DECODING THE ROLE OF PROCESS VARIABLES IN SHAPING THE PROPERTIES OF MAGNESIUM POTASSIUM PHOSPHATE BONE CEMENT: INSIGHTS FROM A SYSTEMATIC STUDY

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Abstract

Magnesium potassium phosphate cement (MKPC) is emerging as a promising alternative to conventional calcium phosphate-based bone cements. However, understanding how processing conditions affect its properties remains a key challenge for medical applications. This study systematically investigates the role of key process parameters, including the type of magnesia powder (normal vs. light), the Mg/P molar ratio (3:1 – 5:1), and the powder-to-liquid (P/L) ratio (2:1 – 3:1) – in shaping the structural, physicochemical, and biological properties of MKPC. Using standardized preparation protocol revealed that each variable, individually or in combination, influences crucial cement characteristics, including setting time and temperature, microstructure diversity, phase composition, k-struvite crystallization, porosity, mechanical strength, biodegradation, injectability, and cytocompatibility. The results revealed that the combination of light dead-burned magnesia, the Mg/P ratio of 4:1, and the P/L ratio of 2:1 provided a balanced setting profile (8-12 min at <50 °C), strong structural integrity, and favorable biological performance. The cement exhibited rapid k-struvite crystallization, well-developed MgP crystal morphology, controlled porosity, and adequate mechanical stability. In vitro assays confirmed good cytocompatibility and osteoblast adhesion. Overall, this systematic study decodes the critical influence of process variables on MKPC biofunctional properties, demonstrating how their controlled adjustment enables fine-tuning of cement performance for minimally invasive orthopedic applications.

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Keywords: *magnesium potassium phosphate, bone cement, optimization, functional properties*

Abbreviations: ANOVA Analysis of variance; BC Bone cement; BS Bending strength; CaP Calcium phosphate; CS Compression strength; hFOB Human Osteoblast Cell Line; JCPDS Joint Committee on Powder Diffraction Standards; KDP Potassium Dihydrogen Phosphate; MPC Magnesium Phosphate Cement; MKPC Magnesium Potassium Phosphate Cement; MTT Thiazolyl Blue Tetrazolium Bromide; PBS Phosphate-buffered saline; PMMA Poly(methyl methacrylate); SEM Scanning electron microscopy; SD Standard Deviations; XRD X-ray Diffractometer.

Introduction

Given the continual advancement of modern medicine, the quest for newer and more advanced treatments for a wide range of human diseases and injuries remains ongoing [1]. Considering the risks associated with living tissue transplants and the limited availability of donor sources, the advancement of bioengineering holds paramount importance, with the development of innovative synthetic substitutes [2]. The progressive aging of society, along with the fast-paced lifestyle, contributes to the prevalence of various skeletal system disorders. These include fractures with critical defects, osteoporosis, bone cancers, and arthritis [3,4]. Bone cement plays a crucial role in the treatment of the aforementioned disorders. These biomaterials may be defined as mixtures comprising liquid and powder phases, which, after mixing, form a paste suitable for application at the specific site of injury. Three prominent categories of bone cements may be listed: polymeric, ceramic, and hydrogels. In contemporary applications, notable types of cements include calcium phosphate and poly(methyl methacrylate) [5-7]. In recent years, the increasing use of magnesium compounds in orthopedic applications is supported by studies showing that Mg^{2+} ions effectively promote osteoblast differentiation while inhibiting osteoclast formation [8]. Magnesium phosphate cements (MPC), originally developed for construction purposes, have also found application as biomaterials for the treatment of human skeletal disorders. Compared to calcium phosphate cements, MPCs exhibit interesting characteristics more closely aligned with the criteria defined for an ideal bone substitute. This encompasses faster setting times, more favorable mechanical strengths, and accelerated degradation in the human body, while maintaining biocompatibility in optimized formulations [9-11]. MPC cements are formulated through a hydraulic acid-base reaction, involving magnesium oxide (or magnesium phosphate) and acid-soluble phosphate (such as $NH_4H_2PO_4$, $(NH_4)_2HPO_4$, NaH_2PO_4, and KH_2PO_4) [12]. Currently, the prevailing production of cement dedicated to medical applications appears to be based on magnesium-potassium phosphate (MKPC; obtained by reacting MgO with KH_2PO_4) due to its suitable setting time and cytocompatibility [13]. This shift was driven by well-recognized limitations of alternative formulations, particularly magnesium-ammonium phosphate cements, whose setting reaction releases NH_4^+/NH_3. These species can induce local pH disturbances, osmotic imbalance, and ammonia-related cytotoxicity [8,12], and such by-products have consistently been linked to reduced cell viability, impaired osteogenic responses, and inflammatory reactions both *in vitro* and *in vivo* [10,12]. In contrast, MKPC yields k-struvite crystals ($KMgPO_4 \cdot 6H_2O$) as their primary hydration product [14]. The formation of these micrometric, biomimetic crystals contributes to the overall cytocompatibility, supporting more favorable cell-material interactions [8,10]. However, a substantial amount of unreacted magnesia is

also preserved within the cement's structure [15]. MKPC technology is strongly influenced by the adopted parameters, which impact the cement's final characteristics, i.e., setting time and temperature, phase composition, paste consistency, reaction pH, mechanical parameters, porosity, and injectability. The following variable parameters can be used: magnesium to phosphate (Mg/P) ratio (customary use: 1-10:1), powder to liquid (P/L) ratio (1-1:7), MgO particle size (5-100 μm), reactivity of MgO (related to calcination; 1100-1600ºC), method of mixing (time and speed) and reaction environment conditions (temperature, humidity etc.) [16,17]. Also, the purity of the reagents will be crucial [18] or the use of additional modifiers or retarders, i.e., borax or carboxymethyl chitosan [19,20]. On the other hand, the functional and biological performance of MKPC can be further enhanced by incorporating natural biopolymers, which improve pH stability, past viscosity, moderate ion release, and promote cell proliferation compared to unmodified formulations [14,20]. Given the multitude of variable combinations in technology, it seems almost impossible to determine the final properties of the cement without experimental testing. Recently, several papers have evaluated different procedures for obtaining MKPC cements, with a primary focus on comparing Mg/P and P/L ratios [21-23]. However, the results in the literature primarily concern cements for construction applications and appear to be inconsistent. This may be due to the fact that any change in technological parameters (such as the selected reagent and its purity, magnesia calcination temperature, MgO particle size, or method of cement production) significantly affects the final characteristics of MKPC, making it difficult to compare available data with each other. Hence, this study aimed to investigate the impact of various process variables on the potential application of MKPC cement in medical settings. The following technological parameters were evaluated: magnesia powder type (normal or light; with different average particle size), Mg/P molar ratio (3, 4, or 5: 1), and P/L ratio (2.0, 2.5, or 3.0: 1) – initially giving 12 research groups. A significant strength of our research is the production and characterization of the tested groups of cements using a consistent methodology and identical conditions (i.e., same calcination protocol, constant mixing procedure, and repeatable test parameters). Furthermore, to the best of our knowledge, this is the first work that simultaneously compares these three key factors influencing the properties of MKPC medical cement (without additional modifiers or retarders), in terms of properties such as setting time and temperature, microstructure, phase composition, porosity, mechanical strength, degradation behavior, injectability, and cytocompatibility.

