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PROPERTIES OF THE HAND MIXED PMMA BASED CEMENT FOR BIOMEDICAL APPLICATIONS

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Abstract: This paper presents insights into the recent trends in development of PMMA bone cements considering their improvements for applications in clinical practice. Experimental investigation of hand mixed PMMA bone cement was realized, aiming to determine mechanical behavior of the material during nanoindentation. Standard multi-cycle indentation tests were applied, with maximum load of 15 N and immediate load relaxation down to 5 N, with sharp Vickers indenter. Indentation curves were obtained and analyzed as the function of the normal load vs penetration depth, for three different numbers of cycles (100, 200 and 300 cycles) and different indentation positions on the sample surface. Resulting indents were analyses from the aspect of the final material structure and its subsequent mechanical behavior. Agglomeration of PMMA beads was observed in the final hardened cement in some surface zones, thus indicating non-homogenous material structure. Changes in the number of cycles did not show significant influence on the mechanical response of the sample. However, sites with agglomerated PMMA beads showed significantly different indentation curves, thus indicating that hand-mixing of PMMA bone cement can produce non-homogenous final material structure.

Keywords: PMMA bone cement; biomedical applications; nanoindentation.

1. INTRODUCTION

Injectable bone cements are essential materials in several medical procedures, such as in fixation of joints (hip, knee, shoulder and elbow joint replacements), percutaneous vertebroplasty (PVP) and percutaneous kyphoplasty (PKP), cranioplasty, eyeglass lenses (contact lenses), soft tissue fillers, and dental prosthetics. Nonresorbable polymethyl methacrylate (PMMA) based bone cements are the oldest material used as bone substitutes, in orthopedics, spine surgeries, and dentistry due to its excellent biocompatibility, density similar to soft tissues, low cost, ease of processing and preparation (also to form complex shapes) and versatile medical applications [1, 2, 3, 4, 5]. PMMA is one of the most produced biopolymers in the world, representing around 50% of all biopolymers used in medical industry. Major producers in the world with annual production (in tons) are [3]: Rohm and Haas (640); Lucite (525); Mitsubishi Rayon (265); Atofina (180); Cyro Industries (132); Asahi Kasei (70); Repsol (45); BASF (36).

In general, PMMA based bone cement is synthetic non-degradable biocompatible solid polymer that is largely studied for clinical applications [6, 7, 8, 9, 10, 11, 12]. Different thermally stable antibiotics are added to provide additional healing and antibacterial properties, such as gentamicin, tobramycin, clindamycin or vancomycin. They are slowly released after implantation during some time period aiming to prevent infections [12, 14]. PMMA [$(C_5O_2H_8)_n$] is isotropic, thus exhibiting same physical and mechanical properties in all structural directions. PMMA does not have a crystal structure. It is amorphous and glassy solid polymer with elasto-plastic behavior.

However, PMMA has certain disadvantages, including low dynamic strength, low flexural modulus, low yield tensile strength, low hardness [3] and accordingly it exhibits the tendency to detach small cement particles from the surface [15]. PMMA might not have the best adhesion to the bone. It belongs to a group of hydrophobic materials. PMMA based bone cements incorporate toxic monomers that can leach to the surrounding tissue and cause inflammation. High heat is generated during the hardening of the material (during polymerization after the mixing of two components) that can produce

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very harmful effects on the surrounding tissue. Precautions are made to insert the bone cement at the right time to avoid the highest generated temperature during exothermal reactions. PMMA bone cement can be sterilized by ethylene oxide. Several literature reviews indicated that traditional PMMA based bone cement do not promote new bone growth and can even inhibit it [2].

