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Development and Characterization of a Gentamicin–Vancomycin-Loaded PMMA Bone Cement for Dynamic Articulating Spacer Fabrication

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Abstract

Background: Periprosthetic joint infection (PJI) is a serious complication of total joint arthroplasty commonly managed by two-stage revision using antibiotic-loaded articulating spacers.

Objective: This study evaluated a dual-antibiotic-loaded PMMA bone cement developed for the fabrication of dynamic spacers.

Methods: In this in vitro experimental study, 4 g of vancomycin hydrochloride was incorporated into a commercially available gentamicin-loaded PMMA bone cement (CEMEX® GENTA). A reusable silicone mold was developed to fabricate anatomically accurate femoral spacer components. The developed cement was compared with the standard formulation regarding macroscopic appearance, color characteristics, polymerization behavior, setting time, maximum polymerization temperature, compressive strength, tensile strength, electrical resistance, and molding performance according to ISO 5833. Statistical analysis was performed using the independent-samples *t*-test ($p < 0.05$).

Results: The addition of vancomycin slightly increased cement opacity without affecting surface morphology or dimensional accuracy. The developed cement exhibited a significantly shorter setting time ($p = 0.03$), whereas no significant differences were observed in doughing time, maximum polymerization temperature, compressive strength, tensile strength, electrical resistance, or molding performance ($p > 0.05$). Both formulations demonstrated excellent moldability and produced anatomically accurate femoral spacer components.

Conclusions: The developed dual-antibiotic-loaded PMMA bone cement preserved the essential physicochemical, mechanical, and molding properties of the original cement while enabling the fabrication of dynamic articulating spacers using a reusable silicone mold. This approach represents a promising strategy for the fabrication of temporary spacers in the management of periprosthetic joint infection.

Keywords: Polymethyl methacrylate (PMMA); Antibiotic-loaded bone cement; Gentamicin; Vancomycin; Dynamic articulating spacer; Periprosthetic joint infection.

1. Introduction

Periprosthetic joint infection (PJI) remains one of the most devastating complications following total joint arthroplasty (TJA), despite continuous advances in implant design, perioperative antimicrobial prophylaxis, and surgical techniques (1). Although the reported incidence of PJI is relatively low, its clinical consequences are profound, often resulting in prolonged hospitalization, repeated surgical procedures, functional impairment, increased healthcare costs, and considerable patient morbidity. Furthermore, the growing prevalence of antibiotic-resistant microorganisms has made the eradication of prosthetic joint infections increasingly challenging, underscoring the need for improved

therapeutic strategies (2-4).

Two-stage revision arthroplasty is currently regarded as the gold standard for treating chronic PJI, particularly in infections caused by resistant or difficult-to-eradicate pathogens. During the first stage of this procedure, all prosthetic components and infected tissues are removed, followed by extensive surgical debridement and implantation of an antibiotic-loaded temporary spacer. After an appropriate course of systemic antibiotic therapy, a definitive prosthesis is implanted during the second stage once infection control has been achieved (5).

Beyond local antibiotic delivery, temporary spacers play a critical mechanical role by preserving joint space, maintaining soft-tissue tension, preventing limb shortening, and facilitating patient mobility during the interval between revision procedures. Compared with static spacers, dynamic (articulating) spacers have demonstrated superior functional outcomes, improved postoperative range of motion, easier second-stage reimplantation, and enhanced patient satisfaction (6). Consequently, considerable attention has recently been directed toward optimizing both spacer design and the properties of the bone cement used to fabricate spacers.

Polymethyl methacrylate (PMMA) remains the most widely used material for manufacturing antibiotic-loaded spacers due to its favorable mechanical properties, handling characteristics, and ability to deliver high local concentrations of antimicrobial agents (7). Commercial PMMA bone cements commonly contain gentamicin as the primary antibiotic; however, supplementary antibiotics, particularly vancomycin, are frequently incorporated to extend antimicrobial coverage against methicillin-resistant Staphylococcus aureus (MRSA), coagulase-negative staphylococci, and other resistant Gram-positive pathogens commonly implicated in PJI (8-10).

