

## ORIGINAL PAPER



## Morphological properties of bone cement mixed with antibiotics

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### Abstract

The aim of this study was to examine the morphology of poly(methyl methacrylate) bone cement manually loaded with meropenem and vancomycin, in order to determine the structural changes in the polymer matrix that occur with antibiotic addition, as well as the relationship between antibiotic particles and the matrix and the changes that occur with cement aging. Samples of SmartSet Endurance™ MV bone cement manually mixed with meropenem, vancomycin and their combinations were examined with scanning electron microscopy after 24 hours storage at room temperature in air and after 28 days of incubation in Ringer's solution at 37°C. Manually prepared bone cement was characterized with microporosity of up to 65 µm and homogenous polymer structure that does not change significantly with incubation of 28 days. Incubation causes changes in mechanical properties that result with more pronounced cracking of the parts subjected to bending stress. Adding vancomycin causes increase in cement porosity and irregularity in shape and size of pores, not only by creation of antibiotic-filled voids, but also by interference with polymer formation and creation of microporosity areas. Incubation of 28 days causes release of antibiotic particles almost completely from the surface of the sample and less towards the center, with more meropenem particles being released compared to vancomycin.

**Keywords:** bone cement, scanning electron microscopy, vancomycin, meropenem.

### Introduction

Infection is one of the most important complications of joint replacement surgery. It has low prevalence of 0.5–3% but is associated with great invalidity and potential lethal outcome [1]. The number of patients with risk factors for postoperative infection, such as obesity and diabetes, is ever increasing in an aging population [2]. Orthopedic implants are foreign bodies prone to bacterial colonization. Bacteria, such as *Staphylococcus* spp. and *Propionibacterium acnes* adhere to implant surface and form biofilms, where they are resistant to the usual minimal inhibitory concentrations of prophylactic antibiotics [3]. In order to overcome systemic toxic effects and establish high local antibiotic concentrations, local antibiotic delivery systems are researched and developed.

Antibiotic-loaded bone cement (ALBC) is often used for local antibiotic delivery for infection prevention or treatment in arthroplasty and other orthopedic procedures. However, with the increase of prevalence of multidrug resistant bacterial strains, antibiotics usually used in ALBC, such as gentamycin, become less effective and there is a need for different antibiotics or their combinations [4]. These antibiotics should be effective against the most frequent

periprosthetic infection causative microorganisms, such as methicillin-resistant *S. aureus* (MRSA) and Gram-negative aerobic bacilli [5]. Snir *et al.* found that vancomycin-loaded poly(methyl methacrylate) (PMMA) inhibited the growth of MRSA for eight days and *S. epidermidis* for 19 days, while it was ineffective in the inhibition of growth of *Escherichia coli*, *Klebsiella pneumoniae* and vancomycin-resistant enterococci (VRE) [6]. Meropenem is a wide spectrum antibiotic with strong antimicrobial activity against most clinically relevant enterobacteria, including extended-spectrum beta-lactamase (ESBL) producing bacteria, as well as MRSA and *S. epidermidis*. Dual antibiotic loading of PMMA with vancomycin and meropenem extends the antimicrobial activity to not only MRSA and enterococci, but to *E. coli* and *Pseudomonas* spp. as well [7]. Antibiotic loading of bone cement causes changes in its mechanical properties, which may be detrimental when the cement is used for implant fixation [8].

PMMA bone cements are two-component systems of powder and liquid. The powder component comprises methacrylate copolymer beads, benzoyl peroxide as initiator of radical polymerization, radiopacifier [barium sulphate

(BaSO<sub>4</sub>) or zirconium dioxide (ZrO<sub>2</sub>)] and sometimes antibiotic. The main ingredient of the liquid phase are methyl methacrylate monomers. It also contains activator for forming radicals, such as *N,N*-dimethyl-*p*-toluidine (DMPT) and inhibitor to avoid premature polymerization (hydroquinone). Mixing of both components causes polymerization activation and PMMA polymers are formed, reaching molecular weights of 100 000 to 1 000 000. After mixing the powder and the liquid components, a doughy mass is formed. Radical polymerization increases the viscosity continuously until the complete hardening/curing of the cement [9]. When antibiotic is added manually to the cement, it is usually mixed in the powder component before adding the liquid component. Antibiotics in powder form are usually used, because liquid antibiotics significantly deteriorate their mechanical properties [10].

### Aim

In this study, we examined the morphology of PMMA bone cement manually loaded with meropenem and vancomycin, in order to determine the structural changes in the polymer matrix that occur with antibiotic addition, as well as the relationship between antibiotic particles and the matrix.

### Materials and Methods

We prepared five groups of samples: PMMA (control group of bone cement without antibiotic), M2.5% (PMMA + meropenem 2.5%, w/w), V2.5% (PMMA + vancomycin 2.5%, w/w), VM2.5% (PMMA + vancomycin 1.25%, w/w + meropenem 1.25%, w/w) and VM5% (PMMA + vancomycin 2.5%, w/w + meropenem 2.5%, w/w).