Materials and methods

Cement preparation

In this study, a powder phase of MPC was made from dead burn magnesia powders (calcined under 1500 °C / 5 h) with two variable powder types (with different average particle sizes): normal (MgO-I; ~52.75 μm; AmBeed, USA) and light (MgO-II; ~7.48 μm; Fisher Chemical, US), and potassium dihydrogen phosphate (KDP; KH_2PO_4, ~78.08 μm, Chempur, Poland). While demineralized water was used as a liquid phase. Mix proportions applied in the experiments are listed in TABLE 1. The cement specimens were prepared by mixing the powder phase with water in a plastic bowl and manually stirring until a homogeneous paste was obtained. Next, the paste was transferred into silicone rubber molds (in two forms: cubic, 6 × 6 × 12 mm and disk, 2 × 15 mm) and stored for curing for a minimum of 24 h. The average particle size of the cement powders was determined after their preparation using the SALD-2300 particle size analyzer (Shimadzu, Japan).

TABLE 1. Mix proportions of tested magnesium potassium phosphate bone cements.

Cement name	MgO type	P/L ratio	Mg/P ratio
MPC-I_MgP3:1	MgO-I	2.5:1.0	3:1
MPC-I_MgP4:1			4:1
MPC-I_MgP5:1			5:1
MPC-I_PL2:1		2.0:1.0	4:1
MPC-I_PL2.5:1		2.5:1.0	
MPC-I_PL3:1		3.0:1.0	
MPC-II_MgP3:1	MgO-II	2.5:1.0	3:1
MPC-II_MgP4:1			4:1
MPC-II_MgP5:1			5:1
MPC-II_PL2:1		2.0:1.0	4:1
MPC-II_PL2.5:1		2.5:1.0	
MPC-II_PL3:1		3.0:1.0	

Characterization

Setting time and setting temperature

The setting time of cement paste (n = 3) was measured using the Vicat MMC-045/E apparatus (Multiserw-Morek, Poland) with a metallic needle (diameter 1.13 mm) and a load of 300 g. This time, designated as the final setting time, was considered the length of time from the combination of cement components to the moment when the specimens were fully solidified, and the indentation mark was no longer visible on their surface. While the setting temperature of cement (n = 3) was tested using a thermocouple (Czah, Poland), placed in a 1.5 mL Eppendorf tube containing a paste of cement (1 g of powder), the maximum value was recorded.

Microstructure analysis

The surface microstructure of the obtained cement was examined using a high-resolution Scanning Electron Microscope (SEM) Quanta 250 FEG (FEI, USA) after curing and drying. Before examination, all specimens were affixed to special holders using conductive stickers and then sputtered with a thin (10 nm) gold layer using a high-vacuum EM SCD500 sputtering machine (Leica, Germany) for electron reflection. SEM images were taken at three different magnifications: 500×, 1000×, and 2000×. The average crystallite size was estimated using ImageJ (National Institutes of Health, USA) and rounded to the nearest whole number.

Phase composition

The cement specimens, after hardening, were crushed and ground in a mortar, and then analyzed using a Phillips X'Pert Pro X-ray diffractometer (Almelo, The Netherlands) with Cu-Kα radiation. Data were collected from 2θ = 20° to 50° with a step size of 0.02°, using a 40 kV voltage and a 40 mA current. Phase identification was undertaken using HighScore Plus software with the International Centre for Diffraction Data (ICDD) database.

Porosity

The initial porosity Φ (%) of the cements (n=3) was calculated by the following equation [24]:

$$\Phi = (m_w - m_d)/(\rho \cdot V) \cdot 100\%$$

where md is the dry mass, and mw is the wet mass (g) after immersion in isopropyl alcohol (Merck, Germany; when a constant weight is achieved), ρ is the density of isopropyl alcohol (g/cm^3), and V is the volume of the specimen (cm^3).

Mechanical properties

The static compressive tests (n = 5) were performed using a Universal Mechanical Testing Machine Z005 (Zwick, Germany) equipped with a 5 kN load cell, at a crosshead speed of 1 mm/min. Before the test, the cured and dried specimens were soaked in phosphate-buffered saline solution (PBS) for 24 hours. The tests were then performed under wet conditions at a temperature of 37 °C. The compressive strength (σ_c) and compressive modulus (E_c) were calculated using the standard method with the integrated software testXpert III (Zwick, Germany). Since there is no ISO standard for testing mineral bone cements, the mechanical testing procedures were adapted from the ISO standard for polymeric bone cements [ISO 5833:2002] whenever possible.

Degradation behavior

The dried and hardened cements (n = 3) were washed in 1 mL of the PBS solution per specimen for 3 h (with a change of solution every hour) to remove possible salt residues in material pores. Then, specimens were dried at 37 °C overnight and weighed (initial mass was determined). Finally, cements were immersed in 2.5 mL of PBS solution (Merck, Germany) and stored for one month at 37 °C with a PBS change every third day. After the immersion, specimens were removed from the solution, dried overnight, and weighed again (the final mass was determined). The relative mass loss was calculated by the following equation [25]:

$$m_{\%} = m_f / m_i \cdot 100\%$$

where m% is the mass change (%), mf is the final mass (g), and mi is the initial mass (g). The analytical balance accuracy of the laboratory scale was 1.0 mg.

Injectability

Injectability was qualitatively assessed by injecting a specified amount of cement paste from a 5 mL syringe. The cement components were mixed and transferred to a syringe. Then, after about 3 minutes, they were hand-squeezed.

Cytocompatibility

The cytocompatibility of developed bone cements was evaluated with a human osteoblast cell line (hFOB 1.9; ATTC CRL-11372). Cells were cultured in F12/Dulbecco-Modified Eagle's Medium (Merck, Germany) supplemented with 0.3 mg/mL geneticin sulfate (G-418, Thermofisher Scientific, UK) and 10% Fetal Bovine Serum (Biowest, France) at 34°C and 5 % CO_2. Before testing, all specimens (n = 4) were sterilized by exposure to UV light (2 × 30 min) and then immersed in 2 mL of the aforementioned medium per specimen for 7 days (pretreatment) to equalize the ion levels [26]. The hFOB cells were seeded at a density of 80 x 10^3 cells/mL on the surface of materials in 1.5 mL of fresh culture medium. The cell viability was analyzed after 3 days of culture using the MTT (thiazolyl blue tetrazolium bromide; Merck, Germany) assay. The development of the colored product metabolized by living cells was assessed colorimetrically using a microplate reader (Victor, PerkinElmer, USA) at 595 nm, with reference to 690 nm. The results were normalized using a cell incubated on a tissue culture plate (TCP) at 100%.

Statistics

Statistical analysis of the data was performed using commercial software (SigmaPlot 14.0, Systat Software, San Jose, CA, USA). The Shapiro–Wilk test was used to assess the normal distribution of the data. All results were calculated as means ± standard deviations (SD) and statistically analyzed using one-way analysis of variance (ANOVA). Multiple comparisons between the control group and the means were performed using the Bonferroni t-test, with statistical significance set at $p < 0.05$.

Results

Setting time

The setting time of cements was strongly dependent on the size of the magnesium powder as well as the Mg/P and P/L ratios (FIG. 1). MgO-I showed a significantly longer time compared to MgO-II. Increasing ratios of Mg to P and powder to liquid contributed to a significant shortening of setting time, but only for MPC-I. The Mg/P ratio showed a greater effect on the time changes than the P/L ratio. It is assumed that the optimal setting time for bone cements is between 10 and 15 minutes [27], hence appropriate groups of cements are: MPC-I_MgP5:1, MPC-II_MgP4:1, and MgP3:1 with a P/L ratio of 2.5. The P/L ratio, on the other hand, allows for small changes in setting time, more significantly for MPC-I in the range of 1-3 minutes and for MPC-II, approx. 1 min.

