



## Bone cement formulation with reduced heating of bone cement resin

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### ABSTRACT

Bone cement material is one of the key materials in bone surgery and orthopedic medicine. In this study, commercial polymethyl-methacrylate bone cement was mixed with boric acid and zinc borate to reduce the reaction temperature of the bone cement. The observation of temperature changes during the polymerization using laser thermometer and thermal camera showed that the use of boron compounds decreased the temperature of the bone cement at least 10°C which is very critical for the biomaterial uses as it affects the biocompatibility of the material. Besides temperature monitoring, microbiological tests showed that the materials have certain antibacterial effect. Water contact angle studies also supported the biocompatibility studies. In the last part, mechanical tests showed that there was not significant change in the tensile strength and tensile modulus values. Antibacterial tests exhibited that zinc borate addition shows antimicrobial activity against *S.epidermidis* as well as boric acid addition over 5% concentration. According to the cell culture studies, boric acid can be interpreted as non-toxic up to 10%, while 10% and 20% zinc borate has toxic effect. This is the first study to use boron compounds in bone cement and it is proved that boric acid at low concentrations can be used for bone cement applications but zinc borate would not be suitable to use in medical applications due to toxic effects.

### 1. Introduction

Biomaterials area is attracting many different scientists from various disciplines including medical doctors, mechanical engineers, materials scientists, and polymer scientists [1]. Additive manufacturing (AM) techniques provides free-form manufacturing and clinical implementation of biomaterials. Materials scientists and engineers can combine their information's to realize of biomaterials by developing new technologies, synthesizing advanced biomaterials and improving medical-image-based digital design [2]. There have been numerous studies on biomaterials with metallic implants, ceramic materials, polymers, and composites [3-5]. Depending on the application, the load carrying capacity of the biomaterial and other medical concerns, different types of materials are preferred [6].

Among many implant surgeries, knee implant surgery has been one of the most commonly done surgeries in the world. For knee implants, a combination of metallic implant and polymeric materials are used. For metallic systems, titanium alloys and cobalt-chromium alloys are generally used. Two metal implants are joint with a polymeric material, ultrahigh molecular weight polyethylene [7]. In knee surgery, metallic implants are supported with certain polymeric materials named as bone cement and this cement layer has been used to provide better compatibility of the metallic implant with bone structure. Furthermore, it provides certain viscoelasticity for the bone replacement [8].

Orthopedic infections can be occurred during or after surgery, especially when foreign material is implanted. Bacteria, mostly staphylococci, are responsible of the-

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se infections by binding damaged tissue and implanted material with immediate formation of biofilms. They can be chronic and last several days or months. These infections are one of the main problems in orthopedic surgery, both for surgeons and patients. They also known with their persistency and resulted with long-term disablement of the patients. All of these problems can cause reducing the patient health quality and remarkable costs [9]. Several different strategies have been utilized to avoid orthopedic infection such as antimicrobial implant coatings and drug delivery systems. But in order to optimize and use these technologies in clinical approaches, there is still great interest and requirement of research. These researches focused on especially developing antibiotic carrier systems like drug loaded polymethyl-methacrylate (PMMA) cement beads or bio-absorbable bone substitute (BBS). With the aid of these novel methodologies, the incidence and severity of infections will reduce [10].

Polymethylmethacrylate (PMMA), is also named as bone cement, and is widely used for fixation of various implants [11]. Bone cement has been used since 1950's [12]. For bone cement, polymethyl-methacrylate has been commonly used polymer and it is a two component system with certain curing conditions and exothermic reaction. This exothermic reaction is quite dangerous for various surgery implants that cause heating and problems for the tissues during the implantation [13].

Boron minerals with a variety of compounds offer numerous solutions for polymeric materials [14-16]. Some boron minerals and compounds have been used as flame retardant and smoke suppressant for different polymers [17,18]. Moreover, anti-microbial properties of the boron compounds have been studied for several years since 1980's [19-21]. Some studies of boron minerals for medical applications show promising results for the biomedical materials in the area of anti-microbial and anti-inflammatory uses [22,23]. Boric acid and zinc borate are well known for antimicrobial and heat resistant properties. Moreover, they are produced in Turkey [24].

