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ORIGINAL ARTICLE

Development and characterization of experimental ZnO cement containing niobophosphate bioactive glass as filling temporary material

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Abstract *Aims:* The aim of this study was to develop and characterize a temporary restorative material based on a zinc oxide matrix containing niobophosphate bioactive glass (NbG) for the caries-affected dentin treatment.

Material and methods: NbG was added to a ZnO_2 matrix in different concentrations (wt%). EDS-SEM, ATR-FTIR and XRD analyses were performed to characterize the cement. Calcium release was evaluated in TRIS solution after 1, 7 and 14 days by colorimetric method (A_{650}). Compressive strengths and setting times were performed to analyze mechanical properties.

Results: EDS spectra confirmed the presence of Ca, P and Nb in the groups containing NbG. EDS mapping exhibit the ZnO_2 homogeneous distribution, and NbG immersed in this matrix. Peaks suggesting interaction between matrix and NbG were not detected in Ftir spectra. Calcium releasing showed to be time-dependent for experimental groups containing 10, 20, 30 and 40%.

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The NbG incorporation progressively increased the compressive strength values in the experimental groups. NbG incorporation seemed to influence the ZnO_2 matrix early setting reaction. No statistical difference was observed in the final setting time.

Conclusion: The addition of NbG particles into zinc oxide matrix could work as a mechanical reinforcement. It is suggested that the calcium released by the cement containing at least 10% NbG could induce apatite formation.

1. Introduction

Encouraging minimal invasive dentistry (Mm et al., 2014), mainly for dental caries treatment (Thompson et al., 2008; Bjørndal, 2018), has led to the development of conservative strategies (McComb, 2000; Pintado-Palomino et al., 2019) that involve the preservation of the affected dentin for lesion treatment (Statement, 2017). In this regard, the development of bioactive restorative materials has become a necessity and it has been the subject of studies (Abuna et al., 2016; Amrollahi et al., 2016, Braga, 2019; Sauro and Pashley, 2016).

The bioactivity concept involves materials capable of promoting apatite crystals precipitation when exposed to a Ca and P-rich solution (Niu et al., 2014; Vallittu et al., 2018). In this context, bioactive glass particles present promising bioactive properties due to their ability to release ions and forming an apatite-like mineral (Fernando et al., 2017). The use of bioactive glass particles as bone graft has been extensively studied and has a recognized capacity for bone adhesion and osteogenic cells stimulation (Braem et al., 2012; El-Rashidy et al., 2017; Schepers et al., 1991). Considering this activity, the use of bioactive particles in dental restorative materials was suggested as an approach that would also be able to stimulate enamel and dentin mineralization (Vollenweider et al., 2007).

The apatite formation on partially demineralized dentin has already been achieved either by the direct application of bioactive particles (Vollenweider et al., 2007; Wang et al., 2011), or by its indirect application, for example, by the addition of bioactive glass to restorative resin composites (Alania et al., 2019; Bauer et al., 2019; Crovace et al., 2016; Proença et al., 2020; Tezvergil-Mutluay et al., 2017; Wang et al., 2014). Among glass particles containing bioactive properties, it was observed that phosphate-based glasses have an excellent Ca/P ratio, similar to human mineralized structures (Karakassides et al., 2004). However, in order to enhance this achievement, authors have added other types of components to the glass formulas.

In this context, the development of bioactive glasses containing niobium was obtained from the addition of niobium oxide in the conventional phosphate glasses structure (niobophosphate bioactive glass - NbG), improving their chemical durability (Carbonari et al., 2003). The application of these particles to resin-based materials or as a dentin rewetting has brought new insights into the treatment of caries lesions, since the addition of niobophosphate bioactive glass (NbG) allowed the increasing of material longevity, besides providing antimicrobial and remineralizing properties for them (Bauer et al., 2016; Carneiro et al., 2018; Carvalho et al., 2015; Proença et al., 2020).

Thus, the development of bioactive materials that may assist in the caries lesions treatment, whether by the remineralizing or antimicrobial capacities, but mainly by their absence of inertia, should be encouraged. Therefore, the objective of this study was to develop and characterize a temporary restorative material for caries affected dentin treatment, based on a zinc oxide matrix containing bioactive NbG particles. The hypothesis tested was that the addition of NbG particle to the zinc oxide matrix would provide Ca ions and structural reinforcement to the experimental cement.