Setting temperature

All tested technological parameters affected the reaction temperature of the cement (FIG. 2). MPC-IIs showed a much higher temperature (in a range of 50-67°C) than MPC-I (40-48°C), and were characterized by a greater impact on varied results when changing one of the ratios. Depending on the magnesium oxide particle size, the ratios had different effects on the reaction temperature. It has

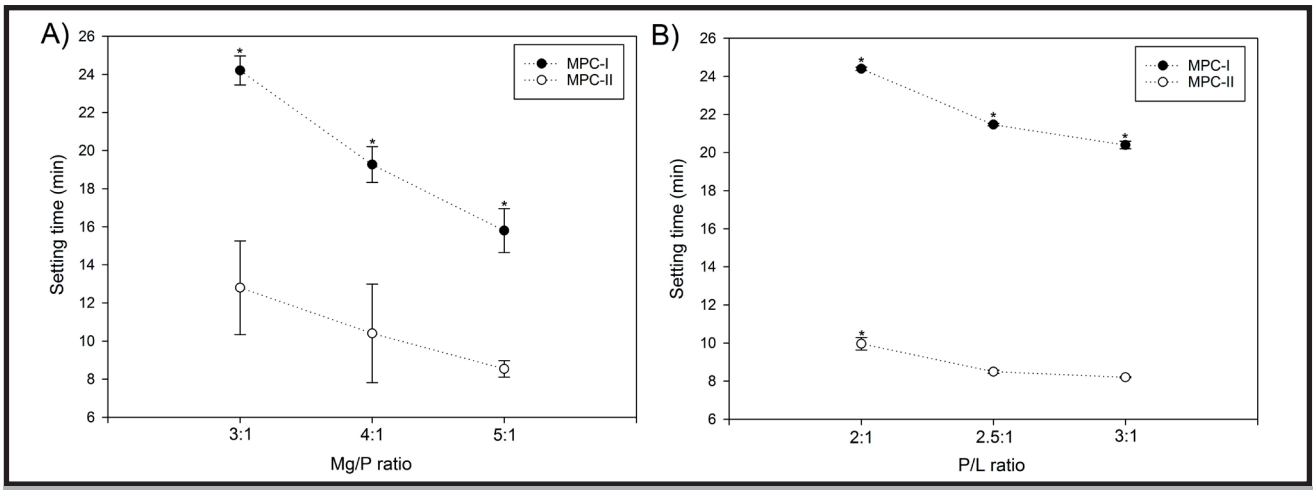

FIG. 1. Setting time of tested magnesium potassium bone cements with A) various Mg/P ratios (P/L ratio constant = 2.5:1) and B) various P/L ratios (Mg/P ratio constant = 4:1) using different types of magnesia powders (n = 3; data are expressed as the mean ± SD; * statistically significant difference between groups (p < 0.05))

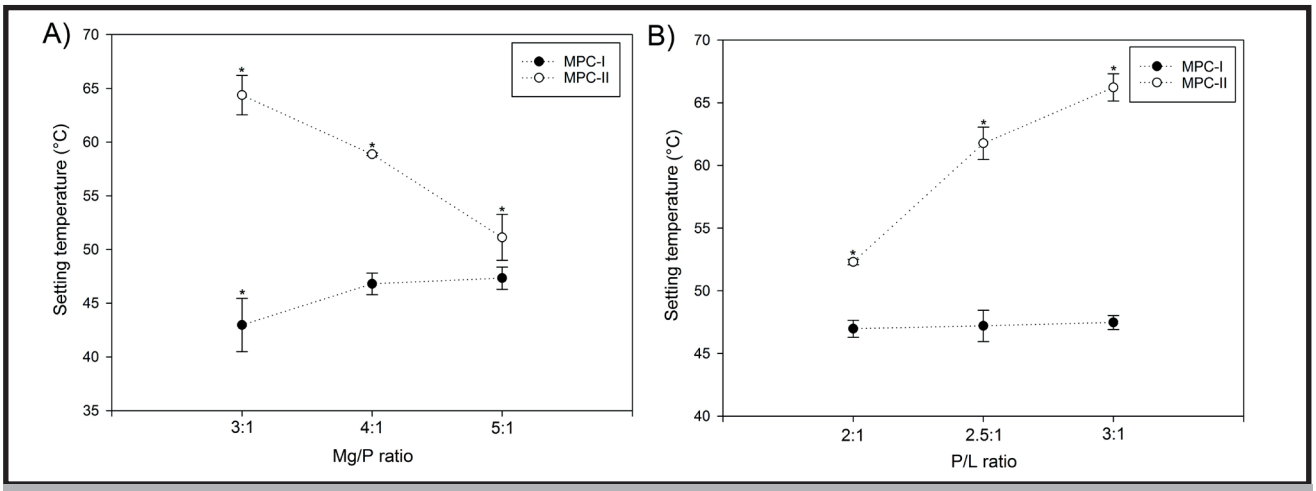

FIG. 2. Setting temperature of tested magnesium potassium bone cements with A) various Mg/P ratios (P/L ratio constant = 2.5:1) and B) various P/L ratios (Mg/P constant = 4:1) using different types of magnesia powders (n = 3; data are expressed as the mean ± SD; * statistically significant difference between groups ($p < 0.05$))

been proven that a temperature above 47°C, maintained for more than 1 min, leads to osteonecrosis [28]; hence, only MPC-I groups seem to be a safe material. However, as the experiment was conducted in the air, it should be assumed that the MPC-II_MgP5:1 and 4:1, especially with P/L_2:1, could not cause a negative reaction at the implantation site, when the cooling agent of tissue fluid comes in.

Microstructure analysis

The use of various magnesium oxides significantly affected the MPCs microstructure and morphology of magnesium phosphate crystals (FIGs. 3 and 4). In the case of MPC-II, a typical structure for ceramic cements was obtained, consisting of numerous crystals. In contrast, for MPC-I, the microstructure was poorly differentiated, especially for P/L = 2.5. For the MPC-II cements, the change in the Mg/P and P/L ratios significantly affected the size and expansion of their crystals. The average size of k-struvite crystals was analyzed for MPC-II cements (FIG. S1; n=20) with a change in the Mg/P ratio and it was noted that the following values: 45 ± 14*, 56 ± 19#, and 77 ± 16*,# µm, respectively for MgP3:1, 4:1 and 5:1 (*,# statistically significant difference between marked groups ($p < 0.05$)).

Phase composition

The XRD spectra of all evaluated cement compositions are shown in FIGs. 5 and 6. Corresponding XRD patterns confirmed the appropriate course of the hydration reaction

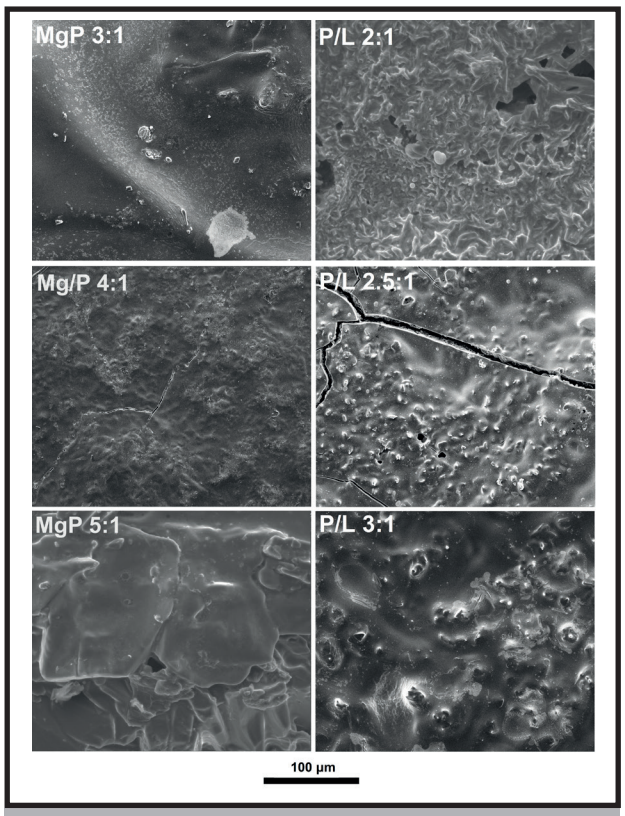

FIG. 3. SEM images of tested magnesium potassium bone cements with various Mg/P (P/L ratio - constant = 2.5:1) and P/L ratios (Mg/P - constant = 4:1) obtained with MgO-I at 500× magnification after curing (the pictures are representative of three specimens)

