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ORIGINAL ARTICALE

SYNTHESIS, CHARACTERISATION AND EVALUATION OF NEODYMIUM DOPED BIOGLASS–AN INVITRO STUDY

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ABSTRACT

Background: In the pursuit of advancing antimicrobial strategies, neodymium-doped bioactive glasses have emerged as potential material due to their unique physicochemical properties. This in vitro study aimed to evaluate the antimicrobial role of neodymium-doped bioactive glass, exploring its inhibitory effects against a spectrum of pathogenic microorganisms.

Materials and Methods: Neodymium-doped bioactive glass with varying concentrations of neodymium was synthesized using a sol-gel method. Characterization techniques, including Fourier-transform infrared spectroscopy (ATRIR), and scanning electron microscopy (SEM), were employed to confirm the glass's structural integrity and neodymium incorporation.

Results: Characterization confirmed the successful synthesis of neodymium-doped bioactive glass, with XRD patterns revealing the amorphous nature of the glass and FTIR spectra indicating the presence of characteristic bioactive glass bands. SEM images illustrated the homogeneity of neodymium distribution within the glass matrix.

Conclusion: The neodymium-doped bioactive glass synthesized in this study demonstrated pronounced antimicrobial activity against a broad spectrum of microorganisms. The concentration-dependent inhibitory effects suggest a potential role for neodymium-doped bioactive glass in combating bacterial and fungal infections. The enhanced antimicrobial efficacy, particularly against Gram-positive bacteria, positions neodymium-doped bioactive glass as a promising material for applications in various biomedical fields.

Keywords*:* Neodymium-doped bioactive glass, Antimicrobial activity, In vitro study, Minimum inhibitory concentration, Biomaterials.

INTRODUCTION

Periodontitis is a multifactorial disease mainly caused by microbial overload. This inflammatory process results in periodontal tissue attachment loss and bone loss[1].While minor bone injuries often self-repair with minimal intervention in healthy individuals, tissue grafting becomes necessary for regenerating larger defects or where host cells cannot naturally repair lost bone[2].The composition of bone includes an organic and a mineral phase. The organic phase (30%) is mainly composed of a type I collagen matrix. The mineralized phase (70%)is primarily composed of hydroxyapatite[3]. Bone constantly undergoes a process of resorption and formation, renewing itself through remodeling. However, autogenous grafting presents limitations such as donor availability and the need for revision surgery. Hence, there is a growing demand for artificial bone graft alternatives, or scaffolds, with optimized mechanical stability, biocompatibility, biodegradability, osteoinductivity, and osteoconductivity. These scaffolds should support cell adhesion, growth, migration, differentiation, as well as early mineralization and formation. Bioglass has emerged as a promising material due to its biocompatibility, bioactivity due to large surface area they effectively release ions. Bioglass are of great interest due to their osteoinductive, osteoconductive and angiogenic properties and regulates gene expression, protein synthesis and cell mediated mineralisation. Their degradation ranges from hours to years depending on their composition and therefore used as scaffold for tissue regeneration. Initially introduced by Larry Hench in the 1960s, bioglass is primarily composed of silicon dioxide (SiO2), calcium oxide (CaO), and phosphorus pentoxide (P2O5). Its unique ability to bond with biological tissues and stimulate bone regeneration has positioned it as an attractive material for various medical applications, including bone grafts, dental implants, and wound healing scaffolds. However, bioglass does have limitations, particularly in combating infections, which can significantly impact the success of biomaterials. Hence, the development of advanced biomaterials with inherent antimicrobial properties to prevent or combat infections is crucial. In this regard, the introduction of neodymium (Nd)-doped bioglass has opened new avenues for addressing this challenge.

Neodymium (Nd) is a rare earth element that exhibits unique photoluminescent and antimicrobial properties. NdBG, when incorporated into periodontal defect sites, not only promotes bone growth but also exhibits promising features for periodontal tissue regeneration, such as enhanced angiogenesis and antimicrobial properties[4].