2. Materials and Methods

2.1. Niobium phosphate glass preparation

NbG glasses were prepared by melting mixtures of diammonium phosphate (33.1 mol%, Reagent Grade - Casa Americana, São Paulo, SP, Brazil), niobium oxide (13.0 mol%, Optical Grade - Companhia Brasileira de Mineração e Metalurgia, Araxá, MG, Brazil), calcium oxide (47.28 mol%, Reagent Grade – Casa Americana) and sodium carbonate (6.62 mol%, Reagent Grade - Casa Americana). The chemical compounds were mixed in a shaker-mixer for 1 h, placed in an alumina crucible, and heated in an electric furnace (Lindberg, Blue M, Il, USA). The heating rate was 10 °C/min up to 500 °C and the blend was kept on air at this temperature for 30 min to eliminate the volatile products. Then, the blend was heated to 1400 °C to completely melt the precursors and it was kept at this temperature for 20 min for homogenization and degassing. The molten blend was poured into a stainless-steel mold and cooled at room temperature. The glass was then crushed in a vibrating system (8000 M, Mixer/Mill, SPEX SamplePrep, NJ, USA) with tungsten carbide grinding vial balls (SPEX SamplePrep, NJ, USA) for 30 min. After grinding, the resultant powder passed through a series of sieves of 150 μm – 75 μm – 53 μm – 38 μm – 20 μm (Hogentogler & Co., Inc, Columbia, MD, USA), and only the powder that passed through the 20 μm sieve was further used to make the experimental cement.

2.2. Cements preparation

The experimental cement was prepared by the mixture of zinc oxide (ZnO_2), zinc sulphate ($ZnSO_4$) and ethoxy-benzic acid ($C_9H_{10}O_3$), to obtain a powder/liquid formulation. At this blend, bioactive particles (NbG: 40.1% Nb_2O_5, 32.8% P_2O_5, 21.2% CaO, Al_2O_3 3.8%, 2.1% Na_2O) were added. Each experimental group was composed by a pre-established amount ZnO matrix varying only the concentration of niobophosphate bioactive glass (Table 1). The mixture of each

specimen was carried out at room temperature (23 °C) and 60 ± 5% of relative humidity. The concentrations of the matrix components were defined based on a previous pilot study.

2.3. Cements characterization

Compositional analyzes were performed on cement samples (n = 3) by energy-dispersive X-ray spectroscopy (EDS) using a scanning electron microscope (SEM, JSM-5600LV; JEOL, Tokyo, Japan) operated at 15 kV. Elemental mapping was obtained for all samples. Chemical interaction between the cement components was characterized by total reflectance Fourier-transform infrared spectroscopy (ATR-FTIR; Tensor 27, BRUKER, Germany). Samples were set over the crystal with a spectral resolution of 4 cm^{-1} and 32 scans for each analysis. All the spectra were recorded three times and an average spectrum was used. The crystalline phases present after components mixing were determined by X-ray diffraction (XRD) operated with Cu Kα radiation (X-ray diffraction constant) λ = 0.15418 nm. The diffraction patterns were obtained in the 2θ range from 10° to 90° in continuous mode at 2°/min (Bruker D8 Advance, Bruker Corp., Billerica, MA, USA).

2.4. Calcium releasing

For ion releasing assessment, TRIS solution was prepared and buffered to pH 7.0 with 50 mmol/L HEPES. Three cylindrical specimens (n = 3) (10 × 1 mm) were made and immediately immersed in 5 mL of pH 7.0 solution, at 37 °C. At each evaluation time point (1, 7 and 14 days), a small amount of the TRIS solution was extracted to calculate the cumulative amount of calcium (Ca^{2+}) released from the cement samples. Calcium concentration was assessed using a colorimetric method (Vogel et al., 1983), as described elsewhere (Costa Oliveira et al., 2017), from a 5 μL sample volume, in duplicate, to estimate the calcium concentration in the solution.

2.5. Setting times

Setting times were performed based on ISO 3107 recommendations (ISO/TC106. Dentistry, restorative materials., 2004 in ISOFDIS 3107). Five cylindrical specimens (n = 5) were used to measure the setting times and a Gillmore needle (diameter 2.0 ± 0.1 mm and mass 100 ± 0.5 g) was vertically positioned onto the surface of the cement every 15 s. Setting time was the

Table 1 Experimental cement composition.

