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Pharmacokinetic and biochemical properties of clindamycin compared with imipenem loaded bone cement

Ban M. ALI [1]*, Orooba M. S. IBRAHIM [2]*, Nibras N.A. ALABBAS [3]*

Department of Physiology, Biochemistry and Pharmacology, College of Veterinary Medicine, University of Baghdad, Iraq.

* Corresponding Author. E-mail: ban.manaf1206h@covm.uobaghdad.edu.iq (B.A.); Tel. +964 781 278 8878

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ABSTRACT: Bone cement is consider as a medical material used to anchor implants to bone in orthopedic and surgical procedures. It is commonly made of polymethyl methacrylate (PMMA), a biocompatible substance that provides mechanical stability. The objective of this study is to examine the elution and biomechanical properties of antibiotics-loaded bone cement. The groups of experiment include, Antibiotic-free bone cement and bone cement containing 5%, 10%, 15%, and 1% of imipenen and Clindamycin, respectively. A total of 35 specimens for compression and tensile testing were acquired. The drug concentration-time curve of imipenem (IMP) and clindamycin was constructed after the eluent drug concentration was measured at 24, 48, 72 h, and 6, 12, and 24 days. All bone cement samples surpassed the ISO 5833 standard for compressive strength (minimum 70 MPa). Clindamycin-loaded cements had higher compressive and tensile strength values compared to IMP -loaded and antibiotic-free cements, particularly at 10% and 15% drug concentrations, Clindamycin-loaded bone cement showed superior elution properties, releasing the drug more consistently over 24 days compared to IMP, which had a rapid release in the first 72 hours and a sharp decline afterward. Clindamycin demonstrated greater antibacterial potency against *Pseudomonas aeruginosa* than IMP, as shown by larger zones of inhibition in agar diffusion assays. Regarder to antibiotic elution, IMP concentrations dropped significantly after 72 hours, while clindamycin maintained a steadier release profile, offering prolonged antibacterial coverage.At the end of 24 days, clindamycin showed a threefold higher cumulative release compared to IMP. In conclusion, Clindamycin-loaded bone cement showed to be more effective than IMP in terms of sustained drug release, mechanical properties, and antibacterial activity, making it a promising choice for treating bone and joint infections.

KEYWORDS: Polymethyl methacrylate; sensitivity; imipenem; clindamycin; mechanical properties; pharmacokinetic.

1. INTRODUCTION

While total knee and complete hip replacements are sophisticated surgical procedures that are often performed worldwide, Unquestionably, one of the most dangerous side effects of total joint arthroplasty is still periprosthetic joint infection (PJI). It frequently means lengthening hospital stays, delays in patient recovery, and treatment cost. As a result of drug resistance and presence of bacterial biofilm, the treatment of peri-prosthetic joint infection is challenging and difficult [1]. The treatment of periprosthetic joint infection (PJI) varies. Debridement, antibiotics and implant retention (DAIR) may be effective treatments for early acute periprosthetic infections; but, the results of DAIR are unquestionably impacted by bacterial drug resistance [2]. Two-stage revision has gained acceptance among academics, even though one-stage revision has been shown to be a good treatment for chronic PJI and has demonstrated success in numerous medical facilities [3].

A common technique in two-stage revision is the use of cement spacers filled with antibiotics for local administration; this approach has a success rate of over 90% [4]. To prepare bone cement, Methyl-methacrylate (MMA) is the primary constituent that undergoes radical polymerization to form poly-methyl-methacrylate when bound to long chains [5[. In order to prevent an infection from spreading or to prevent germs from growing on medical equipment, polymethyl methacrylate (PMMA) bone cement is combined with antimicrobial drugs in high concentrations adjacent to the bone cement. For these antibiotics to be eluted from PMMA, they require the following physical-chemical characteristics: high water solubility,

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stability of heat during polymerization, no chemical reaction, with PMMA or polymerization mediators, little impact on the bone cement's mechanical strength, excellent release from polymerized/cured bone cement, in addition to that the biological characteristics of the antibiotics should be such that they are extremely effective against known or suspected bacterial infections and that the incidence of side effects is minimal in patients receiving local therapy with ALAC [6].