Although dual antibiotic-loaded PMMA bone cements have been increasingly adopted in revision arthroplasty, concerns remain regarding the potential influence of high-dose antibiotics on polymerization behavior, mechanical integrity, thermal characteristics, and handling properties of the cement matrix. Previous investigations have primarily focused on antibiotic elution profiles or antibacterial efficacy. In contrast, relatively few studies have comprehensively evaluated the combined physicochemical, mechanical, thermal, electrical, and molding characteristics of molded dual-antibiotic-loaded PMMA bone cements intended for the fabrication of anatomically accurate articulating spacers (11).

In addition to cement composition, the manufacturing technique itself represents another important determinant of spacer performance. Conventional hand-molded spacers are highly operator-dependent and often exhibit inconsistencies in geometry, surface quality, and dimensional accuracy, potentially compromising joint congruency and postoperative function (12). The use of reusable, anatomically designed silicone molds may overcome these limitations by improving reproducibility, facilitating intraoperative fabrication, and producing spacers with superior dimensional fidelity (13).

Accordingly, the present study aimed to develop a dual-antibiotic-loaded PMMA bone cement containing gentamicin and vancomycin for the fabrication of dynamic articulating knee spacers using a reusable, sterilizable silicone mold. The physicochemical, thermal, mechanical, electrical, and molding characteristics of the developed cement were comprehensively evaluated and compared with those of a commercially available gentamicin-loaded PMMA bone cement to determine its

suitability for temporary spacer fabrication in two-stage revision arthroplasty.

2. Material and Methods

2.1. Study Design

An in vitro experimental study was conducted in two consecutive phases. In the first phase, a dual antibiotic-loaded polymethyl methacrylate (PMMA) bone cement was prepared by incorporating vancomycin hydrochloride into a commercially available gentamicin-loaded PMMA bone cement. In the second phase, a reusable silicone molding system was developed to fabricate anatomically accurate dynamic articulating femoral spacer components. Subsequently, the physicochemical, thermal, mechanical, electrical, and molding characteristics of the developed cement were systematically compared with those of the commercially available gentamicin-loaded formulation (14, 15).

2.2. Materials and Bone Cement Preparation

A commercially available gentamicin-loaded acrylic bone cement (CEMEX® GENTA; Tecres S.p.A., Verona, Italy) was used as the base material throughout the study. This PMMA-based bone cement consists of a powder component containing polymethyl methacrylate (PMMA) and gentamicin, together with a liquid methyl methacrylate (MMA) monomer supplied according to the manufacturer's instructions. According to the manufacturer, the cement is intended for orthopedic applications requiring local antibiotic delivery and prosthetic fixation.

Sterile vancomycin hydrochloride powder for injection was selected as the supplementary antimicrobial agent. To prepare the experimental formulation, 4 g of sterile vancomycin hydrochloride powder was manually blended with 40 g of gentamicin-loaded PMMA cement powder containing 500 mg of gentamicin. The powder components were thoroughly mixed before addition of the liquid monomer to ensure homogeneous distribution of the antibiotics throughout the cement matrix (16,17). The liquid monomer was subsequently added according to the manufacturer's instructions, and manual mixing was continued until a homogeneous dough-like consistency suitable for molding was obtained.

The combination of gentamicin and vancomycin was selected to broaden antimicrobial activity against both Gram-positive and Gram-negative microorganisms commonly associated with periprosthetic joint infection while preserving the handling and mechanical characteristics required for temporary articulating spacers.

2.3. Fabrication of Molded Cement Spacer Components

To enable reproducible fabrication of anatomically accurate dynamic articulating femoral spacers, a reusable silicone molding system was designed and manufactured. A size-4 femoral knee component was used as the master model to reproduce the mold cavity geometry.

