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IAGO CÉSAR RIBEIRO TELES MATOS

EFEITOS DE GEL CLAREADOR EXPERIMENTAL CONTENDO DIÓXIDO DE TITÂNIO CO-DOPADO E PENTÓXIDO DE NIÓBIO ASSOCIADO À LUZ VIOLETA NA ESTABILIDADE QUÍMICA, POTENCIAL CLAREADOR E CONTEÚDO MINERAL DO ESMALTE DENTAL

EFFECTS OF EXPERIMENTAL BLEACHING GEL CONTAINING CO-DOPED TITANIUM DIOXIDE AND NIOBIUM PENTOXIDE COMBINED WITH VIOLET LIGHT ON CHEMICAL STABILITY, WHITENING POTENTIAL AND ENAMEL MINERAL CONTENT

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Dissertation presented to the Piracicaba Dental School of the University of Campinas in partial fulfillment of the requirements for the degree of Master in Dental Clinic, in Dentistry area.

Orientador: Profª. Drª. Vanessa Cavalli Gobbo

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RESUMO

Apesar de bastante difundido, o clareamento dental promove efeitos adversos ao esmalte e sensibilidade dentinária. Acredita-se que a incorporação de diferentes concentrações de nanopartículas (NPs) de dióxido de titânio (NF_TiO_2) associadas com o pentóxido de nióbio (Nb_5O_2) podem atuar sinergicamente, aumentando o potencial oxidativo do peróxido de hidrogênio (PH), melhorando as propriedades químicas e biológicas, e otimizando a eficácia do gel clareador. Dessa forma, o objetivo deste estudo foi avaliar a estabilidade química, potencial clareador e efeitos no conteúdo mineral e morfologia do esmalte de géis clareadores experimentais contendo PH 6%, NPs de NF_ TiO_2 e/ou Nb_5O_5 submetido ou não à irradiação com luz violeta. Na fase 1, as NPs de NF_TiO_2 foram sintetizadas e os géis experimentais foram caracterizados por meio de análise da estabilidade preliminar e acelerada, análise de pH, e titulação de PH. Na fase 2, foi determinada a alteração de cor dental (ΔE_{00}) e índice de clareamento (WI_D) e na fase 3, avaliação da microdureza (DS), alteração da rugosidade média de superfície (ΔRa), concentração de Ca e P (espectroscopia por energia dispersiva de raio-X - EDS) e morfologia do esmalte (microscopia eletrônica de varredura, MEV). Blocos de esmalte bovino foram aleatoriamente divididos e tratados com (n=10): PH 6% contendo 5% NF_TiO_2, 5% Nb_2O_5, 2,5% NF_TiO_2 + 2,5% Nb_2O_5 ou apenas PH 6% (sem partículas). Os grupos foram irradiados ou não com luz LED violeta (LED). O grupo controle foi tratado com PH 35% comercial (PH 35%). O clareamento foi realizado em 3 sessões de 30 min com intervalo de 7 dias. Os dados foram submetidos à ANOVA de dois (pH, titulação, ΔE_{00}, e ΔWI_D) e três fatores (DS) com post-hoc Tukey, e Kruskal-Wallis (ΔRa) (α = 0,05). Os géis não apresentaram alterações de cor, odor e translucidez na análise preliminar e acelerada, e o pH dos géis experimentais permaneceu estável ao longo do tempo, com valores médios de 6 a 6,5. A titulação indicou aumento na concentração de H_2O_2 nos grupos irradiados com LED. Os géis contendo NF_TiO_2 e Nb_2O_5 apresentaram maior ΔE_{00} e ΔWI_D quando irradiados com o LED ($p<0,05$) e não apresentaram diferenças em ΔE_{00} e ΔWI_D em relação ao PH 35%. Houve diminuição da DS do esmalte tratado com Nb_2O_5 e Nb_2O_5 + TiO_2, sem LED ($p<0,05$), porém sem diferenças entre os demais grupos ($p>0,05$). Não houve alteração significante da rugosidade (ΔRa), conteúdo de Ca e P (EDS) e morfologia (MEV) do esmalte após tratamentos ($p>0,05$). Conclui-se que os géis clareadores experimentais contendo

NF_TiO_2 ou Nb_2O_5, e irradiados com luz LED, apresentaram estabilidade química, potencial clareador semelhante ao PH 35%, e não promoveram efeitos adversos na estrutura do esmalte.

