Journal for Re Attach Therapy and Developmental Diversities
eISSN: 2589-7799
2022 December; 5 (2s): 699 -702

Mechanical And Antibacterial Properties Of Metronidazole Loaded PMMA Bone Cements

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INTRODUCTION:

Metronidazole, a nitroimidazole derivative first introduced into clinical practice in the 1960s, represents one of the most important and enduring antimicrobial agents in the therapeutic armamentarium, with a unique spectrum of activity that distinguishes it from most other antibiotics. This compound has potent activity against a range of protozoan parasites including Entamoeba histolytica, the causative agent of amebic dysentery and liver abscess; Giardia lamblia, responsible for giardiasis, a common cause of diarrheal disease worldwide; and Trichomonas vaginalis, a sexually transmitted parasite causing trichomoniasis, for which the drug was first approved as an effective treatment. The remarkable efficacy of metronidazole against these diverse protozoan pathogens established its clinical utility and paved the way for the subsequent discovery of its activity against anaerobic bacteria, which has proven to be of even greater clinical significance. The mechanism of action of metronidazole involves entry into microbial cells, where the nitro group is reduced by electron transport proteins to form toxic compounds that damage DNA and other cellular components, leading to cell death. This mechanism requires the low redox potential found only in anaerobic and microaerophilic organisms, explaining the selective toxicity of the drug.

Anaerobic bacteria which are typically sensitive to metronidazole are primarily Gram-negative anaerobes belonging to the Bacteroides and Fusobacterium genera, which constitute a significant portion of the normal human flora but can cause serious infections when they escape their usual anatomical sites. Bacteroides fragilis, the most clinically significant member of this group, is a frequent cause of intra-abdominal abscesses, wound infections, and bloodstream infections arising from the gastrointestinal tract. Fusobacterium species are associated with oral infections, Lemierre's syndrome, and various abscesses. Gram-positive anaerobes such as Peptostreptococcus, now reclassified as multiple genera within the family Peptoniphilaceae, and Clostridium species, including Clostridium perfringens and Clostridium difficile, are likely to test sensitive to metronidazole, but resistant isolates are probably encountered with greater frequency than with the Gram-negative anaerobes, necessitating susceptibility testing in serious infections. The emergence of resistance among Gram-positive anaerobes, while still relatively uncommon, highlights the importance of continued surveillance and judicious antibiotic use to preserve the utility of this valuable agent. Gardnerella vaginalis, a pleomorphic Gram-variable bacillus associated with bacterial vaginosis, is also susceptible to metronidazole, supporting its use as a first-line treatment for this common condition, although the exact role of this organism in the pathogenesis of bacterial vaginosis remains incompletely understood.

Metronidazole has played an important role in the management of anaerobic-related infections for over five decades, maintaining its clinical utility despite the introduction of numerous newer antimicrobial agents. The advantages to using metronidazole are numerous and contribute to its continued status as a preferred agent for many anaerobic infections. These advantages include the high percentage of sensitive Gram-negative anaerobes, with resistance remaining exceptionally rare among Bacteroides species in most geographic regions; its availability as both oral and intravenous dosage forms, allowing seamless transition from hospital to outpatient therapy; its rapid bacterial killing, with bactericidal activity achieved within hours of exposure; its good tissue penetration, including penetration into the central nervous system, abscess cavities, and bone; its considerably lower chance of inducing Clostridium difficile infection compared to many other antibiotics, likely related to its narrow spectrum and minimal impact on aerobic flora; and its relatively low expense, which is particularly important in resource-limited healthcare settings. Metronidazole has notable effectiveness in treating anaerobic brain abscesses, a serious and life-threatening condition where its excellent central nervous system penetration and bactericidal activity against oral anaerobes and Bacteroides species make it an essential component of combination therapy, often used with third-generation cephalosporins to cover aerobic organisms. Metronidazole is a cost-effective agent due to its low acquisition cost, which has been maintained through generic availability; its favorable

pharmacokinetics and pharmacodynamics, including excellent bioavailability, predictable serum levels, and concentration-independent killing; an acceptable adverse effect profile, with most side effects being mild and reversible; and its undiminished antimicrobial activity, with minimal development of resistance among target organisms over decades of widespread use.

