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Hemocompatibility of Copper oxide with BSA for osteoblast application.

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ABSTRACT

Background: The improvement of the physical structure and biological activity of biomaterials is significantly influenced by copper oxide. As a trace element in the human body, copper (Cu) not only possesses antibacterial properties and a range of biological functions but also has the capability to promote angiogenesis. In comparison to growth factors, copper offers multiple advantages. It could be utilized in conjunction with other inorganic ions to create new intelligent biomaterials that simulate the bone microenvironment. The aim of this study is to evaluate the hemocompatibility of Copper Oxide with BSA for osteoblast application.
Materials and Methods: CuO nanoparticles were prepared by precipitation method using copper nitrate. 100mg of Bovine serum albumin (BSA) protein powder was added. SEM, FTIR and cell viability was assessed. The control taken was blood with a buffer. 'S' represents blood with the sample. Statistical analyses were performed to determine the significance of results.
Results: The scanning electron microscopy study indicates that the morphology was identified as rod-shaped and measured at 1µ in size. A viability of approximately 95.4% was observed in cells regarding cell attachment and toxicity. Improved cell attachment and proliferation were noted.
Conclusion: The study concludes that the prepared copper oxide nanoparticle with BSA was found to be highly compatible and can be taken up for bone regeneration applications.

Keywords: Biocompatibility, Bovine serum albumin, Copper oxide nanoparticles, Cytotoxicity, Cell adhesion, Hemocompatibility.

INTRODUCTION

Copper (Cu) is a vital trace element that plays significant roles in numerous physiology processes, including bone metabolism, connective tissue formation, and redox regulation in human cells [1,2]. Owing to its ability to participate in enzymatic reactions and to modulate angiogenesis, copper has gained considerable interest as a functional component in biomaterials designed for tissue repair and regeneration [2–4]. In particular, copper-containing systems have been reported to accelerate early wound healing and to enhance vascularization, which are key events in successful osseointegration and bone regeneration [5].
Beyond its physiological roles, copper exhibits broad-spectrum antibacterial activity against a range of Gram-positive and Gram-negative pathogens. The antimicrobial effect of copper is attributed to multiple mechanisms, including disruption of bacterial cell membranes, generation of reactive oxygen species, and interference with DNA replication and protein function. Incorporation of copper or copper-based compounds into biomaterial surfaces has therefore been explored as a strategy to reduce implant-associated infections while simultaneously supporting osteogenic and angiogenic responses at the implantation site.
Copper oxide is crucial for enhancing the structure and biological functions of biomaterials. As a tiny element in the body, copper not only fights bacteria and has various biological roles but also supports the growth of new blood vessels [6,7]. Copper has several advantages over growth factors. It doesn't break down easily during processing and stays stable in tough conditions like high temperatures. Additionally, copper has useful physical and chemical properties, including changing porosity, strong mechanical strength, and crosslinking. This makes it possible to combine copper with other inorganic ions to create innovative biomaterials that mimic the bone environment [8].
Bovine serum albumin (BSA) has gained substantial attention in the field of drug delivery as a coating for nanoparticle surfaces. This is credited to its favorable properties, including biodegradability, non-toxicity, high chemical stability, easy accessibility, and an extended half-life [9–11]. Coating metallic or metal oxide nanoparticles with BSA is also a convenient approach to approximate initial protein corona formation and to investigate hemocompatibility under physiologically relevant conditions. For any material intended for orthopedic and bone tissue engineering applications, hemocompatibility

and cytocompatibility with osteoblasts are crucial prerequisites. Materials that contact blood must not induce excessive hemolysis, coagulation, or inflammatory reactions, while also supporting osteoblast attachment, viability, and proliferation on the implant surface. Despite the recognized importance of copper in bone biology, there is still limited information regarding the hemocompatibility of CuO nanoparticles and their direct effects on osteoblast behavior, particularly when combined with protein coatings [12,13].

In this context, the present study aimed to synthesize CuO nanoparticles, coat them with BSA, and evaluate their hemocompatibility and osteoblastic response. Specifically, the objectives were: (1) to characterize the morphology and functional groups of BSA-coated CuO nanoparticles using scanning electron microscopy (SEM) and Fourier transform infrared spectroscopy (FTIR); (2) to assess hemocompatibility through red blood cell (RBC) hemolysis and morphological observations; and (3) to determine osteoblast cell viability, attachment, and proliferation in the presence of BSA-coated CuO nanoparticles. These findings are intended to provide preliminary evidence for the potential use of CuO–BSA systems in bone regeneration applications.