Significant amount of research has been focusing on different improvements and development of new injectable bone substitutes and synthetic bone grafts [2,16,17,18,19]. Proposed solutions include tailoring of PMMA powder micro-beads to mitigate negative effects of nanoparticles, different mixing techniques to reduce porosity from agglomeration of PMMA beads and different new composites, such as composites with bioactive compounds (calcium phosphates, hydroxyapatite - HAp, bioactive glasses - BG) to promote tissue regeneration. PMMA composites with hydroxyapatite (HAp) and nanoparticles of HAp (nHAp) as reinforcing material are important research area because HAp belongs to fully biocompatible material that also promotes material bioactivity [20]. It was suggested that nHAp was the best possible reinforcement for PMMA that is aimed for bone grafts, but effects of HAp reinforcement strongly depend on its production route and is still under investigations. Powder processing techniques during HAp production very strongly influence its final mechanical properties. Sintering is one of the common steps during production and it was proven that different sintering temperatures produce very different mechanical properties of the final HAp. It was suggested that sintering temperature of 1000°C is optimal to produce HAp with low values of Young modulus (around 50 GPa, opposed to 150 GPa value of Young modulus in case of 1200°C sintering temperature). Sintering temperature also significantly influenced hardness and scratch properties. It seems that the type of reinforcement material is not the only influential factor for the final composite properties, but their shape, size and production routes must be strongly considered, as well. Regarding addition of nHAp, it was beneficial up to some percentage, after which it resulted in worsening of the mechanical properties. Major benefit of PMMA matrix reinforcement with HAp is improvement of its biocompatibility and bioactivity, because HAp directly stimulates the living bone tissue to form new cells.

Other means to achieve bioactivity have also been studied. Addition of bioactive glasses, glass ceramic and/or HAp resulted in bioactive PMMA bone cement that promotes bone fixation, osseointegration and long term stability of the cement [18,20]. Strontium ions (Sr) stimulate new bone formation and Sr is frequently added to foster biocompatibility and bone regeneration. Bioactive materials promote bone regeneration due to formation of HAp layer on its surface after the material has been immersed in a body fluid. Such layer is similar to the bone apatite layer, thus forming very strong bond between the implant and the bone. Goñi et al. [18] investigated different bioglasses based on SiO_2–CaO–P_2O_5 combinations and studied them as substitutes for standard radiopaque agent $BaSO_4$ that is added within the most PMMA compositions. Additionally, they studied these bioglasses doped with CaO and SrO. They proposed PMMA bone cement that incorporates SiO_2–CaO–P_2O_5–SrO to improve rheological properties and surface homogeneity and enhance surface adhesion to the surrounding tissue. Bioactive calcium silicate (CS) particles added to PMMA made PMMA/CS hybrid cement that promoted new bone growth, formation of HAp layer and better adhesion and also exhibited much lower temperature during exothermic reaction [17]. The new material significantly degraded during 6 months in animal testing, thus being strongly beneficial for bone regeneration. Micro-pores formed during degradation additionally promoted bone ingrowth and new bone formation. Incorporation of magnetic particles (such as magnetite Fe_3O_4) and bioactive glass-ceramic particles (SC45) was studied to provide a possibility of hyperthermia treatment of cancerous bone cells, beside bioactivity of the cement [21,22]. They produced different composite combinations of SiO_2–Na2O–CaO–P2O5–FeO–Fe_2O_3 ferrimagnetic bioactive glass-ceramic (SC 45 glass-ceramic) with PMMA bone cement, and obtained HAp growth on the surface after 28 days in a simulated body fluid with negligible iron release. This type of hybrid PMMA composite showed promising properties for use in cancer treatment along its main function as the bone filler. Yu et al. [23] obtained similar results with PMMA-Fe_3O_4 composite. Addition of β-tricalcium phosphate (β-TCP) to PMMA resulted in better mechanical properties and bone ingrowth [24]. Addition of tri-calcium phosphate and chitosan to the cement lowered curing temperature, compressive Young's modulus and ultimate compressive strength, prolonged setting time and induced degradability and porosity, thus also enhancing osteo-integration [25].

Different reinforcements (in a form of particles or fibers) are studied aiming at improvement of mechanical properties and to lower the level of heat released during the cement setting, such as silica nanoparticles (average diameter of 200 nm has been proposed as the most suitable). Addition of

biodegradable biopolymeric poly(3-hydroxybutyrate) (PHB) and its copolymer with 3-hydroxyvalerate (PHBV) resulted in prolongation of the setting time and lower heat release [4]. Very small quantities of graphene resulted in significant increase of the cement compressive and flexural strengths [26]. Addition of Ti fibers significantly improved fracture toughness up to 56% [20]. When nanoforms of TiO_2 fibers were incorporated within PMMA matrix, resulting composite showed better properties (63% higher fracture toughness; 20% higher flexural strength; 22% higher flexural modulus), even in case of very small reinforcement quantities (around 1 wt% of n-TiO2 fibers) [20]. Shape of reinforcements also has effects on resulting mechanical properties. For example, PMMA reinforcement by alumina (Al_2O_3) whiskers resulted in better properties than alumina particles. Considering improvements obtained by HAp and alumina when separately added to PMMA matrix, it seems that their combination could provide even better results. Accordingly, hybrid PMMA-HAp-Al_2O_3 composites have been studied aiming at multiple beneficial effects. Other biocompatible compounds were also tried as third reinforcement in hybrid PMMA-HAp composite, such as zinc oxide (ZnO) [27]. Addition of 5% of ZnO to PMMA-HAp resulted in around 250% enhancement of compressive strength. It also improved thermal stability and swelling properties of the composite.