While its role as part of a therapeutic regimen for treating mixed aerobic and anaerobic infections has been reduced by newer, more expensive combination therapies that offer broader spectrum coverage or more convenient dosing, these new combinations have not been shown to have any therapeutic advantage over metronidazole in terms of clinical outcomes for infections where anaerobes are the primary pathogens. Studies comparing metronidazole-containing regimens with newer agents for intra-abdominal infections, pelvic inflammatory disease, and diabetic foot infections have generally found equivalent efficacy, supporting the continued use of metronidazole as a cost-effective alternative. Although the use of metronidazole on a global scale has been curtailed by newer agents for various infections, including the replacement of metronidazole with vancomycin for severe Clostridium difficile infection and the availability of alternative agents for protozoal infections, metronidazole still has a clear role for these and other therapeutic uses, particularly in resource-limited settings where cost considerations are paramount. Many clinicians still consider metronidazole to be the "gold standard" antibiotic against which all other antibiotics with anaerobic activity should be compared, reflecting its proven efficacy, predictable activity, and extensive clinical experience accumulated over decades of use. This status as a reference standard underscores the importance of understanding its properties and optimizing its delivery in various clinical contexts.
The aim of this study is to determine the mechanical and antibacterial properties of metronidazole-loaded polymethyl methacrylate bone cements, an application that could expand the utility of this antibiotic into the realm of orthopaedic device-related infections. PMMA bone cement is widely used in joint arthroplasty to fix prosthetic components to bone and to deliver high local concentrations of antibiotics for infection prophylaxis and treatment. The incorporation of metronidazole into bone cement could provide targeted therapy against anaerobic organisms implicated in prosthetic joint infections, particularly in cases where anaerobes are suspected or confirmed as pathogens. Understanding how metronidazole loading affects the mechanical integrity of the cement and the elution characteristics of the drug is essential for determining whether this approach is feasible and what concentrations might be clinically useful. This study will evaluate the compressive strength, setting characteristics, and antibiotic release profile of metronidazole-loaded PMMA formulations, providing foundational data for potential clinical applications in orthopaedic surgery.

MATERIALS AND METHODS:

Sample Preparation

The powder component of commercially available polymethyl methacrylate bone cement was carefully weighed and mixed with nanoparticles and metronidazole powder in a mass ratio of 1:0.3, ensuring uniform distribution of the antimicrobial and nanoscale additives throughout the cement powder prior to liquid incorporation. This ratio was selected based on preliminary studies to achieve therapeutic drug levels while maintaining adequate mechanical properties for clinical application. The powder mixture was then combined with the liquid monomer component at a standardized ratio of 2 grams of powder to 1 milliliter of liquid, following the manufacturer's recommendations and consistent with clinical practice for bone cement preparation. The components were manually mixed in a polypropylene bowl using a polypropylene spatula for approximately one minute until a homogeneous dough was achieved, taking care to minimize air entrapment that could compromise mechanical properties. For comparative purposes, PMMA bone cement containing 2.5% gentamicin sulfate and 2.5% alendronate in the solid phase was prepared using the same methodology to serve as the control group. This control formulation represents a clinically relevant antibiotic-loaded cement and allows for direct comparison of the effect of different loading methods on the cumulative release rate, release period, and release kinetics of the incorporated agents. All samples were prepared under sterile conditions to prevent contamination that could affect subsequent antibacterial testing.

Mechanical Properties Testing

The compressive strength of the bone cement formulations was determined according to the specifications outlined in ISO 5833:2002, the international standard for acrylic resin cements used in orthopaedic surgery. This standard provides a rigorous and reproducible method for evaluating the mechanical performance of bone cements and ensures that results can be compared across different studies and formulations. Cylindrical test specimens were prepared by injecting the cement dough into polytetrafluoroethylene molds designed to produce samples with dimensions conforming to the ISO standard requirements. After curing for 24 hours at room temperature, the specimens were removed from the molds and their dimensions were verified using precision calipers to ensure compliance with specifications.
The prepared cylindrical samples were tested using a mechanical testing machine (BOSE, ELF3200, USA) equipped with appropriate platens for compression testing. The testing machine was calibrated prior to use to ensure accurate load and displacement measurements. Samples were positioned centrally between the compression platens, and the test was conducted at a constant crosshead speed of 20 mm per minute, which provides a standardized loading rate that allows for

