.5%) of the test material extracts, which were prepared using the ISO 10993-12 [20] extraction procedure following sample sterilization. The plates were then incubated for an additional 24 h to observe cell proliferation.

2.3.2. Extraction Protocol

The test material samples were immersed in 5 mL of the entire DMEM (Dulbecco's Modified Eagle Medium) culture medium under sterile conditions for extraction after being UV-sterilized to correspond with ISO 10993-12:2021 [20] standards. The 100% extract was defined as the medium in this configuration. The 50%, 25%, and 12.5% concentrations of this extract were then made by diluting it in DMEM before being added to the cells.

2.3.3. Cell Proliferation Test (MTT)

The MTT test [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] is used to measure the color change that results from the quantity of MTT converted to formazan. Cells actively absorb MTT, which is then converted into a colorful, water-insoluble formazan product by a mitochondrial-dependent process. Cell viability is determined by a cell's capacity to decrease MTT, and the number of living cells is correlated with the dye intensity obtained from MTT assay. The cytotoxicity test was conducted using the Human Osteoblast (HOB) cell line. Cells were grown in DMEM media supplemented with 10% FBS and 2% L-glutamine, and they were kept in an incubator with 5% CO₂ and 90% humidity at 37 °C. As directed by the HOB Cell Line, a solution of 0.25% trypsin and 0.03% EDTA was used to trypsinize the cells. According to the experiment, the cells were suspended in culture media, transferred to 96-well plates at a density of 10×10^4 cells per well in 150 μ L of medium, and allowed to attach to the surface.

After removing the culture media from the wells and applying a variety of sample concentrations to the cells, the cells were left to culture for 24 h at 37 °C with 5% CO₂ in an incubator. The culture medium was taken out of the wells and the plates were inspected under a microscope after the allotted incubation time. Each test well was then filled with 110 μ L of MTT solution. The plates were incubated at 37 °C for four hours. After that, the formazan crystals were dissolved by removing the MTT solution and adding 100 μ L of SDS to each well. A microplate reader with a 570 nm filter was used to determine optical density, and the findings were utilized for assessment. All samples were tested with a minimum of 4 replicates.

2.3.4. Statistical Analysis

The statistical analysis of the obtained results was analyzed using the Kruskal–Wallis non-parametric test via the GraphPad Prism (v5) program.

3. Results and Discussion

3.1. Microstructure Analysis

Scanning electron microscope images of the composites are presented in Figures 1–8. The CoCrMo/B₄C, Ti/B₄C, and 17-4PH/B₄C composites were subjected to a process of

reinforcement, characterized by an increase in the proportion of B_4C . The compositions demonstrated a consistent distribution of B_4C particles, exhibiting an absence of discernible porosity, cracks, or phase agglomeration. This observation indicates the effectiveness of the mixing and sintering processes.

The metal powders and B_4C reinforcement employed in CoCrMo, Ti, and 17-4 PH alloys are distinguished by their precise dimensional parameters and homogenous distribution, as substantiated by the SEM images, which reveal the presence of complex-shaped structures (Figures 1–8).

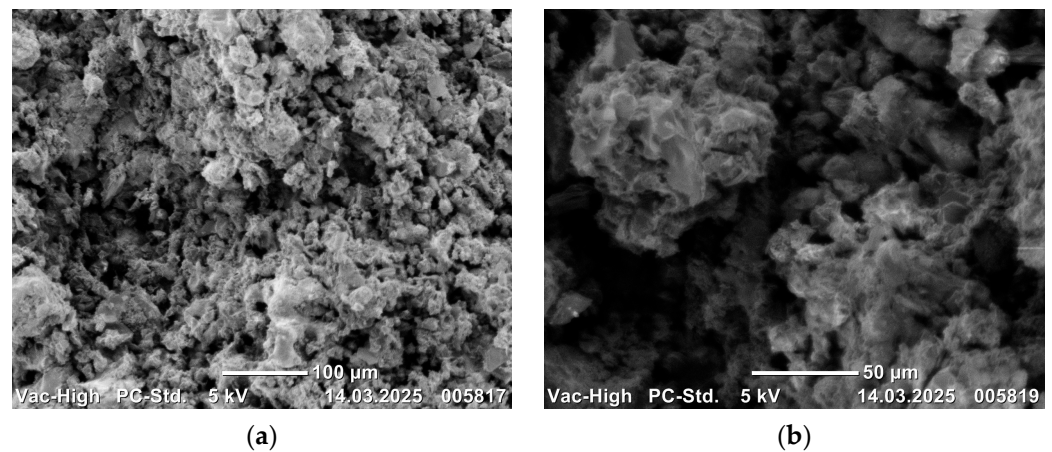


Figure 1. SEM images of CoCrMo/5 B_4C : (a) 100 μm ; (b) 50 μm .

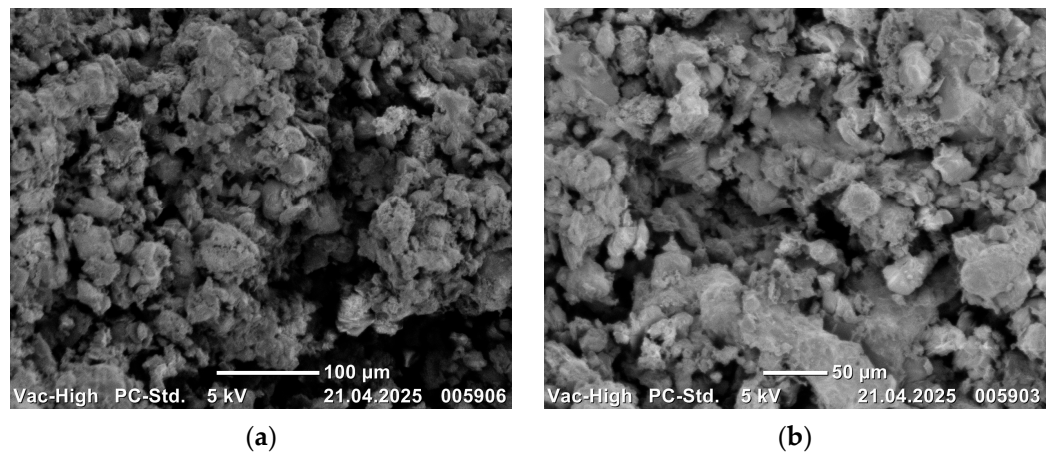


Figure 2. SEM images of CoCrMo/10 B_4C : (a) 100 μm ; (b) 50 μm .

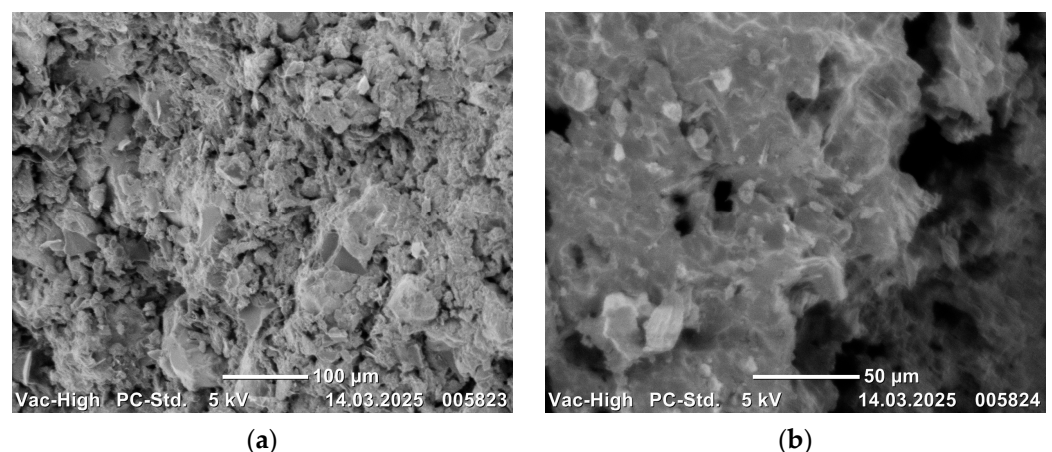


Figure 3. SEM images of Ti/5 B_4C : (a) 100 μm ; (b) 50 μm .