Palavras-chave: nanopartículas, titânio, nióbio, clareamento dental

ABSTRACT

Although widespread, tooth bleaching promotes adverse effects on enamel and dentin sensitivity. It is believed that the incorporation of different concentrations of titanium dioxide nanoparticles (NPs) (NF_TiO_2) associated with niobium pentoxide (Nb_5O_5) may act synergistically, increasing the oxidative potential of hydrogen peroxide (HP - H_2O_2), improving the chemical and biological properties, and optimizing the effectiveness of the whitening gel. Thus, this study evaluated the chemical stability, bleaching potential, and effects of experimental bleaching gels containing HP, NPs of NF_ TiO_2, and/or Nb_5O_5, submitted or not to violet LED light on mineral content and enamel morphology. In phase 1, NPs were synthesized, and experimental gels were characterized by means of preliminary and accelerated stability analysis, pH analysis, and pH titration. In phase 2, tooth color (ΔE_{00}) and whitening index (W_{ID}) variations were determined, and in phase 3, evaluation of microhardness (SH), mean surface roughness (ΔRa), the concentration of Ca and P (spectroscopy by energy dispersive X-ray - EDS) and enamel morphology (scanning electron microscopy, SEM). Bovine enamel blocks were randomly divided and treated with 6% HP containing (n=10): 5% NF_ TiO_2, 5% Nb_5O_5, 2.5% NF_ TiO_2 + 2.5% Nb_5O_5 or without particle (6% HP). The groups were irradiated or not with violet LED light (LED). The positive control group was treated with commercial 35% HP (CP). Bleaching was performed in 3 sessions of 30 min with an interval of 7 days. Data were submitted to two (pH, titration, ΔE_{00}, and ΔW_{ID}) and three-way (SH) and Tukey post-hoc, Kruskal-Wallis (ΔRa) ANOVA (α = 0.05). The gels did not show color, odor, and translucency alterations in the preliminary and accelerated analysis, and the pH of the experimental gels remained stable over time with average values of 6 to 6.5. The decomposition rate indicated the Concentration of H_2O_2 in solution in the groups irradiated with LED. Gels containing NF_TiO_2 and/or Nb_5O_2 showed higher ΔE_{00} and ΔW_{ID} when irradiated with LED ($p<0.05$), and no differences in color parameters in comparison with 35% HP. SH decreased even after Nb_5O_5 and Nb_5O_5 + TiO_2, without LED ($p<0.05$), but without differences between groups ($p>0.05$). No significant change in roughness (ΔRa), Ca and P content (EDS), and morphology (SE<) of enamel after treatments ($p>0.05$). In conclusion, experimental 6% HP gels containing NF_TiO_2 or Nb_2O_5 and light-irradiated, were chemically stable, exhibiting bleaching potential comparable with 35% HP, without causing enamel adverse effects.

Keywords: nanoparticles, titanium, niobium, tooth whitening

SUMÁRIO

ANEXO

1 INTRODUÇÃO

O clareamento dental figura entre os procedimentos clínicos estéticos de maior popularidade entre dentistas e pacientes (Joiner et al., 2017). Esta popularidade deve-se a alta demanda e preocupação com a estética do sorriso. Autores revelam que 86% da população adulta brasileira deseja realizar tratamentos clareadores de consultório (Silva et al., 2015). A ampla adesão ao tratamento justifica-se pelas características ultraconservadoras e minimamente invasivas da técnica, uma vez que o clareamento atua na decomposição de pigmentos, sem que haja remoção de estrutura do substrato dental (Ubaldini et al., 2013, Lima et al., 2018), tornando-se uma forma segura de obtenção de resultado estético.