Medical-grade silicone sheets suitable for spin-casting applications were molded using a hydraulic compression press (Tondar Machin Co., Iran). The silicone material was compressed between independently controlled heated plates at 150°C inside a cylindrical metal chamber. Continuous pressure was maintained throughout the molding process to minimize porosity and preserve dimensional accuracy.

Following fabrication, the mold demonstrated sufficient thermal stability to tolerate repeated steam sterilization using a standard hospital autoclave prior to surgical application. The reusable silicone molding system developed in this study has been registered with the Iranian Patent Office

(Patent No. 108616), highlighting its technological novelty and potential clinical applicability (14).

Following sterilization of the silicone mold, both cement formulations were prepared under sterile operating-room conditions. During the dough phase and before polymerization was complete, the cement was introduced into the mold cavity. After complete curing, the molded femoral spacer components were carefully removed from the mold and visually inspected. The molding performance of both cement formulations was comparatively evaluated according to the following criteria:1- Ease of cement removal from the mold. 2- Adhesion between the cement and silicone mold surface. 3- Surface quality of the molded component. 4- Dimensional fidelity to the original femoral geometry. 5- Presence of visible pores, voids, or incomplete filling. 6- Overall suitability for fabrication of dynamic articulating knee spacer (18,19)

2.4. Macroscopic and Morphological Evaluation

Following complete polymerization, hardened specimens from both cement formulations were evaluated macroscopically and microscopically. Surface morphology, homogeneity, visible porosity, surface roughness, and gross structural defects were assessed using visual inspection and optical microscopy.

Particular attention was given to identifying potential changes in surface integrity resulting from incorporation of vancomycin into the PMMA matrix.

Surface color was quantitatively evaluated using a calibrated digital color analysis system under standardized illumination conditions. Prior to measurement, the system was calibrated using a reference color standard to minimize instrumental variability.

Images of the polymerized cement specimens were captured under identical environmental conditions using a fixed camera position and constant lighting. Color differences between the two formulations were subsequently analyzed to determine whether incorporation of vancomycin altered the visual appearance of the cured PMMA bone cement.

Polymerization kinetics were evaluated by continuously monitoring the temperature generated during cement curing using a calibrated digital thermometer (LiebeWH, CM8550ct). The temperature probe was positioned at the geometric center of the cement mass immediately after mixing, and temperature changes were recorded throughout the polymerization process.

Temperature–time curves were generated for both cement formulations to evaluate the polymerization profile. As PMMA polymerization is an exothermic reaction, doughing time, setting time, and maximum polymerization temperature were considered the principal indicators of handling characteristics and thermal behavior. All measurements were performed in accordance with the recommendations of ISO 5833:2002 (Implants for Surgery—Acrylic Resin Cements)(20)

Mechanical properties were evaluated using a calibrated Shimadzu universal testing machine (Shimadzu Corporation, Kyoto, Japan) at room temperature (25 ± 2°C). Compression and tensile tests were performed in accordance with ISO 5833:2002.

For compressive strength testing, cubic specimens measuring 10 × 10 × 10 mm were prepared, whereas rectangular specimens measuring 10 × 10 × 50 mm were fabricated for tensile testing. Five specimens from each cement formulation were tested (n = 5).

A constant loading rate corresponding to approximately 1 MPa/s was applied until specimen failure. The maximum load sustained before fracture was automatically recorded, and compressive and tensile strengths were subsequently calculated.

Electrical resistance of the fully polymerized cement specimens was measured using a calibrated Megatek benchtop digital multimeter under identical laboratory conditions.

Five independent measurements were obtained from each specimen, and the mean electrical resistance was calculated for statistical analysis. The purpose of this evaluation was to determine whether incorporation of vancomycin altered the electrical characteristics of the polymerized PMMA matrix. Figure 1 shows the experimental equipment.