MATERIALS AND METHODS

Synthesis of CuO nanoparticles

CuO nanoparticles were synthesized by a precipitation method using copper nitrate as the starting salt. Briefly, an aqueous solution of copper nitrate was prepared and subjected to controlled precipitation under appropriate conditions to obtain CuO nanoparticles. The precipitate was collected, washed to remove residual ions, and dried to yield CuO nanopowder suitable for further modification and characterization [14].

BSA coating of CuO nanoparticles

A BSA solution was prepared by dissolving BSA protein powder in distilled water to obtain a final concentration of 100 g of BSA solution (corresponding to 100 mg in the original description, to be adjusted as per your exact protocol). The synthesized CuO nanoparticles were dispersed in the BSA solution and incubated under gentle mixing to allow adsorption and coating of BSA onto the nanoparticle surface. The resulting BSA-coated CuO nanoparticles were collected and used for hemocompatibility and osteoblast studies to simulate interactions with biological proteins [15].

Collection of blood samples and preparation of RBC suspension

Blood specimens were obtained from human subjects following appropriate collection procedures. The samples were processed to separate red blood cells (RBCs) from plasma and other components, and an RBC suspension was prepared for hemocompatibility testing. The control group consisted of blood mixed with buffer alone, while test groups consisted of blood incubated with the BSA-coated CuO nanoparticle samples [16].

Osteoblast cell culture

Osteoblast cells were cultured using standard cell culture techniques. Cells were maintained in appropriate culture medium supplemented with necessary nutrients and antibiotics and incubated under controlled temperature, humidity, and CO_2 conditions. For cytocompatibility testing, osteoblast cells were seeded onto culture plates and allowed to adhere prior to exposure to BSA-coated CuO nanoparticles [17].

Cell viability and cytotoxicity assessment

The effect of BSA-coated CuO nanoparticles on osteoblast viability and cytotoxicity was evaluated using a cell viability assay kit. After exposure of osteoblast cultures to the nanoparticles for the designated incubation period, cell viability was quantified according to the manufacturer's instructions. The assay allowed determination of the percentage of viable cells and assessment of any cytotoxic effects of the CuO–BSA system on osteoblast proliferation and function [18].

Morphological analysis by SEM and microscopy

The morphology and size of the synthesized CuO nanoparticles were examined by scanning electron microscopy (SEM). SEM imaging was used to identify particle shape and approximate dimensions of the nanoparticles. In addition, morphological changes in RBCs and osteoblast cells after exposure to BSA-coated CuO nanoparticles were evaluated using microscopy techniques to detect any structural alterations indicative of toxicity or incompatibility [19].

FTIR characterization

Fourier transform infrared (FTIR) spectroscopy was performed to identify functional groups associated with the CuO nanoparticles and to confirm the presence of BSA coating. The FTIR spectra were analyzed for characteristic peaks corresponding to hydroxyl groups, carbonate groups, and vibrations associated with copper oxide and protein functional groups, indicating successful formation and modification of the nanoparticles [20].

Statistical analysis

All experiments were conducted with appropriate replicates, and data were expressed as mean values with corresponding variability. Statistical analyses were performed to determine the significance of differences between control and test groups. A predefined significance level was applied to interpret the results of hemocompatibility and cell viability assays.

RESULTS

Morphology and structural characterization

SEM analysis revealed that the synthesized CuO nanoparticles were predominantly rod-shaped, with an approximate size of 1 µm **(Figure 1 and 2)**. This rod-like morphology indicated successful formation of CuO structures suitable for further biological evaluation. FTIR spectra confirmed the presence of characteristic peaks corresponding to hydroxyl groups, carbonate species, and copper oxide, consistent with the formation of CuO nanoparticles and interaction with BSA. **(Figure 3)**