SmartSet Endurance™ MV (DePuy Orthopaedic, Inc.) bone cement was used for preparation of cement samples. The cement from 40 g standard packaging was loaded with the above-described quantities of vancomycin and meropenem. Vancomycin was in the form of commercially available lyophilized vancomycin hydrochloride intended for intravenous administration (Vankopol 500 mg, Polifarma), which is a powder of large flaky granules. Meropenem (Meropenem Venus 500 mg, VENUS Pharma GmbH) was in the form of fine powder of meropenem trihydrate for intravenous use.

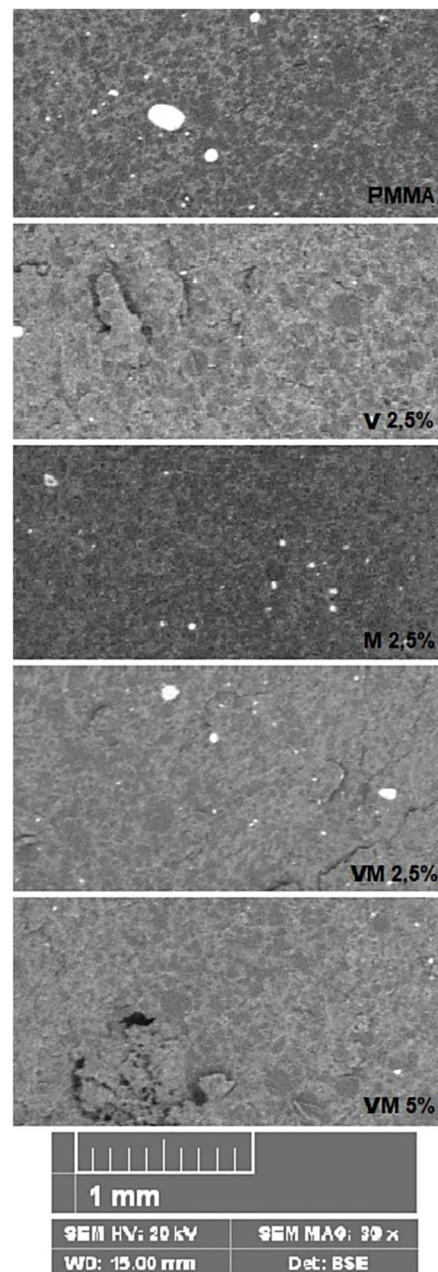
Cement samples were produced according to the procedure described in ISO5833:2002 Implants for surgery – Acrylic resin cements international standard, Annex F: Determination of bending modulus and bending strength of polymerized cement [11]. Half of the samples of each group were subjected to four-point bending test in 24 hours; the other half was tested after 28 days of incubation in Ringer's solution at 37°C.

Morphological analysis of the broken surface of two samples of each group after the four-point bending test was performed with TESCAN VEGA3 LMU scanning electron microscope (SEM) with back-scattered electron (BSE) detector in high vacuum. In addition, we examined the polished surface of samples of VM5% before and after incubation. Sample surface was sputter coated with gold. Energy-dispersive spectroscopy (EDS) was used for confirmation of chemical composition as needed. The analysis was performed at AMBICON Laboratory of

Environmental and Materials Characterization, Faculty of Natural and Technical Sciences, Goce Delchev University, Shtip, Republic of North Macedonia.

### Results

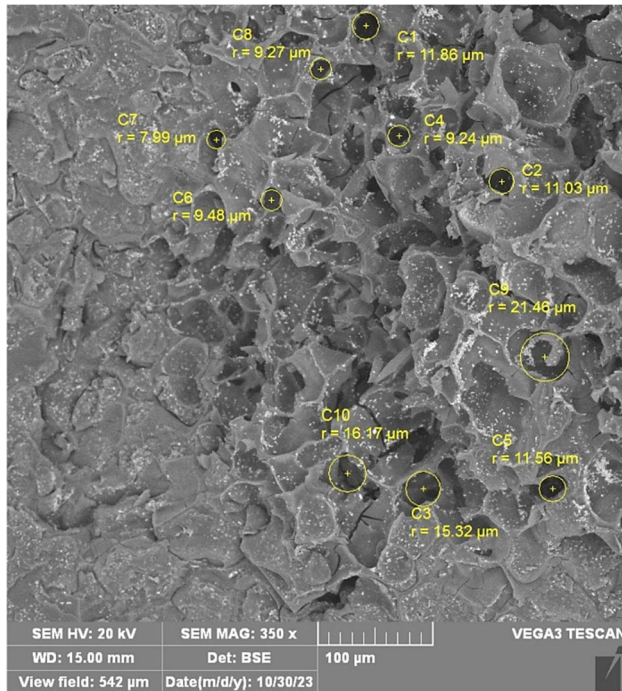
All samples containing vancomycin had larger surface irregularities and pronounced microporosity in the polymer structure as opposed to PMMA and M2.5% samples, which showed greater homogeneity. Figure 1 shows all groups at small magnification of 30×. Surface irregularities were not directly connected to antibiotic granules (Figure 2).