In this study, new types of bone cement materials were prepared using commercial bone cement materials and different boron compounds. The aim of the study was to investigate the effect of boron compounds on the thermal properties of the bone cement. Bone cement is a thermosetting polymer that is cured. During curing, polymer gets heated and while applying to the human, it has a lot of potential harm for the human at high temperature. Moreover, anti-microbial effects of boron minerals and chemicals have been well known and this could be additional effect for the new bone cement. Advanced characterization studies were carried out. Microbial properties were measured to understand the effect of the boron compounds. Furthermore,

biocompatibility tests were conducted to understand the boron compounds with bone cement.

## 2. Materials and Methods

### 2.1. Materials

Bone cement branded AF Cement-1 was used in the study. One packet of bone cement contains 40 grams of powder and 20 ml of liquid parts. Powder part includes 35.04 grams of polymethyl methacrylate, 0.96 gram benzoyl peroxide, 4 grams of barium sulphate and liquid part includes 19.76 milliliters of methyl methacrylate, 0.24 milliliters N, N dimethylmethyl p-toluidine and 18-20 ppm hydroquinone.

Zincborate and boric acid were used as boron derivatives in the experiments. Boric acid were obtained from Eti Maden Affairs General Directorate. Zinc borate (TK.030110.01002) was obtained from Tekkim. MTT (M5655) and DMSO were obtained from Sigma.

### 2.2. Methods

#### 2.2.1. Mixing bone cement and boron derivatives

Samples containing boric acid and zinc borate were produced with a mass of 1%, 5%, 10% and 20%. Boron mixtures were added to the powder part of the ready-made bone cement and then the liquid part of the bone cement was added and polymerized by mixing.

#### 2.2.2. Characterization of developed bone cement formulations

##### 2.2.2.1. Monitoring of the polymerization temperature

Samples containing 1%, 5%, 10% boron additive (boric acid and zinc borate) were produced. The polymerization process was monitored by measuring with a laser thermometer 30 seconds from the center of the samples. In the next experiment, samples were prepared by adding 1%, 5%, 10% and 20% of boron (zinc borate and boric acid) to the mass of the samples. Thermal images were taken every minute during the polymerization. The highest temperature at the time of curing was determined.

##### 2.2.2.2. Fourier transform infrared spectroscopy analysis

Analysis was performed using the Perkin Elmer BX-II FTIR (UK) device. Samples were analyzed in ATR-IR mode in the spectral range of 400-4000  $\text{cm}^{-1}$  at 2  $\text{cm}^{-1}$  resolutions.

##### 2.2.2.3. Dynamic mechanical analysis

The samples were examined by Perkin Elmer Instruments DMA Q800 (UK), with a 1 Hz frequency scan at

a heating rate of 3°C/min. from room temperature to 180°C. The samples had 4 cm length and 1 cm width with a 0.5 cm thickness.

#### 2.2.2.4. Tensile test

The tensile strength and elasticity modulus were determined using a Shimadzu (Japan) brand universal tensile tester. Experiments were carried out at a draw speed of 0.1 mm/min. The samples according to the standard were prepared. At least 5 samples were tested. The test specimens were prepared according to ASTM D-638 (Tensile testing for plastics). The load cell was 5 kN.

#### 2.2.2.5. Contact angle

For the contact angle test, the specimens were produced with care that the surfaces are flat. Contact angle measurements were carried out at room temperature with a manual optical tensiometer Attension Theta. The liquid used was pure water and a microsyringe was used to obtain a volume of about 5 µL drop. The contact angle measurements are repeated at least five different points.

#### 2.2.2.6. Scanning electron microscope (SEM) analysis

Scanning electron microscopy Carl Zeiss 300VP (SEM) was used to observe the polymer microstructure in 500 kV. The fracture surfaces were covered with gold and SEM images were taken.