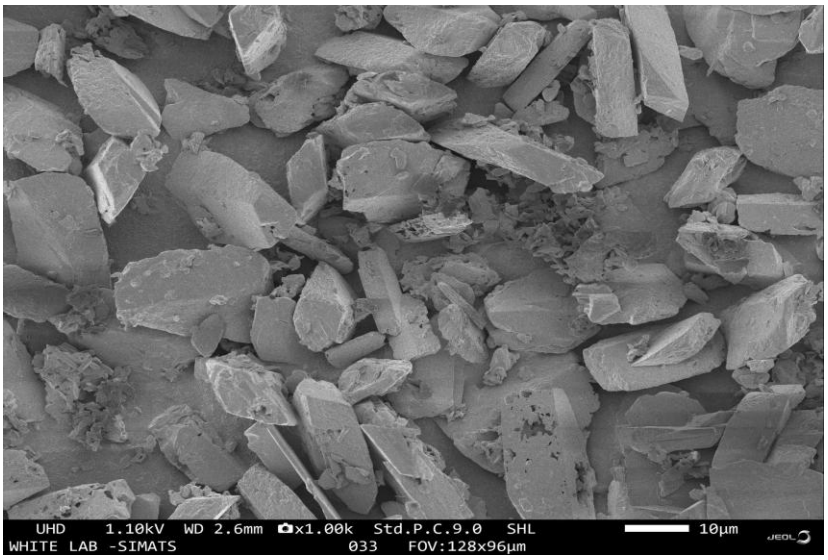

Figure 1: Represents the scanning electron microscopy image which indicates that the morphology was identified as rod-shaped and measured at 1µ in size.

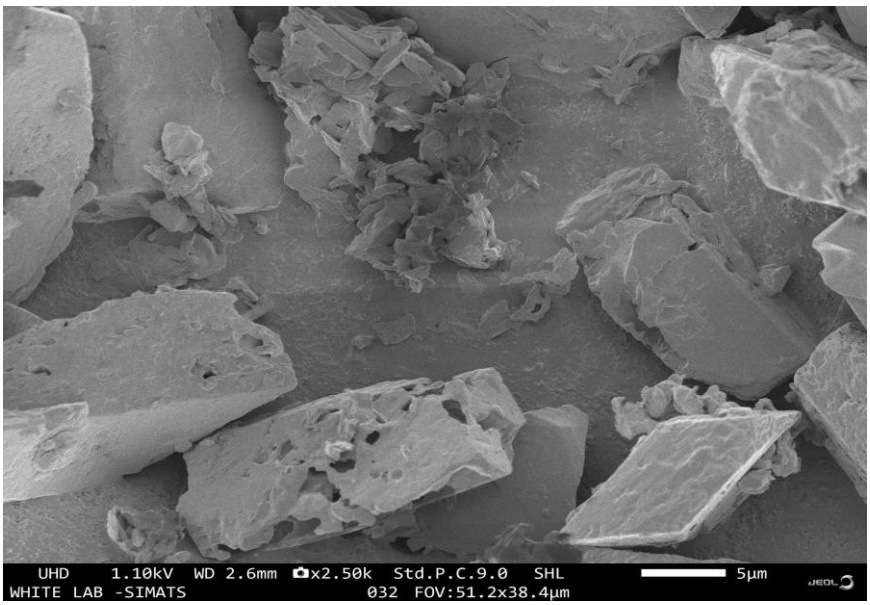

Figure 2: Represents the scanning electron microscopy image which indicates that the morphology was identified as rod-shaped and measured at 1µ in size.

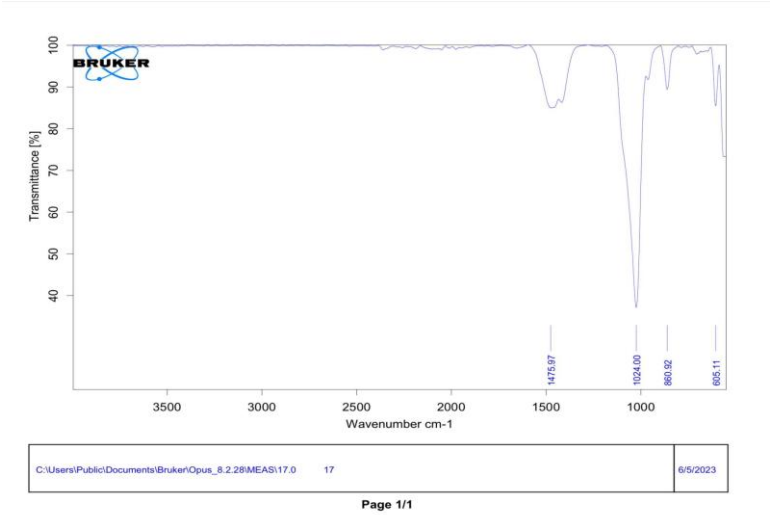

Figure 3: Represents FTIR results which confirms the presence of hydroxyl groups, carbonate, and the formation of copper oxide nanoparticles.