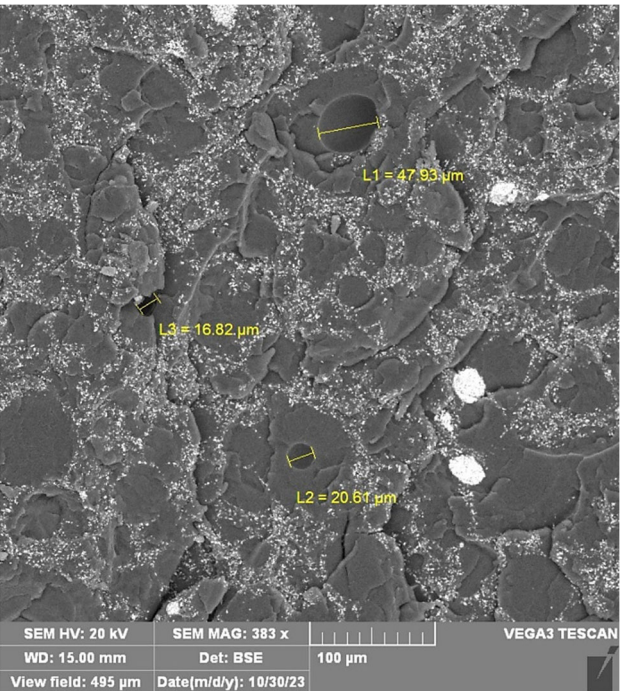
**Figure 1** – Broken sample surface of all examined groups before incubation with original magnification of 30×.

Figure 3 represents the broken surface of a nonincubated PMMA sample enlarged 383 times. The grey cloudy areas are zones of polymerized PMMA, while the white grainy structures and larger white circles represent the BaSO<sub>4</sub> radiopacifier, as confirmed by EDS analysis (Figure 4). The visualized zone of the PMMA sample has several pores

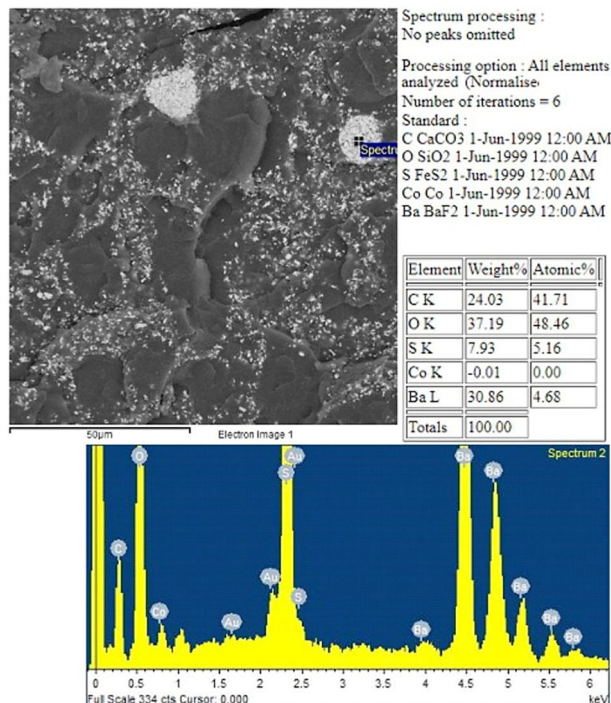
and gas bubbles with dimensions ranging from 16.82  $\mu\text{m}$  to 47.93  $\mu\text{m}$ , depicted in yellow in Figure 3. Dimensions of gas bubbles we detected throughout the sample surfaces, achieved by manual cement mixing go up to 65  $\mu\text{m}$ .



**Figure 2 – Zone of irregularity in polymer structure of VM5% sample surface. Dimensions of some of the pores in yellow. No visible antibiotic granules in this area.**



**Figure 3 – Broken surface of PMMA sample with magnification of 383 $\times$ . PMMA: Poly(methyl methacrylate).**



**Figure 4 – EDS analysis of single point (Spectrum 2) of sample surface of PMMA sample. EDS: Energy-dispersive spectroscopy; PMMA: Poly(methyl methacrylate).**

Vancomycin granules embedded in the polymer had irregular, often needle-like shapes with great span of different dimensions, while meropenem granules had rectangular shapes with greater uniformity in size. All antibiotic granules

BaSO<sub>4</sub> is not always homogeneously distributed and does not incorporate in polymerized zones. It is found between polymer areas, sometimes forms larger clumps and does not fill pores or gas bubbles.

were clearly delineated from surrounding polymers and had multiple cracks in their structure. Vancomycin granules appear smooth, and have many cracks perpendicular to their longer axis, while meropenem particles have longitudinal lines on larger magnification with structure resembling wood splinters (Figure 5, A and B). The granules depicted in Figure 5 (A and B) have similar length but are shown with different magnification.