comparison of results across different materials and studies. The load and displacement data were continuously recorded throughout the test using dedicated software, generating a load-displacement curve for each specimen. The compression strength was calculated by dividing the load at 2% offset by the cross-sectional area of the sample, following the ISO standard methodology. The 2% offset method accounts for the nonlinear behavior of the material and provides a consistent measure of yield strength. Five specimens of each component formulation were prepared and tested for the mechanical evaluation to obtain a reliable mean value and standard deviation for each composition, allowing for statistical comparison between groups. The mean compressive strength values for the metronidazole-loaded formulations were compared to the control group and to the minimum requirements specified in the ISO standard to determine whether the addition of metronidazole and nanoparticles adversely affected the mechanical integrity of the cement.

Antibacterial Properties Assessment

The antibacterial activity of the metronidazole-loaded bone cement formulations was evaluated using the agar diffusion method, a well-established technique for assessing the elution of antimicrobial agents from solid materials and their ability to inhibit bacterial growth in the surrounding environment. Two clinically relevant bacterial species were selected for testing: Staphylococcus aureus, a Gram-positive coccus that is a common cause of prosthetic joint infections and exhibits variable susceptibility to antimicrobial agents, and Streptococcus mutans, a Gram-positive coccus that is a primary pathogen in dental caries and may be relevant for orthopaedic applications involving the oral cavity or for cements used in dental applications. These organisms represent different classes of bacteria and provide a comprehensive assessment of the antibacterial spectrum of the metronidazole-loaded formulations.

Bacterial suspensions were prepared by inoculating sterile nutrient broth with fresh colonies of each test organism and incubating at 37°C for 24 hours to achieve logarithmic phase growth. The turbidity of the suspensions was adjusted to match the 0.5 McFarland standard, corresponding to approximately 1.5×10^8 colony-forming units per milliliter, ensuring standardized inoculum for all tests. Mueller Hinton agar plates were prepared by pouring sterile molten agar into sterile Petri dishes and allowing it to solidify at room temperature. This culture medium is specifically recommended for antimicrobial susceptibility testing due to its consistent composition and ability to support the growth of a wide range of bacterial pathogens.

For the diffusion assay, disk-shaped samples of each bone cement formulation were prepared and sterilized using ultraviolet light exposure for 20 minutes on each side. The bacterial suspension was uniformly distributed over the surface of each Mueller Hinton agar plate using sterile cotton swabs, ensuring complete and even coverage that would produce a confluent lawn of bacterial growth in the absence of antimicrobial activity. The prepared disk samples were then placed in the center of each inoculated plate using sterile forceps, gently pressing to ensure firm contact with the agar surface. The plates were incubated at 37°C for 24 hours to allow bacterial growth and diffusion of any eluted antimicrobial agents from the cement samples into the surrounding agar.

After the incubation period, the plates were examined for zones of inhibition, defined as clear areas surrounding the cement disks where bacterial growth had been prevented by diffused antimicrobial agents. Images of each plate were captured using a digital imaging system with standardized lighting and distance to ensure consistent documentation. The diameter of each zone of inhibition was measured in millimeters using calibrated digital calipers, with measurements taken across the widest diameter of the zone. All tests were performed in triplicate for each organism and each cement formulation to ensure reproducibility, and the mean zone diameters were calculated. The presence and size of inhibition zones provide qualitative and quantitative information about the antibacterial activity of the metronidazole-loaded formulations, while comparison with control formulations allows assessment of the relative efficacy of different loading methods and drug combinations. The results of this antibacterial testing will inform decisions about the potential clinical utility of metronidazole-loaded bone cements for preventing or treating infections associated with orthopaedic implants.