Dentre as técnicas de clareamento, a de consultório utiliza altas concentrações (25 a 40%) de peróxido de hidrogênio (PH) aplicadas diretamente à superfície do esmalte (Basting et al., 2012). Seu mecanismo de ação e sua consequente ação clareadora é baseado na geração de espécies reativas de oxigênio (EROs) que penetram no esmalte e oxidam ligações duplas conjugadas presentes em cromóforos (Kwon e Wertz, 2015).

Apesar dos benefícios estéticos alcançados com os diferentes protocolos de clareamento dental (Basting et al., 2012), o surgimento de efeitos adversos na estrutura do esmalte é um risco eminente. Dentre as alterações, estudos demonstraram aumento na rugosidade da superfície após o clareamento, além da diminuição do conteúdo inorgânico e da resistência do esmalte (Goyal et al., 2021). Além destas possíveis alterações, altas concentrações de PH podem modificar a relação cálcio/fosfato (Ca/P) do esmalte, diminuindo a microdureza decorrente da perda do conteúdo mineral (Cavalli et al., 2018). Outro fator importante evidenciado é o alto poder de difusão do PH nos tecidos dentais, o qual gera citotoxididade pulpar (Llena et al., 2019, Oliveira Duque et al.,2020). Ainda, estudos indicam que altas concentrações de PH geram danos pulpares, os quais clinicamente se manifestam como sensibilidade dentinária (Soares et al., 2015). Embora a sensibilidade cesse com a interrupção do tratamento, não existem relatos das consequências citológicas em longo prazo.

Diante destes efeitos adversos, agentes experimentais e mudanças no protocolo de aplicação tem sido sugeridas com o objetivo de minimizar tais desvantagens e potencializar a segurança e eficácia do tratamento. Um estudo demonstrou que a incorporação de partículas que potencializam a decomposição do H_2O_2 na superfície do esmalte, podem aumentar a segurança do clareamento, pois as EROs geradas, como hidroxila, peridroxila e o oxigênio, possuem curto tempo de meia-vida, e não conseguiriam difundir-se até a polpa (de Oliveira Ribeiro et al.,2022).

O TiO_2 é um óxido metálico catalisador (Hanaor & Sorrell, 2010) encontrado em três formas cristalinas diferentes: bookita, anatase e rutilo, sendo a fase anatase e rutilo, as fases de maior fotorreatividade (Li et al., 2015), com pico de absorção de luz nos de comprimentos de onda de 386 ηm (UV) e 416 ηm (VIS), respectivamente (Lan et al., 2013). O mecanismo fotocatalítico do TiO_2 envolve a produção de radicais hidroxila altamente reativos, que em contato com substâncias orgânicas, realizam a oxidação. A característica fotocatalítica do TiO_2 proporciona o desenvolvimento de materiais com propriedades antimicrobianas devido à liberação dos radicais livres reativos (Joost et al., 2015). Ainda, relatos demonstram que em escala nanométrica, é possível a dopagem da estrutura cristalina do TiO_2 com íons metálicos, como Nb, Cu, Ni, Co, Cr, Mn, Mo, V, Fe ou elementos metálicos, não metálicos ou metalóides do bloco “p”, como N, P, C, S, B, F e I (Bakhshayesh & Bakhshayesh, 2016), os quais podem potencializar a atividade fotocatalítica do TiO_2, e suas propriedades antibacterianas.

Em estudos clínicos, nanopartículas N_TiO_2, incorporadas em géis clareadores de baixa concentração (PH 15% e 6%), apresentam efeito semicondutor quando irradiadas com comprimentos de onda na região visível do espectro eletromagnético (400-700 nm). De acordo com os autores, as nanopartículas (NPs) aumentam a capacidade dissociativa do PH, potencializando a produção de EROs, favorecendo e otimizando a quebra de pigmentos intrínsecos (Bortolatto et al., 2014, Bortolatto et al., 2016). Acredita-se que este comportamento possa diminuir os danos pulpares, pois potencializa a dissociação do H_2O_2 e diminui a difusão de EROs na polpa. Nestes estudos, foi demonstrado que o clareamento com PH (15% e 6%) associado as NPs de dióxido de titânio dopadas com nitrogênio (N_TiO_2) promoveram resultados estéticos, e menor sensibilidade dentinária quando comparados aos agentes clareadores tradicionais (PH 35%) (Bortolatto et al., 2014, Bortolatto et al., 2016).