Osteoblast viability, attachment, and proliferation

Osteoblast cell viability in the presence of BSA-coated CuO nanoparticles was approximately 95.4%, indicating minimal cytotoxicity and favorable conditions for cell survival. The high viability suggested that the CuO–BSA system supported osteoblast attachment and proliferation rather than impairing cell function. Microscopic observations corroborated these findings, demonstrating improved cell attachment and active proliferation on the surfaces exposed to the nanoparticles **(Figure 4)**.

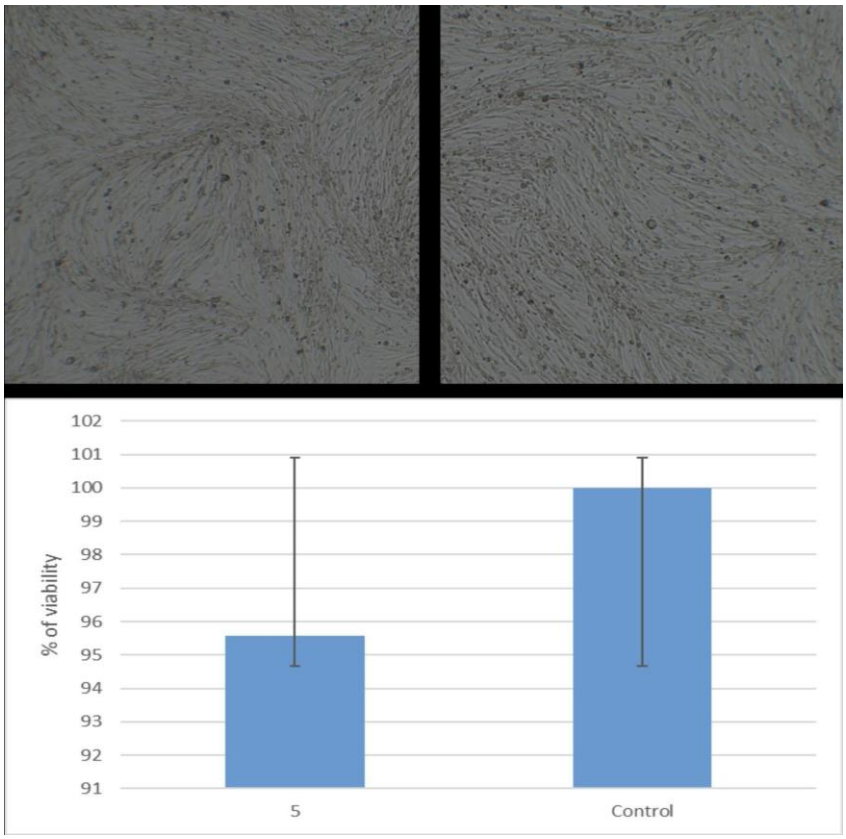

Figure 4: Represents the cell attachment and toxicity. In assessing cell attachment and toxicity, osteoblast cells were utilized, revealing favorable results with 95.4% viability. This high viability suggests conducive conditions for osteoblast cells, facilitating their attachment and proliferation. This implies that the cells not only adhered successfully to the substrate or surface under investigation but also displayed active growth and division, indicating a positive and supportive environment for osteoblast cells in this specific experimental context.

DISCUSSION

In the past few years, there has been an increasing emphasis on tissue engineering as an alternative strategy for mending defects [21,22]. This method utilizes cells, scaffolds, and growth factors to direct the development of bone and cartilage. Diverse biomaterial-based scaffolds act as a platform to transport cells and growth factors, inserted into bone or cartilage defects to promote regeneration [23–28]. Cu has been identified as crucial for bone growth; its deficiency may lead to bone abnormalities and diminished strength. Copper-doped scaffolds within biomaterials hold promise for advancing bone tissue engineering, contributing to both bone healing and infection prevention, making them pivotal in the field of regenerative bone tissue engineering [29–33]. Beyond simple ion release, copper can modulate key cellular pathways involved in osteogenesis and angiogenesis, enhancing the recruitment and differentiation of progenitor cells while supporting neovascularization within the defect site. This coordinated effect is particularly valuable for large or poorly vascularized defects, where simultaneous stimulation of bone formation and blood vessel ingrowth is essential for stable regeneration.