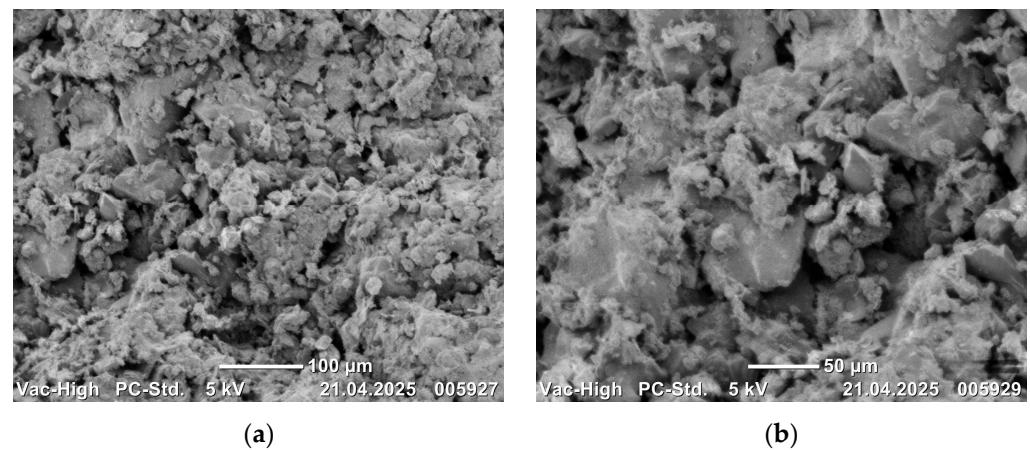


Figure 4. SEM images of Ti/10B₄C: (a) 100 μm; (b) 50 μm.

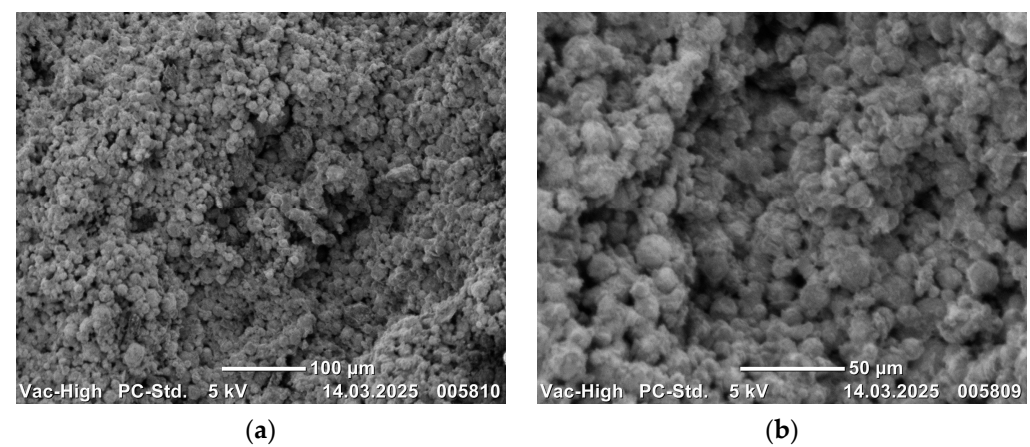


Figure 5. SEM images of 17-4PH/3B₄C: (a) 100 μm; (b) 50 μm.

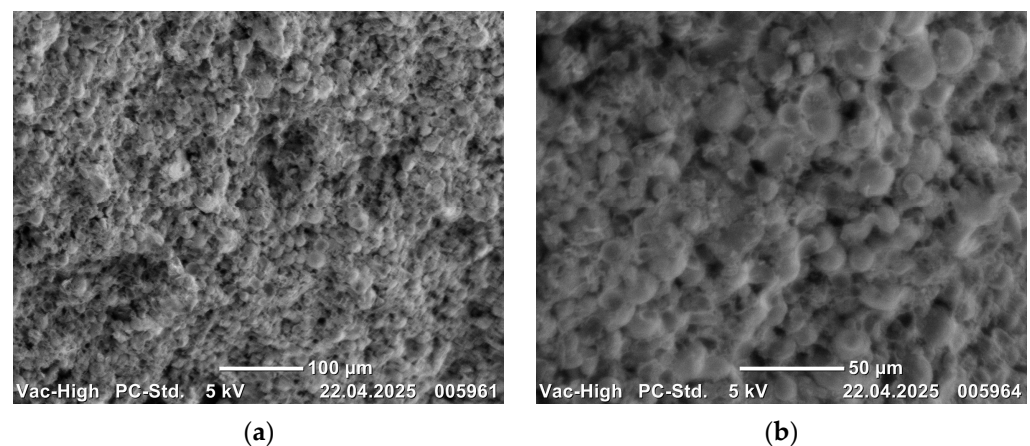


Figure 6. SEM images of 17-4PH/6B₄C: (a) 100 μm; (b) 50 μm.

The SEM images (see Figures 1–8) illustrate the presence of increasing B₄C reinforcement in the composite structures. The metal powders have formed suitable bonds with each other and with the B₄C-reinforcement. SEM images show the composites homogeneous microstructures. The observed bond formation and homogeneous distribution suggest that the composites have undergone sufficient sintering. A thorough examination of the microstructures of the composites revealed the absence of any defects, such as macro or micro pores or cracks/porosity, that could potentially compromise their mechanical properties. The microstructure results obtained from SEM images are consistent with the findings reported in Güder et al. [10].

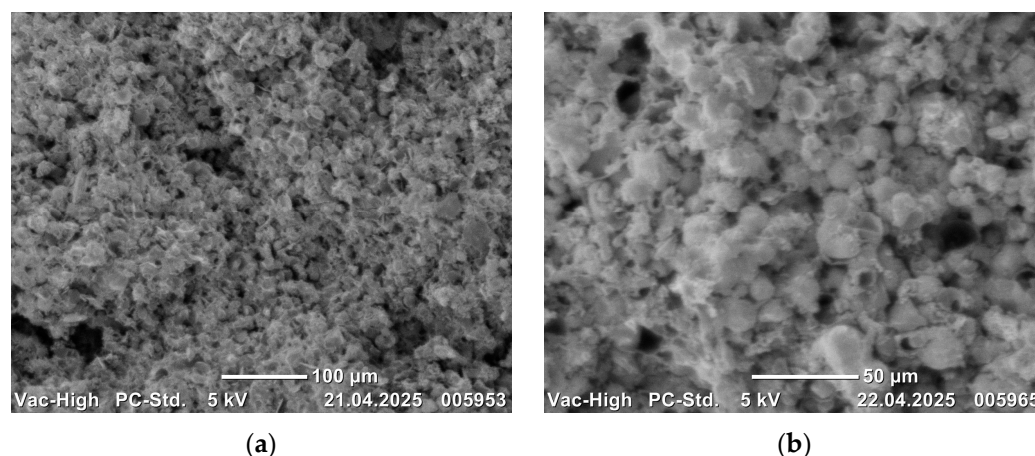


Figure 7. SEM images of 17-4PH/9B₄C: (a) 100 μm; (b) 50 μm.