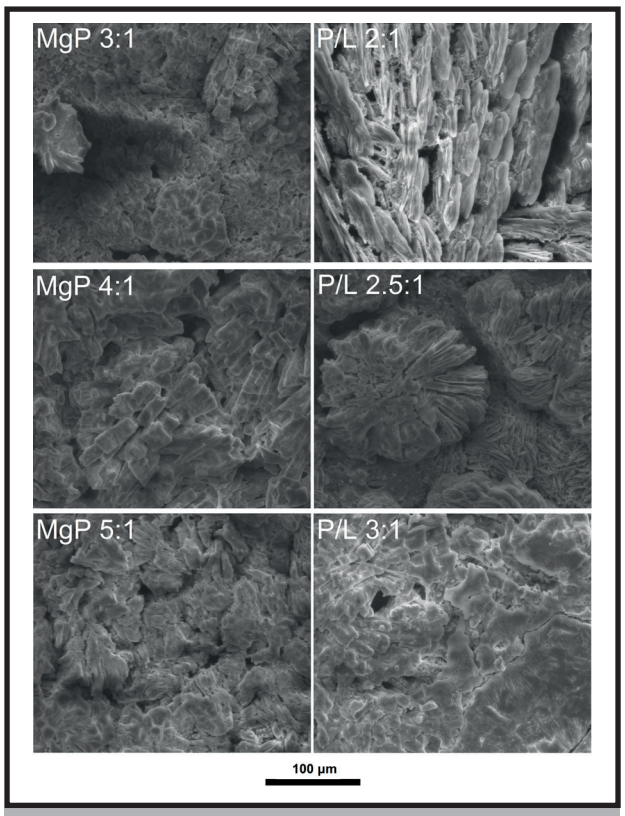

FIG. 4. SEM images of tested magnesium potassium bone cements with various Mg/P (P/L ratio - constant = 2.5:1) and P/L ratios (Mg/P - constant = 4:1) obtained with MgO-II at 500× magnification after curing (the pictures are representative of three specimens)

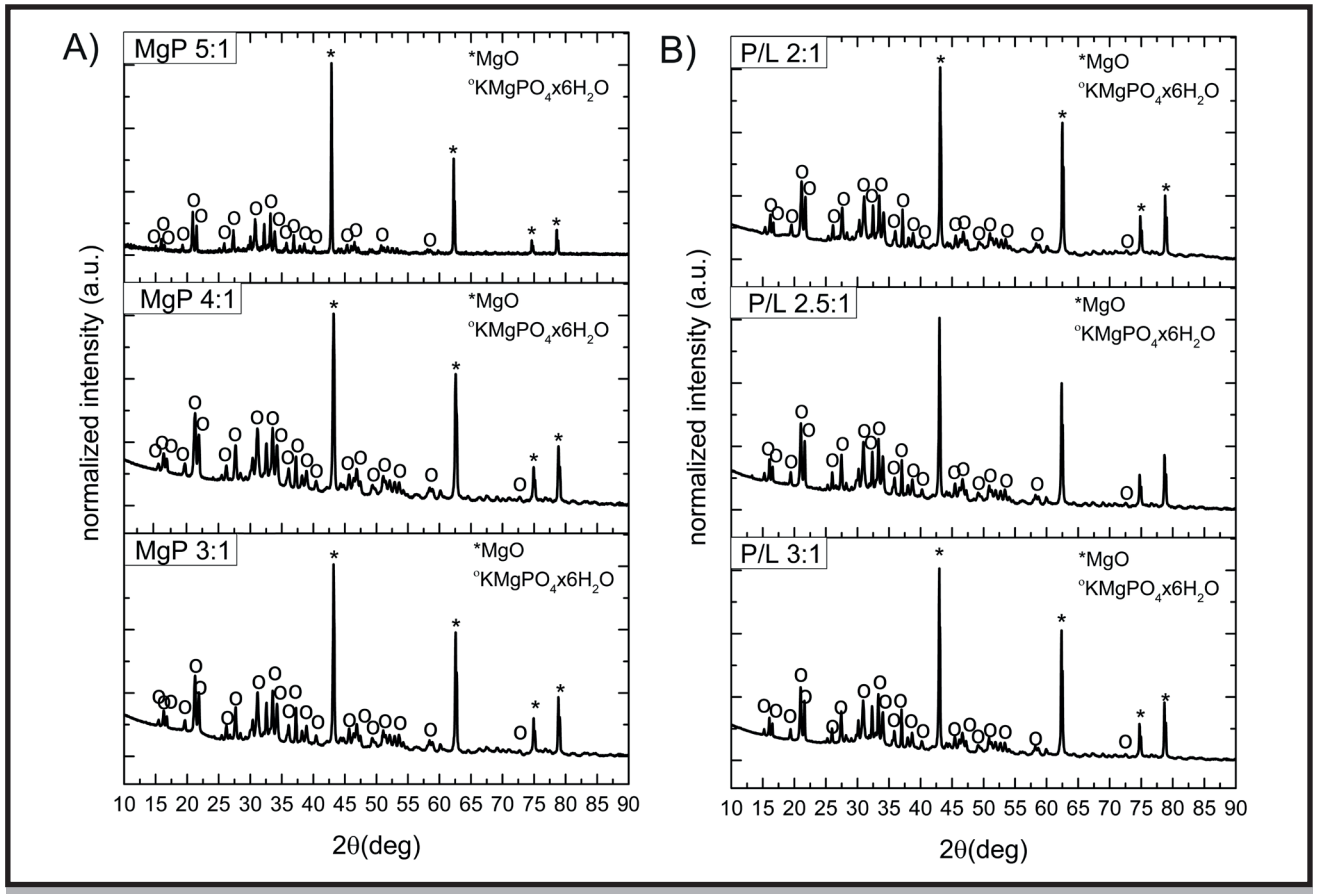

FIG. 5. XRD patterns of the tested bone cements obtained with MgO-I after curing 24h under 37°C, 100% humidity. Characteristic reflexes are marked as: $KMgPO_4 \times 6H_2O$ and MgO