Different combinations obtained by blending PMMA powder with different particles or fibers resulted in improvements of bone cements, but they are mainly in research stage and not clinically applied. Significant efforts have been realized to find better PMMA-bone cement compositions, mainly focusing on better compressive, dynamic, and flexural properties in order to improve resistance to complex loading conditions that are present within the body and the implantation zone. On the other side, bioactivity and lower heat releases during hardening of the final material are also in a focus of research in order to prevent tissue damage during the implantation, as well as to provide healing properties, beside better acceptance of the implant by the surrounding tissue. PMMA bone cements are long in use, but they still have some drawbacks that need to be corrected by new compositions and also tailoring of the production process.

This paper presents insights into the mechanical behavior of PMMA-based bone cement that is clinically used today in joint arthroplasty. Mechanical properties of hand-mixed PMMA-bone cement were studied, by using nanoindentation. Material behavior, depending on the position of the indentation and number of cycles, is discussed.

2. MATERIALS AND METHODS

Bone cement was made by hand-mixing two main components: polymer powder (PMMA) and liquid methylmethacrylate (MMA) monomer, as per instructions by the manufacturer. Polymer powder consists of smooth spherical round particles that can be of different diameters, but smaller beads are more favorable from aspect of dissolution time within liquid monomer. Commercial PMMA bone cement produced by Palacos R, Schering Corporation, USA, was used in indentation tests [28].

Mechanical properties of the cement were studied by using nanoindentation (CSM nanoindenter). Uniform mode was used with compressive indentation up to the maximum load (15 N) and immediate load relaxation down to 5 N. Sharp Vickers indenter was applied. Deep indents were made and analyzed, in order to avoid ambiguity due to the dimensions of the indenter tip. Indentation curves were obtained and analyzed, as well as changes of the normal load during the test as the function of indentation depth, with different times to reach the maximum load, by changing the number of indentation cycles.

3. RESULTS AND DISCUSSION

The structure of PMMA bone cement prepared by hand-mixing two components is shown in Figure 1. PMMA beads are clearly seen (left arrows in Figure 1). Agglomeration of beads resulting in zones where large voids can be found within the material is shown in Fig 1, by the right arrow. Mixing time of the components is limited to around maximum of 3 min, because the total preparation time of PMMA cement should be around 10 min, after which it is supposed to be inserted into implantation site in a form of its final shape. Shaping and molding of PMMA cement to the final model is also done within those 10 min. Hence, mixing time of components cannot be long, because the prolonged exothermic reactions would make the cement too hard to be applied after 10 min. Hand mixing usually results in certain amount of agglomerated beads which is not good for the final mechanical behavior of the cement. It can be seen from Figure 1 that sharp edges exist around surface voids (agglomerated beads shown by the right arrow) that certainly represent crack initiation site.