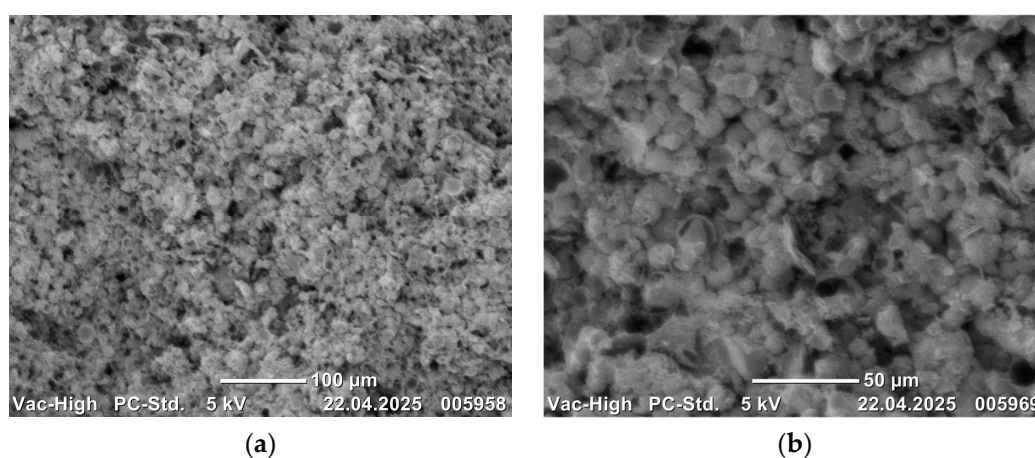


Figure 8. SEM images of 17-4PH/12B₄C: (a) 100 μm; (b) 50 μm.

3.2. Characterization of B₄C-Reinforced Composites

The mechanical and corrosion test results shown here are based on five experiments. The data distributions are illustrated in Figures 9–14, along with the maximum and minimum points. Standard deviations for the experiments are: hardness 25 HV3, wear 0.1%, elastic modulus 40 GPa, conductivity 2% (%IACS), corrosion rate 0.3 mm/year, and surface oxide resistance 40 Ω cm² [10].

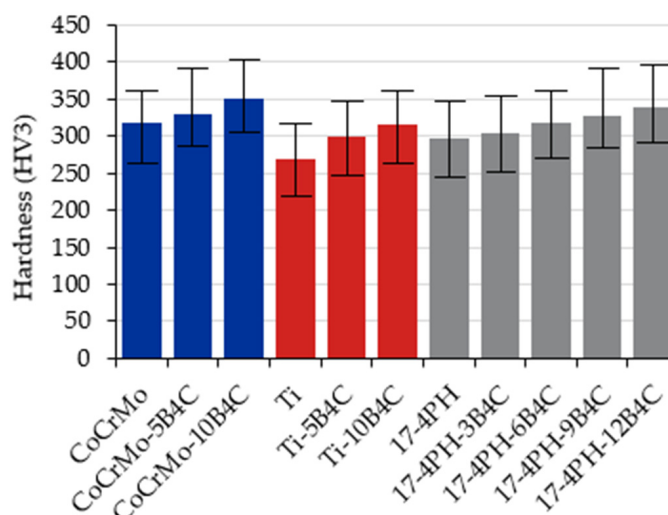


Figure 9. Hardness values of composites [10].

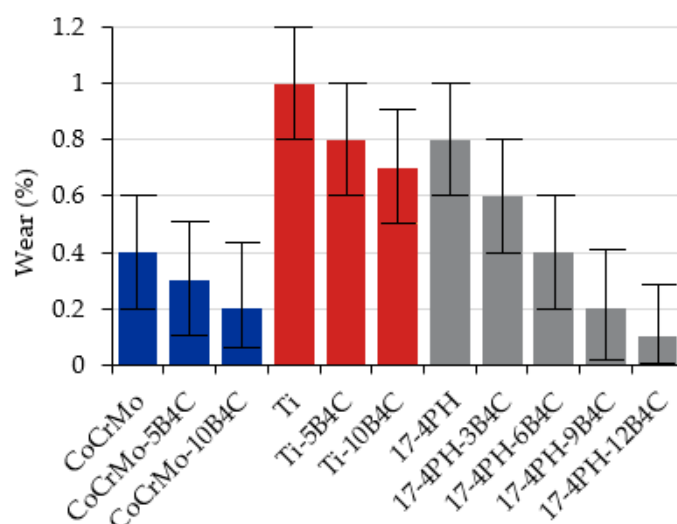


Figure 10. Wear (%) of composites [10].

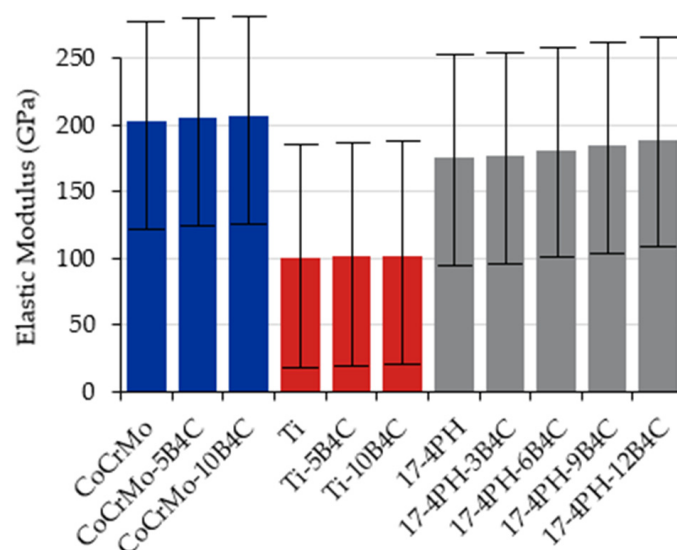


Figure 11. Elastic modulus values of composites [10].

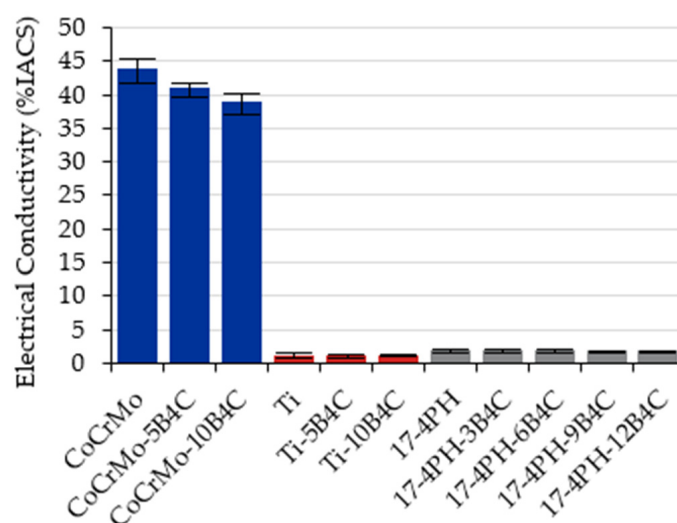


Figure 12. Electrical conductivity values of composites [10].

The results of the Vickers microhardness test (see Figure 9) demonstrate a consistent increase in hardness with increasing B₄C content. The wear test results (see Figure 10)

demonstrate a substantial decrease in wear rates across all composite groups following the incorporation of B_4C . These findings align with the trends documented by Yoganandam et al. [3], and Mohanavel-Vijayakumar [21].