The type and quantity of antibiotic, the surface of contact, the compound's conditions, and the cement's viscosity all affect how easily the antibiotic is released from the cement [7]. Because of the polymer's nature, fluids can pass through it and the incorporated antibiotic can release. However, even if the hydrophobicity of the cement limits this release to less than 10%, the majority of the antibiotic is released in the early hours and days after surgery [8]. Periprosthetic joint infection are primarily caused by Gram-positive bacteria, but Gram-negative bacterial infections are now becoming more frequent [9]. Antibiotics added to bone cement are most likely needed to combat anaerobes, drug-resistant negative bacteria, and positive bacteria. Imipenem (IMP) is a beta-lactam agent from the carbapenem family which is slightly water soluble and presents as polydisperse crystalline particles [10]. As IMP disrupts the formation of cell walls, it has bactericidal effects on both aerobic and anaerobic Gram positive and Gram-negative bacteria, such as *Enterococcus* and *Pseudomonas aeruginosa* [11]. On the other hand, clindamycin has been used and loaded in bone cement to treat PJI as a result of his ability to diffuse well into bone, reaching good bone concentrations [12]. Theaim of this study is to evaluate the elution, mechanical properties, and antibacterial efficacy of clindamycin and IMP -loaded bone cement to enhance treatment outcomes for bone and joint infections.

2. RESULTS

2.1. Identification of *pseudomonas aeruginosa* on nutrient agar

The bacterial colonies on nutrient agar revealed smooth greenish coloration due to the release of pyoverdin dye as shown in Figure 1.

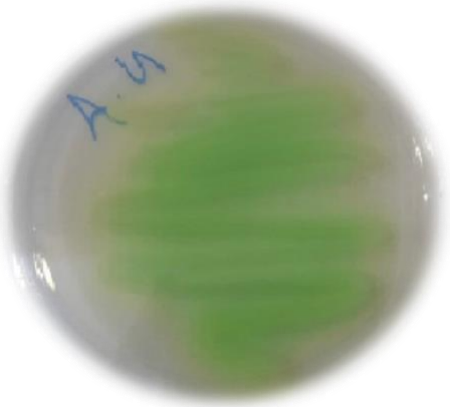

Figure 1. *Pseudomonas aeruginosa* on nutrient agar

2.2. Imipenem and Clindamycin standard curve

A range of standard solutions for Clindamycin and IMP of 10.0, 20.0, 40.0, 60.0 and 80.0 µg/ml were assayed through agar well diffusion method as illustrated in Figure 2. Different concentration of clindamycin and IMP induced zones of inhibition in varying degrees. The standard curves for IMP and clindamycin were constructed using concentrations ranging from 10–80 µg/ml to evaluate their antibacterial activity through the agar diffusion method. IMP's regression equation was with a value of 0.9958, indicating a strong linear relationship. Clindamycin's regression equation was, with a value of 0.9993, demonstrating excellent linearity. The steeper slope of clindamycin's curve suggests greater antibacterial potency, as smaller concentration changes produced larger zones of inhibition compared to IMP, highlighting clindamycin's superior effectiveness against *Pseudomonas aeruginosa* (Figure 3 and 4).

