RESEARCH PAPER

Assessment of the Cytocompatibility of a Novel 45S5 Bioactive Glass Based Intracanal Medicament with Human Periodontal Ligament Fibroblasts Using MTT Assay

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Abstract

Objectives:To evaluate the short-term cytocompatibility of a 45S5 bioactive glass (BG-45S5) intracanal medicament with human periodontal ligament (PDL) fibroblasts using the microplate MTT assay and phase-contrast morphological observation.Materials and Methods:

Primary human PDL fibroblasts were cultured in Dulbecco's Modified Eagle Medium (DMEM) and exposed for 24 h to BG-45S5 at 1, 5, 10, 25, and 50 µg/mL. Doxorubicin served as the cytotoxic reference. MTT solution (0.5 mg/mL) was incubated for 4 h; formazan crystals were dissolved in DMSO and optical density (OD) recorded at 570 nm. Viability was normalized to untreated controls. Data were analyzed by one-way ANOVA ($\alpha = 0.05$).Results:

A significant group effect was observed ($F(5,60) = 12.59$; $p \ll 0.001$). Mean viability (%) for each group: Doxorubicin 14.6 ± 25.9; BG-45S5 50 µg/mL 27.3 ± 43.7; BG-45S5 1 µg/mL 91.7 ± 5.5; BG-45S5 5 µg/mL 81.6 ± 24.5; BG-45S5 10 µg/mL 76.5 ± 27.7; BG-45S5 25 µg/mL 76.2 ± 27.9. Micrographs confirmed confluent spindle morphology at low concentration and reduced confluence at higher doses.Conclusion:

BG-45S5 showed good short-term cytocompatibility at 1–10 µg/mL with concentration-dependent metabolic suppression at 25–50 µg/mL. The medicament may be suitable for intracanal application at biologically acceptable concentrations.

Keywords: Bioactive glass, Cytotoxicity, Intracanal medicament, MTT assay

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Introduction

The quest for the perfect intracanal medicament remains a central theme in endodontic research. The goal is clear: to ensure effective microbial control within the intricate root canal system while keeping the periapical tissues healthy. For a long time, calcium hydroxide has been the gold standard due to its strong alkalinity and wide-ranging antimicrobial properties. However, it has a high pH which can harm nearby connective tissue, and it struggles to combat resistant bacteria like *Enterococcus faecalis* [1,2]. These shortcomings have led to the development of biomaterials which combine antimicrobial potential and biocompatibility.

Bioactive glass (BG), which was first formulated by Hench in 1969, is the first material shown to bond chemically with bone and dentin [3]. The 45S5 composition, which consists of 45 wt% SiO_2, 24.5 wt% Na_2O, 24.5 wt% CaO, and 6 wt% P_2O_5, has set the standard for all bioactive glass systems. When it comes into contact with physiological fluids, it quickly exchanges Na^+ and H^+ ions, leading to a localized increase in alkalinity and the release of Ca^{2+}, phosphate, and soluble silica. These ions then form hydroxy-carbonate apatite (HCA), creating a mineral layer that closely resembles biological apatite, promoting integration with dentin and bone. [4–6].

Beyond its ability to mineralize, 45S also has an antibacterial action; the elevated pH level, along with the osmotic stress caused by the ionic dissolution products, disrupts bacterial enzyme systems and affects how their membranes work. [7]. Investigations

have shown that nano-sized 45S particles completely eradicated *E. faecalis* biofilms within 24 hours and effectively prevented bacterial leakage through dentin tubules [8,9]. These findings show that bioactive glass may serve as a promising replacement or alternative to calcium hydroxide, especially when processed into a nanoscale or mesoporous formulation which allows the controlled ion release and improvement in surface reactivity [10].

It is important to ensure that medicaments are compatible with the tissues around the apical region. The periodontal ligament (PDL) fibroblast serves as a key in-vitro model since these cells come into direct contact with the medicaments that may be pushed beyond the apex during treatment. Previous studies on S53P4 and 45S variants indicate that fibroblasts can thrive at low concentrations, but higher doses may temporarily hinder their metabolic activity due to ionic and osmotic stress. [11–14]. This highlights the requirement of standardized cytotoxicity evaluation under ISO 10993-5 guidelines before clinical translation.

The MTT assay is a reliable method of biocompatibility analysis. It measures the activity of mitochondrial dehydrogenase, providing a gauge of cell metabolism after exposure to different materials. Its consistency, ease of use, and adherence to international biocompatibility standards make it particularly well-suited for research on dental biomaterials[15–17].