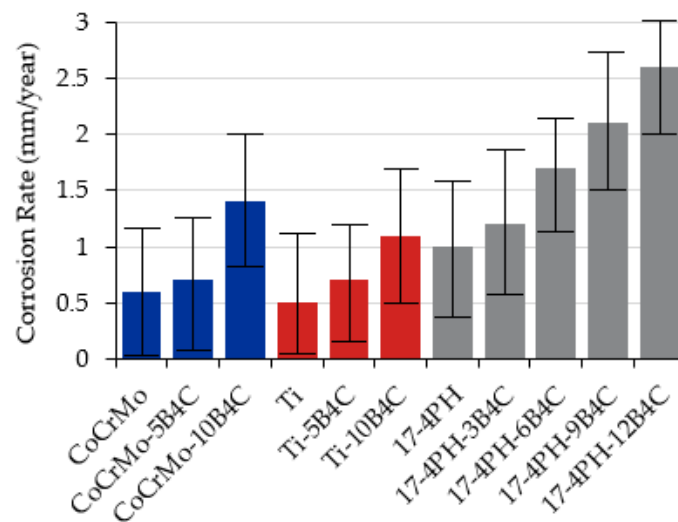


Figure 13. Corrosion rates of composites [10].

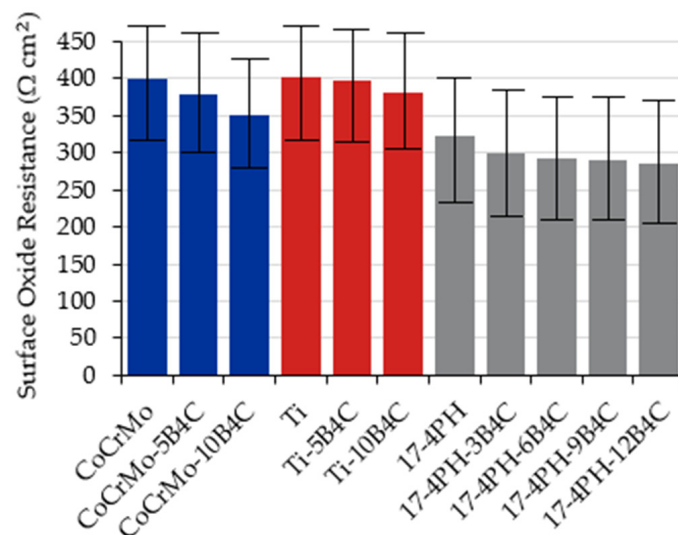


Figure 14. Surface oxide resistance values of composites [10].

The elastic modulus values (see Figure 11) exhibited positive correlation between the elastic modulus and the B_4C content. CoCrMo/ B_4C composites demonstrated the highest values; however, the elastic modulus of Ti/ B_4C composites approximates that of bone, thereby potentially mitigating the stress-shielding effect. This is crucial for ensuring biomechanical compatibility between the implant and the bone [10,22].

Electrical conductivity values (see Figure 12) exhibited a decrease in conductivity across all composites, attributable to the insulating nature of B_4C . This decline was particularly evident in the Ti/ B_4C composite samples. In biomedical applications, implants primarily function to bear mechanical loads and to be biocompatible. To avoid effects from magnetic fields, the conductivity of implant materials must match and be low [10].

The morphology, particle size, and particle size distribution of the B_4C particles utilized in composites were maintained constant throughout the production process, with the reinforcement ratio being the sole variable. The effects of these factors on the corrosion behavior of B_4C particles was not addressed in this study.

The corrosion rate values (see Figure 13) demonstrate that the B_4C additive increases the corrosion rate in each composite group. This phenomenon is attributable to the formation of microgalvanic cells and augmented surface interactions between B_4C and the matrix. It was found that the corrosion rate was highest in the 17-4PH/12 B_4C specimen. The lowest corrosion rates were measured in CoCrMo/5 B_4C and Ti/5 B_4C composites. The advantageous properties of composite that contain low percentages of B_4C reinforcement, such as their reduced corrosion rates, render them well-suited for various applications [10].

Surface oxide resistance values (see Figure 14) demonstrated that an augmentation in the B_4C ratio led to a reduction in surface oxide resistance across all composite groups. This decline was especially evident in the 17-4PH/ B_4C composite group. Notwithstanding the effect of B_4C on increasing the corrosion rate and decreasing surface oxide resistance, the Ti/ B_4C composites demonstrated better corrosion resistance. The findings of Toptan et al. [8] provide additional evidence in support of these results.

3.3. In Vitro Cytotoxicity Assessment of B_4C -Reinforced Composites

Cell Viability (MTT) test results systematically examined and demonstrated the concentration and time-dependent effects of extracts from B_4C -reinforced CoCrMo, Ti, and 17-4 PH alloys on human osteoblast cells. A clear dose-dependent relationship was observed in all analyzed composite groups, with cell viability increasing as the extract concentration decreased; this suggests that extracts at high concentrations have more pronounced cytotoxic effects due to ions or particles released from the reinforcement or matrix phase.

3.3.1. CoCrMo Matrix Composites

It was observed that a 100% concentration of CoCrMo/5 B_4C extracts caused a strong suppression of viability; cell viability remained low in the 100% group for 24–48–72 h (Figure 15). However, cell viability improved significantly with extract dilution (50% → 25% → 12.5%), and values close to the control level were obtained in the 12.5% group, particularly in the 48 h and 72 h measurements. This result supports that the CoCrMo matrix does not cause cellular toxicity in low-concentration extracts.

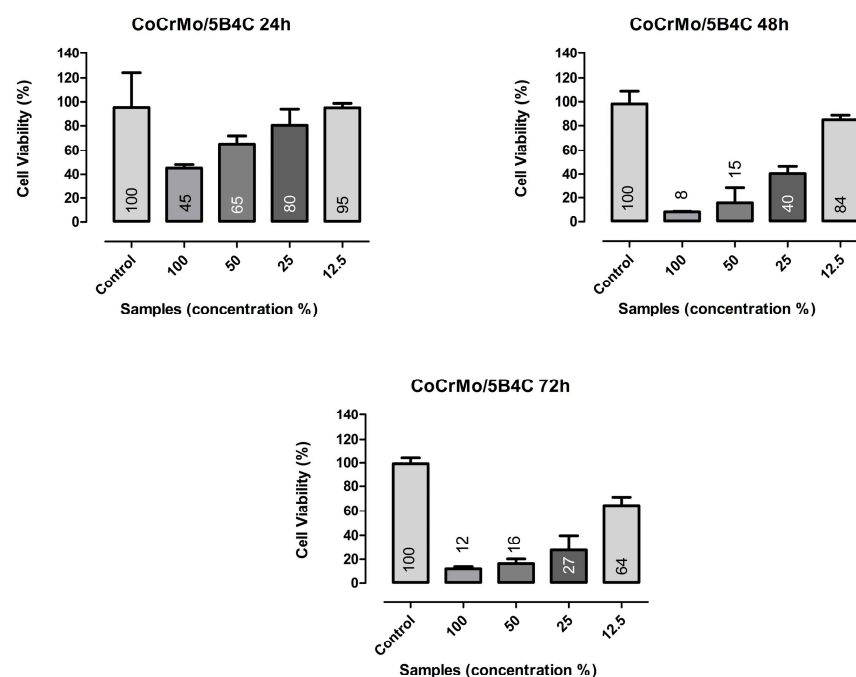


Figure 15. Cell viability analysis of HOB cells after 24–48–72 h of incubation with different concentrations of CoCrMo/5 B_4C samples (p -value < 0.05 was considered statistically significant).

In CoCrMo/10B₄C composites, the 100% extract showed marked cytotoxicity at all time points (Figure 16). While partial recovery was observed in the 50% group, cell viability increased significantly in the 25% and especially the 12.5% groups; at 48 and 72 h, the 12.5% extract was reported to show biocompatibility levels consistent with the control. In the CoCrMo/10B₄C sample, the lower cell viability values observed at the 48 h and 72 h time points, particularly due to the increase in the B₄C reinforcement ratio (compared to CoCrMo/5B₄C), suggest that the release of B₄C may cause cumulative cytotoxicity.

CoCrMo/5B₄C and CoCrMo/10B₄C composites exhibited more pronounced cytotoxicity levels compared to Ti alloys, but more acceptable levels compared to 17-4 PH alloys.