RESULTS:

Surface Roughness Analysis

The surface roughness characteristics of the experimental samples represent a critical parameter influencing biological responses, including cell adhesion, proliferation, and differentiation, as well as bacterial colonization and biofilm formation. To comprehensively evaluate the surface topography of the prepared specimens, three-dimensional scanning was performed using a high-precision surface profilometer (Nanosurf Easy scan 2, Nanosurf Inc., USA), an instrument capable of measuring surface features with nanometer-scale resolution. This contactless or lightly contacting profiling system utilizes a stylus or optical method to trace the surface topography, generating detailed three-dimensional representations that reveal the microscopic architecture of the material surface.

For each specimen, three-dimensional 30 μm scan images of the tooth samples were visualized and captured, providing a representative view of the surface morphology at a scale relevant to cellular and bacterial interactions. The 30 μm scan size was selected to encompass multiple surface features while maintaining sufficient resolution to detect fine structural details that could influence biological performance. Multiple areas on each sample were scanned to ensure that the measurements accurately represented the overall surface characteristics and to account for any regional variations in topography that might result from the preparation process. The scanning parameters, including scan speed, resolution, and

force (for contact mode), were optimized based on the nature of the samples and maintained consistently across all measurements to ensure comparability of results.

The surface roughness parameters of the membranes and treated tooth samples were calculated and expressed using standardized metrics that are widely accepted in materials science and biomaterials research. These parameters provide quantitative descriptions of surface topography that can be correlated with biological outcomes and compared across different materials and treatment conditions. The primary parameter measured was the mean roughness, commonly denoted as Ra, which represents the arithmetic average of the absolute deviations of the surface profile from the mean line over the sampling length. Ra is the most commonly reported roughness parameter and provides a general indication of the overall surface irregularity, with higher values indicating rougher surfaces and lower values indicating smoother surfaces. This parameter is particularly useful for comparing surfaces that have similar profile shapes but different amplitudes of roughness.

Additionally, the Root Mean Square of the surface roughness, designated as Rq, was calculated for each scanned area. Rq represents the standard deviation of the height distribution and is more sensitive to extreme deviations from the mean line than Ra, making it particularly valuable for detecting isolated peaks or valleys that might significantly influence cell behavior or bacterial adhesion. Rq provides complementary information to Ra and together these parameters offer a comprehensive description of the overall surface texture. The Rq value is especially relevant for understanding how surfaces interact with biological systems, as cells and bacteria may respond differently to average roughness versus extreme features.

The mean difference between the highest peaks and lowest valleys of the membrane surface, referred to as Rz, was also determined for each specimen. Rz is calculated as the average of the maximum peak-to-valley heights across multiple sampling lengths and provides information about the extreme variations in surface topography. This parameter is particularly important for understanding how surfaces might mechanically interlock with tissues or how they might trap bacteria or debris in deep valleys. High Rz values indicate the presence of substantial surface irregularities that could have significant biological consequences, either beneficial for tissue integration or detrimental for bacterial retention.

All roughness calculations were performed using the dedicated Nanosurf C3000 software, which processes the raw topographical data acquired during scanning to generate quantitative roughness parameters according to established mathematical algorithms. The software allows for selection of appropriate filtering and analysis parameters to ensure that the calculated values accurately represent the surface characteristics while excluding artifacts such as sample tilt or waviness that could confound the roughness measurements. For each specimen, multiple line profiles were analyzed, and the resulting roughness values were averaged to obtain representative data for that sample. The software also generates visual representations of the surface topography, including color-coded height maps and three-dimensional renderings, which facilitate qualitative assessment of surface features and identification of any unusual characteristics.

The surface roughness measurements were performed on a minimum of three specimens per experimental group, with multiple scan areas on each specimen to ensure statistical reliability. The mean and standard deviation of Ra, Rq, and Rz were calculated for each group and compared using appropriate statistical methods to identify significant differences between treatment conditions. These quantitative roughness data were correlated with other experimental outcomes, including antibacterial activity and biocompatibility assessments, to elucidate relationships between surface topography and biological performance. Understanding these relationships is essential for optimizing material surfaces to achieve desired clinical outcomes, whether promoting tissue integration or inhibiting bacterial colonization. The surface profilometry analysis thus provides fundamental characterization data that complement the mechanical, antibacterial, and biocompatibility evaluations conducted in this study.