Multiple microcracks were detected on the sample surfaces examined. These cracks often started or ended at an antibiotic granule or cement void or connected such structures (Figure 6, A and B). In most instances, based on these images we could not determine the direction of crack propagation.

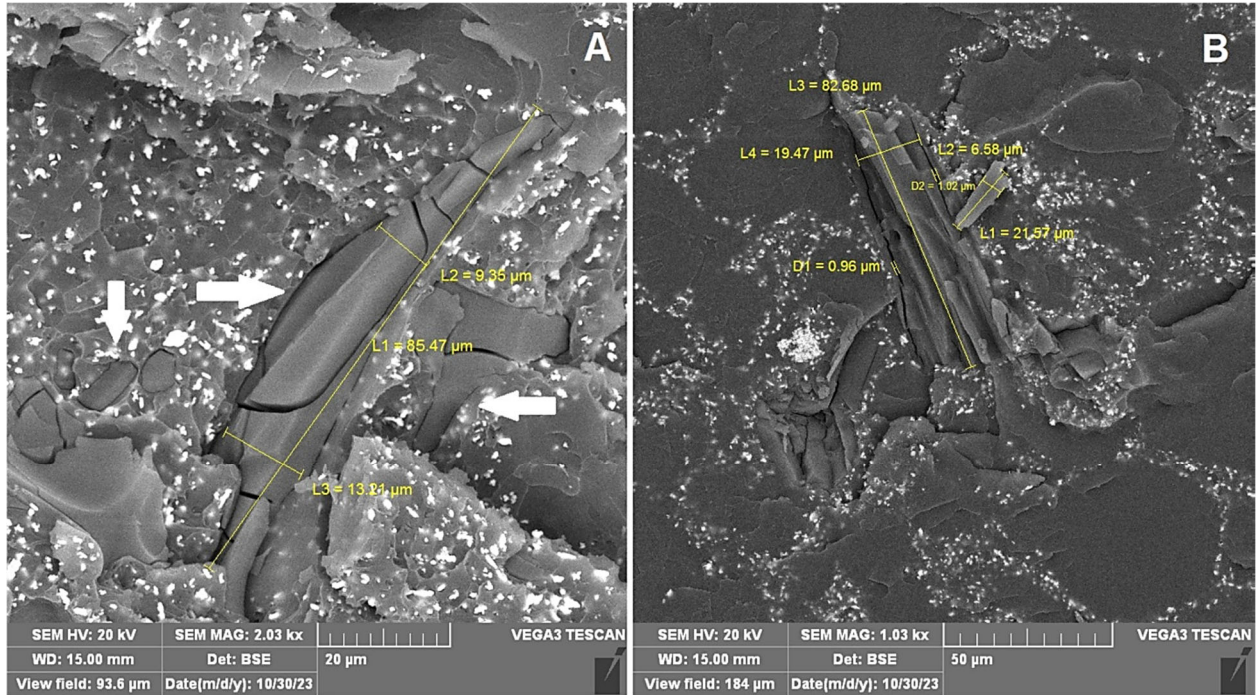
Images taken from incubated samples show that incubation in Ringer's solution for 28 days causes release of antibiotic, which is indirectly visualized as voids in the polymer matrix that correspond in shape and size to the identified antibiotic granules. Figure 7 (A and B) shows the polished surface of VM5% samples before (A) and after (B) incubation. Multiple voids can be seen on the surface of the incubated sample. Such voids were not detected on the surface of incubated PMMA samples.

Antibiotic particles were released from sample surface first. This was demonstrated by identification of multiple voids near the sample surface and non-released antibiotic particles towards the center of the sample on the images of the broken surface. There was greater release of meropenem compared to vancomycin. This was shown by identification of greater number of voids (Figure 8A) and smaller number