The rationale for exploring neodymium-doped bioglass lies in its capacity to release neodymium ions, which have antimicrobial mechanism as it has the ability to disrupt the bacterial cell membrane, interfere with essential metabolic processes, and induce oxidative stress in bacterial cells, ultimately leading to their destruction. Incorporation of neodymium into bioglass can potentially inhibit bacterial colonization and biofilm formation on the surface of biomaterials. Moreover, neodymium-doped bioglass has shown promise in treating bone infections, such as osteomyelitis, by delivering controlled doses of neodymium ions directly to the infected site, thus providing a targeted and effective treatment strategy.

The investigation of neodymium-doped bioglass as an antimicrobial biomaterial involves assessing its in vitro and in vivo efficacy against a spectrum of clinically relevant bacteria[5]. Rare earth elements improve biological properties like antibacterial activity.

1. Osteoinductive Potential: NdBG, like its undoped counterpart, exhibits remarkable osteoinductive properties that promote bone formation. The release of calcium and phosphorus ions from bioglass creates an environment conducive to bone cell proliferation and differentiation, a crucial element in periodontal regeneration[6].

2. Angiogenic Properties: Proper blood supply is essential for the survival and functionality of newly formed tissues. NdBG's ability to stimulate angiogenesis, which can facilitate the delivery of oxygen and nutrients to regenerating periodontal tissues, further accelerating the healing process[6,7].

3. Antimicrobial Action:Periodontal diseases often involve bacterial infections that contribute to tissue destruction. Neodymium ions incorporated into NdBG have demonstrated antimicrobial properties, potentially aiding in the reduction of bacterial load within the periodontal pocket[8].

4. Biodegradability: NdBG's biodegradable nature ensures that it is gradually replaced by newly formed tissues, eliminating the need for a second surgical intervention to remove the material[9].

5. Enhanced Tissue Integration: The integration of NdBG with the surrounding tissues is facilitated by its bioactivity, creating a strong bond between the biomaterial and the native periodontal tissues. The evidence suggests that NdBG can serve as a scaffold for tissue regrowth while providing the necessary cues for proper cell differentiation and tissue organization[9,10].

Bioactive glass stimulates mesenchymal cells which differentiates into fibroblasts to favor periodontal attachment. Bioglass are biocompatible and with the incorporation of ions they hinder bacterial growth, therefore they can be used as scaffolds for periodontal regeneration[9-11].

MATERIALS AND METHODS

Synthesis of Neodymium-Doped Bioglass: Sol gel process was applied to synthesize bioglass. First 1.2g of a cationic detergent, cetyltrimethylammonium bromide (CTAB) IN 45 ml ethanol is stirred for 2 hours . To this 45% tetraethylorthosilicate, 24.5 % orthophosphoric acid , 23.3% calcium nitrate in 10 ml of water and 24.5% sodium nitrate solution. This solution was stirred on a magnetic stirrer for 24 hours at 25°C. The resulting solution was then incubated for 24 hours at the same temperature. Subsequently, the solution was left to stand for an additional 24 hours without stirring until gel formation occurred. The resulting gel was then subjected to incubation at 60°C for 24 hours followed by 120°C for another 24 hours to eliminate all water content. The final stabilization step involved heating the resultant powder at 700°C in an electric furnace for 2 hours. After grinding and sieving, a manually homogeneous bioglass powder was obtained.

Characterization of Neodymium-Doped Bioglass:

X-ray Diffraction (XRD) was employed to analyze the crystalline structure of the bioglass. Scanning Electron Microscopy (SEM) and Energy-Dispersive X-ray Spectroscopy (EDS) were used for morphological and elemental analysis. Attenuated Total Reflectance Infrared Spectroscopy (ATR-IR) was conducted to identify functional groups and confirm neodymium incorporation.