Figure1: The experimental equipment.

2.5. Quality Control

To minimize experimental variability, all cement formulations were prepared by the same operator under identical laboratory conditions. Standardized mixing procedures, ambient temperature (25 ± 2°C), humidity, curing conditions, and testing protocols were maintained throughout the study. All measuring instruments were calibrated before each experimental session according to the manufacturers' recommendations. Each experimental procedure was repeated independently, with five specimens per group (n = 5) to ensure reproducibility and improve the reliability of the results.

The proposed molding technique was designed to simulate the intraoperative workflow of two-stage revision arthroplasty closely. Accordingly, all fabrication procedures were performed using sterilizable materials under clinically applicable handling conditions. This approach enhances the translational potential of the proposed system and facilitates future preclinical and clinical investigations.

2.6. Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). Quantitative data are presented as mean ± standard deviation (SD). The normality of data distribution was assessed using the Shapiro–Wilk test. Comparisons between the commercially available gentamicin-loaded PMMA bone cement and the dual-antibiotic-loaded formulation were performed using an independent-samples t-

test. A two-tailed p-value < 0.05 was considered statistically significant.

3. Results

3.1. Macroscopic and Morphological Evaluation

Macroscopic inspection revealed no noticeable differences in the overall geometry or dimensional accuracy of the two cement formulations following complete polymerization. Both the commercially available gentamicin-loaded PMMA bone cement and the developed dual antibiotic-loaded formulation successfully reproduced the geometry of the femoral mold without visible deformation, structural defects, or dimensional distortion. Microscopic examination further demonstrated comparable surface morphology, homogeneity, and structural integrity in both groups. No apparent differences were observed in surface roughness, visible porosity, or gross structural irregularities following incorporation of vancomycin into the PMMA matrix (Figure 2).

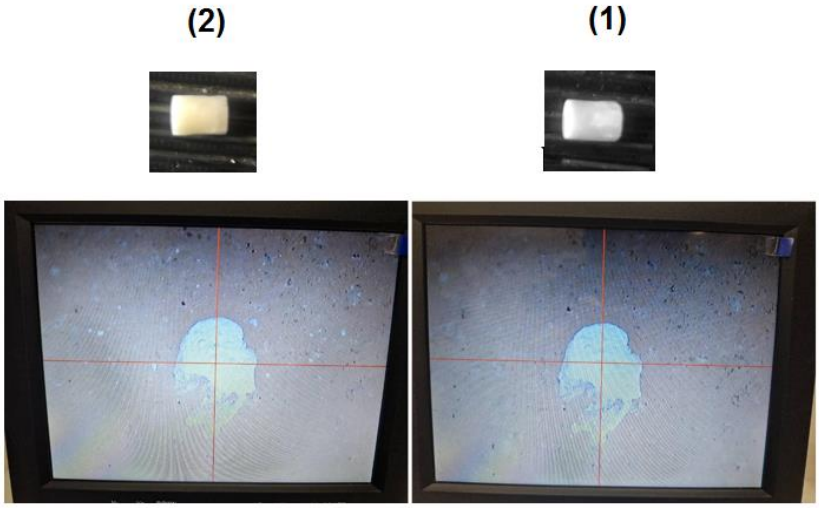

Figure 2. Macroscopic and dimensional appearance of the standard cement (1) and the cement developed in the present study (2).

Quantitative color analysis demonstrated a slight increase in opacity in the developed cement compared with the commercially available formulation. The dual antibiotic-loaded cement exhibited a slightly cream-colored appearance after polymerization, consistent with the incorporation of vancomycin powder. In contrast, the standard cement maintained its original appearance.

3.2. Polymerization Kinetics and Thermal Behavior

Representative temperature–time curves obtained during polymerization are presented in Figure 3. Both cement formulations exhibited similar polymerization profiles, characterized by a rapid increase in temperature followed by gradual cooling after the exothermic reaction. The overall thermal behavior remained comparable between the two formulations throughout the polymerization process.