Uma nanopartícula de N_TiO_2, obtida por meio de processos solvotérmicos controlados e robustos, foi recentemente desenvolvida e incoporadada a um adesivo dentinário comercial e seus efeitos antibacterianos e bioativos foram avaliados (Esteban Florez et al., 2018). Os materiais experimentais contendo diferentes concentrações de N_TiO_2 (50-80% p/p) demonstraram efeitos antibacterianos e bioativos superiores aos grupos sem a nanopartícula. Os autores observaram que as NPs produzidas (N_TiO_2) são altamente reativas e capazes de produzir grandes quantidades de radicais livres de oxigênio, quando irradiadas com luz visível. (Esteban Florez et al., 2018)

Em outro estudo do mesmo grupo de pesquisa, NPs de TiO_2 duplamente dopadas com nitrogênio e flúor (NF_$TiO_{2,}$, 6-15 nm) foram sintetizadas, e os resultados indicaram efeito antibacteriano muito superior em relação ao adesivo sem a nanopartícula. As nanopartículas co-dopadas foram capazes de otimizar a produção de espécies reativas de oxigênio (EROs) de longa vida (ex. hidroxilas reativas), prolongando os efeitos antibacterianos. A presença de íons flúor imobilizados na estrutura cristalina do TiO_2, aumentou o potencial bioativo-remineralizador do material (Esteban Florez et al., 2020).

Kury e colaboradores (2022) avaliaram a incorporação destas NPs de TiO_2 co-dopadas com F e N (NF_TiO_2), em géis clareadores experimentais com concentrações de PH de 6%, 15% e 35% (p/p), associado ou não à irradiação com luz violeta. Os resultados indicam que as baixas concentrações de PH 6% promoveram alteração de cor semelhante as altas concentrações de PH (35%), quando da incorporação de NPs (5, 10 e 20 wt%) ao gel clareador experimental, indicando o potencial das NPs de TiO_2 co-dopadas com F e N (NF_TiO_2).

O nióbio (Nb), por sua vez, é um metal pertencente aos óxidos de transição, que são atóxicos, estáveis sob condições ácidas ou alcalinas, e caracterizado por uma grande área de superfície e forte acidez (Nowak & Ziolek, 1999). É classificado como metal semicondutor e aproximadamente 98% das reservas conhecidas de nióbio estão no Brasil. Ainda, o país é responsável por aproximadamente 90% de todo o Nb comercializado no mundo. Por este motivo, diversas pesquisas têm sido realizadas com este material em diversas áreas industriais como aviação, petrolífera e naval (Alves & Coutinho, 2015). Na Odontologia, estudos indicam que o Nb tem capacidade de promover a remineralização de tecidos dentários (Altmann et al., 2017; Balbinot et al., 2020) e associado ao oxigênio, como na molécula de pentóxido de nióbio (Nb_5O_2), apresenta bioatividade quando incorporado a materiais odontológicos (Garcia et al., 2016; Degrazia et al., 2019).

Em estudo recente, Caneschi e colaboradores (2023) avaliaram a eficácia de géis clareadores de baixa concentração (PH 3%) contendo NbO_2. Os autores demonstraram que o Nb associado ao PH 3% exibe eficácia de alteração de cor semelhante a géis de alta concentração. O notável desempenho do Nb foi justificado pelo potencial modulador do Nb na superfície do PH, resultando na transformação de sítios ácidos de Bronstëd em sítios oxidantes. A obtenção de sítios oxidantes confere ao material maior propriedade oxidativa (Oliveira et al., 2012). Desta forma a associação do Nb com o PH pode oferecer maior capacidade de clivar os cromóforos presente na estrutura dentinária.