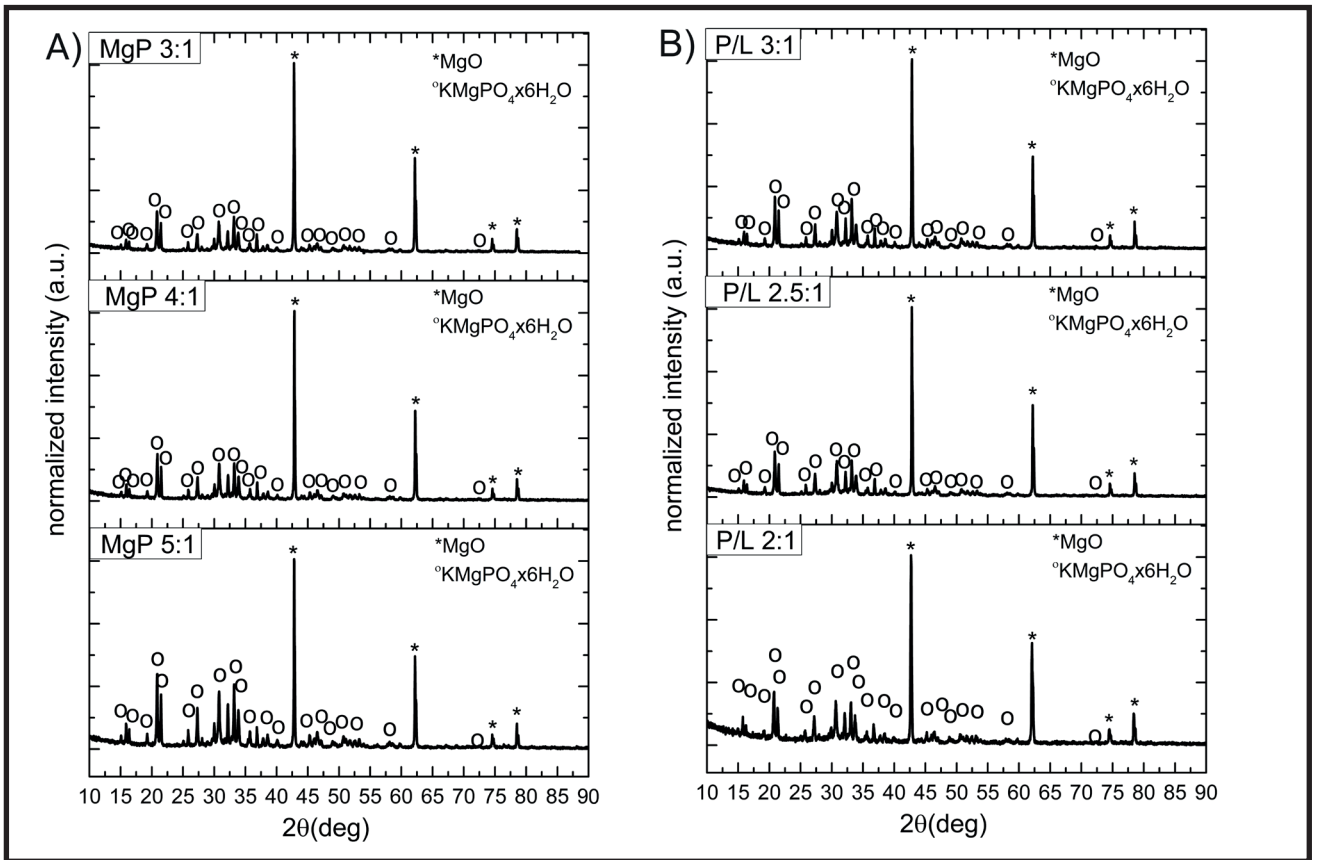

FIG. 6. XRD patterns of the tested bone cements obtained with MgO-II after curing 24h under 37°C, 100% humidity. Characteristic reflexes are marked as: $KMgPO_4 \times 6H_2O$ and MgO

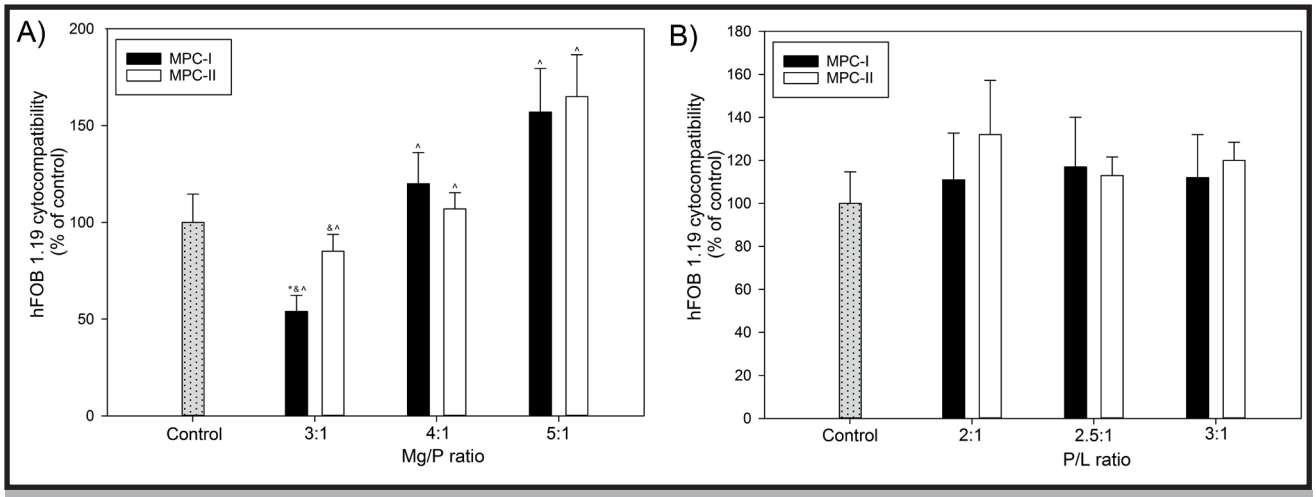

FIG. 7. Cytocompatibility of the tested magnesium potassium bone cements with A) various Mg/P ratio (P/L ratio - constant = 2.5:1) and B) various P/L ratio (Mg/P ratio – constant = 4:1) obtained using different types of magnesia powders (n = 4; data are expressed as the mean ± SD; * statistically significant difference compared to control, & statistically significant difference between MgO type, ^ statistically significant difference between Mg/P or P/L ratio ($p < 0.05$))

as all groups consisted of a well-crystallized phase of k-struvite – $MgKPO_4 \cdot 6H_2O$ (ICDD 01-075-1076). However, all groups also exhibited the presence of unreacted magnesium oxide (ICDD 01-075-0447), a typical phenomenon for MKPC cements.

Qualitative analysis of the normalized diffractograms, by comparing the peak relations for both phases, allowed us to determine that the highest ratio of magnesium phosphate crystallization was obtained for the groups with an Mg/P ratio of 4:1, with no significant influence related to the type of applied magnesium oxide or the selected P/L ratio. Furthermore, only Mg/P ratios of 3:1 exhibited a significant deterioration in MPC crystallization. However, it should be considered that k-struvite also typically occurs in the amorphous phase, which was not apparent in diffractograms.

Cytocompatibility

Cytocompatibility studies were performed on human osteoblasts hFOB 1.19, and the results are shown in FIG. 7. Both magnesium oxide size and Mg/P ratio showed a significant influence on the number of tested bone cells. There is a visible trend of increased cell viability in samples grown on different Mg/P ratios compared to the control (TCP). However, there was no significant difference in the cytocompatibility of cements, except for Mg/P3:1 and between MPC-I and MPC-II. Additionally, changing the P/L ratio only slightly affects (without statistical significance) cell viability. Generally, the viability was more pronounced in MPC-II samples (FIG. 7B). The cements MPC-I and MPC-II_Mg/P5:1 and P/L2:1 had the most favorable cytocompatibility. Further, only cements based on Mg/P3:1 were characterized by cytotoxicity (cell viability compared to control below 70%), especially MPC-I.

Based on the research conducted, we decided to choose MgO-II **(a light type of magnesia**) as a more suitable base for producing cements dedicated to medical applications, and additional research was carried out focusing on this group.