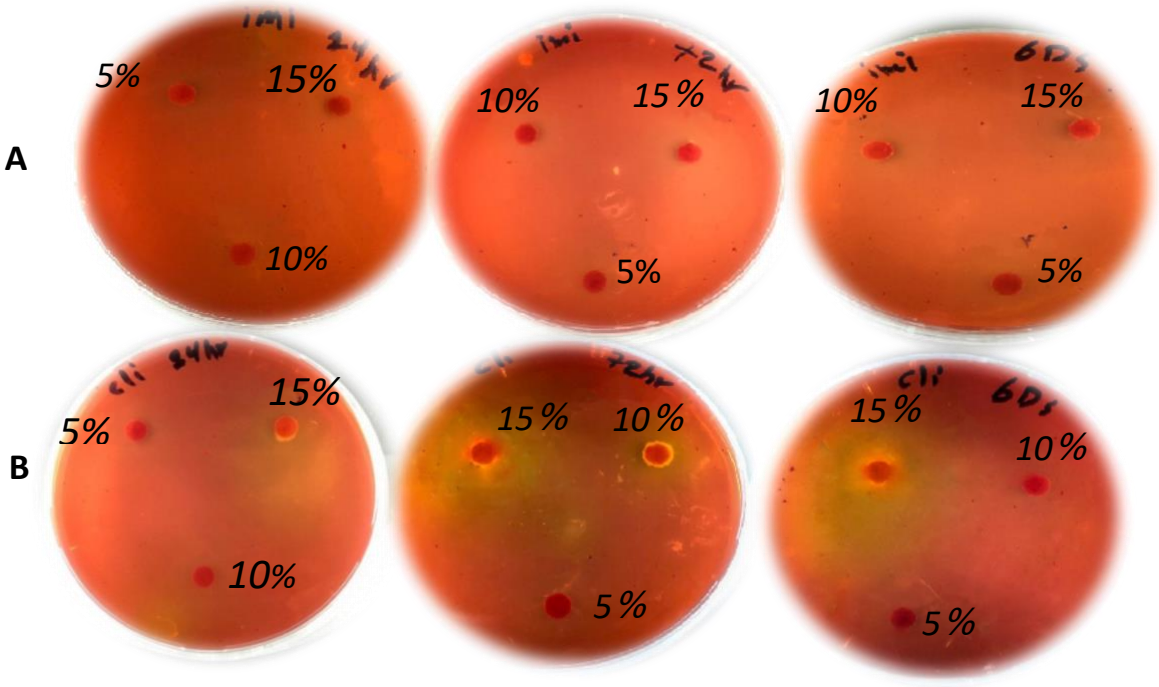

Figure 2. A. zone of inhibition of different concentrations of IMP at different times; B: zone of inhibition of different concentrations of clindamycin at different times