The developed dual antibiotic-loaded cement exhibited a shorter setting time than the commercially available formulation. At room temperature, incorporation of vancomycin reduced the final setting time by approximately 20 s (0.3 min), indicating a slightly faster curing process. At a lower ambient temperature(15°C), the difference in

polymerization behavior became more pronounced. The commercially available cement completed polymerization after approximately 10.5 min, whereas the developed formulation required approximately 12 min, corresponding to a 14% difference in curing behavior under reduced-temperature conditions.

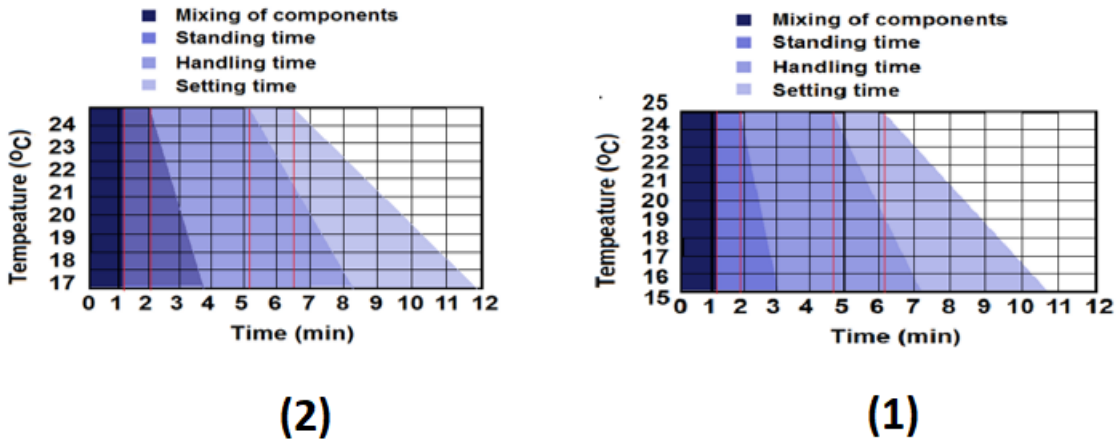

Figure 3. Temperature–time curve of the developed cement, the standard cement (1) and the cement developed in the present study (2).

3.3. Electrical Resistance

Electrical resistance measurements were performed on fully polymerized specimens using a benchtop digital multimeter. The mean electrical resistance of the commercially available gentamicin-loaded cement was 5.92 ± 1.22 MΩ, whereas the developed dual antibiotic-loaded cement exhibited a mean electrical resistance of 5.31 ± 1.56 MΩ. Statistical analysis demonstrated no significant difference between the two formulations ($p > 0.05$), indicating that incorporation of vancomycin did not measurably influence the electrical behavior of the polymerized PMMA matrix.

3.4. Physicochemical and Mechanical Evaluation According to ISO 5833

The physicochemical and mechanical properties of both cement formulations were evaluated in accordance with ISO 5833, and the results are summarized in Table 1.

Table 1. Comparison of physicochemical and mechanical properties of the commercially available gentamicin-loaded PMMA bone cement and the developed dual antibiotic-loaded formulation according to ISO 5833.

Parameter	Developed Dual Antibiotic-Loaded Cement	Commercial Gentamicin-Loaded Cement	P-value
Doughing time (min)	5.15 ± 0.61	4.79 ± 0.63	0.36
Setting time (min)	6.66 ± 0.21	6.06 ± 0.18	**0.03***
Maximum polymerization temperature (°C)	93.17 ± 4.23	89.11 ± 3.16	0.25
Compressive strength (MPa)	76.14 ± 6.12	81.23 ± 7.05	0.11
Tensile strength (MPa)	59.33 ± 8.53	61.33 ± 6.61	0.51

Values are presented as mean ± standard deviation (n = 5).
*Statistically significant difference ($P < 0.05$).