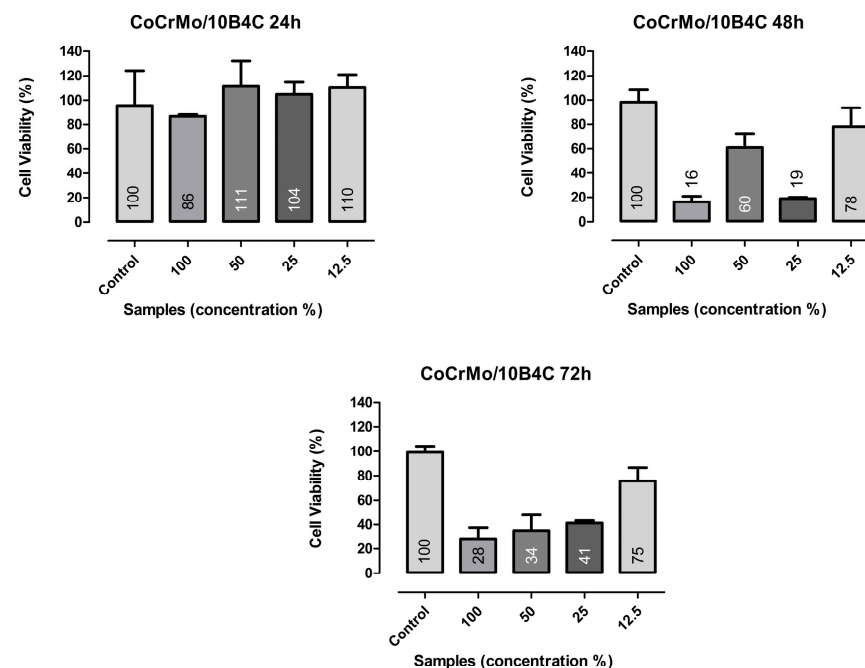


Figure 16. Cell viability analysis of HOB cells after 24–48–72 h of incubation with different concentrations of CoCrMo/10B₄C samples (p -value < 0.05 was considered statistically significant).

3.3.2. Titanium (Ti) Matrix Composites

Ti/5B₄C and Ti/10B₄C composites were observed to exhibit the highest biocompatibility among all alloy matrices studied. This result indicates that the natural biocompatibility of Ti alloys is largely preserved with B₄C reinforcement. In MTT tests performed with Ti/5B₄C extracts, cell viability decreases depending on the extract concentration; viability is preserved as the concentration decreases (Figure 17). In particular, a marked decrease in viability was recorded at the 24 h, 48 h, and 72 h measurements in the 100% extract applications; in contrast, at the 48 h and 72 h, cell viability at the 25% and 12.5% concentrations remained close to or slightly above the control levels. The preservation of metabolic activity over time (72 h) in low-diluted extracts indicates that the Ti matrix largely maintains cell tolerance despite the addition of B₄C. A similar concentration dependence was observed in Ti/10B₄C samples. The 100% extract group showed the lowest viability values at all time points; however, viability increased steadily as the concentration decreased from 50% to 25% to 12.5% (Figure 18). Viability was particularly high in the 12.5% and 25% groups at 48 and 72 h, indicating that bioadhesion persists at low extract concentrations despite the doubling of the B₄C ratio in the Ti matrix.

When comparing Ti/10B₄C with Ti/5B₄C, it was noted that Ti/10B₄C exhibited slightly lower viability at high concentrations. These findings confirm that B₄C-reinforced Ti composites possess highly promising biocompatibility properties for orthopedic implant applications.

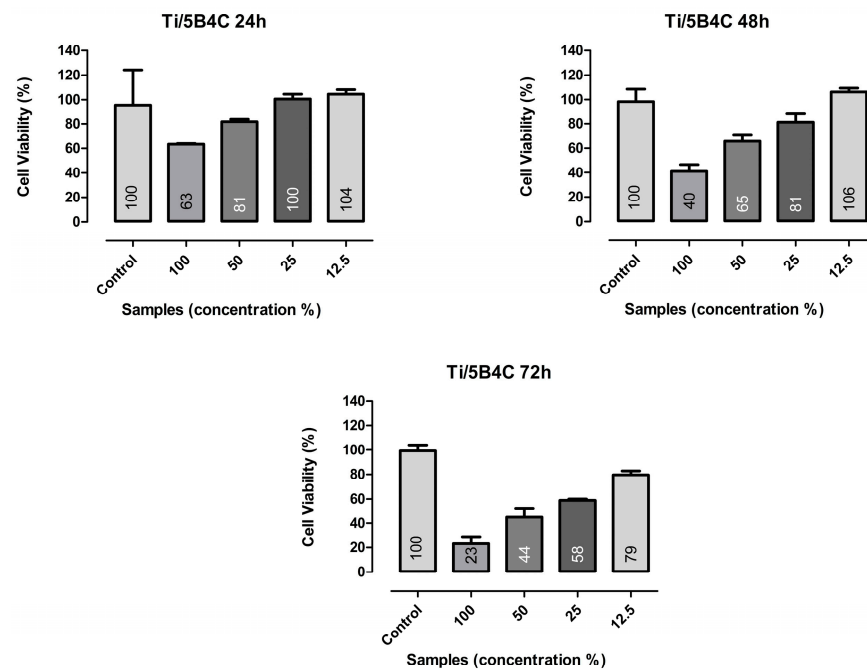


Figure 17. Cell viability analysis of HOB cells after 24–48–72 h of incubation with different concentrations of Ti/5B₄C samples (*p*-value < 0.05 was considered statistically significant).

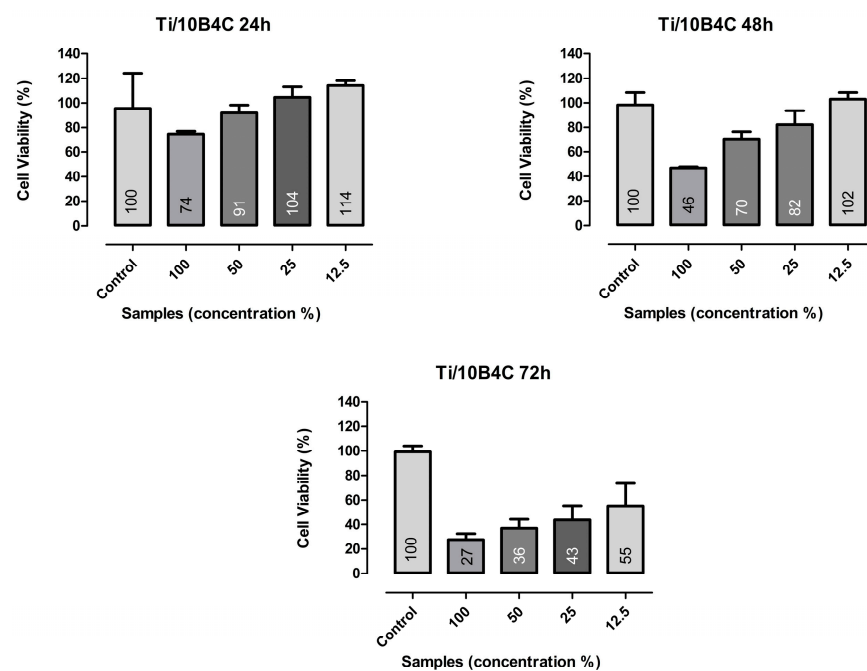


Figure 18. Cell viability analysis of HOB cells after 24–48–72 h of incubation with different concentrations of Ti/10B₄C samples (*p*-value < 0.05 was considered statistically significant).