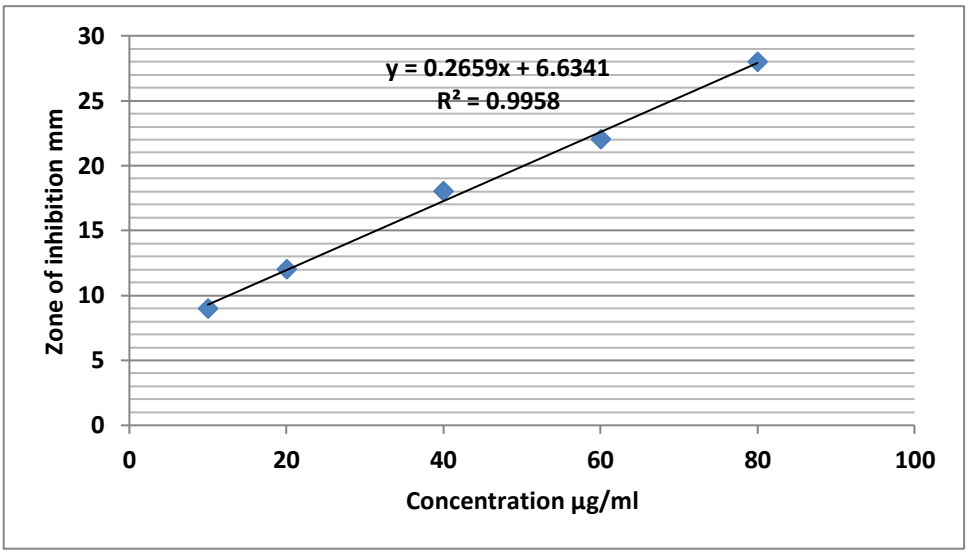

Figure 3. Standard curve of IMP

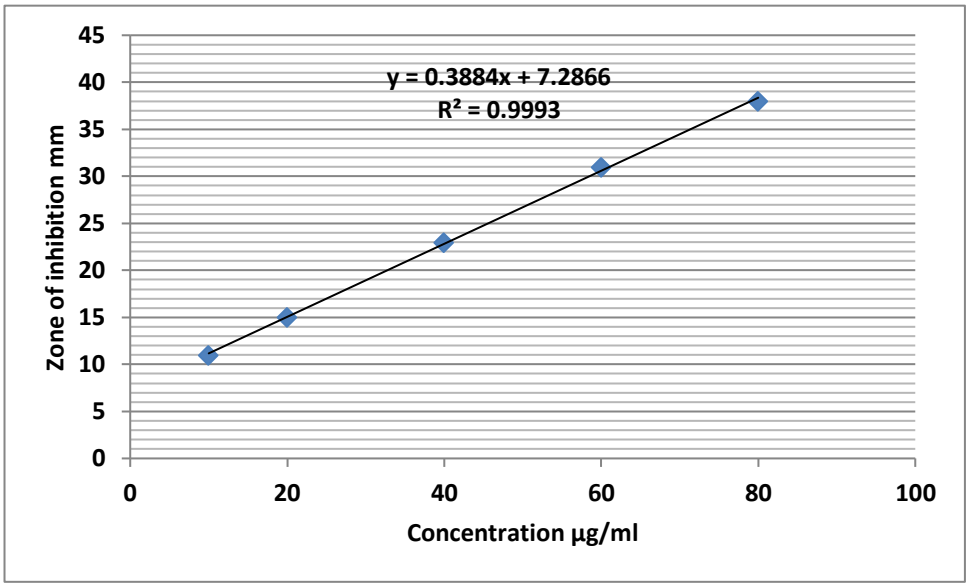

Figure 4. Standard curve of Clindamycin

2.3. Drug Concentration Elution of the Imipenem

The samples M1, M2, and M3 mean concentration of eluted IMP at 37C⁰ at various time intervals are shown in Table 1. During the first 72 hours, IMP was released quickly. IMP concentrations in samples M1, M2, and M3 started to drop after 72 hours and reached 0.49±0.43), 0.78±0.07, and 3.12 ±0.54) µg/ml, respectively, after 24 days of immersion. They kept going down throughout the rest of the trial. The elution concentration of IMP at various sampling intervals at 37Co is displayed in Figure 5.

Table 1. Elution drug concentration of imipenen (µg/mL) at 37C°

Time / days	Sample 5%	Sample 10%	Sample 15 %
1	35.84 ± 0.72	65.82 ± 0.15	98.54 ± 0.12
2	22.69 ± 0.41	35.42 ± 0.22	45.29 ± 0.17
3	9.82 ± 0.06	13.69 ± 0.31	18.78 ± 0.02
6	4.58 ± 0.07	7.59 ± 0.18	11.41 ± 0.19
12	1.67 ± 0.51	3.98 ± 0.94	7.62 ± 0.06
24	0.49 ± 0.43	0.78 ± 0.07	3.12 ± 0.54