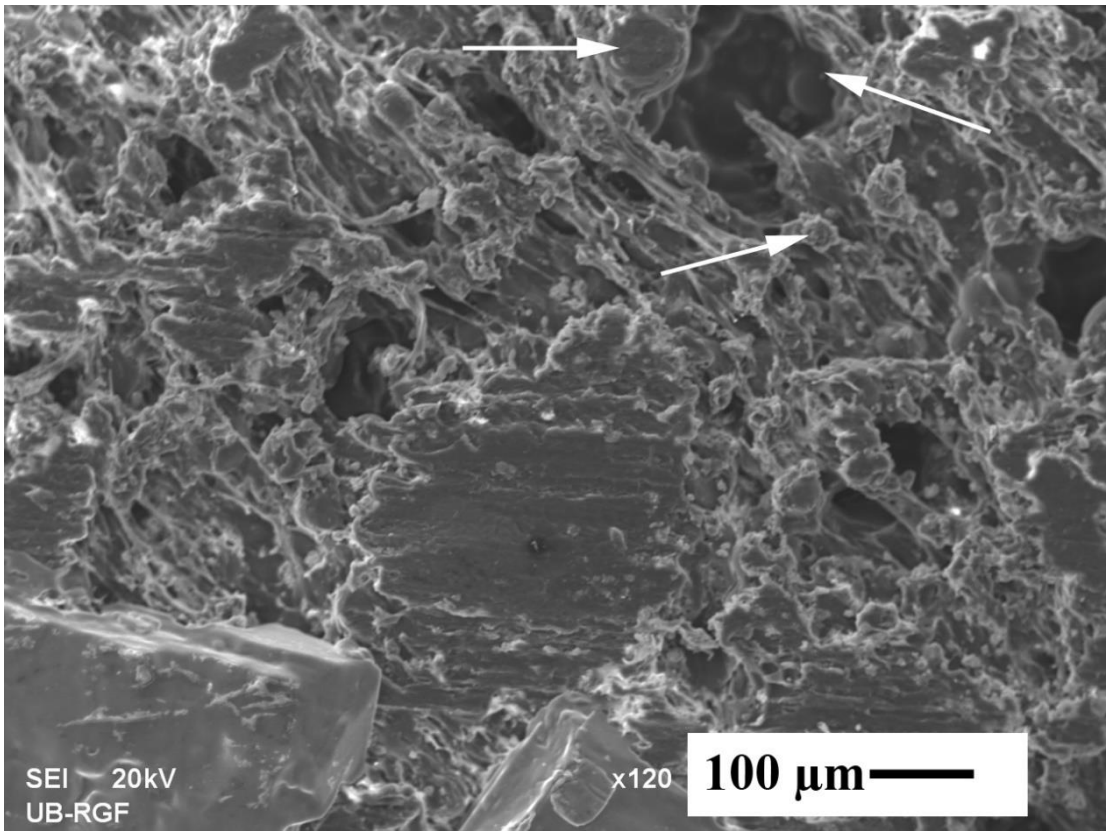

Figure 1. SEM image of PMMA bone cement surface: a) Two left arrows show polarized PMMA bead within the cement structure; b) Right arrow shows surface void formed due to agglomeration of many PMMA beads

Indentation curves for different number of cycles at three different positions are shown in Figure 2. It can be clearly seen that the same mode of indentation and the same normal load produced different penetration depths, depending on the position of the indentation. This is the consequence of non-homogenous material properties over the sample surface, due to the previously mentioned agglomeration of PMMA beads. It can be assumed that deeper penetration depth was achieved at the surface zone where PMMA beads were agglomerated, thus forming certain degree of irregular voids, such as the one shown in Figure 1, by the right arrow. In case of well-prepared bone cement with smooth surface and regular distribution of material constituents (like the left part of the sample shown in Figure 1), there was no significant difference in penetration depth for different number of cycles, as shown in Figure 2a (100 cycles) and 2c (300 cycles).

It can be seen that there are two distinct parts during one load-unload cycle: elastic reversible zone followed by irreversible plastic deformation. Applied load and depth have been measured dynamically during a load-unload cycle. Accordingly, the surface surrounded by the indentation curve represents plastic work of the indentation, whereas the remaining surface beneath outer maximum indentation curve and the normal line to the horizontal axis represents elastic part of the work.