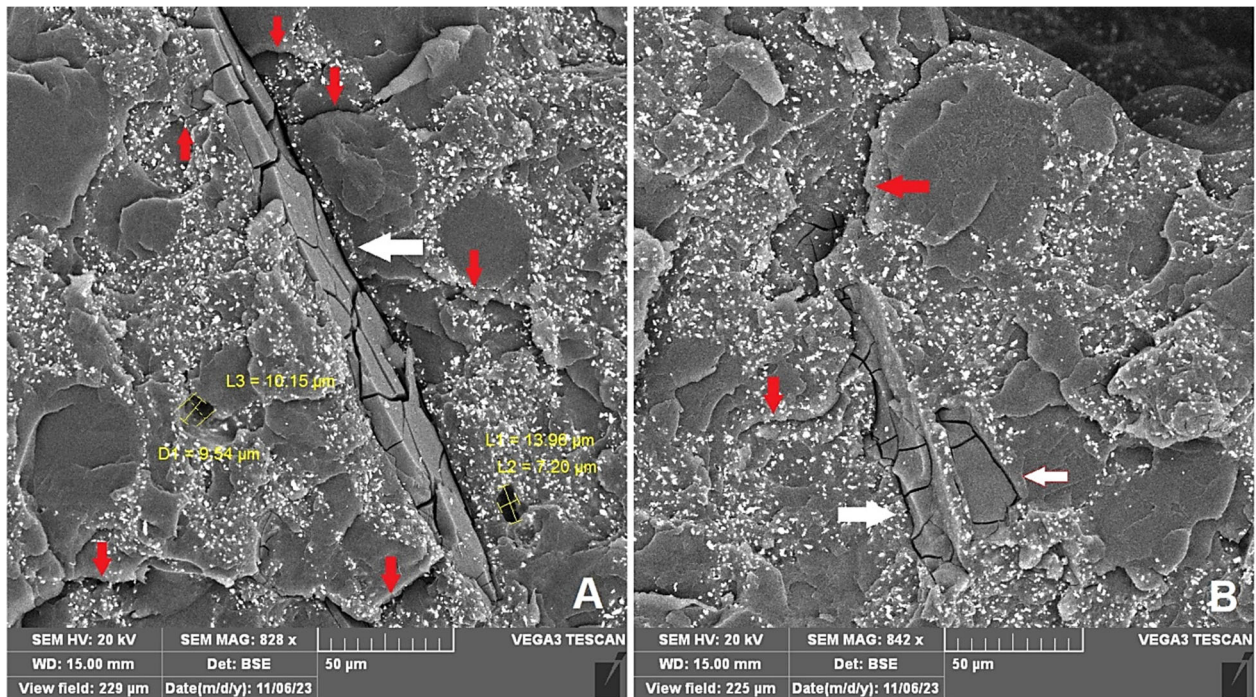
of meropenem particles in the incubated samples compared to vancomycin. It was difficult to identify unreleased meropenem particles in the incubated samples, as they were scarce. Voids that corresponded to vancomycin particles or were partially filled with vancomycin (Figure 8B) were detected only very close to the sample surface, while the deeper parts had unreleased vancomycin particles.

Figure 9 shows a section of the broken surface of incubated VM2.5% sample, where several different features

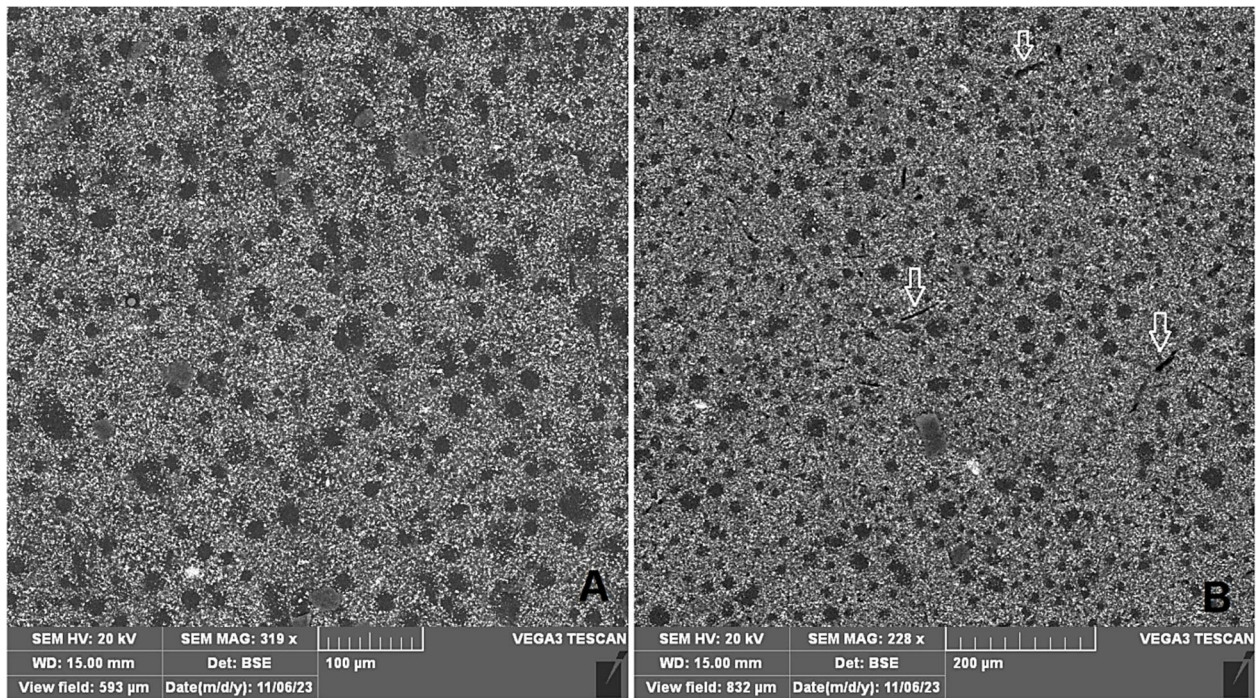
can be identified. There are unreleased antibiotic particles and voids we consider to be formed by antibiotic release. These voids are irregular, as opposed to the round or oval micropores found in PMMA samples and in antibiotic samples before incubation. Multiple zones of microfractures in the polymer substance can be seen (some are marked with red outline arrows). These zones are more frequent in incubated samples.