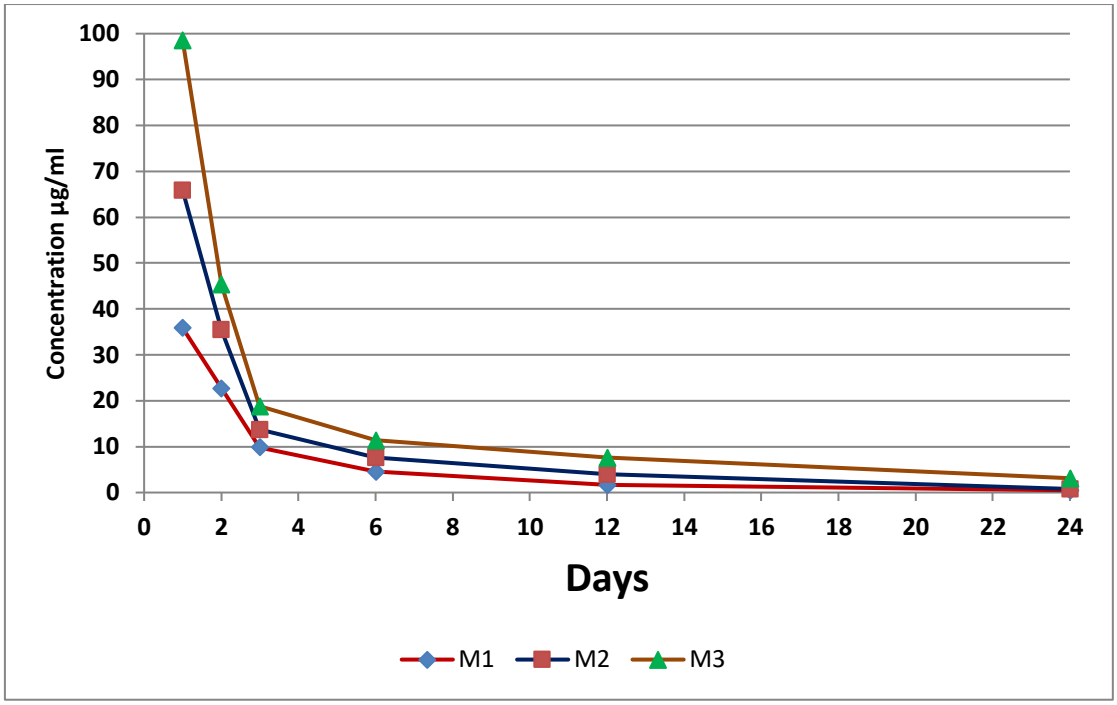

Figure 5. Drug concentration – time curve of IMP eluted from IMP – loaded bone cement samples

2.4. Drug Concentration Elution of the Clindamycin

Table 2 represents the average eluted Clindamycin concentration for samples C1, C2, and C3 at 37C^0 throughout different time intervals. Clindamycin's release was fast at the first 72 hr. After 72hr, Clindamycin concentration of samples C1, C2, C3 remained declining and reached at 24 days of immersion (0.62 ± 0.47), (1.68 ± 0.54) and (4.11 ± 0.02) µg/ml respectively, and continued to decline throughout the rest of the study time. Figure 6 displays the elution concentration of Clindamycin at various sampling periods at 37C^o.

Table 2. Clindamycin elution drug concentration (µg/mL) at 37°C

Time / days	Samples 5%	Samples 10%	Samples 15%
1	48.72 ± 0.03	72.23 ± 0.09	108.48 ± 0.18
2	29.25 ± 0.22	42.15 ± 0.19	56.27 ± 0.08
3	12.92 ± 0.15	23.84 ± 0.04	33.79 ± 0.09
6	6.58 ± 0.11	12.35 ± 0.16	16.21 ± 0.48
12	1.88 ± 0.52	7.87 ± 0.87	11.82 ± 0.25
24	0.62 ± 0.47	1.68 ± 0.54	4.11 ± 0.02

2.5. Compression strength and tensile strength of bone cement

The bone cement exhibited a notably high compressive strength, registering an impressive result ranging between (80-98 MPa) in the conducted compression test. This strong performance indicates the material's remarkable ability to withstand and resist axial stresses under compression, which was exceeding the minimum criterion of ISO 5883 [70 MPa]. While, the tensile test was determined to be between the range 25-34 MPa, this test measure the ability of material to withstand pulling forces without breaking or fracturing. Table 3.