No statistically significant differences were observed between the two cement formulations regarding doughing time, maximum polymerization temperature, compressive strength, or tensile strength ($p > 0.05$). The only parameter demonstrating a statistically significant difference was the setting time, with the developed formulation exhibiting a shorter curing period than the commercially available cement ($p = 0.03$). The comparative results are illustrated in Figure 4.

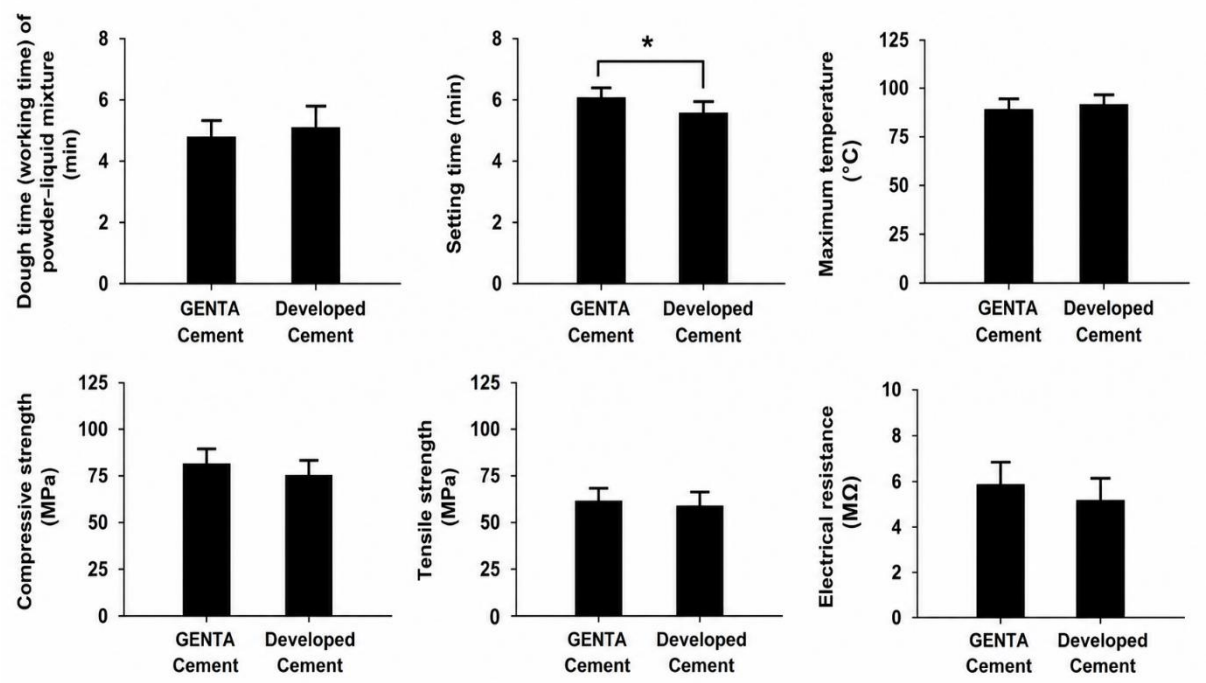

Figure 4: Bar chart of the evaluated parameters

3.5. Evaluation of Silicone Mold Performance

The performance of the reusable silicone molding system was evaluated during fabrication of the femoral spacer components. Both cement formulations filled the mold cavity, with no evidence of incomplete filling or air entrapment. No adhesion between the polymerized cement and the silicone mold surface was observed during demolding. Consequently, all femoral spacer components were removed without fracture, deformation, or surface damage. Macroscopic examination demonstrated excellent surface smoothness, accurate reproduction of anatomical contours, and high dimensional fidelity in both groups. Incorporation of vancomycin did not adversely affect moldability or the ability of the cement to reproduce the geometry of the original femoral component. The only observable difference between the two groups was a slight increase in opacity of the developed dual-antibiotic-loaded cement, consistent with the quantitative color analysis .Figure 5 shows the antibiotic-loaded cement prosthesis. Table 2 shows the qualitative evaluation of molding performance.