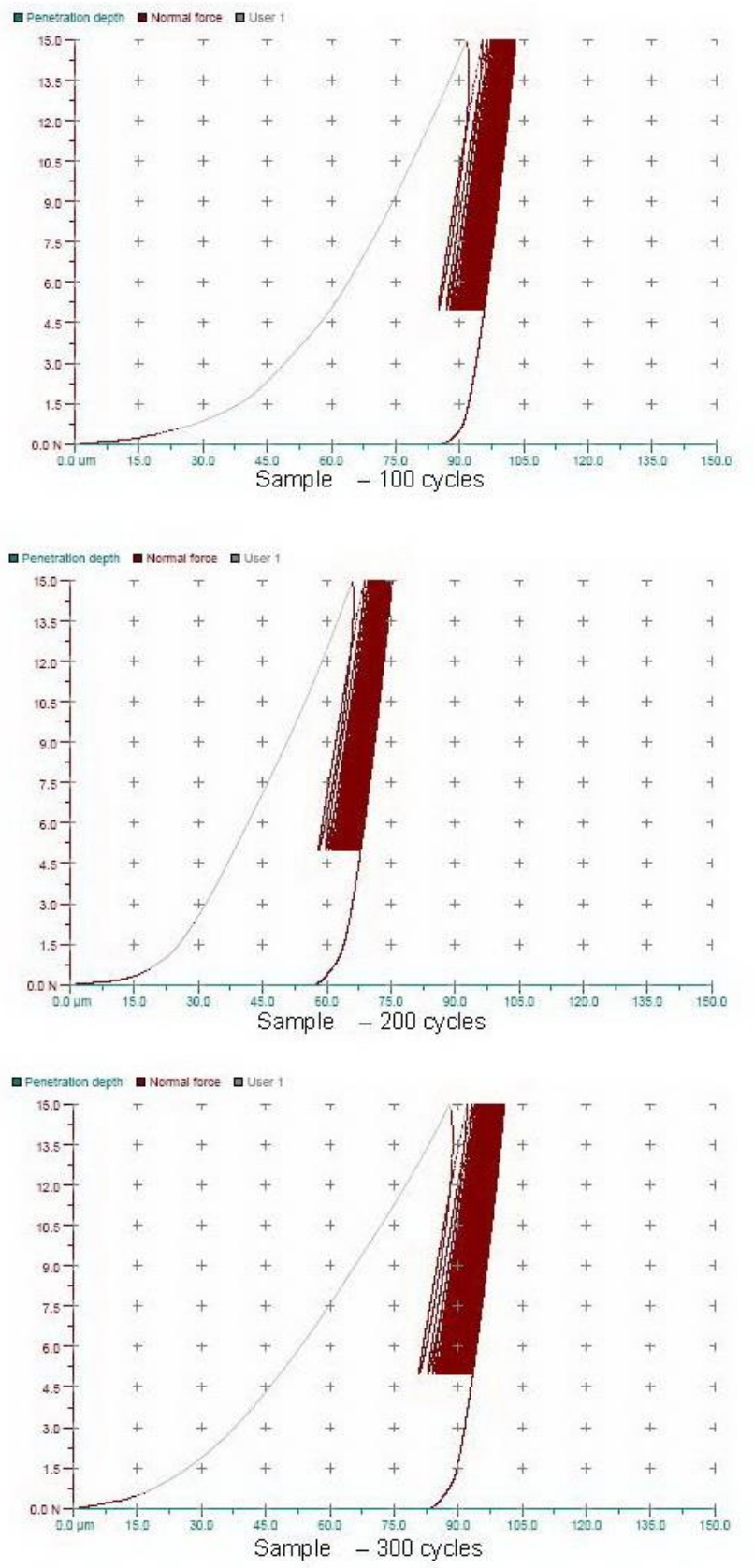

Figure 2. Indentation curves of PMMA bone cement for three different numbers of indentation cycles at three different positions on the sample surface

Optical images of the indents are shown in Fig 3, for two different numbers of cycles (100 cycles and 300 cycles). It can be seen that edges are ragged thus clearly showing intensive plastic deformation. Number of micro cracks can be seen along the outer edges of the indents. "Stress whitening" is visible as the white color of the material, and this is common to appear prior to the initial material cracking in those zones. Further loading within these "stress whitening" zones would produce material cracking.