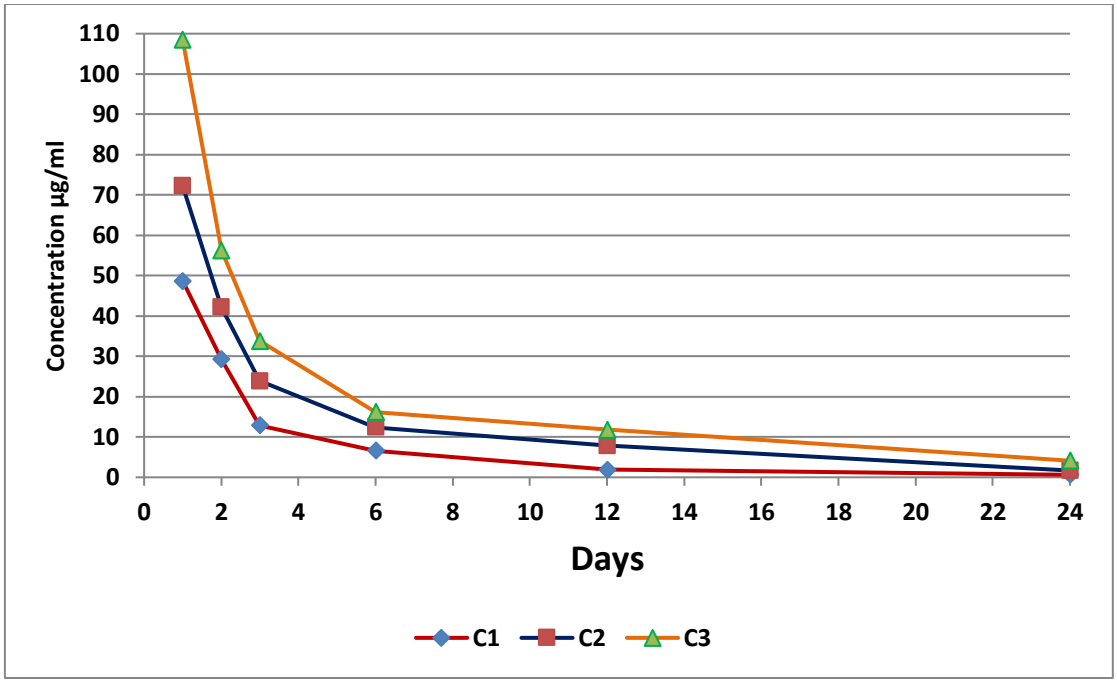

Figure 6. Drug concentration – time curve of Clindamycin eluted from Clindamycin – loaded bone cement samples

Table 3. Compressive strength and tensile strength estimates (MPa) of all Designed antibiotic-loaded bone cement samples.

Antibiotic-loaded cement sample	Compressive test	Tensile test
C0	80 ± 3.7 de	25 ±1.3 c
Bone-cement loaded with 5% IMP **(Im5%)**	73 ±2.6 e	20 ±0.87 d
Bone-cement loaded with 10% IMP **(Im10%)**	85 ±3.7 cd	24 ±1.7 cd
Bone-cement loaded with 10% IMP **(Im15%)**	89 ±4.1 c	28 ±1.5 bc
Bone –cement loaded with 5% Clindamycin (CL5%)	90 ±3.8 bc	25 ±1.2 c
Bone –cement loaded with 10% Clindamycin (CL10%)	102 ±6.2 a	32 ±2.3 a
Bone –cement loaded with 15% Clindamycin (CL15%)	98 ±4.8 ab	34 ±2.6 a
LSD value	8.029 *	4.913 *

Means having different letters in same column differed significantly, * (P≤0.05).

3. DISCUSSION

With tests conducted under physiological conditions, the current study aimed to demonstrate how the concentration, characteristics, and kind of antibiotic added to cement affect antibiotic release, the fluid uptake process, and the mechanical properties of bone cement. Numerous studies have been conducted on the release of antibiotics from bone cement and the factors, such as antibiotic quantity and type, have an influence on the antibiotic efficacy, the porosity of the cement, the environment, or cement preparation [13,14]. The selection of antibiotics was based on their inexpensive cost, broad availability, frequent application in infections of prosthetic joints, and biochemical profiles with varying molecular weights and solubilities [15].