Even though there is evidence showing the antimicrobial effectiveness and remineralizing abilities of 45S bioactive glass, there is laccunae in research on how the cytocompatibility varies with different doses when used as an intracanal medicament. It's crucial to determine a safe concentration range that strikes a balance between its antibacterial strength and how well cells can tolerate it. With that in mind, this study set out to assess the cytocompatibility of a 45S5 bioactive glass-based intracanal medicament on human periodontal ligament fibroblasts, using the MTT assay and looking at morphological changes. The goal is to establish biologically acceptable concentration limits for clinical use and to highlight the material's potential in regenerative endodontic therapy.

Materials and methodology-

Study Design

The research paper is an experimental study conducted in vitro on the biocompatibility of a bioactive 45S glass based medicament in relation to human periodontal ligament fibroblasts. The experimental design entailed 6 groups; a positive control and five experimental cohorts with varying material concentration.Cytotoxicity was measured through a microplate based MTT test, but morphological evaluation provided a qualitative evaluation. All operations were performed and compliant with the ISO 109935:2009 standard of in vitro biocompatibility testing and performed according to the guidelines of the Good Cell Culture Practice (GCCP 2020).

Sample Preparation and Characterization of Bioactive Glass

The precursor material used was the Standard 45S5 bioactive Glass (Perioglass ™; US Biomaterials Corp., Alachua, FL, USA) which consists of 45 wt% SiO_2, 24.5 wt% Na_2O, 24.5 wt% CaO, and 6 wt% P_2O_5. To increase surface reactivity and also recreate clinically relevant size of the particles, nano-sized bioactive glass powders were made through a sol–gel pathway. The silicon organosilicate tetraethyl orthosilicate (TEOS) and phosphorus ester triethyl phosphate (TEP) were hydrolyzed in the presence of sodium hydroxide and calcium hydroxide to give the desired 45S5 oxide stoichiometry. The ethanol and deionized water were used as the solvent system, thus maintaining a uniform hydrolysis and further condensation. The sol was kept at 70 °C with a pH of 2, which were favorable to form the network and gel it.Subsequently, the gel was allowed to dry over a period of one week in order to undergo polycondensation to achieve structural stability. The residual organics were removed by calcination at the temperature of 800 °C to obtain phase-pure bioactive Glass nanoparticles (BAG-np). The product of the grinding was carefully ground to fine, sifted and placed in airtight, desiccated sterile vials. The Fourier-transform infrared spectroscopy revealed the existence of typical SiOSIOCI suppose a full network to be formed and that no unreacted alkoxides are present. Before biological assessment, the powder was dried-heat at 180 °C for 2 hours. . Prior to use, the fresh suspensions were prepared in a fresh cell culture medium so as to maintain the ionic reactivity.

Cell Line and Cell Conditions.

Primary human periodontal ligament (PDL) fibroblasts (ATCC® CRL-2241™) - were chosen in order to study the responses of periapical tissue. The cells were kept in The Dulbecco Modified Eagles Media (DMEM) containing the 10% fetal bovine serum (FBS), 1% penicillin streptomycin, and 2mM L-glutamine.Incubation of cultures was done at 37 °C in a moist environment, having 5 percent of CO_2. Passages four to six were utilized to maintain cellular properties. After trypsinization, cells were seeded at a density of 1×10^4 cell per well in sterile 96 well flat bottom plates and left to stabilize after 24 hours.

Exposure Protocol

As per the experimental design, the growth medium was replaced with test (100 µL/well) or control solutions. These preparations were incubated on cells for over 24 hours to simulate the exposure of the cells to intracanal medicament eluates that may occur in the periapical area in clinical practice. Every concentration was measured in triplicates wells and the whole assay was repeated thrice (n = 4 -14 per group).

MTT Viability Assay

The viability of the cells was measured using MTT assay which measures the mitochondrial dehydrogenase activity [1,2]. After 24 to 16h exposure, the culture medium was substituted with 100 uL of an MTT solution at the final concentration of 0.5mg/mL. The plates were then incubated at 4 h at 37 C so as to help convert the MTT to purple formazan crystals by the metabolically active cells. Reaction was stopped by aspirating the supernatant and adding 100 0M dimethyl sulfoxide (DMSO) to each well. A slow agitation of 10 min was conducted to dissolve all the formazan and the optical densities were recorded at 570 nm in the presence of a reference wavelength of 630 nm with a microplate reader (BioTek Instruments, USA).

Cell viability (%) was calculated as:

Viability (%) = (OD_sample / OD_control) × 100

Cytotoxicity (%) = 100 - Viability (%)

Results were expressed as mean ± standard deviation (SD).