Matrix composition	Experimental group/NbG %	
Zinc oxide (ZnO_2) 50%	Control	0
Zinc Sulphate (Zn_2SO_4) 15%	1	5
Ethoxybenzoic acid-2 ($C_9H_{10}O_3$) 20%	2	10
Ethoxybenzoic acid-4 ($C_9H_{10}O_3$) 15%	3	20
	4	30
	5	40

Niobium Phosphate Bioactive Glass (NbG) 40.1% Nb_2O_5, 32.8% P_2O_5, 21.2% CaO, Al_2O_3 3.8%, 2.1% Na_2O.

time from the start of mixing until the time in which the indenter failed to completely penetrate the depth of the cement.

2.6. Compressive strength

Five cylindrical specimens (n = 5) with 6 mm of height and 4 mm of diameter were made using silicon molds for each group. After one hour-mixing, the specimens were lapped in their molds with 1200-grit silicon-carbide paper and purified water. All specimens were maintained in purified water at 37 °C until the time of testing. Testing was then performed 24 h after specimen production on a universal testing machine (Model 5544, Instron, Massachusetts, USA) at a crosshead speed of 1.0 mm/min.

2.7. Statistical analyses

For statistical analysis, the GraphPad Software (GraphPad Prism, version 8, La Jolla, CA, USA) was used. Kolmogorov-Smirnov test was used to check the data normal distribution and transformations were performed when needed. Mechanical properties data were analyzed by One-way ANOVA and Tukey's test. Calcium release data were analyzed by RM Two-way ANOVA followed by Tukey's test. The significance level α was set in 5% and a test power of 80%.

3. Results

3.1. Cements characterization

Energy-dispersive X-ray spectroscopy analysis showed the presence of the elements Ca, P and Nb (components of the NbG particles) in the cement samples, except for the control group (Fig. 1). In the mapping performed by EDS, the homogeneous distribution of the matrix obtained from the mixture of ethoxybenzoic acid and zinc oxide (Fig. 2A), and the presence of NbG particles immersed in the matrix were observed (Fig. 2B).

Peaks of 1673, 1110, 754 cm^{-1} were observed in the spectra obtained by FTIR, corresponding to Zn-O binding. Meanwhile, peaks of 921, 851, 641 cm^{-1} were representative of the different types of Nb-bindings. Changings were not observed at peaks related to Zn-O binding after addition of the particles in the matrix. In addition, peaks suggesting interaction between matrix and NbG particles were not detected.

The X-ray diffraction patterns indicated the presence of zincite (ICSD 31052), a compound related to the crystallization of zinc oxide, in all experimental groups (Fig. 3).