First proposed the idea of using antibiotic-loaded bone cement to administer antibiotics locally in 1970 [16]. A member of the carbapenem family, IMP has a broad spectrum of bactericidal activity. Its broad spectrum of in vitro activity makes it efficient against a variety of Gram-negative infections, such as those that produce extended-spectrum beta-lactamase (ESBL) and Enterobacteriaceae that produce ampicillin [17]. Although the antibiotic clindamycin, a semi-synthetic lincosamide, is used to treat a number of serious infections brought on by both gram positive and gram-negative microbes [18]. According to our research, imipenem elutes from bone cement at pharmacologically detectable concentrations over a period of one to twenty-four days, depending on the amount of antibiotic injected. A thorough description of the features of antibiotic elution from bone cement has been provided; it exhibits a quick initial release that diminishes

exponentially with time [19]. In comparison to the group receiving the same dosage of imipenem, the group receiving clindamycin saw somewhat higher release within the first 24 hours, when the same amount of antibiotic was given, the total clindamycin eluted after 24 days was more than three times higher in the groups who received imipenem than in the non-imipenem groups, the fact that both medications behaved differently after 24 hours and 24 days was a significant finding. After 24 hours, the imipenem groups displayed very little antibiotic elution. In contrast, the clindamycin group's elution was more persistent over time and had a noticeably higher cumulative release up to 24 days [20]. Because clindamycin has a higher bioavailability and better diffusion in bone tissue than imipenem, it has a more effective effect on bacteria and may be a viable alternative antibiotic for the treatment of infections in the bones and joints [21]. The results demonstrated a notable discrepancy in their antimicrobial activities. Clindamycin exhibited a larger inhibition zone compared to imipenem, indicative of its heightened potency against *Pseudomonas aeruginosa* strains under investigation. The larger inhibition zone implies a greater capacity to inhibit bacterial growth. These findings strongly suggest that clindamycin may be a more effective treatment option against *Pseudomonas aeruginosa*. For the biomechanical properties of bone cement, compression and tensile strength have been done, the compression test is the easiest to control accurately, and has been used as a basis for comparing strengths of the various cements [22]. While the tensile test refers to its ability to withstand loads that tend to elongate or stretch it [23]. PMMA bone cement exhibits a compressive strength that surpasses its tensile strength. Thus, the evaluation of this arrangement was noted in numerous polymer studies. This indicates that, in comparison to compressive loading, tensile loading may be regarded as an observed risk aspect for failure [24]. The compressive strength and tensile strength of bone cement vary from 78 to 96 MPa and 20 to 35 MPa, respectively, and as biomaterials are intended to serve as substitutes to bone, it is crucial to refer to many research with referenced values [25].

4. CONCLUSION

In conclusion, the antibiotic-loaded bone cement exhibited greater efficacy than antibiotics alone. Potent and locally delivered antibiotic- eluting polymers may assist against antimicrobial resistance. In addition, these *in vitro* investigations represented the superior biomechanical qualities of clindamycin-loaded bone cement compared to imipenem. Clindamycin may be released from bone cement for up to 24 days at a steady 37 ^{o}C.

5. MATERIALS AND METHODS

5.1. Materials

5.1.1. Polymethyl Methacrylate

Commercial polymethyl- methacrylate bone cement, consisting of 40g powder and 20 ml liquid, was selected as both the antibiotic admixture's base and as a control.

5.1.2. Antibiotics

The impact of Imipenen (Kabi) and Clindamycin (Vitapure), two commercial drugs, on the mechanical properties of PMMA bone cement were studied. Following that, the elution properties of bone cement loaded with antibiotics were examined. The antibiotic-loaded cement was made by combining PMMA powder and Imipenen, also known as cindamycin powder, using a mixer for two minutes under aseptic circumstances. PMMA liquid was then added. A temperature of 25±1C and a humidity of 40% to 60% were used to mix the components equally.

5.2. Grouping

Investigations were conducted on seven formulations: Control, C: free-antibiotics bone cement. Bone-cement loaded with 5% imipenem (2 gm/ 40 gm); Bone- cement loaded with 10% imipenem (4 gm/40 gm); Bone -cement loaded with 15% imipenem (6 gm/40 gm); Bone –cement loaded with 5% Clindamycin (2 gm/40 gm); Bone- cement loaded with 10% Clindamycin (4 gm/40 gm); and Bone- cement loaded with 15% Clindamycin.