#### 2.2.3. Antibacterial tests

Antibacterial analysis experiments were carried out in accordance with JIS Z 2801 with slight modification. Bone cement samples with 5%, 10% and 20% zinc borate added (3) and 5%, 10% and 20% boric acid added (3) bactericidal activity tests were performed [25].

*S. epidermidis* [ATCC® 12228™] culture was used. The samples were prepared in the form of a thin plate 5x5 cm<sup>2</sup>. withal materials were subjected to surface sterilization with ethanol (70% v/v). Bacteria were added to the sample surface and the tops were sealed with film and allowed to incubate for 24 hours (h) in a humidified atmosphere. Samples were than diluted serially and inoculated with Nutrient agar. After incubation at 35±1°C for 24 h bacterial counts were calculated. Additive-free cements were used as controls.

#### 2.2.4. In vitro cytotoxicity test with MTT

The cytotoxicity test of bone cements were performed according to ISO 10993-5 standards at Katip Celebi University Biomedical Engineering Cell Culture Laboratories. The samples were incubated in serum-free Dulbecco's Modified Eagle Medium (DMEM) cell culture medium for 24 h at 5% CO<sub>2</sub> 37°C. After 24 h, the extracts were taken from the media for cell proliferati-

on analysis. L929 cells were seeded on 24 well plates and incubated in DMEM medium supplemented by 10% Fetal Bovine Serum (FBS), 1% Penicillin Streptomycin for 24 h. The extract of the material was added to the cells. MTT (3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2Htetrazolium bromide) assay was applied for evaluating the cell proliferation of bone cements for day1, day4, and day7. At each time point, proliferation assay was performed. Briefly, the MTT solution was added to each well and incubated for 2 h at 5% CO<sub>2</sub> 37°C. After 2 h, the MTT solution was removed from the cells and 500 µL Dimethyl Sulfoxide (DMSO) was put on the cells. The cell numbers were obtained by absorbance reading at 570 nm by using a plate reader [26,27]. The cell number for all samples were compared to negative control which contains no FBS to calculate the percentage of viable cells.

### 3. Results and Discussion

#### 3.1. Thermal Measurements

During thermal measurements, reproducible measurements were obtained. In Figure 1, maximum temperature values are given. The maximum temperature value seen in unadulterated sample is 84°C. It was observed that with increased content of boric acid and zinc borate additives, the curing temperature of the bone cement decreased. With the addition of 20% boric acid and zinc borate, the temperature during this curing time has been reduced to 59.7°C and 56.5, respectively. The thermal stability and flame retardancy of the zinc borate has been quite well known and this finding has also supports this important impact of the boron minerals in the bone cement. This finding is very critical for the biomedical materials. The bone cement is a two-component curing material but the high temperature for this material can cause severe problems for the body to accept the material. It can create various problems as infections and other diseases. This