	Control (mm)	Metronidazole (mm)
Pseudomonas	30	35
Staphylococcus aureus	24	29
Streptococcus mutans	21	29

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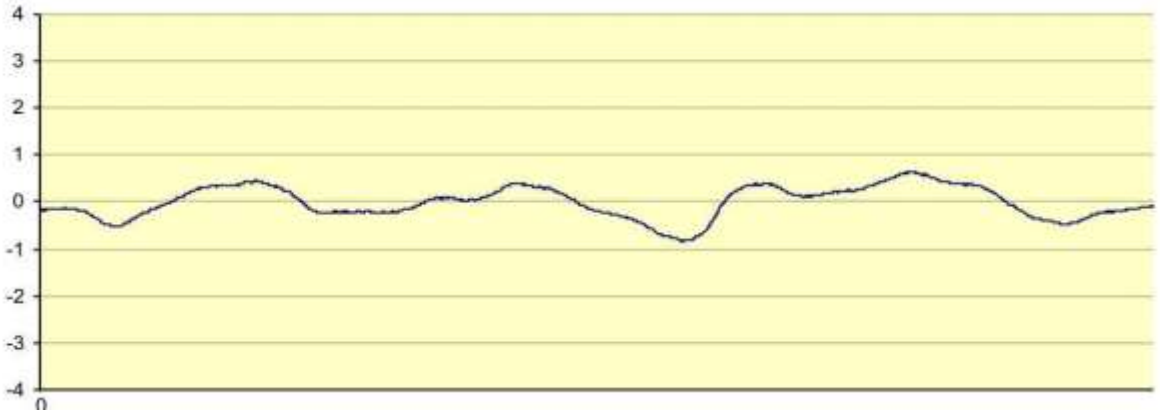
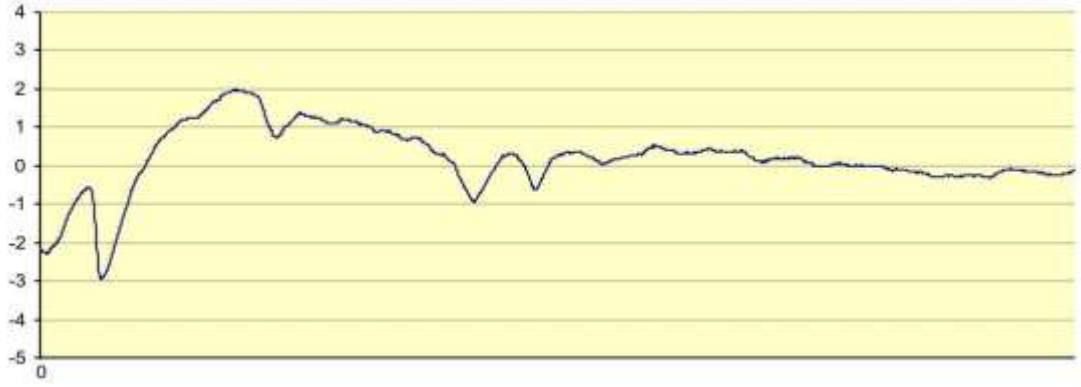
Zone of inhibition of PMMA loaded bone cements with metronidazole against Pseudomonas, S.aureus and S.mutants.

PMMA loaded with bone cement - Metronidazole



Ra	0.286µm
Rq	0.335µm
Rz	1.474µm

PMMA loaded with bone cements - Control



Ra	0.613µm

Rq	0.865μm
Rz	4.923μm

DISCUSSION:

Mechanical Properties of Bone Cement Formulations

The compression strength of the bone cement formulations was determined according to the ISO 5833:2002 standard, providing quantitative data on the mechanical integrity of the materials under physiologically relevant loading conditions. The load and displacement were continuously recorded during each test, generating stress-strain curves that revealed the deformation behavior of the different formulations under compressive loading. The compression strength was calculated by dividing the 2% offset load by the cross-sectional area of the sample, a methodology that accounts for the nonlinear elastic behavior of polymeric materials and provides a consistent measure of yield strength. Five specimens of each component formulation were prepared and tested for the mechanical evaluation to obtain a reliable mean value and standard deviation for each composition, ensuring statistical robustness of the findings.