Porosity

FIG. 8 presents the porosity results of the tested cements obtained with MgO-II, which exhibit various technological properties. The P/L ratio showed a significant effect on the specimen's porosity, showing a decreasing trend as the ratio increased. Changing the Mg/P ratio in the range of 3.0-5.0: 1.0 did not significantly affect these properties. The highest porosity (~8%) was found for the MPC-II_PL2:1_MgP_4:1.

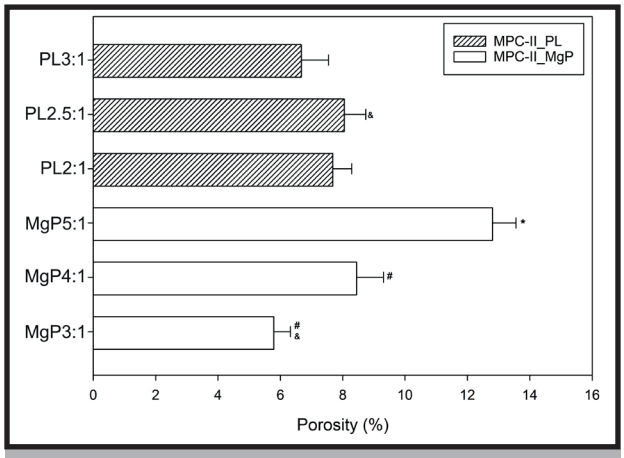

FIG. 8. Porosity of the tested magnesium potassium bone cements based on MgO-II with various Mg/P (P/L ratio - constant = 2.5:1) and P/L ratio (Mg/P ratio – constant = 4:1) (n = 3; data are expressed as the mean ± SD; #, & statistically significant difference between marked groups ($p < 0.05$))

Injectability

The injectability of the cement's pastes was determined qualitatively to check whether all tested groups could be applied in minimally invasive procedures. The results obtained are presented in TABLE 2 and in the example photo in FIG. 9.

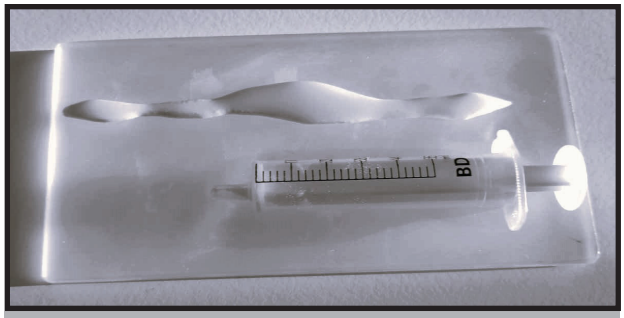

FIG. 9. An example photo of an injectable cement paste (representative for groups defined as injectable in TABLE 2; n=3)

TABLE 2. Injectability of tested bone cements pastes (the results are representative of three experiments)

Cements	Qualitative assessment of injectability
MPC-II_MgP3:1	injectable paste
MPC-II_MgP4:1	injectable paste
MPC-II_MgP5:1	**non-injectable paste**
MPC-II_PL2:1	injectable paste
MPC-II_PL2.5:1	injectable paste
MPC-II_PL3:1	**non-injectable paste**

The experiments showed that two cement groups are not suitable for injection applications – these were MPC-II, with the highest Mg/P ratio (5:1), and MCP-II, with the highest P/L ratio (3:1). The other cements were defined as injectable.

Degradation behavior

All tested cements, except MPC-II_MgP5:1, showed a similar biodegradation of rate about ~4.5-6.0% per month (FIG. 10). Only the group with the highest Mg/P ratio (5:1) showed a significant increase in mass loss (close to ~7.5-9.0%).

Mechanical properties

The results of the mechanical properties of the tested specimens based on MPC-II are shown in FIG. 11. The tests were carried out under liquid conditions (in PBS solution at body temperature), which had a significant impact on the obtained values. Generally, the cements showed relatively similar values of compressive strength (~10-20 MPa) and Young's modules (~900-1300 MPa); the only statistically significant difference was observed in compressive strength between the PL2:1 and PL3:1 group.

Discussion

The manipulation of the technological process enables the regulation of the ultimate properties of magnesium phosphate cements, such as: setting reaction, microstructure – especially MgP crystal size and distribution, phase composition, porosity, mechanical strengths, paste cohesion and its leaching resistance, biodegradation rate, cell viability, injectability, and also antibacterial properties [9]. The following variable parameters can be applied: the type of reagents (kind of Mg and P substrates), their particle size, Mg/P molar ratio, P/L ratio, reactivity of Mg substrate, method of mixing, as well as reaction environment conditions [29,30]. Different MKPC-based cements were obtained and characterized using three indicators (magnesia type, Mg/P molar ratio, and P/L ratio) to evaluate their effect on the main material properties and select the most beneficial bone cement for medical applications.

The influence of magnesia type on the MKPC properties

Magnesium oxide has a foundational role as the main component of magnesium potassium phosphate cement. Consideration must be given to the fact that the properties of the MKPC will be influenced by its source (such as salt lakes, dolomite ores, magnesite, or sea salt), reactivity (dependent on calcination), and average particle size [9]. Here, we decided to evaluate two types of commercially available

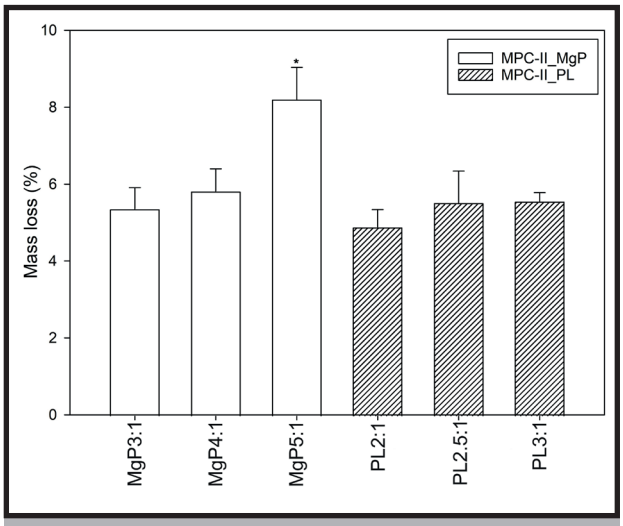

FIG. 10. Degradation of the tested magnesium potassium bone cements based on MgO-II with various Mg/P (P/L ratio constant = 2.5:1) and P/L ratio (Mg/P ratio constant = 4:1) (n = 3; data are expressed as the mean ± SD; * statistically significant difference between all other groups (p < 0.05))