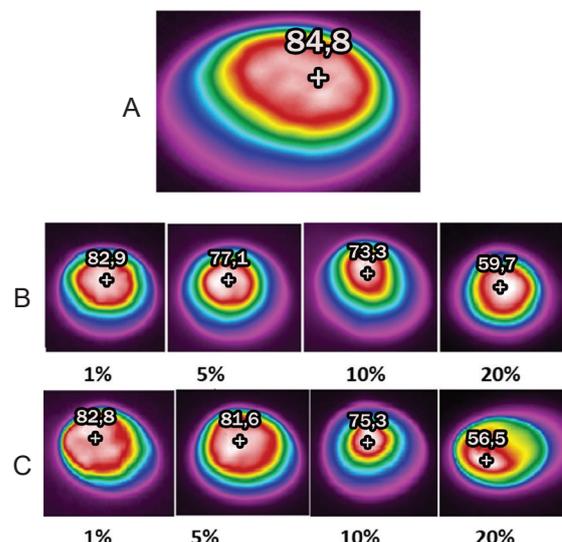
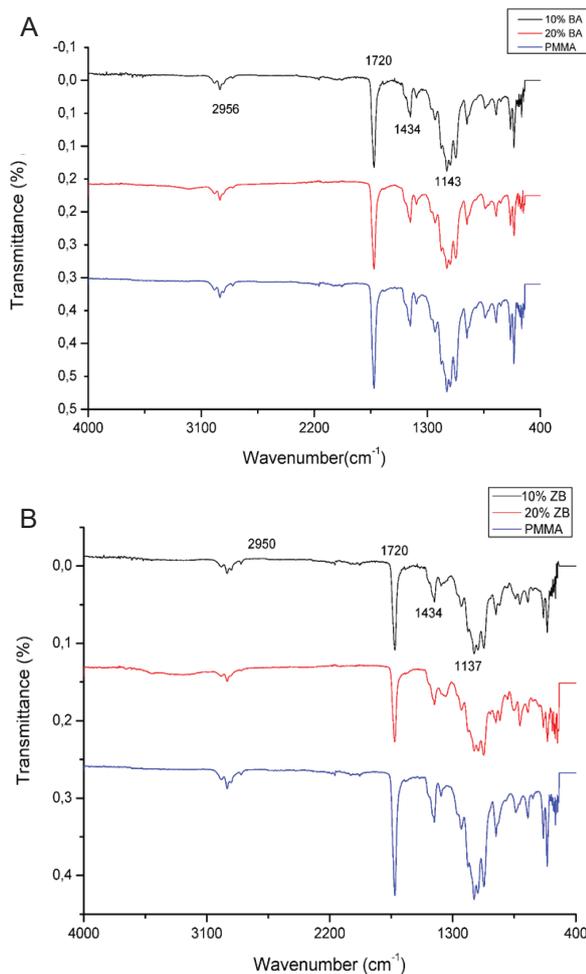


Figure 1. Maximum temperature values of A) unadulterated sample, B) BA addition, C) ZB addition.

finding will open many new possibilities for the medical device design. The thermal stability of the polymers was carried with other polymer characterization tools as well.

### 3.2. FTIR Results

According to FTIR spectrums in Figure 2A and Figure 2B, the band at  $1720\text{ cm}^{-1}$  indicates the presence of the acrylate carboxyl group. All spectrum shows that addition of BA and ZB resulted with decreasing in the transmittance of the band comparison with unadulterated PMMA. The bands at  $1434\text{ cm}^{-1}$  can be interpreted to the bending vibration of the C-H bonds of the  $-\text{CH}_3$  group and they changed with the alteration of additives percentages. The band at  $987\text{ cm}^{-1}$  is the characteristic absorption vibration of PMMA's  $\text{BO}_4$  groups, together with the bands at  $1062\text{ cm}^{-1}$  and  $843\text{ cm}^{-1}$  [28]. The band of  $1407\text{ cm}^{-1}$  was related to stretching vibrations of trihedral borate ( $\text{BO}_3$ ) groups. The peak observed between  $754$  and  $650\text{ cm}^{-1}$  wavelengths can be interpreted as in-plane bending vibrations of  $\text{BO}_3$  groups [29]. The bands at  $2956\text{ cm}^{-1}$  can be interpreted in the C-H bond stress vibrations of the  $-\text{CH}_3$  and  $-\text{CH}_2-$  groups. Moreover, absorption bands at  $3490\text{ cm}^{-1}$  can be

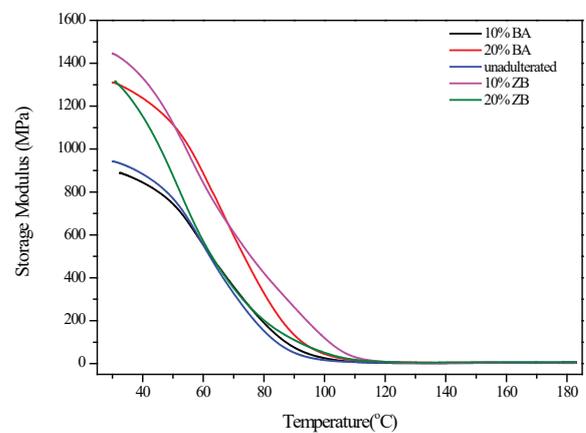


**Figure 2.** FTIR spectrums of A) comparison of unadulterated PMMA and BA additives of cement and B) comparison of unadulterated PMMA and ZB additive of cement.

interpreted to the stretching and bending vibrations of the  $-\text{OH}$  group. It can be said that these bands at  $3490\text{ cm}^{-1}$  increase with boron contribution. Also, FTIR peaks show that full curing was achieved at mild temperatures as well.