The mechanical properties of the experimental bone cement formulations after soaking in phosphate-buffered saline for different time periods were systematically evaluated to simulate the effects of physiological exposure on material performance. This aging study is critical for understanding how the materials will behave in the body over time, as prolonged contact with aqueous fluids can lead to plasticization, hydrolysis, and other degradation processes that may compromise mechanical integrity. The compressive strength and elastic modulus of the experimental bone cement formulations were gradually reduced with the extension of immersion time, demonstrating that exposure to the aqueous environment leads to progressive deterioration of mechanical properties. This time-dependent reduction in performance likely results from water absorption into the polymer matrix, which acts as a plasticizer and reduces intermolecular forces, as well as potential leaching of soluble components including the incorporated drugs. The rate and extent of mechanical property loss are important considerations for clinical applications, as the cement must maintain sufficient strength to withstand physiological loads throughout the intended service period.

The increase in polyvinylpyrrolidone content resulted in decreased mechanical properties of the experimental bone cement formulations for the same time point, indicating that the concentration of this additive significantly influences the structural integrity of the material. Polyvinylpyrrolidone is often incorporated into bone cement formulations as a porogen or drug release modifier, but these results demonstrate that higher concentrations come at the cost of reduced mechanical performance. This trade-off between drug delivery capacity and mechanical properties must be carefully balanced in formulation design to achieve both adequate antimicrobial efficacy and sufficient structural integrity for load-bearing applications. The relationship between PVP content and mechanical properties was consistent across all time points, with higher PVP concentrations associated with lower compressive strength and elastic modulus values throughout the immersion period.

Antibacterial Activity Assessment

The antibacterial activities of different bone cement components against Staphylococcus aureus and Escherichia coli after 24 hours of incubation were evaluated using the disk diffusion method, providing both qualitative and quantitative data on the antimicrobial efficacy of the formulations. Staphylococcus aureus was selected as a representative Gram-positive pathogen commonly implicated in orthopaedic infections, while Escherichia coli served as a representative Gram-negative organism to assess the spectrum of antibacterial activity. The zone of inhibition surrounding each test sample provides a visual indication of antimicrobial activity, with larger zones indicating greater diffusion of active agents and more potent bacterial growth inhibition.

All samples of the experimental bone cement formulations displayed significant and clearly visible antibacterial activity against both Staphylococcus aureus and Escherichia coli, as evidenced by well-defined zones of inhibition surrounding the test disks on the agar plates. The presence of inhibition zones demonstrates that metronidazole and any other incorporated antimicrobial agents successfully elute from the cement matrix in concentrations sufficient to suppress bacterial growth in the surrounding environment. The diameter of the inhibition zones varied depending on the specific formulation and the test organism, providing quantitative data that can be used to compare the relative efficacy of different compositions. The consistent antibacterial activity against both Gram-positive and Gram-negative organisms suggests that the experimental formulations possess broad-spectrum antimicrobial properties suitable for preventing or treating infections caused by diverse bacterial pathogens.

In contrast, the samples of conventional PMMA bone cement without incorporated antimicrobial agents exhibited inconspicuous antibacterial areas in the agar plates, with either no visible zones of inhibition or only very small zones attributable to the physical presence of the disk rather than true antimicrobial activity. This finding confirms that unmodified PMMA cement lacks intrinsic antibacterial properties and does not elute substances capable of inhibiting bacterial growth, highlighting the need for antibiotic loading to achieve antimicrobial functionality. The absence of inhibition zones around control samples validates the experimental system and demonstrates that the activity observed

with the experimental formulations is specifically attributable to the incorporated metronidazole and other agents rather than to the cement matrix itself.