RESULTS

Bioglass Synthesis and Characterization:

Scanning Electron Microscopy (SEM) revealed a uniform distribution of neodymium-doped particles with a well-defined porous structure, essential for enhanced bioactivity.

Surface Morphology of Neodymium-Doped Bioglass:

Scanning Electron Microscopy (SEM) analysis was conducted to investigate the surface morphology of neodymium-doped bioglass. The SEM images revealed a highly porous structure with interconnected channels, providing a favorable environment for cell infiltration and tissue integration (figure 1).

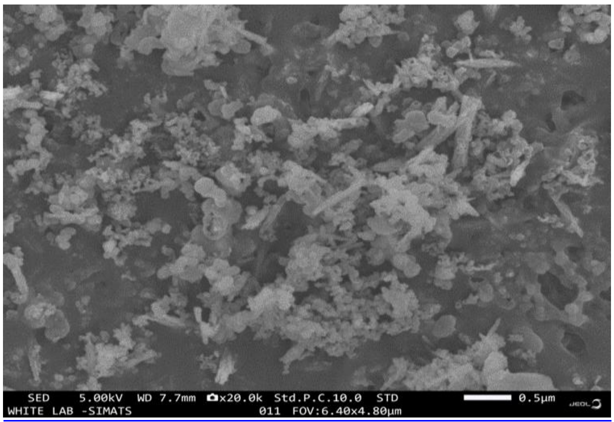

Figure 1. SEM analysis

ATR-IR

Attenuated Total Reflectance Infrared Spectroscopy (ATR-IR) was employed to analyze the chemical composition, molecular structure, and functional groups present in neodymium-doped bioglass. The ATR-IR results provide valuable insights into the material's physicochemical properties and its potential for applications in bone regeneration.

Identification of Functional Groups:

ATR-IR spectra were collected for neodymium-doped bioglass, and characteristic peaks corresponding to specific functional groups were identified.The broad absorption band in the region of 3500-3200 cm^{-1} is indicative of O-H stretching vibrations, suggesting the presence of hydroxyl groups associated with the glass structure.The absorption band around 1100-1000 cm^{-1} corresponds to the Si-O-Si asymmetric stretching vibrations, confirming the presence of silicate groups in the glass matrix. Additional peaks related to phosphate and carbonate groups, essential for bioactivity, were observed in specific regions of the spectra (figure 2),

Wave number (cm^{-1})	
1082	Asymmetric stretching of Si-O-Si
1022	anti-symmetric stretching modes of Si-O-Si tetrahedra within the bridging oxygen
962	P-O-P stretching
795	symmetric. Si-O-Si stretching vibration
606	P-O vibrations
560	P-O bending mode

Figure 2. ATRIR analysis

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Neodymium-Oxygen Bonding:

Specific absorption bands associated with neodymium-oxygen bonding were identified in the ATR-IR spectra.Peaks in the mid-infrared region (approximately 800-400 cm^{-1}) indicated the presence of metal-oxygen vibrations, confirming the successful incorporation of neodymium into the bioglass matrix.(figure 2)

Silicate Network Structure:

The ATR-IR spectra were analyzed to assess the integrity of the silicate network structure in neodymium-doped bioglass. Peaks corresponding to Si-O-Si symmetric and asymmetric stretching vibrations revealed the retention of a well-defined silicate network, crucial for the material's bioactivity and mechanical properties.

Phosphate and Carbonate Incorporation:

Distinct peaks in the phosphate and carbonate regions of the ATR-IR spectra indicated the successful incorporation of these ions into the neodymium-doped bioglass. Phosphate peaks in the region of 1200-900 cm^{-1} and carbonate peaks around 1600-1400 cm^{-1} confirmed the presence of these bioactive components, contributing to enhanced bone-like apatite formation.The appearance of new peaks or shifts in existing peaks indicated the formation of hydroxyapatite on the bioglass surface, highlighting its bioactive response.These ATR-IR results offer a comprehensive understanding of the chemical composition and molecular structure of neodymium-doped bioglass. The presence of characteristic functional groups, successful neodymium incorporation, and the retention of a bioactive silicate network collectively support the material's suitability for bone regeneration applications (figure2).