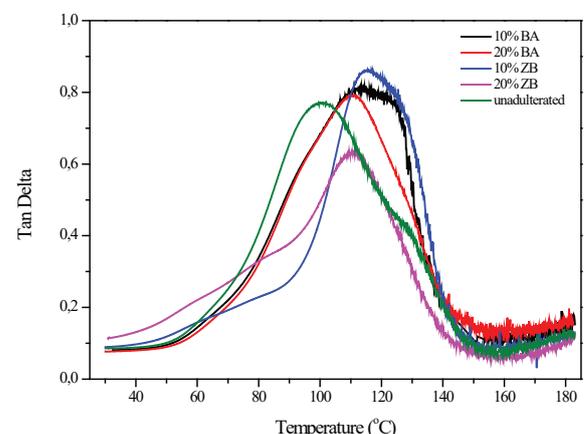
### 3.3. DMA Results

It is seen that in Figure 3 of storage modulus graph, while it was around  $900\text{ MPa}$  in the unadulterated sample, it increased to around  $1300\text{ MPa}$  with  $20\%$  ZB and  $20\%$  BA contribution. Storage modulus values at elevated temperatures show another important aspect of thermal processes for these materials. The increase of the storage modulus values was also clearly seen at elevated temperatures which is a very important information we can get with dynamic mechanical analysis [30]. This has been done first time for the bone cement analysis in the literature.



**Figure 3.** DMA Results of  $10\%$  BA,  $20\%$  BA,  $10\%$  ZB,  $20\%$  ZB and unadulterated samples (Storage modulus vs Temperature).

Tan-Delta data can give information about the glass transition temperature. It is seen in Figure 4, glass transition temperature is increased from  $100$  to  $110$  with  $20\%$  BA contribution and to  $120$  with  $20\%$  ZB contribution. The shift of glass transition temperature



**Figure 4.** DMA results of  $10\%$  BA,  $20\%$  BA,  $10\%$  ZB,  $20\%$  ZB and unadulterated samples (Tan Delta vs Temperature).

shows the bonding and the rigidity of the samples. The addition of boron compounds significantly increased the glass transition temperature which shows that the materials can be stable at higher temperatures. This is also supporting the findings of thermal measurements.

While the curing temperature of the bone cement decreases, the thermal stability of the materials increases as well. This is a very important finding that can shed a light for various biomedical materials research.

### 3.4. Tensile Test Results

The tensile test was made by preparing a sample in molds in accordance with the "ASTM F451-08 Standard Specification for Acrylic Bone Cement" standard and the results in Figure 5 were obtained. When the shape is interpreted considering the standard deviations, it can be interpreted that the maximum tensile values are approximately the same except for the 20% boric acid addition, and that the boron additive does not change the mechanical properties of the bone cement. Especially, when the standard deviations are taken into consideration, they were almost equal. This kind of result was also presented in one of our studies showing that boron compounds do not alter the mechanical properties of the polymers. This is an important outcome of this study. As we decrease the temperature of the bone cement, the mechanical properties are not altered much.