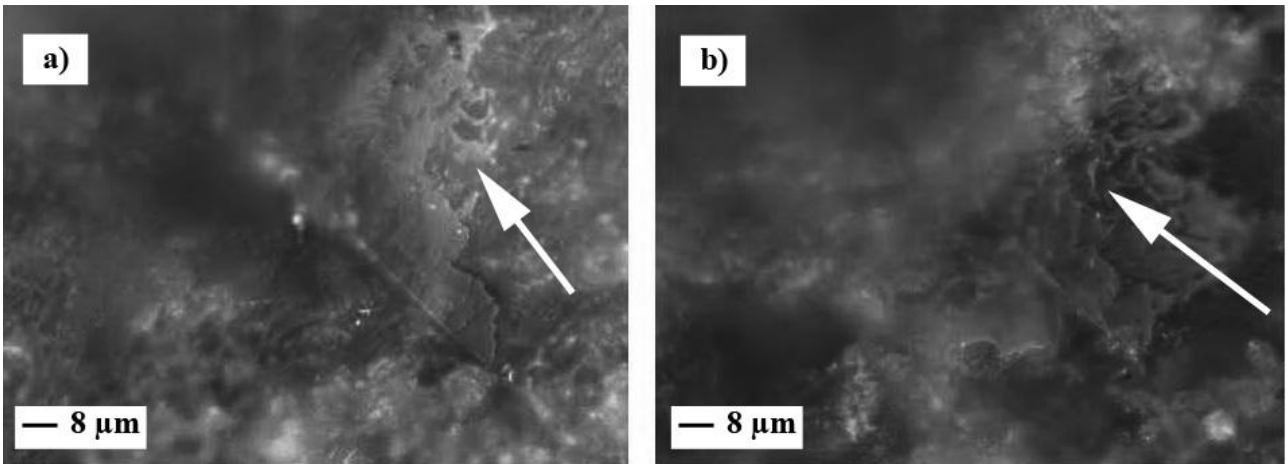

Figure 3. Optical images of the indents at PMMA bone cement: a) 100 indentation cycles and b) 300 indentation cycles

It is clear that hand-mixing of PMMA bone cement, during its preparation, has a significant influence on the final material properties. It is evident that non-homogenous material structure was obtained, as shown by large void in Fig 1, even after the strict following of the predefined manufacturer procedure from aspect of time. Agglomeration of pearls at one zone will, in time, lead to some degree of material failure within that zone. There are different techniques that can be used to avoid this, such as vacuum treatment [28] or automatic mixing of the cement by using some of the newly developed devices that exist at the market today. Experimental results evidently showed that hand-mixing is not the most optimal method to prepare PMMA based bone cement in clinical practice, even though it is sometimes unavoidable. Indentation curve in Fig 2b, also showed significant difference of mechanical response depending on the position on the material surface what, in ideal case, should be avoided, because such non-homogenous behavior prevent prediction of its behavior during functioning and probably lead to some degree of material failure in later stages.

4. CONCLUSION

PMMA bone cement was prepared by hand mixing the components. Standard multi-cycle indentation tests showed that mechanical response of the material was highly dependent on the position of the indentation. It was not significantly dependent on the number of cycles. Agglomeration of PMMA beads was observed in the final hardened cement in some surface zones, thus indicating non-homogenous final material structure. Around those agglomerated beads, sharp edges could be observed that represent crack initiation sites within the final PMMA cement. Indentation tests exhibited clear elastic and plastic part of the work. "Stress whitening" zones could be observed around the indents' edges indicating crack initiation sites within those zones. It can be concluded that hand mixing of PMMA bone cement can produce non-homogenous material structure. Accordingly, some advanced preparation techniques are recommended, such as vacuum curing or automated mixing of components.

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КАРАКТЕРИСТИКЕ РУЧНО МЕШАНОГ ЦЕМЕНТА ЗА БИОМЕДИЦИНСКЕ ПРИМЕНЕ

Сажетак: У раду су представљени трендови развоја коштаног цемента на бази PMMA узимајући у обзир унапређење његове примене у клиничкој пракси. Реализована је експериментална студија ручно припремљеног коштаног цемента на бази PMMA, фокусирано на утврђивање механичког понашања материјала применом метода наноиндентације. Примењен је стандардни вишециклични тест индентације, са максималном силом од 15 N и тренутном релаксацијом силе до 5 N без задржавања на максималној вредности, оштрим Викерсовим индентером. Добијене криве индентације су анализиране с аспекта зависности нормалне силе од дубине продирања, за три различита броја циклуса индентације (100, 200 и 300 циклуса) и за три различите позиције утискивања на површини узорка. Резултујући трагови утискивања анализирани су узимајући у обзир структуру материјала и резултујуће механичко понашање. Уочена је агломерација PMMA куглица у финалној очврснутој структури цемента у неким зонама површине, што указује на нехомогеност структуре материјала. Промене броја циклуса нису показале значајнији утицај на механички одзив код узорака. Међутим, зоне у којима је присутна агломерација PMMA куглица, дале су значајно различите криве индентације, што указује на то да ручно мешање цемента може произвести нехомогену финалну структуру материјала.

Кључне речи: PMMA коштани цемент; биомедицинске примене; наноиндентација.

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