Morphological Analysis

After the exposure, the morphology of fibroblasts was assessed with the help of an inverted light microscope (Olympus CKX53, Japan; magnification ×200). A photomicrograph of representative fields of the control, BG-45S5 1 µg/mL and BG-45S5 50 µg/m were taken. The parameters highlighted by the assessment included the cell density, morphology, adherence, and possible morphological expression of cellular stress, including rounding and detachment (Figure 1).

Results

MTT Viability

Significant variability in viability was seen across all the six included groups ($p \ll 0.001$). Doxorubicin saw pronounced cytotoxicity (≈ 15% mean viability). BG-45S5 at 1–10 µg/mL preserved around 75–92% viability, whereas 25–50 µg/mL showed moderate suppression (≈ 27–76%). Standard deviations were less at low concentrations, indicating a stable metabolic activity.

Morphological Findings

As shown in Figure 1, control and BG-45S5 1 µg/mL cells revealed spindle-shaped fibroblasts creating confluent monolayers. At 50 µg/mL, cell density is reduced with occasional rounding, consistent with metabolic suppression but without gross necrosis.

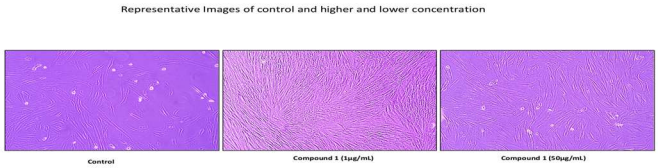

Figure 1 - Phase-contrast images showing human periodontal ligament fibroblasts in the control group and after exposure to 1 µg/mL and 50 µg/mL of the 45S5 bioactive glass–based intracanal medicament. Cells remained healthy and well spread at the lower concentration, while mild morphological changes were noted at the higher dose.

Statistical analysis

ANOVA confirmed highly significant differences among groups (F = 12.59). Post-hoc interpretation suggests the two lowest-viability groups correspond to cytotoxic conditions (Doxorubicin, BG-45S5 50 µg/mL), while remaining groups showed acceptable compatibility. The results of the statistical analysis are cited in table 1.

Table 1 : Mean cell viability (± SD) of human PDL fibroblasts after exposure to varying concentrations of 45S bioactive glass–based intracanal medicament.

Group	Concentration (µg/mL)	n	Mean ± SD Viability (%)	Variance
Doxorubicin (Positive control)	—	**4**	**79.34 ± 1.99**	**1.82**
BG-45S Compound	**1**	**4**	**99.8 ± 1.92**	**3.68**
BG-45S Compound	**10**	**4**	**95.4 ± 0.94**	**0.88**
BG-45S Compound	**25**	**4**	**92.1 ± 0.82**	**0.67**
BG-45S Compound	**50**	**4**	**87.6 ± 1.19**	**1.19**
Control	**0**	**4**	**100 ± 0.56**	**0.56**

ANOVA: F(5,18)=6.29, p=0.0015 (significant)

Discussion

In this study the assessed cytocompatibility of a 45S5 bioactive glass-based intracanal medicament (BG-45S5) was done with the use of human periodontal ligament fibroblasts with MTT assay being a quantitative metric of cellular metabolic activity. This data indicated a distinct concentration-dependent effect: at the low concentration of (1–10 µg mL -1) the cell viability was not lower than 75 per cent, and at the high concentrations (25-50 µg mL -1) the mitochondrial activity was relatively reduced. The doxorubicin generated in the positive control exhibited the anticipated high cytotoxicity consequently confirming the sensitivity of the assay. These findings support the evidence that BG-45S5 shows acceptable short-term biocompatibility when used at relevant concentrations, consistent with the general safety profile reported for bioactive glass compositions in dental and orthopedic applications [3–6].

It is possible to attribute the biocompatibility of BG -45S5 to its regulated ionic dissolution profile, which allows to control the cellular microenvironment without causing an excessive alkalinity or osmotic stress.When it is exposed to aqueous media, BG-45S5 releases sodium, calcium and phosphate ions, and, thus, increases the local pH to about 10-11. Although this temporary alkalinity also helps in its antimicrobial property, the high ion release rate at high concentrations of the substance can negatively affect mitochondrial activity due to its oxidative stress or the transfer of the membrane potential [7,8]. The present results align with the hypothesis that optimal biological response occurs within a narrow range of ion concentrations, beyond which cytotoxicity may develop due to ionic imbalance or elevated osmolarity. Previous studies have shown that bioactive Glass preparations, including S53P4 and 45S5, can be used to create layers of hydroxycarbonate apatite (HCA) on the surfaces of dentin and bone, and thus serve as an intermediate chemical bond between the restorative material and the biological tissues [4,5,9]. The newly generated Ca 2+ and silicate species of these glasses stimulate the expression of osteogenic transcriptional activity, enhances collagen synthesis, and promotes mineral deposition through osteoblastic signaling pathways activation, such as alkaline phosphatase and osteocalcin expression [25,26]. The ions released within populations of fibroblasts probably mediate intracellular signaling bouts, including ERK1/2 and p38 MAPK, which are involved in cell division and extracellular matrix dynamics [24]. High cell viability at low cell concentrations in the current study shows that the ionic environment generated by BG-45S5 supports normative cellular processes of metabolism and can also enhance reparative signaling pathways.