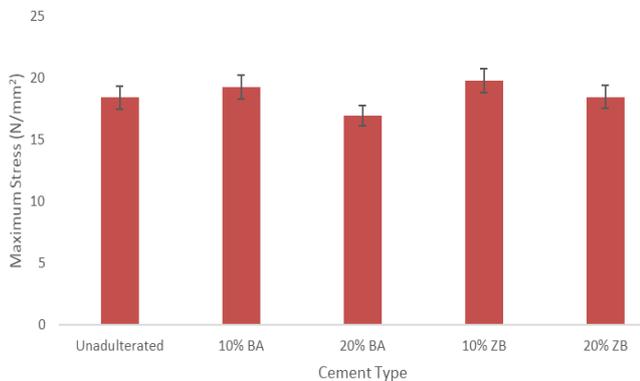


Figure 5. Maximum stress due to cement types.

### 3.5. Contact Angle Results

In literature, the contact angle value of PMMA has been found as 68-70 degrees, and there are studies suggesting that this value can be made super hydrophobic and increased to 154 degrees [31].

According to measurements, it is seen in Table 1, the average contact angle of the unadulterated bone cement was calculated to be 92.71 degrees, and with the addition of boric acid and zinc borate, this value was slightly decreased to an average of 87°C. It can be said that the (-OH) groups in the boron additive cause hydrophilic properties. Bone cement, which is permanent in the body, is in contact with body fluids such as

joint fluid. Considering that this material used in the biomedical field is used in the body, it is advantageous to have hydrophilic properties. For biomaterials used in the body, high hydrophilicity or hydrophobicity is undesirable.

Table 1. Contact angle results.

Sample Name	Average Contact Angle (Degree)
Unadulterated	92.71
1% BA	90.63
5% BA	88.42
10% BA	87.79
20% BA	87.38
1% ZB	90.48
5% ZB	89.57
10% ZB	88.67
20% ZB	87.52

### 3.6. Scanning Electron Microscope (SEM) Results

According SEM images in Figure 6, boron addition did not cause significant differences in porous structure, morphology, aggregation, heterogeneous distribution. When compared with the control sample, it was interpreted that mechanical properties did not change negatively.