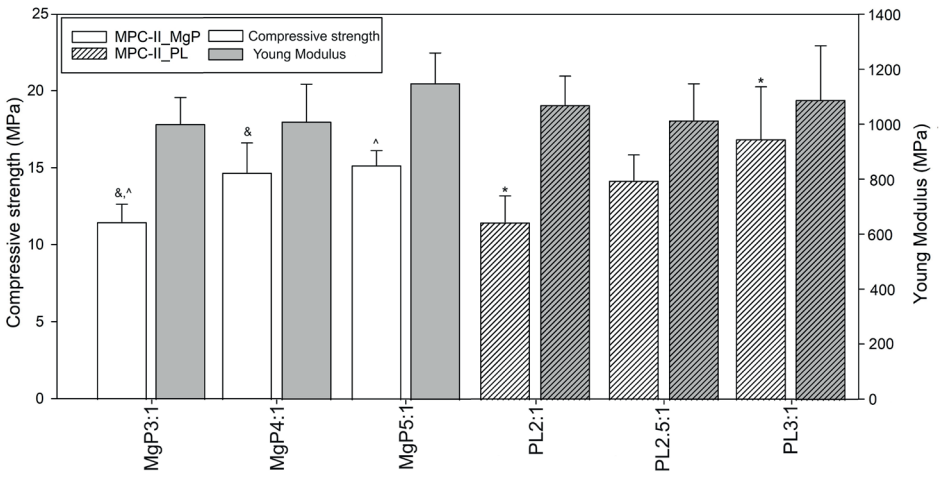

FIG. 11. Mechanical properties (compressive strength and Young's Modulus) of the tested bone cements carried out in wet conditions (n = 8; data are expressed as the mean ± SD; *,&,^ statistically significant difference between groups (p < 0.05))

magnesium oxide powders: normal (MgO-I) with particle size ~52.75 μm and light (MgO-II) with ~7.48 μm, calcined using the repeatable protocol (1500 °C / 5 h) and used to produce cements by the same procedure. The selected calcination temperature is a standard for MPC dedicated to medical applications and is referred to as 'heavily calcined' or 'dead-burn' magnesia (range 1500-1700°C) [29]. Regardless of the technology, the main final product of the hydration reaction, MgO and KH_2PO_4, should be k-struvite [31], which may exist in both crystalline and amorphous forms [32]. Our results clearly indicate that the type of magnesium oxide had a key influence on the following properties of MKPC cement: setting reaction (hardening time and reaction temperature; FIGs. 1, 2) and microstructure (FIGs. 3, 4). For MgO-I (with higher particle size), the initial stages of the hydration reaction were much less effective – cement's setting time was 2× higher than in the case of MgO-II, while the temperature did not exceed 50°C (and was even lower for ~15 °C than MgO-II). The microstructure of MKPC cements differs dramatically between the two groups. For MPC-II, typical magnesium phosphate crystals are observed, whereas MPC-I has a dense structure with numerous cracks and slight porosity present. Additionally, in the case of MPC-I, we observed a phenomenon of efflorescence – the formation of intermediate hydrates based on various phases on the surface of specimens [33], which necessitated more frequent mixing of the cement paste during hardening. Furthermore, there was no significant effect of the MgO type used on the crystallization of k-struvite or the percentage ratio with unreacted magnesium oxide (FIGs. 5, 6). Additionally, the cytocompatibility of the obtained materials, as tested on osteoblasts (FIG. 7), did not change significantly depending on their type, except for the Mg/P3:1 group, where a slightly more favorable trend for MgO-II may be observed. The differences may be attributed to the hydraulic reaction itself. It can be assumed that light magnesium oxide with a smaller particle size allows KDP to dissolve and achieve a more acidic pH more quickly, and its dissolution is also more efficient [34]. However, the crystallization process (the final stage of the hydraulic reaction), associated with a change in pH towards alkaline, is similar for both MgO types. Hence, the conclusion is that the type of magnesium oxide is only crucial for the first phases of the cement reaction. Simultaneously, MgO type has a significant impact on the microstructure of cements. The literature mentions that k-struvite crystals are predominantly observed in acicular, platelike, or prismatic forms with micrometer sizes [29]. Here, only for the MPC-II group, the occurrence of MgP crystals was observed, and they had an acicular-prismatic shape with a size of less than 50 μm. Viani et al. also found that the diversity of MPC microstructure depends on the hydration reaction, which is influenced by changes in calcination temperature [35]. Further, Pang et. al. stated that the physical and chemical properties of MgO significantly affect the properties of MKPC. Finally, as the microstructure and internal porosity have a key impact on cell adhesion [36], slightly different results were also observed in cytocompatibility research. Due to the functional requirements for bone cement (the optimal setting time of 10-15 min [27]) and a more favorable microstructure (characterized by diverse microstructure and internal porosity), having a positive effect on osteoblast cell adhesion and viability, in our opinion, light magnesium oxide will be more suitable as a base of MKPC for medical applications.

The influence of the Mg/P molar ratio on the MKPC properties

The ratio of magnesium to phosphorus in MPC cements is one of the most frequently studied parameters in the scientific research of these materials [10,15]. This is because it has the greatest influence (of course, with the right liquid-to-powder ratio) on the hydration reaction. This process is strongly dependent on pH changes, and it is crucial for the dissolution of magnesium oxide and its subsequent crystallization [37,38]. With an inappropriate Mg/P ratio, the hydraulic reaction may not take place properly, and k-struvite may not occur or occur only in amorphous form. Further, the effectiveness of crystal formation is limited by the availability of reagents, i.e., magnesia, phosphate (and also water) [39]. Hence, an inappropriate Mg/P ratio may significantly disturb the hydration process and significantly deteriorate the properties of cement due to the residual amount of KH_2PO_4 or unreacted MgO [40]. Here, we preselected three Mg/P ratios, based on the literature as optimal for cement medical applications [12], and we confirmed that a change in the range of 3-5: 1 MgP molar ratio is crucial for the material properties; however, we found that the results are different for types of magnesium oxide. Generally, the increase in the ratio contributed to a more effective hydration reaction (faster setting times; FIG. 1), greater growth of k-struvite crystals (FIG. 4; FIG. S1), more appropriate crystallization (FIGs. 5, 6), faster biodegradation (FIG. 10), injectability (TABLE 2) and better osteoblasts adhesion and their viability (FIG. 7). However, the results for the setting temperature (FIG. 2) and the obtained microstructure (FIGs. 3, 4) are significantly different for the MgO-I and MgO-II types. The results obtained are partially consistent with current knowledge. It was also previously confirmed that with increasing Mg/P ratio (in the range of 1-10: 1), the setting and hardening speed of cement increased [41], which we also observed for both types of magnesium oxide. Xu et al. found that a lower Mg/P ratio (< 4:1) leads to a denser microstructure with better crystallization and growth of the k-struvite by sufficient time to properly proceed with the hydration reaction [33], which is consistent with our results for MgO-II (of XRD and SEM analysis; and also Xu et al. used this MgO type a base), while in case of MgO-I there is no such tendency on SEM microstructure. On the other hand, Chau et al. stated that MPC cement with a low Mg/P ratio (< 5:1) had poor crystal growth [42], which we agree with, but only for MPC-I SEM evaluation. For MPC-II, all groups (3-5: 1 Mg/P ratio) exhibited the expected microstructure with well-crystallized k-struvite. However, in our case, the least effective crystallization reaction was observed for a Mg/P ratio of 3:1 (FIGs. 5 and 6), regardless of the type of MgO used. Furthermore, Li et al. observed a cracking phenomenon in cement with a lower Mg/P ratio (<3:1), which is attributed to the high hygroscopicity of KH2PO4 salt [43]. We observed numerous cracks only in the MPC-I specimens, but in the MPC-II specimens, we did not find this problem. In terms of cement's porosity, we did not find statistically significant differences; however, a trend is observed that aligns with the literature, specifically the result of Ma et al. [44], which indicates that a higher Mg/P ratio results in higher porosity. Moreover, in our studies, we did not observe differences between the mechanical properties of the tested MgP ratios (FIG. 11). While Wang et al. found that low (<2) and high (≥ 5) Mg/P ratios decrease the compressive strength of cements, and the optimal Mg/P ratio was 4:1 (but g:g). They believe that the residual amount of salt in a low ratio or bad cohesion between grains at a high ratio contributes to such results [40]. Also, Le Rouzic et al. stated that the high-strength MKPC cement should be prepared with Mg/P ratio in the range of 4-5:1 [41], which we also confirm. All the above differences in results may be due to the use of different parameters (such as calcination temperature, MgO type, and its size), but may also be caused by variations in testing methods. Here, we perform experiments under wet conditions, but based on our previous observations, we also know that these results are worse than those for

dry conditions. To sum up, the most favorable Mg/P ratio for medical applications for MKPC cements obtained from light magnesium oxide is 4:1.