3.2. Calcium releasing

As shown in Fig. 4, the Ca^{2+} release from cements showed to be time-dependent for experimental groups containing 10, 20, 30, and 40% NbG. These formulations exhibited the same release pattern, differing from the control group and increasing linearly over time. For 5% NbG cement samples, low Ca^{2+} concentration was observed, not differing statistically from the control group. No Ca^{2+} was released from the control group samples.
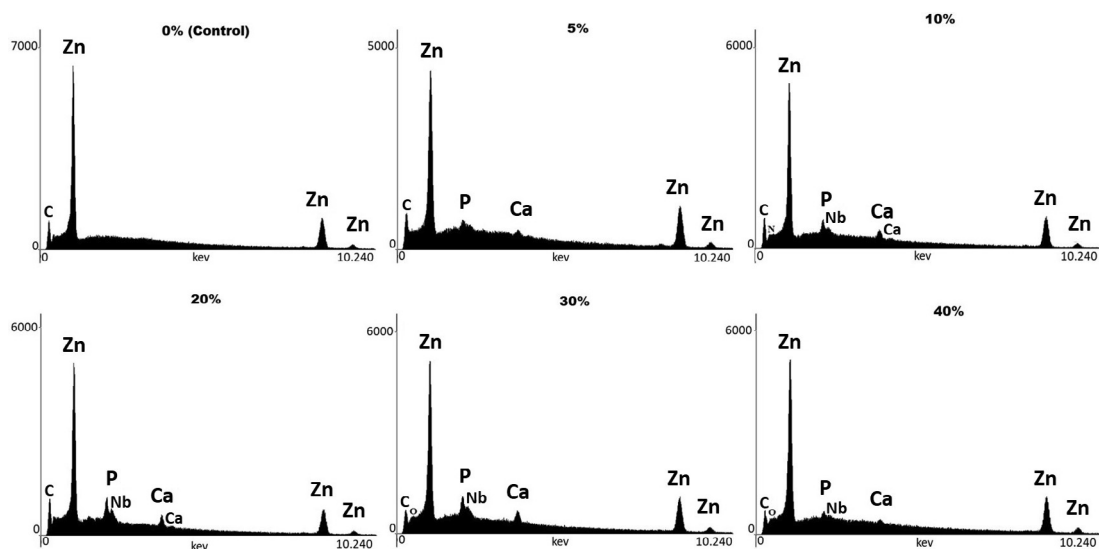
Fig. 1 Energy Dispersive X-ray Spectroscopy (EDS) analysis showing the Ca, P and Nb elements present in the cement composition for all experimental groups containing NbG particles. The control group spectrum shows only the presence of Zn and C ions related to the formation of the zinc oxide matrix.
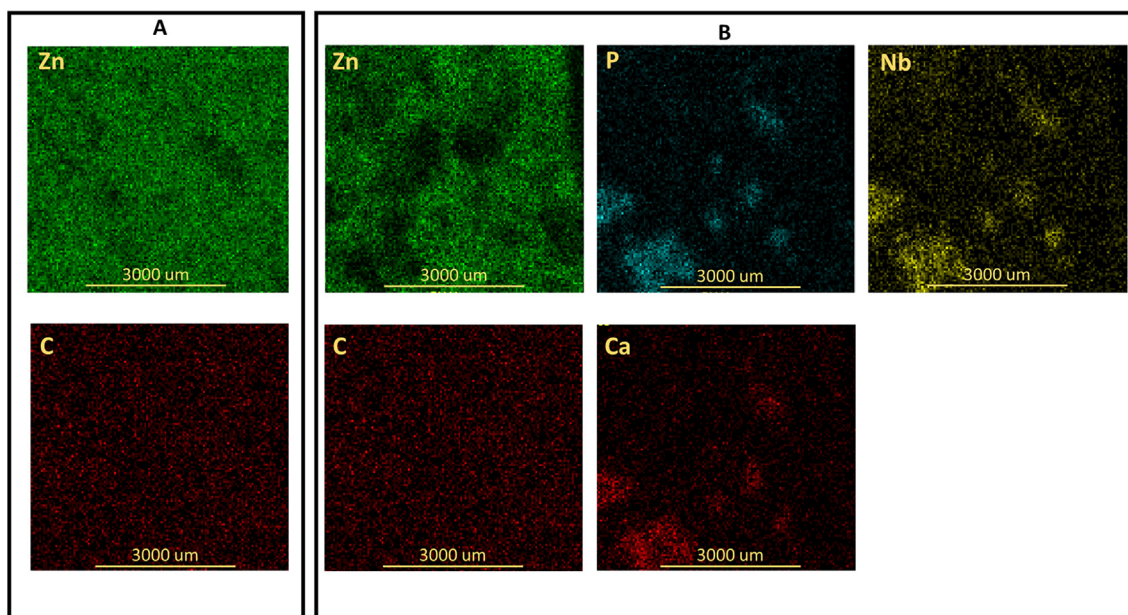

Fig. 2 EDS mapping images showing presence of Zn and C elements in the control group cement sample (A) and experimental cement groups showing the presence of Ca, P and Nb (NbG components) immerse in a ZnO matrix (B).

3.3. Physical properties

The average of final setting times is described in Table 2. Albeit a slight increase in values had been observed as the concentration of NbG increased, a statistically significant difference was not found among groups ($p < 0.05$). A similar result was found in the compressive strength data (Table 2). The incorporation of NbG progressively increased compressive strength values in the experimental groups (Table 2). A statistically significant difference was observed between control and the experimental group containing 40% NbG particles.

4. Discussion

The conservation of dental tissue, either intact or subject to remineralization, has been basing the concept of minimally invasive dentistry (Ismail et al., 2013; Philip, 2019). In this way, clinical interventions should be limited to the removal of friable enamel and softened dentin (caries-infected dentin), preserving enamel and partially demineralized dentin (caries-affected dentin) regions (Pintado-Palomino et al., 2019).