3.3.3. 17-4 PH Matrix Composites

The MTT profiles obtained for each B₄C added to the 17-4 PH matrix at different weight percentages (3, 6, 9, 12%) are summarized in detail in the following subsections. Measurements at 24, 48, and 72 h are included in every sample (Figures 19–22).

The 17-4PH/3B₄C sample showed a concentration-dependent decline pattern: viability considerably dropped over a period of 24–48–72 h in the 100% extract (Figure 19). However, at 50% and lower concentrations, cell viability gradually recovered; particularly at 25% and 12.5% concentrations, metabolic activity was observed to be quite close to control levels at

48–72 h. The low B₄C ratio allows for acceptable biocompatibility even in low extracts for the 17-4 PH matrix.

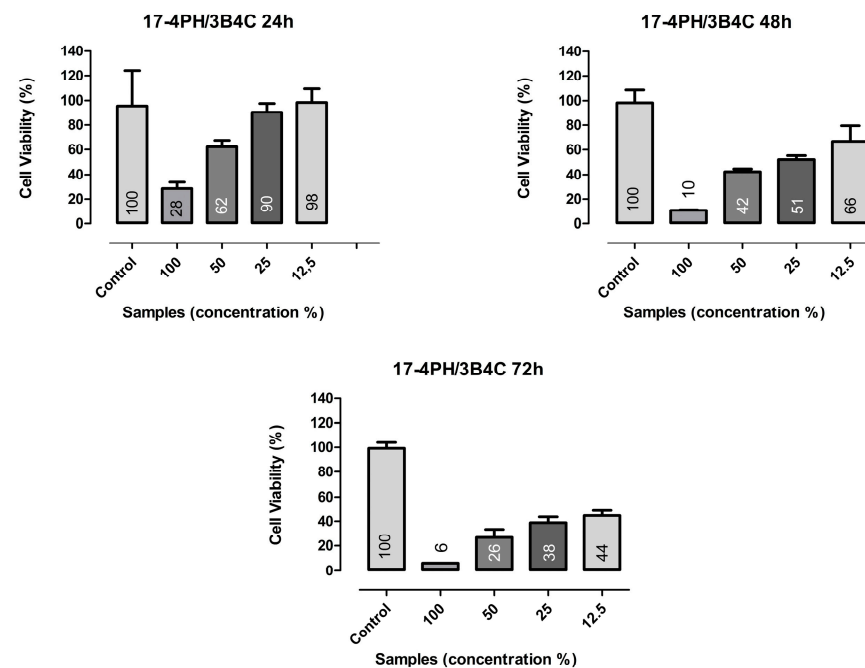


Figure 19. Cell viability analysis of HOB cells after 24–48–72 h of incubation with different concentrations of 17-4PH/3B₄C samples (p -value < 0.05 was considered statistically significant).

A similar behavior was observed in the composite containing 6% B₄C; viability suppression was more pronounced at high concentrations, but viability suppression was more noticeable at high doses (Figure 20). Compared to 3%, the 6% reinforcement exhibited slightly more pronounced toxicity in high extracts, supporting the effect of reinforcement amount on toxicity.

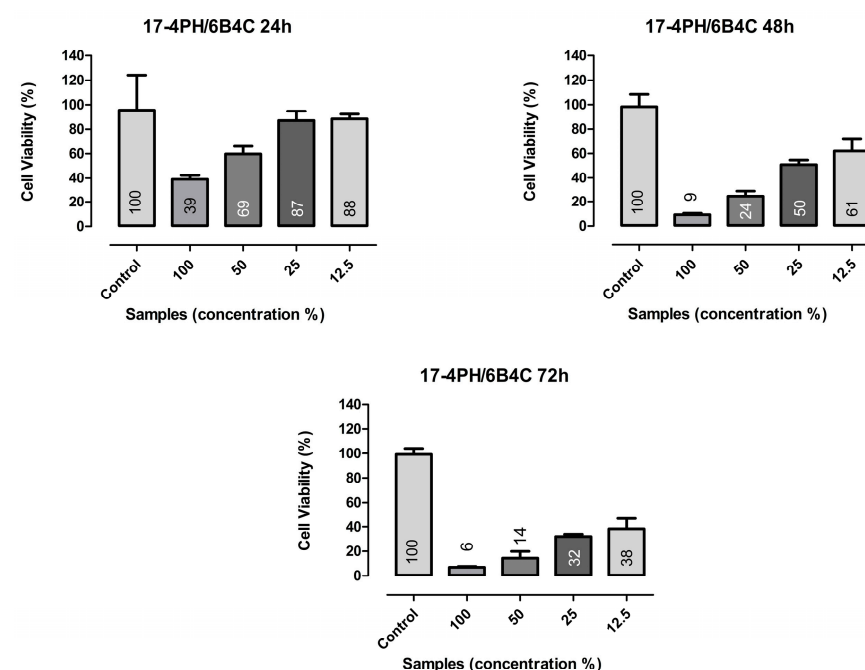


Figure 20. Cell viability analysis of HOB cells after 24–48–72 h of incubation with different concentrations of 17-4PH/6B₄C samples (p -value < 0.05 was considered statistically significant).

Although partial recovery was shown in the 25% and 12.5% groups, cell viability was decreased in the 9% B₄C composite, especially in the 100% and 50% extracts. It is known that the 9% supplement contains a higher level of cellular suppression potential (Figure 21). Viability declined considerably in certain groups over time (48–72 h), indicating that excessive B₄C dosage may have greater negative effects in long-term extracts.

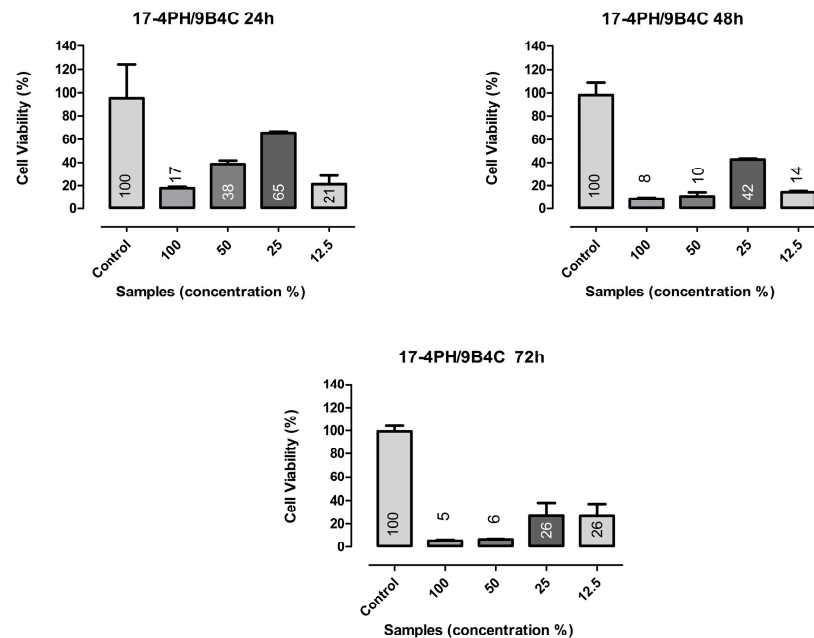


Figure 21. Cell viability analysis of HOB cells after 24–48–72 h of incubation with different concentrations of 17-4PH/9B₄C samples (p -value < 0.05 was considered statistically significant).

The group with the highest supplementation rate, 17-4PH/12B₄C, also had the most pronounced cytotoxicity (Figure 22). Statistically, the 100% extract had the lowest viability values; even in diluted extracts (25%, 12.5%), viability was often lower than in samples containing 3–6%. This result suggests that potential ion/particle release is successful and that high-ratio B₄C reinforcement in the 17-4 PH matrix may lower cellular tolerance.