The minor cytotoxicity that was measured at 25–50 µg/mL could be explained by the increased rate of dissolution, creating the condition of local alkalinisation. Bakry et al. also reported similar results and reported reduced fibroblast proliferation caused by high levels of the 45S5 desensitising paste but stimulated cell attachments and morphology at lower levels [22]. According to Waltimo et al. nanometric 45S5 particles killed E. faecalis after 24 hours, but caused a slight permanent reduction in fibroblast metabolic activity at concentrations above 100 µg/mL [6]. These data are supported in the current study, which emphasizes the idea that bioglass has a therapeutic window, in which antimicrobial activity and cytocompatibility are co-existing. In clinical practice, intracanal medicaments need to balance the antimicrobial effect with biocompatibility to avoid periapical irritation. Although effective in most of the pathogens of the canal, calcium hydroxide can cause necrosis and inflammatory reactions when extruded past the apex due to its elevated pH (>12.5) [1,2]. The advantage of bioactive glass is that it achieves the moderate level of alkalinity that is neither too high that it discourages the growth of microbes nor too low that it fails to address the physiologic tolerance of the periapical tissues [9,10]. Besides, its ability to release Ca^{2+} and phosphate ions enhances the dentin remineralisation process and can speed up the recovery of periapical lesions [17,18].

The MTT test used in this paper provides a sensitive and reproducible test of the mitochondrial dehydrogenase activity, which is a valid proxy of cell viability [13,15]. However, this assay is mostly indicative of metabolic ability, as opposed to prolonged survival or proliferation kinetics. Additional assays such as Live/Dead staining, lactate dehydrogenase (LDH) release assay or flow cytometric analysis would allow distinguishing between apoptotic and necrotic responses and improve the interpretation of the cytotoxic effects [19,20]. However, the combination of quantitative viability measures and morphological analyses generates a strong initial evaluation of biological tolerance in line with the requirements of ISO 10993-5 standards [12]. A critical mechanistic factor is the contact of bioactive Glass ions with the culture medium. The buffering properties of DMEM and the existence of serum proteins have the potential of adjusting kinetics of ion-exchange and affecting pH elevation [14,16].

Thus, the variation in viability, which was found with varying concentrations, probably reflects the balance between the rate of dissolution and the buffering power of the medium. Future studies must hence include real-time ion-release profiling and continuous pH

measurements to be able to relate physicochemical variables to cellular responses. Additionally, the molecular evidence of markers (COL1A1, ALP, RUNX2) of BG-induced mineralization and tissue regeneration would be molecularly supported [25,27]. BG-45S5 regenerative capability represents a research field that is becoming more relevant.

The ionic components of it have been shown to induce stem-cell differentiation, angiogenesis, and development of mineralized tissue with the release of calcium and silicate under a controlled mode [25,28]. In this regard, in addition to playing the role of a disinfecting intracanal medicament, BG45S5 may also play a functional role in tissue repair, which would be a rational combination of disinfection and biomimetic repair. Such materials incorporated in regenerative endodontic protocols can thereby increase antimicrobial effectiveness and increase healing of the periapical. Despite these promising results, the current study is limited due to its short exposure period and in vitro model, which can not model the complex biological processes occurring in periapical tissues. The effects of host immune responses, vascular perfusion, and dentin buffering on material behavior may have a significant effect in vivo. In turn, extended culture periods and animal in-vivo models would be critical phases of measuring chronic tissue reactions and confirming biocompatibility in a clinical setting. Finally, this paper defines that 45S5 bioactive Glass has a concentration-dependent cytocompatibility with an acceptable cell viability of ≤10 µg/mL. The twofold nature of the material, i.e. ability to release therapeutic ions and at the same time be tolerated by the cell, points to the future as a next-generation intracanal medicament. Following additional streamlining, BG 45S might be utilized as a biologically active compound that would also assist in disinfection and tissue regeneration during endodontic treatment.

Conclusion

Within the limitations of this study, **BG-45S5 intracanal medicament demonstrated good cytocompatibility at concentrations ≤ 10 µg/mL** and a concentration-dependent decline in fibroblast viability at higher levels. The material meets the required preliminary ISO 10993-5 biocompatibility criteria for in-vitro evaluation and merits further investigation as a biologically favorable intracanal medicament.

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