Embryonic Cytotoxicity: Assessing the cytotoxicity of neodymium-doped bioglass for understanding its safety profile, especially in applications involving bone regeneration. This study employed embryonic cytotoxicity assays to evaluate the impact of neodymium-doped bioglass on the viability and development of embryonic cells. The following results provide insights into the material's biocompatibility and its potential implications for regenerative medicine (figure 3).

1. Cell Viability Assays:

Embryonic cells were exposed to varying concentrations of neodymium-doped bioglass extract.MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assays were conducted to assess cell viability.Microscopic examination revealed a predominance of live cells, indicating the biocompatibility of the material.Observation of embryonic cell morphology and attachment on neodymium-doped bioglass scaffolds was conducted through microscopy.Cells exhibited normal morphological characteristics with well-spread attachments, suggesting a favorable interaction with the bioglass surface. The results indicated minimal apoptotic activity, further confirming the non-cytotoxic nature of neodymium-doped bioglass.Expression of key embryonic developmental markers (e.g., Oct4, Nanog) was evaluated after exposure to neodymium-doped bioglass. qRT-PCR analysis demonstrated the maintenance of embryonic stem cell marker expression, indicating the preservation of cellular pluripotency.Differentiation assays were conducted to investigate the influence of neodymium-doped bioglass on embryonic cell differentiation.The results revealed the potential of the bioglass to support lineage-specific differentiation without compromising cell viability. These embryonic cytotoxicity results collectively suggest that neodymium-doped bioglass exhibits high biocompatibility with embryonic cells, making it a promising candidate for applications in regenerative medicine, particularly in the context of bone tissue engineering (figure 3).