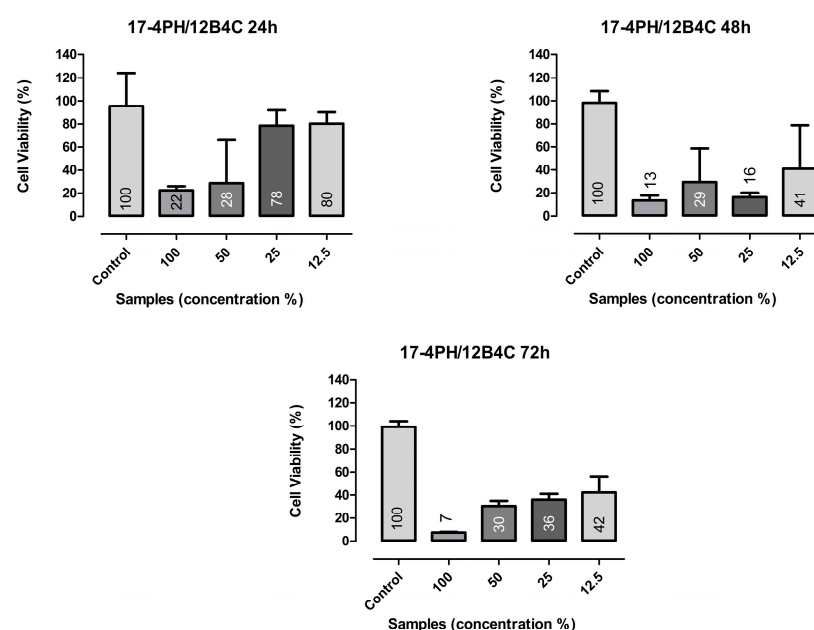


Figure 22. Cell viability analysis of HOB cells after 24–48–72 h of incubation with different concentrations of 17-4PH/12B₄C samples (p -value < 0.05 was considered statistically significant).

Güder et al. [10] reported that B_4C addition increased the elastic modulus and hardness in CoCrMo matrix MMCs. B_4C has been demonstrated to enhance hardness and wear resistance while concomitantly reducing corrosion rate and decreasing the surface oxide film resistance. The enhanced hardness and elastic modulus resulting from the B_4C reinforcement induce a mechanical stress accumulation at the interfaces between the B_4C particles and the matrix. These stress regions affect the interface's mechanical behavior, leading to the formation and increased density of micro-galvanic cells in localized areas, thereby inducing local Co/Cr ion release. This phenomenon indicates an increase in local metal ion release. B_4C reinforcement improves hardness and wear resistance in 17-4 PH matrix MMCs, while increasing the elastic modulus and deteriorating the corrosion behavior. B_4C reinforcement has been demonstrated to induce microstructural alterations in 17-4 PH matrix MMCs, resulting in diminished passive film stability and accelerated corrosion rate. As the B_4C content increases, the elastic modulus of 17-4 PH MMCs increases, leading to increased mechanical incompatibility between the metal matrix and the ceramic phase. Mechanical incompatibility creates biological risks by causing stress concentrations, microcrack formation, and particle detachment at matrix-reinforcement interfaces. Local stress fields accelerate microcrack formation at matrix-reinforcement interfaces. The resultant microstructural damage initiates the detachment and separation of B_4C particles from the surface. 17-4 PH SS mainly contains Ni and Cr. Increasing the B_4C reinforcement ratio leads to mechanical incompatibility, an increase in micro-galvanic cells, and increased corrosion, which accelerates the migration of Fe, Cr, and Cu ions into the cell environment. The micro- and nano-scale B_4C particles and metallic ions result in a biological response from the cells. The biological response is associated with mechanical wear and particle-induced cytotoxicity. This situation has been observed to exert an indirect effect on the level of cell viability, thereby contributing to the decrease in cellular metabolic activity that has been documented in MTT tests.

Han and Chen [23,24] demonstrated the effect of galvanic pairs formed between the Al matrix and B_4C particles on corrosion behavior of Al/ B_4C MMCs. A rising galvanic effect, concomitant with an elevated B_4C ratio, has been demonstrated to be associated with diminished corrosion resistance. It is theorized that this mechanism occurs similarly in CoCrMo/ B_4C MMC systems, affecting cellular viability through increased ion release. Han and Chen [24] showed Al/ B_4C composites are less corrosion resistant than the basic Al alloy and that the corrosion resistance of the composites decreases as the B_4C particle volume ratio increases. The researchers have posited the potential for the formation of galvanic cells within Al/ B_4C composites. Zhang et al. [25] demonstrated that the B_4C reinforcement in Al/ B_4C composites enhanced the yield and tensile strength, while also improving the load-carrying capacity and mechanical properties of the composites. Ghandvar et al. [26] demonstrated that the addition of B_4C to Al/ B_4C MMCs enhances their hardness and wear resistance. The incorporation of 5% by weight of B_4C reinforcement resulted in an enhancement of pitting on the fracture surface. Research has demonstrated that the incorporation of B_4C reinforcement leads to a transformation in the wear mechanism, which was previously dominated by wear and delamination, into a moderate level of wear. Huang et al. [27] examined the mechanical properties of 17-4PH/TiC MMCs. The grain size underwent a substantial reduction in size with an increase in TiC content. Increasing the TiC weight ratio resulted in a greater number of microcracks and TiC aggregation, showing only a limited improvement in wear resistance. B_4C reinforcement has been found to increase the hardness and elastic modulus of the 17-4 PH matrix, thereby creating mechanical incompatibility at the interfaces between the B_4C particles and the matrix. This has been linked to interface damage, micro-galvanic corrosion, and a potential toxic effect due to the combined effect of Ni and Cu ion release.

Boron carbide (B_4C) ceramics are known to have biocompatibility together with exceptional hardness, low friction coefficient, and superior corrosion resistance and have recently attracted considerable attention as promising materials for biomedical applications [28]. Chepelava et al. [29] tested porous B_4C ceramics produced by pressureless sintering at 1900–2100 °C for cytocompatibility of osteoblast progenitor mesenchymal stem cells (MSC-DP1) according to ISO 10993-12 [20] in direct cytotoxicity testing and demonstrated cell viability were 102.1% (24 h) and 99.1% (72 h) for the samples autoclaved; 110.0% (24 h) and 94.4% (72 h) for those treated with ethylene oxide. To enhance the clinical performance of 316 L stainless steel, composite coatings based on B_4C , B_4C /chitosan, and B_4C /chitosan/ SiO_2 were fabricated using a liquid spraying technique and wear and corrosion resistance, bioactivity and antibacterial behaviors were tested [28]. Among the coatings, the B_4C /CS/ SiO_2 system exhibited the most favorable overall performance, providing a denser and harder surface that markedly decreased wear rate and corrosion while supporting calcium–phosphate deposition in simulated body fluid. Moreover, its increased hydrophilicity, surface roughness, and the stimulatory effect of released Si^{4+} ions promoted MC3T3-E1 mouse osteoblast cell proliferation, and the coating showed a very high antibacterial efficiency (99.58%), highlighting its strong potential for orthopedic implant applications.

Öksüz [30] investigated B_4C incorporated α -alumina (Al_2O_3) matrix highly porous bioceramic foams for hard tissue defects. Structural analyses reported a homogeneous, interconnected pore architecture and the successful integration of B_4C , while the gradual increase in compressive strength with higher B_4C content indicated its reinforcing effect on the ceramic framework. In vitro findings revealed favorable L929 murine cell viability and enhanced proliferation, suggesting that B_4C -doped foams combine improved mechanical performance with a supportive biological response, making them promising candidates for bone tissue engineering applications. Any cytotoxic effect was reported for B_4C on human cervical cancer (HeLa) and human embryonic kidney cells (HEK 293-T) for the concentrations of 100–800 $\mu g/L$ [31]. Amorphous B_4C powder has been previously evaluated with various cell lines, such as Hs680 fibroblasts, RAW 264.7 macrophages and no statistically significant variation in cell viability between samples were reported [32].