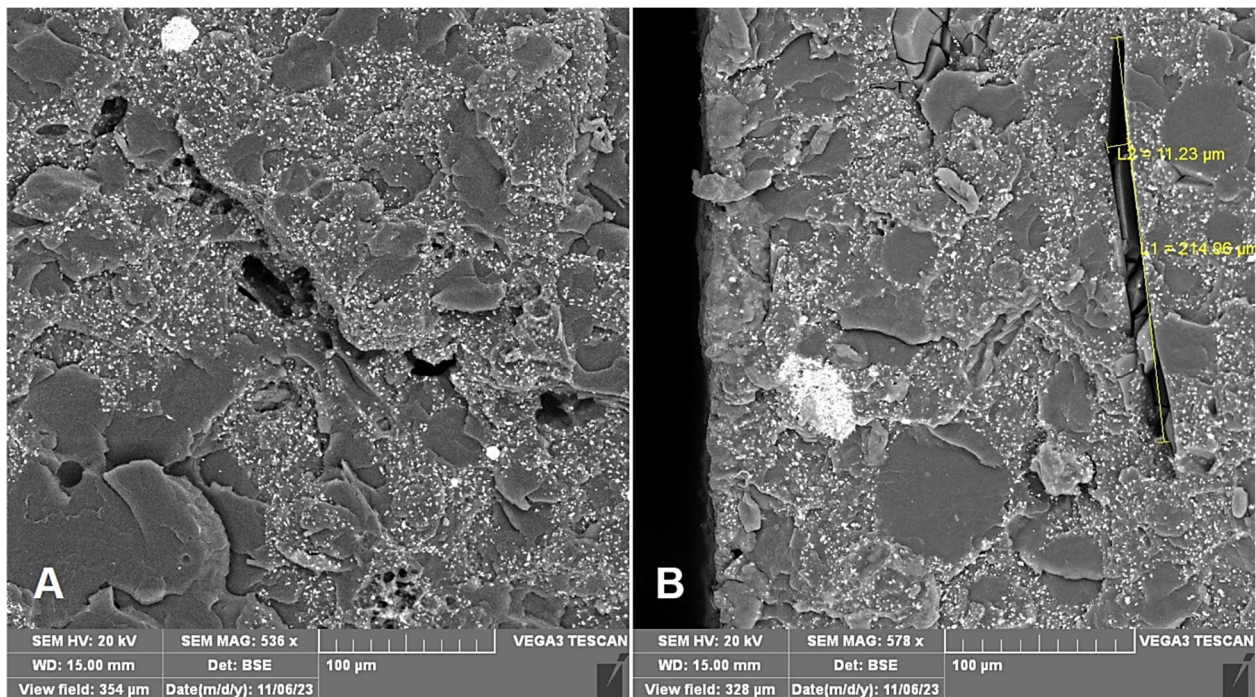
**Figure 5 – Antibiotic granules in ALBC: (A) Vancomycin granules (white arrows) in V2.5% sample; (B) Meropenem granules in M2.5% sample. Dimensions in yellow. ALBC: Antibiotic-loaded bone cement.**



**Figure 6 – Microcracks on broken cement surface: (A) Needle-like vancomycin granules (white arrow) with multiple microcracks (red arrows) spreading from it through the polymer in a radial fashion in an incubated VM2.5% sample; (B) Vancomycin granules in an incubated V2.5% sample (white arrows) with microcracks (red arrows) of which the upper one connects the granule with a larger micropore.**



**Figure 7** – Polished surface of VM5% samples: (A) Nonincubated; (B) Incubated. Arrows showing some of the voids on the sample surface.

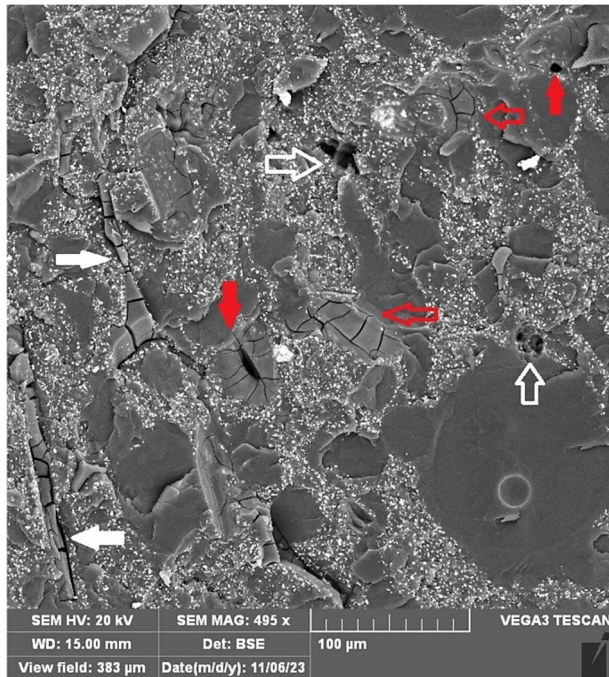


**Figure 8** – SEM images of incubated samples with 500×+ magnification: (A) M2.5% sample – multiple voids with morphology of meropenem particles are visible; (B) VM5% sample – void that is filled with remains of vancomycin is visible in vicinity of sample surface. Its dimensions are highlighted in yellow. SEM: Scanning electron microscopy.