However, due to the bacterial action, these regions present changings in their morphological, chemical, and consequently
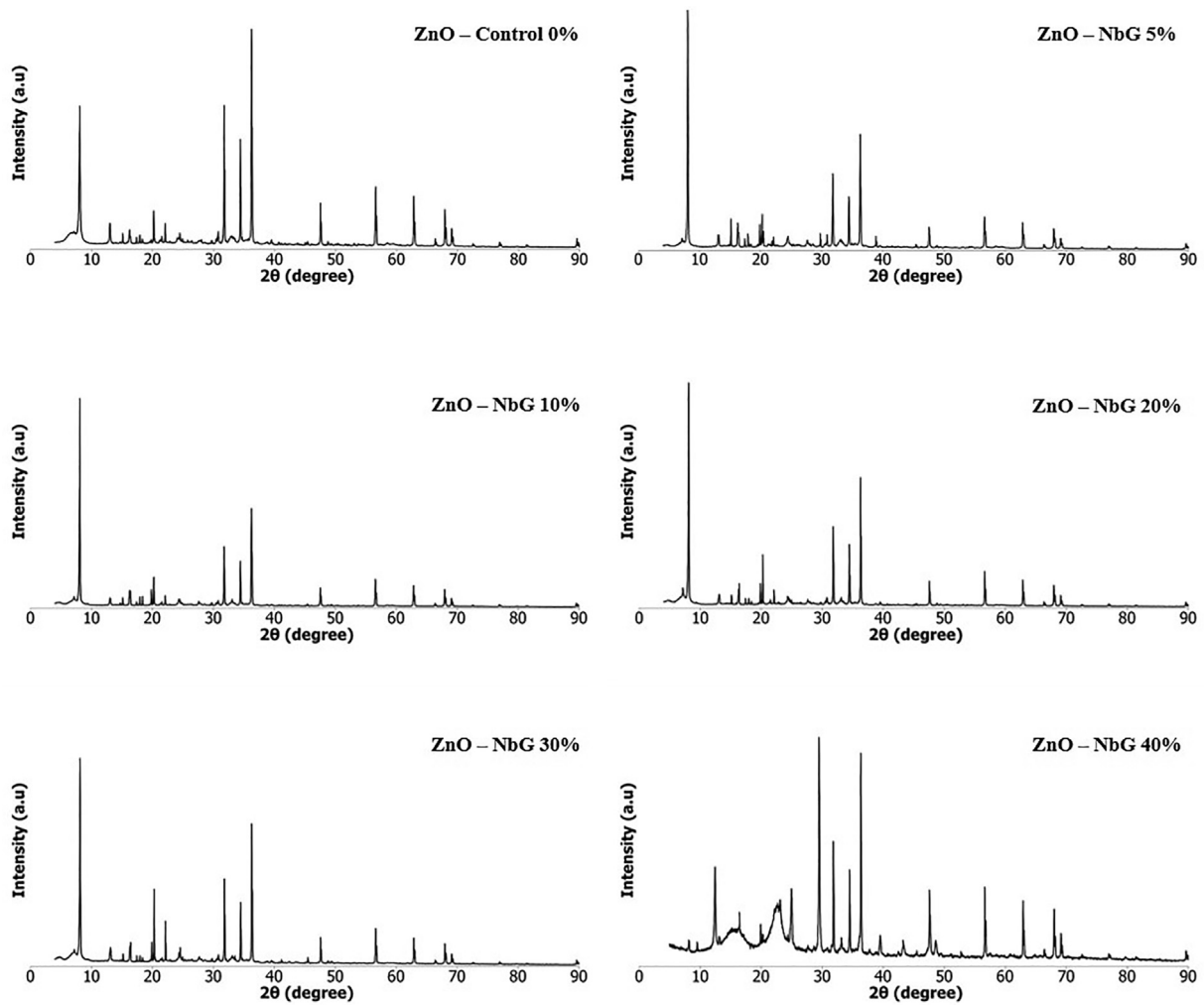
Fig. 3 X-ray diffraction patterns of experimental cement containing different NbG concentrations. The diffractogram indicates the presence of zincite and sodium potassium niobate minerals related to the zinc matrix and the NbG particle, respectively.
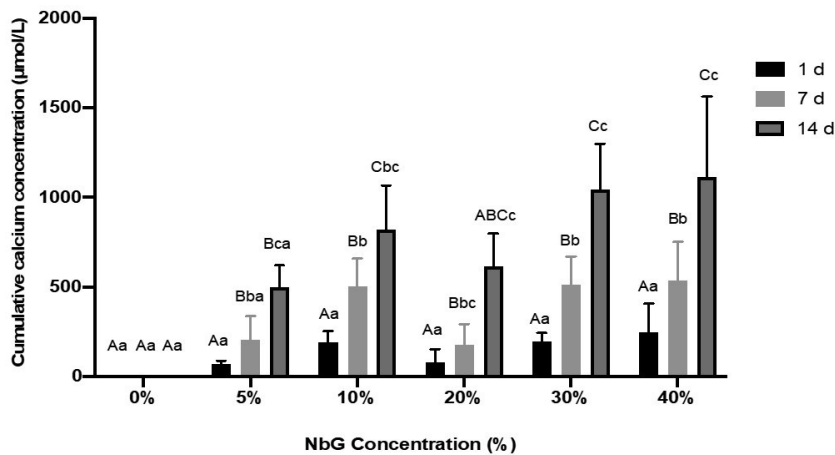