Ti–Cu/ B_4C composites produced by powder metallurgy is evaluated for their microstructure, mechanical performance, and biocompatibility by Islak et al. [11]. The incorporation of B_4C reported to lead to the formation of reinforcing phases (Ti_2Cu , α -Ti, TiB, and B_4C), resulting in marked increases in hardness and wear resistance, while surface analyses indicated a dominant abrasive wear mechanism. Bioactivity tests with bone marrow mesenchymal stem cells (MSC) of Wistar Albino rat revealed T0B alloy, not reinforced with B_4C , showed the highest cytotoxic effect with a viability rate of 37.62% on the first day. The lowest cytotoxicity was calculated as 53.40% for the T6B composite. The cytotoxicity value approached that of a pure titanium alloy after an increase in the amount of B_4C in the structure was more than 6% additive. As a result, the highest cytocompatibility at 6% B_4C , suggested improved osteointegration potential, although an initial acute cytotoxic effect—likely related to copper release—decreased over time, demonstrating the overall promise of B_4C addition for enhancing the osteogenic performance of Ti–Cu alloys. The results demonstrated that the composite containing 6% B_4C showed the most favorable biocompatibility. Moreover, applying a pre-washing step to the fabricated samples prior to implantation is expected to further enhance their cellular compatibility by reducing the release of residual or potentially cytotoxic components.

In the light of literature, the resulting MTT data indicate that diluted extracts of B_4C -reinforced Ti and CoCrMo composites (12.5% and 25%) provide high cell viability within acceptable limits for implant materials, demonstrating a good biocompatibility

profile. In particular, Ti/5B₄C and Ti/10B₄C composites offer the most promising biocompatibility results. However, 17-4 PH composites exhibit significant cytotoxicity at high extract concentrations, even at high B₄C reinforcement ratios. According to ISO 10993-5 [33], a material is considered cytotoxic when cell viability falls below 70% in in vitro assays, whereas values above this threshold indicate acceptable cytocompatibility for direct or indirect biological contact. In this context, all tested samples exhibited an initial cytotoxic response on the days of evaluation at higher doses of sample extracts. And similar with Islak et al. [11], 17-4PH/6B₄C showed higher cell viability results with the dilution of sample extracts indicating that pre wash before usage/examination can increase cellular viability. These findings reveal the biological interaction of these new-generation composite implants, establishing an important scientific basis for clinical potential assessments.

In 5% B₄C-reinforced CoCrMo composites, the limited interfacial area and low galvanic cell density restricted metal ion release. Increasing the B₄C reinforcement ratio from 5% to 10% increased the reinforcement-matrix interface area, intensifying and continuing the galvanic effect in the cell culture medium. This increased the release of Co and Cr ions. The suppressive effect of these ions on cell metabolism is the primary reason for the decrease in cell viability observed in MTT tests. Metal ion release from orthopedic implants on nearby bone cells may lead to cytotoxicity and metabolism affecting results. Bone marrow stromal cells (BMCs) were cultured for 48 h with metal ions found in commonly used orthopedic implants, that is, Ti6Al4V, CoCrMo, and 316 L SS and at the end of cultivation period Cr⁶⁺ was reported to be highly cytotoxic (65% cytotoxicity); Co²⁺, Mo⁶⁺ were moderately cytotoxic (24% and 31% respectively) and Ti⁴⁺, Al³⁺, V⁵⁺, and Mn²⁺ were minimally toxic. Notably, ion combinations corresponding to CoCrMo and 316 L SS alloys demonstrated moderate toxicity at physiologically relevant concentrations, with rapid and irreversible effects observed even after short exposure times [34]. Gurel et al. [35] investigated biocompatibility, toxicity, and cellular responses biocompatibility, toxicity, and cellular responses of CoCrMo alloys before and after surface modifications with SaOS-2 cells and concluded that TiN coating and porous surface modification significantly increased cell viability compared to the unmodified CoCrMo alloy (50% viability at day 5), demonstrating that surface characteristics directly influence osteoblast behavior and improve biocompatibility and Mo release in FBS is reported at the highest at day 1. Importantly, none of the tested surface modifications exhibited any cytotoxic effects, supporting their safety. Additionally, TiN, porous, and polished surfaces led to a significant reduction in integrin subunit expression associated with cell adhesion, while fibronectin expression remained unaffected. These surfaces also promoted an anti-inflammatory response, suggesting a more favorable interaction between the material and surrounding tissue. Upon contact with body fluids Co, Cr and Mo oxide release to surrounding environment from passive layer of CoCrMo is reported previously [36,37].

In light of both the existing literature and the present findings, it can be concluded that CoCrMo-based composites exhibit a measurable cytotoxic response under in vitro conditions, particularly when evaluated through extract-based assays in FBS-containing cell culture media. This effect is largely attributed to the release of metal ions such as Co, Cr, and Mo, which is intensified by micro-galvanic interactions at the reinforcement-matrix interfaces, especially with increasing B₄C content. The presence of serum proteins may further facilitate ion mobilization and bioavailability, thereby amplifying their impact on cellular metabolism and viability. Accordingly, although CoCrMo/B₄C composites demonstrate promising mechanical properties, their biological performance remains limited by ion-induced cytotoxicity. Therefore, prior to their consideration as viable implant materials, these systems require further optimization strategies—such as surface modification, coating approaches, or compositional tuning—to effectively minimize ion

release. Moreover, comprehensive biological assessments, including long-term cytotoxicity, ion release kinetics, and in vivo validation studies, are essential to fully elucidate their safety profile and clinical applicability.

4. Conclusions

In this study, conventional powder metallurgy methods were employed to synthesize B₄C-reinforced CoCrMo, Ti, and 17-4 PH, and the in vitro biocompatibility and cytotoxicity of the MMCs were systematically evaluated using human osteoblast (HOB) cells. The results demonstrated that the incorporation of B₄C ceramic reinforcement into CoCrMo, Ti, and 17-4 PH matrices resulted in enhancements in hardness and wear resistance. However, an increase in the amount of B₄C additive also introduced a disadvantage in terms of elastic modulus, corrosion rate, and surface oxide resistance. Observations have been made that the increased stiffness and elastic modulus with B₄C reinforcement can result in a buildup of mechanical stress, leading to a mismatch at the interfaces among the reinforcement particles and the matrix. This acceleration of processes can promote the formation of micro-galvanic corrosion in local areas and the migration of ions into the cell environment. A notable dose-dependent cytotoxic effect was observed in all composite systems reinforced with B₄C.

The following key findings can be distilled from the present study:

- CoCrMo/B₄C composites exhibited moderate cytotoxicity, which diminished upon dilution of the extract, suggesting compatibility at low concentrations.
- Ti/B₄C composites exhibited the highest degree of biocompatibility, and cell viability was largely preserved, even at higher B₄C ratios.
- 17-4PH/B₄C composites were cytotoxic at higher concentrations of extract, which was exacerbated by increasing B₄C content due to potential ion/particle release. However, the low B₄C ratio allows for acceptable biocompatibility even in low extracts for the 17-4 PH matrix.

These findings indicate that diluted extracts of CoCrMo and Ti composites maintained cell viability at a biocompatible range consistent with ISO 10993-5 [33] cytocompatibility criteria, thereby suggesting potential for biomedical applications.

Ti/5B₄C composite, which exhibited an optimal balance in mechanical performance, corrosion resistance, and biomechanics, demonstrated the highest biocompatibility. This composition demonstrates considerable promise in orthopedic, dental, and weight-bearing biomedical applications due to its ability to interact with biological systems in a compatible manner.

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