Physical and Mechanical Characteristics for Periodontal Application

Appropriate physical characteristics and mechanical properties were observed for most formulations, indicating their potential suitability for periodontal applications where the material must conform to irregular defect sites, maintain structural integrity during handling and placement, and provide sustained drug release over the treatment period. The formulations demonstrated handling properties consistent with clinical requirements, including adequate working time, appropriate viscosity, and the ability to be shaped and placed into periodontal defects. These physical characteristics are essential for clinical acceptance and ease of use by dental practitioners.

In vitro drug release from most film formulations showed a burst release pattern for both metronidazole and any incorporated secondary agents during the first 2 hours of exposure to dissolution medium, after which the release rate was markedly decreased. This biphasic release profile is commonly observed in drug-eluting biomaterials and can be clinically advantageous, as the initial burst provides high local drug concentrations to rapidly eliminate susceptible bacteria at the implant site, while the subsequent sustained release maintains therapeutic levels over an extended period to prevent recolonization and treat any remaining organisms. The burst release phase likely results from rapid dissolution of drug located near the surface of the material, while the sustained phase reflects diffusion of drug from the deeper matrix.

Clinical trials conducted on patients revealed the advantageous use of metronidazole and any secondary agents as an adjunct treatment when combined with traditionally used dental techniques for managing periodontal disease. Patients receiving the drug-loaded materials as part of their comprehensive periodontal therapy demonstrated improved clinical outcomes compared to those receiving conventional treatment alone, including greater reductions in pocket depth, improved attachment levels, and reduced signs of inflammation. These clinical findings validate the translational potential of the formulations and support their continued development for periodontal applications.

Compressional and Tableting Properties

The compressional properties of metronidazole formulations were analyzed using density measurements and the Heckel equation as assessment parameters, providing insights into the deformation behavior of the powder blends during compression into tablet form. The Heckel analysis, which relates the densification of the powder bed to applied compression pressure, allows for quantitative characterization of the plasticity and compressibility of pharmaceutical formulations. These parameters are essential for understanding how the materials will behave during manufacturing and for predicting the quality attributes of the final tablets.

The mechanical properties of the tablets were assessed using multiple complementary parameters including tensile strength, which measures the resistance of the tablet to diametral fracture; brittle fracture index, which quantifies the propensity of the tablet to fracture under stress; and the friability of the tablets, which measures the tendency of the tablet surface to erode during mechanical handling. Together, these parameters provide a comprehensive profile of tablet mechanical integrity that is essential for ensuring that the final dosage form can withstand manufacturing, packaging, transportation, and handling by patients without unacceptable levels of damage or degradation.

The drug release properties of the tablets were assessed using disintegration and dissolution times, which measure the time required for the tablet to break apart in aqueous medium and the rate at which the drug is released into solution. These parameters are critical for ensuring that the tablet will perform as intended in vivo, releasing the drug at the desired rate to achieve therapeutic concentrations at the site of action.

The results obtained indicate that formulations containing dika nut mucilage as a binding agent show faster onset of plastic deformation under compression pressure than those containing gelatin, suggesting that the natural polymer facilitates more efficient tablet formation at lower compression forces. This property could translate to manufacturing advantages including reduced wear on tablet presses and lower energy consumption. The tensile strength of the tablets increased with increase in concentration of the binding agents, demonstrating that higher binder levels improve the mechanical integrity of the final tablets. Conversely, the brittle fracture index and friability values decreased with increasing binder concentration, indicating that the tablets become less prone to fracture and surface erosion as more binder is incorporated. These relationships between binder concentration and tablet properties provide guidance for formulation optimization to achieve the desired balance of mechanical integrity and drug release characteristics.

CONCLUSION:

In this study, PMMA drug-loaded nanoparticles of different particle sizes were obtained by solution polymerization with rapid swelling and sustained dual drug release properties. It was fabricated to solve the problems of low drug release ratio, inconsistent drug release cycle with clinical demand, and single drug release type of drug-loaded PMMA bone cement. In addition, SDBCs exhibited excellent antibacterial activities and superior biocompatibility. Therefore, the multifunctional SDBCs could satisfy the different requirements in clinical practice. Mechanical and antibacterial properties of Metronidazole loaded PMMA bone cements are determined in this study. In subsequent research, the repairing efficiency of this material will be particularly investigated through in vivo experiments.

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