Fig. 4 Cumulative calcium concentration released by the experimental cements. Different capital letters indicate statistically significant differences among concentrations, evaluated in the same time point. Different lowercases indicate statistically significant differences among times, into each NbG concentration.

Table 2 Mean (SD) values of physical properties of the experimental cement containing different concentration of Niobium phosphate glass (NbG) (One-way ANOVA; $p < 0.05$; $n = 5$).

NbG (%)	Setting time (min) Final	Compressive strength (MPa)
0	7.3 (0.3) A	10.95 (2.6) A
5	6.46 (0.4) A	14.22 (1.8) AB
10	7.46 (0.3) A	18.35 (3.3) BC
20	7.08 (0.3) A	18.11 (2.5) BC
30	7.16 (0.5) A	19.09 (1.7) BC
40	8.13 (0.2) A	23.19 (3.8) C

For each physical property distinct capital letters indicate statically significance ($p < 0.05$) differences among groups (rows).

in their mechanical properties (Pugach et al., 2009). Studies indicate that such changings may negatively affect the longevity of definitive restorations performed on these regions (Nakajima et al., 2011). This fact, along with the progressive development of remineralization strategies (Philip, 2019), converges to the development of materials able to recover the affected tissue before the definitive restorative treatment. In this study, we developed and characterized a ZnO-based temporary restorative material containing NbG bioactive particles, which could potentialize the effect of this material, contributing to the dental tissue remineralization under a minimally invasive dentistry context. Additionally, elemental analysis demonstrated the presence of the NbG particles immersed into the ZnO matrix (Figs. 1 and 2). In the obtained FTIR spectra, no peak pointed out possible chemical groups related to the chemical interaction between the particle-forming elements and the matrix.

Similarly to commercial ZnO cements (Wong et al., 2011), the reaction of experimental material formation can be summarized in two phases: 1) ZnO hydrolysis and zinc hydroxide formation, and 2) Reaction of zinc hydroxide with polymerized fatty acids (ethoxybenzoic acid), forming a chelate. In this way, an amorphous matrix is formed, as demonstrated in the X-ray diffraction patterns (Fig. 3), in which particles of zinc oxide and NbG not consumed during the reaction are found (Figs. 1 and 2).

The results obtained in the setting time and compressive strength mechanical tests (Table 2) reinforced the evidence of absence of interaction between NbG particles and the matrix, during the setting reaction. Before carrying out the experiments, a sample size calculation was done in order to reach a test power of 80%. Previous studies were used as parameters for the calculation based on average and standard deviation thereby allowing us to use 5 specimens per group (Wong et al., 2011). The addition of different concentrations of NbG particles showed no influence on the final setting time of the reaction. Moreover, the compressive strength results complied with the requirements of a minimum 5 MPa value, described in ISO standard 3107 for type II materials set for bases and temporary restorations (ISO 3107:2011). The values presented direct relationship with the concentration present in the particles, suggesting the particles are working as a mechanical reinforcement for the cement. Similar behavior was observed when NbG particles were applied in resin matrix of dental adhesives or composite (Carneiro et al., 2018; Carvalho et al., 2015; Proença et al., 2020). These results can