5.3. Standard Curve of Imipenem and Clindamycin

Imipenem and Clindamycin standard solutions were made in increments of 0.0, 10.0, 20.0, 40.0, 60.0, and 80.0 µg/ml. The standard solutions' peak regions were quantitatively measured. The standard curve was constructed by using linear regression analysis to examine the drug concentrations and peak regions.

5.4. Antibiotic-Loaded Bone Cement Elution Specimens and Sampling

For every group of 5%, 10%, and 15% for Imipenem and 5%, 10%, and 15% for Clindamycin, Six-cylindrical specimens, each measuring 12 mm in diameter and 17 mm in length, were molded in sterile settings at a consistent 37 ^{o}C. After that, each group's specimens were individually placed, without stirring, in sterile containers with 100 mL of saline solution. One, two, three, six, twelve-, and twenty-four-days following immersion were sampled. 1.5 milliliters of the solution were taken out of the container and subjected to an agar well diffusion method analysis after it had been on a magnetic stirrer for a minute prior to sampling. Following the separate, rinse by using saline solution (10 ml), the specimens were submerged in 100 mL of saline solution in sterile containers.

5.5. Detection of Antibiotic- loaded Bone Cement

To evaluate the antibiotic activity of the produced specimens, the agar diffusion assay was used **[26].** Using the Standard McFarland solution No.0.5, the volume of 5 milliliters of standardized bacterial stock suspensions was calculated. *Pseudomonas aeruginosa* (1.5×10^8 cfu/ml) was well mixed with 500 ml of sterile Mueller Hinton agar. Each sterile Petri dish received 25 ml of the inoculated Mueller Hinton agar. The agar was allowed to solidify for ten minutes. There were five discs in each of these plates, and the agar discs were removed using sterile forceps. Next, the discs were filled with 0.1 ml of each concentration of all samples using a micro-titer pipette, and they were left to diffuse at room temperature for two hours.

The samples in the discs were then incubated for 24 hours at 37oC with the plates in the upright position. For every concentration sample, three duplicates were used, and the activity was measured by comparing the diameter of the inhibitory zone surrounding each well to the tested organism in millimeters. As controls, the appropriate solvent (distilled water) was added concurrently with the sample. Values for the standard errors and results were tabulated.

5.6. Specimens for Biomechanical Tests

Five specimens were molded for every formulation. Specimens were created by molding. For each of the seven groups, a total of 35 specimens for compression and tensile testing were acquired. The specimens were 12-mm-tall and 6-mm-diameter cylinders. Following testing, due to mechanical characteristics that don't meet ISO standard requirements.

5.7. Compression strength and tensile test

Crushing and tensile tester machines that illustrated in Figure 7 were used to perform the compression and tensile testing. Five specimens were evaluated for each formulation and test type. Plus, compressive and tensile strength averages were calculated. Compression strength is the maximum compression that a material can withstand per unit area without failing under normal temperature conditions. Typically, it is given as MPa, or N/mm2. ISO 5833 states that bone cement should have a compressive strength of at least 70 MPa and a tensile strength of between 20 and 35 MPa [24].

Figure 7. A; Crush tester for bone cement. B; Tensile tester

5.8. Statistical analysis

The statistical analysis involved linear regression for the standard curves of imipenem and clindamycin, confirming strong linearity for accurate antibiotic quantification. Elution profiles were analyzed using mean and standard deviation, showing significant differences in release patterns, with clindamycin exhibiting higher cumulative release over 24 days. ANOVA revealed statistically significant differences in compressive and tensile strength among groups, with clindamycin-loaded cements (10% and 15%) showing superior mechanical properties compared to imipenem-loaded and antibiotic-free cements. All the statistical analysis were performed using SPSS 26 and the difference between groups were determined using ANOVA test with LSD post hoc test to assess the multiple comparisons between all studied groups considereng $p<0.05$ as a significant difference [27,28].

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