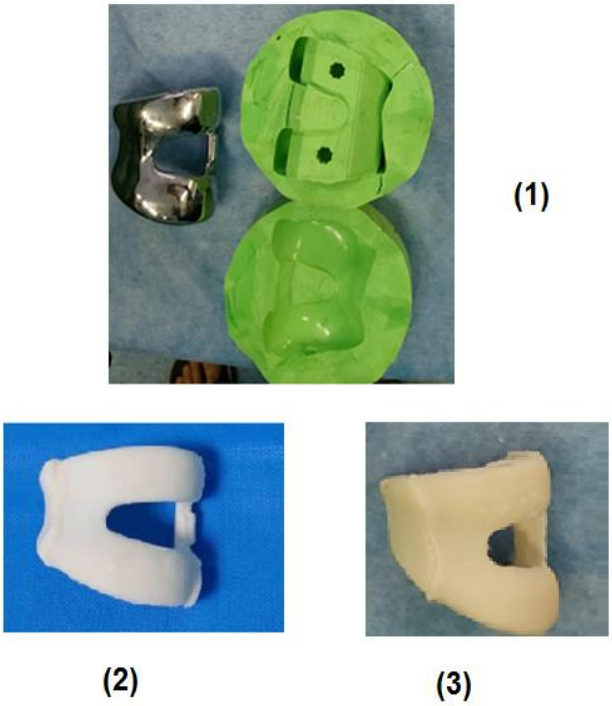

Figure 5. Size-4 ATA femoral prosthesis with its silicone mold (1), standard cement prosthesis (2), and antibiotic-loaded cement prosthesis containing additional vancomycin (3).

Table 2. Qualitative evaluation of molding performance of the reusable silicone mold.

Evaluation Parameter	Commercial Gentamicin-Loaded Cement	Developed Dual Antibiotic-Loaded Cement
Mold filling	Complete	Complete
Ease of demolding	Excellent	Excellent
Adhesion to silicone mold	None observed	None observed
Surface quality	Excellent	Excellent
Surface smoothness	Excellent	Excellent
Visible porosity	None observed	None observed
Surface defects	None observed	None observed
Incomplete filling	None observed	None observed
Dimensional fidelity	Excellent	Excellent
Anatomical reproduction	Excellent	Excellent
Suitability for fabrication of dynamic articulating spacers	Suitable	Suitable

3.6. Clinical Applicability

Repeated fabrication of femoral spacer components demonstrated excellent reproducibility of the proposed molding technique. No measurable differences in cement handling, mold filling, demolding behavior, surface quality, or final component geometry were observed among repeated fabrication cycles. The reusable silicone mold consistently produced anatomically accurate femoral spacer components with uniform surface characteristics and dimensional reproducibility, indicating that the proposed manufacturing technique may reduce operator-dependent variability commonly associated with manually fabricated antibiotic-loaded cement spacers. The proposed fabrication method closely simulated the intraoperative workflow of two-stage revision arthroplasty. The reusable sterilizable silicone mold enabled rapid production of anatomically accurate femoral spacer components while maintaining excellent moldability, dimensional accuracy, and surface quality. Overall, incorporation of 4 g of vancomycin hydrochloride into the commercially available gentamicin-loaded PMMA bone cement did not adversely affect its physicochemical, thermal, mechanical, electrical, or molding characteristics. The developed formulation preserved the handling and structural properties of the original cement while providing a reproducible manufacturing process for anatomically accurate, dynamically articulating knee spacers.

