Cerium Oxide-Enabled Multifunctional Calcium Phosphate–Hyaluronic Acid Cement for Antibacterial Bone Regeneration

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Abstract

Calcium phosphate cement (CPC) is a promising bone substitute; however, its susceptibility to bacterial colonization remains a critical limitation. Here, cerium oxide (CeO_2) was incorporated into hyaluronic acid (HA)-modified CPC to develop an antibacterial and multifunctional bone cement. The antibacterial performance of CPC-HA-CeO_2 was particularly remarkable, achieving bacterial inhibition of 99.97% against Gram-positive and 99.98% against Gram-negative bacteria, highlighting its potential to mitigate bacterial contamination. Beyond antibacterial efficacy, CeO_2 incorporation exhibited concentration-dependent biological and mechanical responses. The 2.5% CeO_2 formulation demonstrated the highest cell viability, whereas 5% CeO_2 yielded the greatest compressive strength. Apatite-like flake formation following simulated body fluid immersion further confirmed the material's in vitro bioactivity. These findings establish CeO_2 incorporation as a promising strategy for developing antibacterial CPC-based bone cement that combines bacterial inhibition, cytocompatibility, bioactivity, and mechanical reinforcement for bone tissue engineering.

Keyword: Bone tissue engineering, cerium oxide, calcium phosphate cement, hyaluronic acid

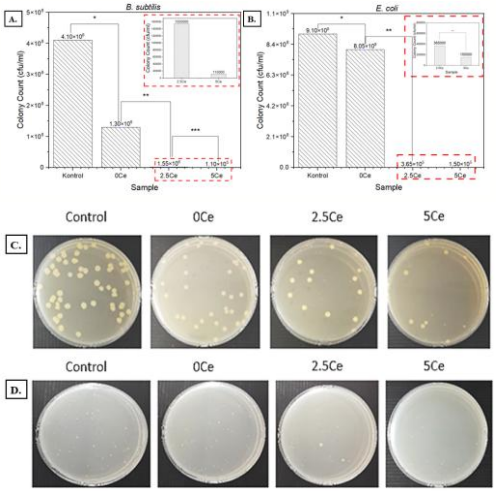
Introduction

Osteoporosis is a skeletal disorder characterized by reduced bone mass and deteriorated bone microarchitecture, increasing fracture risk. Bone cement, particularly calcium phosphate cement (CPC), is widely used for bone repair due to its biocompatibility. However, its mechanical and biological properties remain limited. Incorporating hyaluronic acid (HA) into CPC has been reported to improve compressive strength and osteogenic activity, but its antibacterial performance remains insufficient.

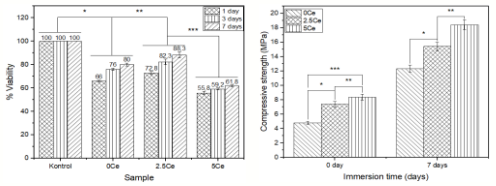
Cerium oxide (CeO_2) has emerged as a promising multifunctional material due to its antibacterial activity, redox properties, and potential to enhance mechanical performance. Its Ce^{3+}/Ce^{4+} redox transitions contribute to bacterial inhibition, while cerium ions may support osteoblast proliferation and differentiation. Therefore, this study incorporates CeO_2 into CPC-HA to develop multifunctional bone cement with improved antibacterial activity, cytocompatibility, bioactivity, and mechanical properties.

Research Method

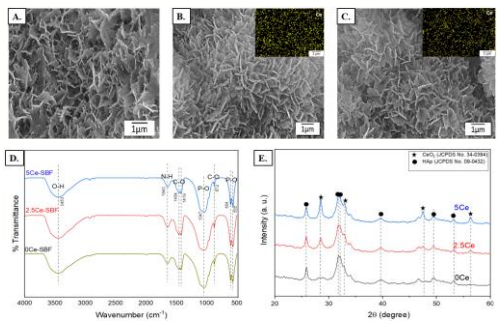
Tetra calcium phosphate (TTCP) was synthesized from catfish bone waste (*Clarias gariepinus*) through alkaline hydrolysis. The synthesized TTCP was then combined with dicalcium phosphate anhydrous (DCPA, 92%, Sigma-Aldrich) to produce calcium phosphate cement (CPC), incorporating hyaluronic acid (HA, 4% w/v) and cerium oxide (CeO_2) at concentrations of 0%, 2.5%, and 5%. The cement samples were characterized using SEM, FTIR, and XRD, followed by initial setting time and compressive strength measurements. Antibacterial activity against *Bacillus subtilis* and *Escherichia coli*, as well as cytocompatibility using UC-MSCs, was evaluated. Bioactivity was assessed by immersion in simulated body fluid (SBF) at 37°C for 7 days.



Picture 1. Antibacterial activity of bone cement with different Ce concentrations against B. subtilis and E. coli. (AB) Colony count results and (CD) representative agar plate images showing reduced bacterial growth with increasing Ce concentration.



Picture 2. Cell viability of bone cement and Compressive test results before and after soaking SBF for 7 days



Picture 3. Surface morphology, FTIR spectra, and XRD patterns of bone cement with different Ce concentrations after SBF immersion.

Discussion & Result

CeO_2 incorporation enhanced the antibacterial performance of CPC-HA cement in a concentration-dependent manner. The antibacterial activity increased with increasing CeO_2 concentration against both Gram-positive *Bacillus subtilis* and Gram-negative *Escherichia coli*. The 5% CeO_2 formulation achieved the highest bacterial inhibition, reaching 99.97% and 99.98%, respectively. This improvement may be associated with the redox activity of CeO_2, which can contribute to bacterial growth inhibition.

Cell viability results showed an increase over the 7-day observation period. Among the tested formulations, 2.5% CeO_2 exhibited the highest cell viability of 88.3% on day 7. This result suggests that moderate CeO_2 incorporation provides a favorable balance between antibacterial activity and cellular compatibility, whereas higher concentrations may influence cellular responses.

Following 7 days of immersion in simulated body fluid (SBF), SEM images revealed the formation of apatite-like flake structures on the cement surface. These morphological changes were supported by FTIR and XRD analyses, indicating the development of calcium phosphate-related mineral phases. The Ca/P ratio increased from 1.56 in 0Ce to 1.76 in 2.5Ce and 1.87 in 5Ce, suggesting changes in the surface mineral composition with increasing CeO_2 content.

Compressive strength increased with CeO_2 concentration, both before and after SBF immersion. The 5% CeO_2 formulation exhibited the highest compressive strength, increasing from 8.35 ± 2.65 MPa before immersion to 18.38 ± 5.45 MPa after 7 days. This improvement may be related to mineral deposition and changes in the cement structure during SBF exposure. Overall, 5% CeO_2 provided the strongest antibacterial and mechanical performance, while 2.5% CeO_2 showed the highest cell viability.

Conclusion

CeO_2 incorporation enhanced the antibacterial and mechanical performance of CPC-HA cement. The 5% CeO_2 formulation demonstrated the highest bacterial inhibition and compressive strength, while 2.5% CeO_2 provided the highest cell viability (88.3%). Apatite-like formation after SBF immersion further indicated in vitro bioactivity. Overall, CPC-HA-CeO_2 shows promising potential as a multifunctional bone cement for bone regeneration, warranting further biological and in vivo evaluation.