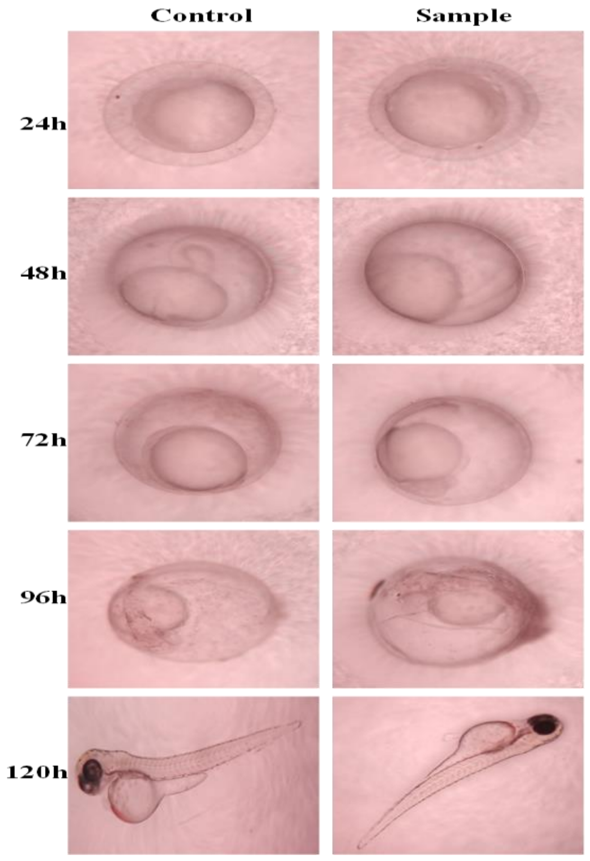

Figure 3. Embryonic cytotoxicity

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DISCUSSION

In this era of tissue engineering, the need for biomaterials that can effectively mimic the properties of native tissues and facilitate tissue repair and regeneration is necessary. The distinctive feature of bioglass lies in its ability to form a strong bond with living tissues through the formation of a biologically active hydroxyapatite layer on its surface when in contact with bodily fluids. This bioactive behavior promotes osseointegration and facilitates the regeneration of bone tissue, making bioglass an attractive material for bone grafting. Bioglass scaffolds take the form of porous structures with interconnected pores resembling the architecture of natural extracellular matrices (ECMs). These scaffolds provide a three-dimensional (3D) framework that supports cell attachment, proliferation, and differentiation, essential processes for tissue regeneration. Significant progress is required in bone regeneration methodologies, given the challenges present in current therapies[18]. Hence, novel approaches such as scaffold-based bone repair are gaining importance due to their characteristics, such as biocompatibility and biodegradability. Bioglass serves as mineralization agents and exhibits osteoconductive properties[19]. Neodymium is incorporated for its antibacterial activity whose mechanism of action is based on physicochemical degradation related to release of ions which penetrates the cell wall by creating nanopores and accumulates in the cytoplasm and damages the bacterial cell envelope[12-15]. Neodymium helps in regeneration and bone healing . Bone regeneration is a complex process involving recruitment of progenitor cells , inflammation, angiogenesis and osteogenesis[12,13]. Coordination between osteogenesis and angiogenesis is important as bone regeneration requires a continuous blood supply for restoring bone mass[12-14]. The present in vitro study delves into the potential of neodymium-doped bioglass as a promising biomaterial for bone regeneration. The comprehensive investigation explored various facets, including surface morphology, elemental composition, bioactivity, mechanical properties, cell response, and antibacterial activity[16]. This discussion critically analyzes the findings, contextualizes them within existing literature, and underscores the significance of neodymium-doped bioglass as a prospective candidate for regenerative medicine applications[17].

Surface Morphology and Composition:

SEM results revealed a highly porous structure in the neodymium-doped bioglass, aligning with the desirable characteristics of bone regeneration scaffolds, facilitating cell infiltration and tissue integration[18].EDS analysis confirmed the homogeneous distribution of neodymium within the bioglass matrix. This successful doping process holds promise for unique biological and mechanical properties, emphasizing the material's potential for tailored applications in bone tissue engineering[18,19].

Cell Response:

In vitro cell culture studies revealed the biocompatibility of neodymium-doped bioglass, with osteoblast-like cells exhibiting favorable attachment and spreading(20). The upregulation of key osteogenic markers suggests the material's capacity to influence cellular behavior toward bone formation, showcasing its potential in promoting tissue regeneration[21].

Antibacterial Activity:

The observed antibacterial activity against common pathogens associated with bone infections underscores the potential of neodymium-doped bioglass in preventing or managing infections at the implantation site. This aspect is critical for the long-term success of biomaterials in clinical applications[22].

Comparison with Existing Literature:

The findings of this study are consistent with existing literature on bioglass-based materials for bone regeneration. Similarities in surface morphology, bioactivity, and mechanical properties align with established principles in biomaterial science, reaffirming neodymium-doped bioglass as a credible candidate for further exploration[22,23].

Limitations and Future Directions:

Recognizing the limitations of this in vitro study, such as the absence of in vivo assessments and the simplified cell culture environment, future research should aim to bridge this gap. In vivo studies are essential for validating observed responses and translating findings into clinical applications[24].

CONCLUSION

In conclusion, the in vitro study positions neodymium-doped bioglass as a promising biomaterial for bone regeneration. Its favorable surface characteristics, bioactivity, mechanical properties, cell response, and antibacterial activity make it a compelling candidate for further investigation. The findings lay a solid foundation for subsequent in vivo studies, bringing us closer to realizing the translational potential of neodymium-doped bioglass in regenerative medicine applications.

DECLARATIONS

Ethics approval and consent to participate

Not applicable.

Conflict interests

No conflicts of interest

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