The current study assessed the hemocompatibility of copper oxide nanoparticles with BSA and determined their osteoblastic properties. The use of BSA as a stabilizing agent may further improve the biological interface by enhancing protein adsorption and mimicking aspects of the native extracellular environment, thereby facilitating integrin-mediated cell adhesion. Such a protein-rich corona around the nanoparticles can influence cell–material interactions, potentially contributing to the high viability and robust attachment observed in osteoblast cultures. During the assessment of cell attachment and toxicity, osteoblast cells were utilized, revealing positive outcomes with a viability rate of 95.4%. This high viability implies favorable conditions for osteoblast cells, fostering both their attachment and proliferation. It suggests that the cells not only successfully adhered to the substrate or surface under investigation but also exhibited active growth and division, highlighting a positive and supportive environment for osteoblast cells in this particular experimental setting. Moreover, the preservation of cell morphology and the absence of overt signs of stress or apoptosis suggest that the tested formulation remains within a biologically acceptable concentration window, where copper provides bioactivity without inducing oxidative or inflammatory damage to osteoblasts.

Despite the essential role Cu plays in the physiological processes of bone cells, there is a scarcity of research regarding its influence on osteoblast behavior. This gap is particularly important because osteoblast response determines not only initial cell survival but also subsequent matrix deposition, mineralization, and long-term integration of the implant with host bone. A clearer understanding of how copper concentration, nanoparticle size, and surface chemistry jointly regulate these processes is therefore critical for the rational design of next-generation bone substitutes. Hang et al. discovered that elevated Cu levels in nanotubes may pose harm to osteoblasts, yet cytotoxicity becomes negligible at relatively low Cu content (1.01 at.%). Furthermore, observations indicate that hydroxyapatite coatings substituted with a low concentration of Cu, including Cu^{2+}, demonstrate positive cytocompatibility and pose no toxicity to osteoblasts [34]. Ewald et al. reported that the incorporation of copper in calcium phosphate cements is associated with increased activity and proliferation of osteoblastic cells [5]. The above studies are in accordance with the results of the present study. Taken together, these findings indicate that carefully controlled copper incorporation can shift the balance from potential cytotoxicity toward pro-regenerative signaling, reinforcing the concept of a narrow but exploitable therapeutic window for copper-based biomaterials in bone tissue engineering.

The utilization of scanning electron microscopy in the study reveals that the morphology was identified as rod-shaped, measuring 1μ in size. FTIR confirmed the presence of hydroxyl groups, carbonate, and the formation of copper oxide nanoparticles. Correlating these structural and chemical characteristics with the favorable biological responses observed in vitro underscores the importance of integrated physicochemical and biological evaluation. Such an approach provides a more complete framework for optimizing copper oxide nanoparticle formulations that are both functionally effective and safe for future translational applications in bone repair.

CONCLUSION

The BSA-coated copper oxide nanoparticles demonstrated excellent hemocompatibility, with no significant hemolysis observed in red blood cells, and supported robust osteoblast viability (95.4%), attachment, and proliferation. These findings highlight the dual benefits of CuO's antibacterial properties and its role in promoting osteogenic responses, making it a promising component for bone tissue engineering scaffolds. Future studies should explore long-term in vivo implantation, dose-dependent effects, and mechanical integration within composite biomaterials to validate clinical translation potential. Overall, this CuO-BSA system offers a stable, biocompatible platform for advancing bone regeneration therapies while mitigating infection risks.

AUTHORS CONTRIBUTIONS

Reenu Joshy: Literature search, data collection, analysis, manuscript drafting. Dr. Bargavi P: Aided in conception of the topic, has participated in the study design, statistical analysis and has supervised in preparation and final correction of the manuscript, Data verification, manuscript drafting, preparation of manuscript.

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CONFLICT OF INTEREST
The author declares that there were no conflicts of interest in the present study.

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