The influence of the P/L ratio on the MKPC properties

In the case of the parameter P/L ratio, the literature is rather consistent. A lower P/L ratio results in a longer setting time, improved paste workability, increased porosity, and reduced mechanical strengths [15,45]. In our research, we managed to confirm that increasing the P/L ratio (in the range of 2.0-3.0: 1; with a constant 4:1 Mg/P ratio) had an influence on setting reaction time (slightly shorter setting time and higher setting temperature; FIGs. 1, 2), growth and shape of k-struvite crystals (only for MPC-II; FIG. 4), mechanical properties (FIG. 11), porosity (FIG. 8) and also enables injectability of the paste (TABLE 2, FIG. 9). However, we have found that this parameter, in its tested range, had no significant effect on cement's degradation rate (FIG. 10), k-struvite crystallization process (FIGs. 5,6), and cytocompatibility of cements (FIG. 7). It was previously confirmed that the P/L parameter has a key influence on hydration reactions – using too high a ratio can lead to incomplete dissolution of the salt and its remaining in the structure, pH too low to dissolve MgO or disruption of k-struvite crystallization [46]. Further, Lothenbach et. al. showed that pH occurring during the hydration reaction (which also depends on P/L ratio) significantly affects the formation of various phases different than k-struvite [47]. While Xu et al. reported that efflorescence was strongly dependent on the P/L [33]. However, in our case, we did not observe such a relationship, which may be related to the P/L range we chose for our research, which was confirmed as suitable for medical applications. Moreover, in the review of Zheng et al., they found that the MPC cement with the highest mechanical strength is obtained with a P/L ratio of ~ 1.54 (w/c = 0.65) [48]. On the other hand, Li and Chen found that the most favorable cement in the mechanical aspect was with a P/L ratio of about 6:1 (w/c = 0.14-0.16) [49]. It is also worth noting that here, the P/L ratio showed relatively smaller changes in setting time (i.e., 1-3 min for MPC-I and 1 min for MPC-II) compared to the Mg/P ratio. However, the literature indicates that the P/L ratio significantly influences the setting time of MPC – these differences may arise from the application of a relatively narrow P/L ratio range (2–3 : 1) with constant other technological parameters. Finally, it is essential to note that in most available works, researchers have tested construction cements whose parameters are not suitable for medical applications, and the resulting differences may be attributed to the technology itself. To sum up, based on our study, the most favorable P/L ratio for medical applications of MKPC cements was found to be 2:1 for the light magnesium oxide type.

Choosing the most favorable MKPC cement

The research conducted enabled us to select the optimal technology for producing bone cement based on magnesium-potassium phosphate, which possesses the appropriate properties for medical applications. The cement composition was based on two reagents: dead-burned magnesium oxide (light type; calcined at 1500 °C for 5 h) and a phosphate salt with a 4:1 Mg/P ratio and a 2:1 P/L ratio. This proposed cement hardened in the range of 8-12 min, with a reaction temperature lower than ~53 °C, consisted of well-crystallized k-struvite, had a diverse microstructure with clearly visible MgP crystals, its porosity was ~8%, it was injectable, its biodegradation rate was ~6% / month, had compressive strength ~12 MPa and Young Modulus ~1.0-1.2 GPa, and finally this cement showed good cytocompatibility for osteoblasts. Hence, we believe that this optimized MKPC cement may be widely used, without the need for additional retards, in various medical applications, especially in minimally invasive orthopedic procedures.

Limitations

In this work, 12 groups of MKPC cements were characterized, differing in the type of magnesium oxide and the used Mg/P and P/L ratios used, which allowed for a broader analysis of the MKPC cement technology (with constant MgO calcination temperature and cement production procedure). However, our work still has its limitations. Firstly, it focuses on cement based on magnesium potassium phosphate, dedicated to medical applications. Secondly, only specific ranges of Mg/P (3-5: 1) and P/L (2-3: 1) ratios were selected based on the literature. Increasing these ranges could allow us to draw different or more accurate conclusions. Thirdly, some technological factors were not considered, and according to reports, they also affect the properties of cements, e.g., type of water [50], source of MgO [9], light or medium burned magnesia [29]. Moreover, the applied methodology also has its limitations. The conducted injectability study was only preliminary and qualitative in nature. For a more detailed analysis and comparison with the literature, it would be recommended to use a standardized method to determine the force required for paste extrusion and the percentage of paste injected. Further, it will be particularly interesting to correlate the injectability of the cement pastes with their rheological properties. Also, as a limitation, the setting temperature measurement may be overestimated due to the use of a simple model, with the thermocouple placed at the center of the hardening cement paste without simulating body fluids. Finally, more in-depth studies on cell-cement interactions in relation to biodegradation, as well as the evaluation of antibacterial properties (previously reported for MPC [51]) of the investigated cement groups, represent valuable directions for further research.

Conclusions

In the present study, we examined the influence of various process variables, such as magnesia powder type, Mg/P molar ratio, and P/L ratio, on the properties of magnesium potassium phosphate cement to select the optimal technology for its medical applications. The following conclusions were drawn up after our research:

1) Changing any one technological parameter significantly affects the hydraulic reaction and results in different properties of the cement; the selection of the optimal MKPC should consider: the type of reagents, their particle size, calcination protocol of MgO, molar ratio of Mg/P, and P/L ratio.

2) Magnesia type (normal vs light) has a significant effect on the initial stages of hydraulic reaction (hardening time and setting temperature), diversity of microstructure, and formation of visible k-struvite crystals, the occurrence of the efflorescence phenomenon, while exhibiting negligible influence on crystallization process and cytocompatibility.

3) Mg/P molar ratio (3 vs 4 vs 5:1) has a significant impact on hydraulic reaction (hardening time), k-struvite crystallization, and MgP crystals growth, biodegradation rate, injectability, compressive strength, and also adhesion and viability of osteoblasts. However, this is not a key parameter in the case of setting temperature, efflorescence, and diversity of microstructure.

4) P/L ratio (2 vs 2.5 vs 3:1) significantly affects hydraulic reaction (hardening time and setting temperature), growth and shape of MgP crystals, porosity, mechanical properties, and injectability, while it has no meaningful effect on biodegradation rate, the crystallization process, efflorescence, and cytocompatibility.

5) It is possible to obtain MKPC cement with properties suitable for medical applications without the addition of retardants by optimizing the process of its technology.

Based on our research, we found that the most favorable bone cement based on magnesium potassium phosphate may be obtained using dead burn light magnesia (~7.48 μm average particle size; calcinated at 1500 °C / 5h) and the following parameters: 4:1 Mg/P molar ratio and 2:1 P/L ratio.

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Author Contributions

Conceptualization. M.W.; methodology. M.W., A.R.; formal analysis. M.W., AM.-G., A.R.; investigation. K.S., A.M.-G., A.R., and M.W.; resources. M.W.; data curation. A.M.-G. and M.W.; writing – original draft preparation. M.W.; writing – review and editing. A.R., A.M.-G., and M.W.; visualization. M.W. and A.M.-G.; project administration. M.W.; supervision. M.W. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT to improve language and readability. After using this tool, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the publication.

Data availability

The XRD datasets analysed during the current study are available in the "Bridge of Knowledge" repository of the Gdańsk University of Technology at https://doi.org/10.34808/gwpr-ns40. All other data are available from the corresponding author upon reasonable request. Please note that the corresponding author can be contacted for further information regarding the datasets.

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