be explained by the chemical stability of NbG bioactive glasses (Carbonari et al., 2003). Such capacity is only possible due to the addition of Nb ions in the conventional phosphate glass structure (Knowles et al., 2001; Lopes et al., 2014). The presence of this element leads to the formation of mixed chains O-P-O-Nb-O-P-O (Carbonari et al., 2003), responsible for structural changes that affect the chemical stability and solubility of the particles (Altmann et al., 2017).

The bioactivity of glass particles is directly related to their dissolution and the biochemical interactions involved in this process, such as the calcium ions releasing, changings in the pH of the medium, and the formation of mineral precipitates (Brauer, 2015; Hench, 1991). Regarding dissolution, NbG particles presented slow/low ions release when compared to conventional silicate glasses (Bauer et al., 2016). However, this characteristic does not compromise the bioactivity of these particles (Carneiro et al., 2018). Here, the Ca^{2+} ion release readings demonstrated a direct relationship with the time, when considering concentrations above 5% (Fig. 4). As expected, all experimental groups containing bioactive particles released Ca^{2+} ions, favoring the interactions between the free ions and the dental structures. When the dentin mineral induction capacity was evaluated in the literature, it was observed the use of calcium in concentrations above 200 μM was able to induce mineral formation in about 10 h (Saito et al., 2003). In this context, all experimental groups containing NbG particles, starting at 10%, would be capable of releasing enough Ca^{2+} ions for mineral induction from the 7th day. The graphs show a trend of increasing the Ca^{2+} releasing over time. Despite of these results, it is important to consider that in many countries, temporary materials are used in periods longer than 14 days (Milani et al., 2017) and a long-term evaluation of the experimental material is encouraged.

The mineralization process induced by bioactive glass particles involves a cascade of interactions between particle and body fluids (Andersson and Kangasniemi, 1991; Brauer, 2015; Martin et al., 2009). Thus, from 45S5 bioactive glasses use, it would initially occur an ion exchanging, and increasing of the medium pH followed by hydrolysis of Si—O—Si bonds (Hench et al., 2006). Afterwards, a condensation reaction between Si—OH groups would occur, generating a polymerized particle layer (Brauer, 2015). On NbG particles, this process occurs similarly, except by the surface layer that would be formed by Nb-OH groups. As in the silicate particles, the layer would act as a nucleation template for apatite formation. initially forming calcium phosphate (Ca/P) that later becomes hydroxycarbonate apatite with the course of the process (Bauer et al., 2016; Lopes et al., 2014). Additionally, studies have highlighted the ability of niobium to induce mineral (Karlinsey et al., 2006), which also would work as a hydroxyapatite crystals nucleator (da Rocha et al., 2013).

Here we showed the development of a temporary restorative material based on zinc oxide and different concentrations of NbG particles. The properties presented by the material are suitable for its use as a temporary dental restorative material. The NbG content attributes bioactivity to the material, which may contribute for dentin mineralization, as demonstrated by Bauer et al, 2019. Compositions containing 30 and 40% of particles are those indicated for invention development, since they had better mechanical and ions releasing results. Further studies should be carried out in order to analyze the bioactive properties of the material and possible applications.

5. Conclusions

The addition of NbG particles into zinc oxide matrix is chemically feasible and could work as a mechanical reinforcement for the restorative material. In addition, the amount of calcium released by the cement samples containing at least 10% NbG could induce apatite mineral formation in caries-affected dentin.

6. Patents

This work has a patent registered under BR 10 2016 013838-8 number.

Ethical Statement

For this publication does not apply.

CRediT authorship contribution statement

Paulo Vitor Campos Ferreira: Conceptualization, Methodology. **Gabriel Flores Abuna:** Conceptualization, Methodology, Data curation, Writing - original draft. **Bárbara Emanoele Costa Oliveira:** Data curation, Writing - original draft. **Simonides Consani:** Visualization. **Mário Sinhoreti:** Supervision, Investigation. **Ceci Nunes Carvalho:** Validation. **José Bauer:** Data curation, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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