## Discussions

ALBC has been used for implant fixation in arthroplasty procedures for decades. However, the exact mechanisms of the process of antibiotic incorporation, stability, relationship and elution from PMMA, as well as levels of its antimicrobial activity *in vivo* are still researched and debated and vary for different antibiotics.

In this paper, we examined the morphology of bone cement with added antibiotics, the relationship of antibiotic particles with the polymer as well as changes that occurred with incubation in Ringer's solution at 37°C. We examined PMMA samples loaded with vancomycin, meropenem and their combination in different doses. These formulations can potentially be used for primary and secondary infection prevention in procedures of cemented arthroplasties.



**Figure 9 – Incubated VM2.5% sample under 495× magnification. Full white arrows: vancomycin particles. White outline arrows: voids are most likely created by antibiotic (meropenem) release. Full red arrows: micropores. Red outline arrows: microcracks in the polymer structure.**

Bone cement porosity is considered to be the most important determinant of its mechanical behavior *in vivo*. Fractographic analyses of cement samples retrieved during revisions showed that cement failure occurs primarily due to fatigue and propagation of cracks with micropores influencing these events [12]. Fatigue cracks in cement have been shown to originate at micropores and decrease of cement microporosity has delayed onset of fatigue [13, 14]. *In vitro*, there is strong negative correlation between porosity and number of loading cycles to cement fatigue [15]. However, these results are not confirmed by clinical outcomes. An analysis of data from the *Swedish Hip Register* showed that femoral component fixation with vacuum mixed low viscosity cement with significantly lower porosity had worse clinical outcomes compared to high viscosity cement, with risk for revision being higher in the first four years after implantation [16]. The absence of translation of experimental evidence into clinical practice can be explained by the complexity of cement loading. In experimental environments, cement samples are subjected to uniform stresses, which do not occur *in vivo*, where it is important whether porosity occurs in areas of local stress singularities.

Kim *et al.* investigated fracture toughness (K1C) and its relation to porosity of ALBC. They found that pore size rather than pore volume fraction was the dominant factor for K1C reduction. According to them, 1 mm pores have critical size and begin impacting fracture evolution, while micropores did not significantly impact fracture evolution [17]. According to Allahyari *et al.*, in bone cement models, increasing porosity reduced the maximum stress needed to start crack propagation and pores had the greatest effect on ultimate strength by altering the crack propagation path [18].

The sample surfaces we examined with SEM had

multiple micropores with dimensions ranging from several micrometers to several hundred micrometers. Small spherical voids represent gas bubbles formed by air entrapment or monomer evaporation. Larger irregular voids with protruding polymer beads (as seen in the upper right corner of Figure 5B) may represent defects in filling or may form with polymer shrinkage. Only one macropore with diameter of 1 mm was detected in a PMMA sample. However, during sample production, samples with large visible defects were discarded and were not included in the study. Multiple secondary microcracks were discovered on the broken sample surface as well. These cracks sometimes connected neighboring voids and/or antibiotic particles and sometimes were not connected with them. The pattern of multiple cracks spreading from antibiotic particles (Figure 5, A and B) suggest that antibiotic particles may act as stress concentrators. For most cracks we could not identify the direction of spreading, but there were instances where it was clear that they started from a pore and spread in a radial fashion as well as several that ended at a pore, suggesting that voids and pores in the polymer matrix may serve as both crack initiators and crack stoppers.

Cement porosity has some beneficial clinical properties as well. Increased surface roughness and porosity improve antibiotic elution from ALBC [19]. In latest years, various micro- and nanoscale materials that increase porosity and level of antibiotic elution while preserving the mechanical properties of PMMA have been researched with different results [20]. So far, there are no studies that support clinical use of these materials in arthroplasty procedures.

In this study, samples containing vancomycin had more frequent, larger pores with greater variance of dimensions, as well as some zones of dense microporosity without antibiotic inclusions. The structure of PMMA and meropenem samples was homogenous, with smaller, round micropores or rectangular voids in the incubated meropenem samples. We did not find microcrack concentration around BaSO<sub>4</sub> agglomerates, although rare cracks did cross them. Type and concentration of radiopacifier may influence cement porosity and its mechanical properties. Increasing BaSO<sub>4</sub> fraction causes increase of porosity [21]. Also, there is evidence that BaSO<sub>4</sub> agglomerates cause fatigue cracks in cement samples [22].