4. Discussion

The present study evaluated a dual-antibiotic-loaded polymethyl methacrylate (PMMA) bone cement for the fabrication of dynamic articulating knee spacers using a reusable silicone mold. The principal finding was that incorporation of 4 g of vancomycin hydrochloride into a commercially available gentamicin-loaded PMMA bone cement did not adversely affect its physicochemical, thermal, mechanical, electrical, or molding properties. Although the addition of vancomycin resulted in a slightly shorter setting time and a minor change in cement color, the developed formulation maintained mechanical performance comparable to that of the standard cement while potentially providing broader antimicrobial coverage. Antibiotic-loaded PMMA bone cement is widely used during two-stage revision arthroplasty because it provides temporary mechanical support while delivering high local antibiotic levels (21-23). However, increasing antibiotic content may alter polymerization behavior and reduce mechanical strength (24).

In the present study, no significant differences were observed in compressive strength, tensile strength, maximum polymerization temperature, or electrical resistance between the two formulations. These findings indicate that the investigated vancomycin concentration preserved the structural integrity of the PMMA matrix while maintaining its handling characteristics. The results are consistent with previous studies demonstrating that therapeutic concentrations of vancomycin can be incorporated into PMMA bone cement without compromising clinically acceptable mechanical properties (25). Similar observations have been reported for dual antibiotic-loaded bone cements containing aminoglycosides and vancomycin, supporting the use of combination antibiotic therapy to improve antimicrobial coverage against resistant microorganisms commonly associated with periprosthetic joint infection. A major strength of the present study is the evaluation of a reusable sterilizable silicone mold designed for fabrication of anatomically accurate dynamic femoral spacers. Unlike conventional hand-molded spacers, which are highly dependent on surgical experience, the proposed molding system consistently produced components with excellent dimensional fidelity, smooth surface quality,

and no adhesion to the mold. These findings suggest that the proposed manufacturing technique may improve the reproducibility of spacer fabrication while reducing operator-dependent variability during surgery (26).

Another important aspect of this study is the comprehensive characterization of the developed cement. In addition to mechanical properties, the present investigation evaluated thermal behavior, polymerization characteristics, electrical resistance, surface morphology, and molding performance. Such a comprehensive assessment provides a broader understanding of material behavior than studies that focus solely on antibiotic release or mechanical testing (27). Despite these promising findings, several limitations should be acknowledged. This study evaluated only the initial physicochemical and mechanical properties of the developed cement. Antibiotic release kinetics, antibacterial efficacy against clinically isolated microorganisms, fatigue behavior, wear resistance, cytocompatibility, and in vivo biological performance were not investigated. Future studies should therefore include microbiological assays, long-term elution analysis, biomechanical fatigue testing, finite element modeling, and preclinical animal studies to further validate the proposed system before clinical application (28).

5. Conclusion

This study demonstrated that incorporating vancomycin into a commercially available gentamicin-loaded PMMA bone cement produced a dual-antibiotic-loaded formulation that preserved the essential physicochemical, thermal, mechanical, and handling characteristics required for temporary articulating spacers. In combination with a reusable sterilizable silicone molding system, the developed approach enabled reproducible fabrication of anatomically accurate femoral spacer components without compromising structural integrity or molding performance. Rather than introducing only a modified bone cement, the present work proposes an integrated platform that combines material formulation, reproducible manufacturing, and comprehensive material characterization to fabricate dynamic articulating spacers. This approach has the potential to improve the consistency and practicality of temporary spacer production during two-stage revision arthroplasty while supporting broader local antimicrobial delivery. Future microbiological, biomechanical, and clinical studies are required to validate further the long-term performance and clinical translation of the proposed system.

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Conflicts of interests: The authors declare no conflicts of interest.

Consent for publication: Not applicable.

Ethics approval and consent to participate: This experimental study was approved by the Ethics Committee of North Khorasan University of Medical Sciences, Bojnurd, Iran (IR.NKUMS.REC.1403.069). The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

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