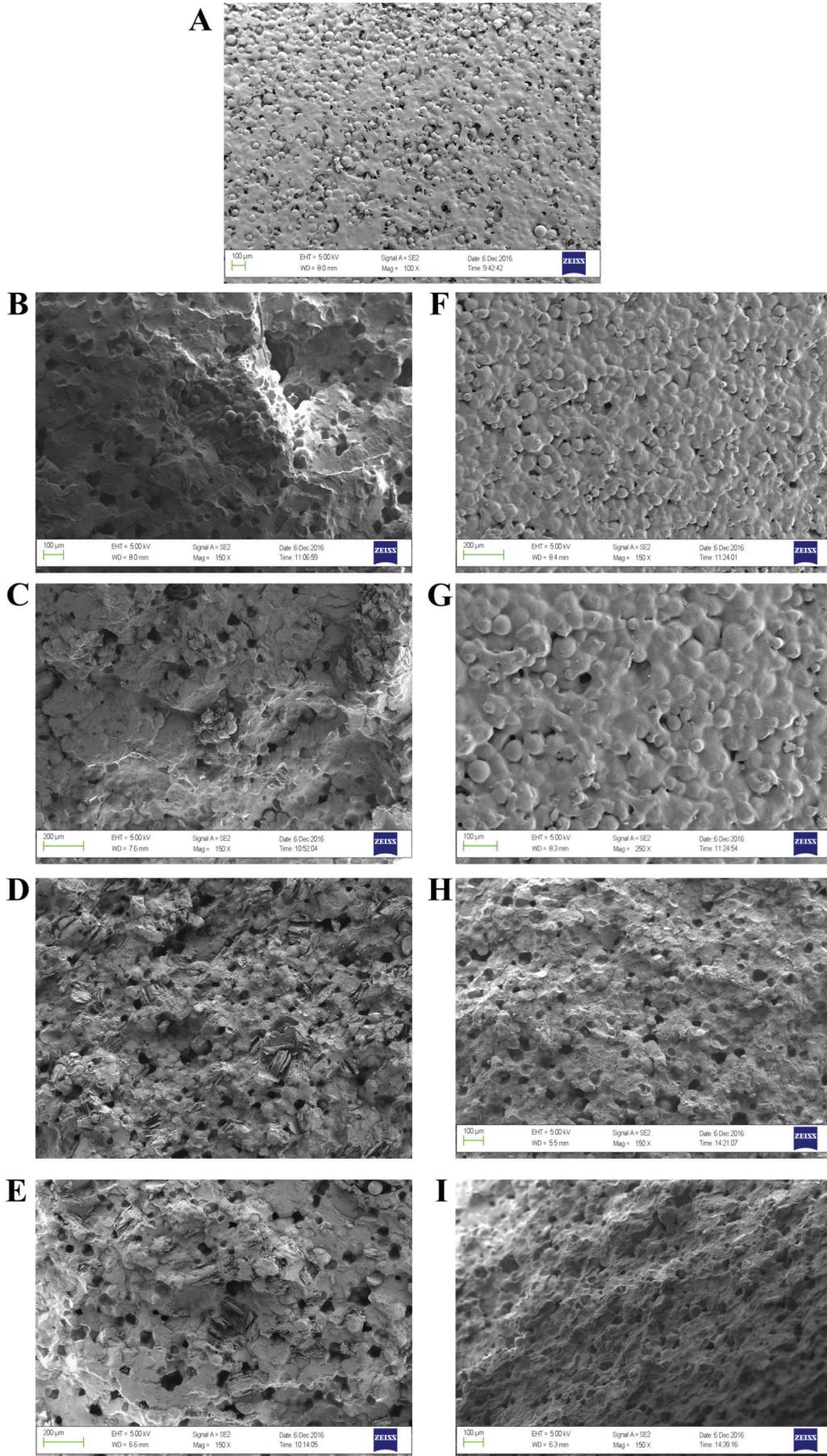
### 3.7. Antimicrobial Tests

*S. epidermidis* is very common contamination agent and it is a risk for patients with insufficient immune systems and permanent catheters. This bacterial risk also settles on the surface of medical prostheses and it is resistant to a wide range of antibiotics, including penicillin and methicillin. Antimicrobial test results are listed in Table 2 according to JIS Z 2801 Standard.

According to Table 2, zinc borate addition shows antimicrobial activity against *S. epidermidis* as well as boric acid addition over 5% concentration. These results suggested that boron-added bone cements will be an effective surface coating biomaterial to prevent bacterial growth. Also borate addition to bone cement can be used as an effective bioactive filler in order to increase antibiotic elution from the cement [32].

### 3.8. In Vitro Cytotoxicity Test With MTT

The results of cell viability obtained by MTT assay showed that 10% BA had no cytotoxic effects on L929 cells at each time point, while 20% BA, 10% ZB had cytotoxic effect on L929 cells at each time point. Although, the cytotoxic effect of 20% BA, 10% ZB, and 20% ZB, it was observed that bone cement formulations have positive effect on cell growth. Cell numbers were increased up to 7 days for each sample. Boric acid can be interpreted as non-toxic up to 10%, while 10%



**Figure 6.** SEM Images of A) unadulterated, B) 1% BA, C) 5% BA, D) 10% BA, E) 20% BA, F) 1% ZB, G) 5% ZB, H) 10% ZB, I) 20% ZB samples in 150 X magnitude.