Alimohammadi *et al.* used micro-computed tomography ( $\mu$ CT) to investigate bone cement porosity and determined that sample porosity increased with increasing the dose of added telavancin [23]. According to their study, there was largest increase of 0.1 to 0.5 mm pores, which they attribute to antibiotic release. They consider clusters of micropores more important for crack initiation and propagation compared to macropores. This contradicts the results of the above mentioned study of Kim *et al.*, who found that macropores and vicinity of the pores (pore-pore interactions) cause crack propagation [17]. In another study examining the effects of different doses of vancomycin on mechanical properties of bone cement, Kim *et al.* determined that macropores usually appear when adding vancomycin in doses above 1 g [24]. They also found that microporosity is scarce in Simplex bone cement, while it is pronounced in Palacos<sup>®</sup> R. Their findings correspond to the absence of macroporosity in our samples, where we added maximum 1 g of vancomycin per 40 g PMMA.

Miola *et al.* analyzed SEM micrographs of low and high viscosity Palacos® prefabricated with gentamycin or manually loaded with gentamycin. They found greater porosity in the commercially prepared ALBC. They did not find connections between pores. They found differences of pore morphology in cements with different viscosity and determined that low viscosity PMMA undergoes changes when incubated in buffered physiological solution with appearance of filaments in the polymer structure [25].

We did not observe any connections (other than cracks) between pores as well. We used medium viscosity cement and the morphology of the pores we observed is more similar to the high viscosity cement pores. The polymer structure of SmartSet Endurance™ MV cement is more homogenous even at high magnification compared to the micrographs of Palacos® presented in the paper of Miola *et al.* [25]. No changes in the structure of polymer were observed after incubation. The dominant change we observed after incubation was appearance of voids which corresponded to antibiotic particles, mainly meropenem, in terms of shape and size. We also observed higher incidence of cracks in the structure of the polymer. We believe this finding corresponds to the changes of mechanical properties of bone cement with aging.

During incubation in Ringer's solution, antibiotic particles are released first from cement surface and later from the deeper layers. In 28 day-long incubation, more meropenem particles were released compared to vancomycin. There were rare meropenem particles on the examined broken surface and a large number of voids that corresponded to meropenem particles in nonincubated samples. Samuel *et al.* found that meropenem elutes from acrylic bone cement for a period of 3–27 days depending on the concentration of antibiotic [26]. According to them, for samples containing 2.5% meropenem, only 0.83% of antibiotic is released during five weeks.

In incubated vancomycin containing samples, there were voids with the shape and size of vancomycin particles near the surface sample and partially filled voids, but towards the middle of the sample there were many identifiable vancomycin particles and no voids of similar shape. We hypothesize that vancomycin elution may continue with longer incubation, but measurement of eluted concentrations or their antibacterial activity requires different methodology. Numerous studies report different time durations of vancomycin elution, ranging from several days up to six weeks [27]. Our findings suggest that the surface and thickness of the cement construct play important role in the dynamics of antibiotic elution, which corresponds to findings of previous studies [28, 29].

We did not find any differences between samples containing only one antibiotic and samples containing both antibiotics that would add insight into the proposed mechanism of “passive opportunism” [30] of antibiotic release.

The limitation of this study is the inability to quantify the porosity, so the estimate of increased porosity is subjective. Porosity was not homogeneously distributed across sample surface, which made it unreliable to estimate porosity based on images of small areas of the sample. Release of antibiotic was deduced by inspection and comparison of voids and pores. Antibiotic concentration was not measured in incubation fluid.

These findings show that antibiotic loading causes morphological changes in the structure of the cured bone cement, which may impact the mechanical performance of the cement. The effects are more pronounced for vancomycin than meropenem, but do not seem to be synergistic for antibiotic combination. This fact, combined with the larger release of meropenem particles in the fluid, makes it a safer choice for PMMA loading for arthroplasty procedures. Vancomycin loading for joint replacement, or dual antibiotic combination should be used after careful consideration of the changes of the mechanical properties of the bone cement.

## ☞ Conclusions

We found that manually prepared SmartSet Endurance™ MV bone cement as indicated in ISO5833:2002 Implants for surgery – Acrylic resin cements international standard, Anex F, is characterized with microporosity of up to 65 µm and homogenous polymer structure that does not change significantly with incubation of 28 days. Incubation causes changes in mechanical properties that result with more pronounced cracking of the parts subjected to bending stress. We found that adding vancomycin causes increase in cement porosity and irregularity in shape and size of pores, not only by creation of antibiotic-filled voids, but also by interference with polymer formation and creation of microporosity areas. Incubation of 28 days causes release of antibiotic particles almost completely from the surface of the sample and less towards the center, with more meropenem particles being released compared to vancomycin.

## Conflict of interests

The authors declare that they have no conflict of interests.

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