**Table 2.** Antimicrobial test results according to JIS Z 2801 Standard.

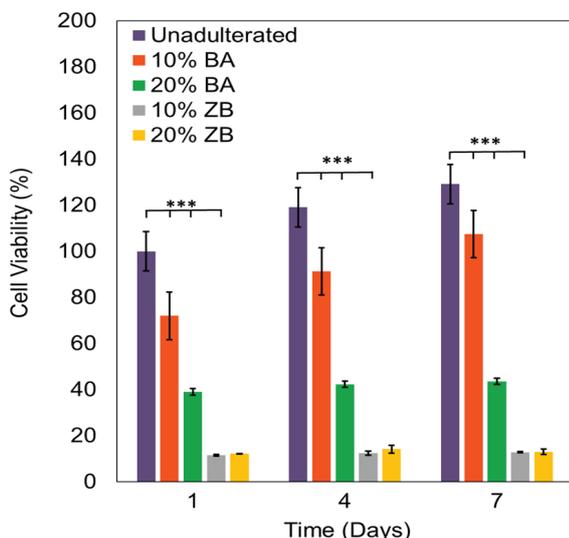
Sample	Test Organism	Test Sample 24 h (cfu/log)	Control 0 h (cfu/log)	Control 24 h (cfu/log)	R	Acceptance Criteria
5% ZB	<i>S. epidermidis</i>	0/0	396/2.60	123/2.09	2,09	≥2 log
<b>5% zinc borate added sample effective on bacteria</b>						
10% ZB	<i>S. epidermidis</i>	0/0	396/2.60	123/2.09	2,09	≥2 log
<b>10% zinc borate added sample effective on bacteria</b>						
20% ZB	<i>S. epidermidis</i>	0/0	396/2.60	123/2.09	2,09	≥2 log
<b>20% zinc borate added sample effective on bacteria</b>						
5% BA	<i>S. epidermidis</i>	81/1.91	396/2.60	123/2.09	0,18	≥2 log
<b>5% boric acid added sample NOT effective on bacteria</b>						
10% BA	<i>S. epidermidis</i>	0/0	396/2.60	123/2.09	2,09	≥2 log
<b>10% boric acid added sample effective on bacteria</b>						
20% BA	<i>S. epidermidis</i>	0/0	396/2.60	123/2.09	2,09	≥2 log
<b>20% boric acid added sample effective on bacteria</b>						

N (0<sup>th</sup> hour): The number of live microorganisms in the sample, cfu/cm<sup>2</sup>

N (24<sup>th</sup> hour): The number of live microorganisms in the sample, cfu/cm<sup>2</sup>

R: Antibacterial activity (logarithmic reduction)

and 20% zinc borate has toxic effect. Similarly, Hsu et al. evaluated the cytotoxicity of BA on L929 and UMR-106 cell by applying MTT assay and observed that increased BA concentration inhibited cell proliferation in a dose-dependent manner [33]. Furthermore, Uğur et al. reported that although there was no significant difference between zinc borate treated groups and non-zinc borate treated groups, zinc borate addition decreased the cell viability compared to control group [34]. This is the first study to use boron compounds in bone cement. This was a basic research trying to understand the effects of boron compounds in terms cell viability. It was understood that besides reducing temperature boric acid at low concentrations can be used for bone cement applications. It is also realized that zinc borate would not be suitable to use in medical applications due to toxic effects.



**Figure 7.** The percentage of increase in cell number at 1, 4 and 7 days after cultivation in extracts of bone cements.

#### 4. Conclusions

Boric acid and zinc borate were added to the bone cement and their effects on polymerization process and characteristic properties were evaluated. In the polymerization process in unadulterated bone cement, the temperature increased to 80-95°C, while this value decreased to 45-65°C with boron additive. This process was monitored and photographed with a thermal camera. In addition, bone cements produced with boron additives were tested for *S. epidermidis* in accordance with the standard of "ISO 22196 Measurement of antibacterial activity on plastics surfaces" and it was found that they show antimicrobial activity. This study was the first study to use boron minerals in the bone cement formulation. We found that the incorporation of bone cement improved the thermal properties by means of reducing the heating of the bone cement. Boron minerals also provided antimicrobial properties and also the biocompatibility studies revealed that boron minerals affect the compatibility very slightly. Boron minerals also improved the hydrophilic character of the bone cement which is very critical for the biomedical applications. SEM images revealed that effective dispersion of the boron compounds was succeeded. Mechanical property measurements at elevated temperatures also proved that boron minerals have positive effect for the reinforcement of the bone cement.

There are many studies about boron-containing bioactive bone cements in the literature. According to these studies, boron addition has positive effects especially enhancing of angiogenesis, wound healing, osteogenesis as well as antimicrobial properties. These developments are quite new and these findings are key of the utilizing of boron-based bone cements in biomedical applications in the future.

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