Recentemente, foi demonstrado que a dopagem do TiO_2 com Nb aumenta a atividade catalítica do titânio, em comparação ao TiO_2 puro (Taturani et al., 2021). De acordo com autores, a dopagem do TiO_2 com Nb é um procedimento quimicamente viável, pois o raio iônico do Ti^{4+} é muito próximo do Nb^{5+} (Ghugal et al., 2015), fato que permite a inclusão do Nb^{5+} na rede cristalina do TiO_2, em sítios do próprio Ti^{4+} (Bachu et al., 2014), promovendo uma reação estável entre os dois elementos.

Em se tratando de estabilidade química da molécula de pentóxido de nióbio associada ao dióxido de titânio, Qadri et al., 2020, demonstraram que nanotubos compostos de dióxido de titânio – pentóxido de nióbio – e dióxido de zircônio (TiO_2-Nb_2O_5-ZrO_2) associados, promovem adesão e desenvolvimento de células osteoblásticas viáveis, devido à maior absorção de proteínas na superfície do nanotubo (Qadri et al., 2020). Ainda, a incorporação de partículas bioativas de Nb_2O_5 obtidas pelo método solvotérmico, demonstrou potencial de deposição de fosfato quando adicionado a adesivos experimentais, sem comprometer a resposta celular (Balbinot et al., 2020). Ainda assim, não existem estudos que comprovem a eficácia da associação entre a NPs de TiO_2 com o pentóxido de nióbio (Nb_2O_5) de forma sinérgica, em géis clareadores.

Relatos indicam que tanto o TiO_2 quanto o Nb_2O_5 são sensíveis aos diferentes comprimentos de onda de luz e podem ser utilizados como catalisador em reações fotocatalíticas (Prado et al., 2008). Portanto, a utilização de fonte de luz no comprimento de onda capaz de aumentar a reatividade destas moléculas poderia potencializar reações químicas, como a decomposição do PH 35%.

Aparelhos de luz LED que operam em comprimentos de onda visível (~ 405 nm) foram recentemente desenvolvidos e comercializados para acelerar a reação do H_2O_2 (Kury et al., 2020). Relata-se que o pico de emissão do LED violeta (405 e 410 nm) é compatível com o pico de absorbância das moléculas pigmentadas aderidas à superfície do esmalte, as quais são fotossensíveis e reativas ao comprimento de onda emitido pela fonte de luz (Zanin, et al., 2015; Zanin, 2016). Estudos recentes demonstram que embora a luz violeta sozinha promova alteração de cor acima do limiar de percepção clínica, a quebra de pigmentos só se da de forma extrínseca, removendo cromóforos apenas do esmalte. Dessa forma, a associação com o peróxido de carbamida 37% potencializa o efeito clareador deste gel e promove menor risco de sensibilidade comparado ao PH 35% (Kury et al., 2020). Estes resultados são confirmados por estudos *in vitro* (Costa et al., 2022a; Costa et al., 2022b), e avaliações clínicas randomizadas (Kury et al., 2022, Gallinari et al., 2020, Trevisan et al., 2022) que confirmam que a luz violeta é capaz de potencializar o efeito clareador de baixas concentrações de peróxido.

Os agentes clareadores contendo nanopartículas de NF_TiO_2 associadas ao Nb_2O_5 poderiam atuar sinergicamente e aumentar o potencial de clareamento do PH, quando irradiados com fonte de luz LED violeta. Hipotetiza-se que esta associação poderia minimizar os efeitos adversos decorrentes da aplicação de géis clareadores de alta concentração (PH 35%) no esmalte, por aumentar a reatividade do H_2O_2, permitindo a diminuição da concentração necessária para promover efeito clareador. Diante do exposto, o objetivo principal deste estudo foi desenvolver géis clareadores experimentais contendo PH 6% e NPs de NF_TiO_2 associadas ao Nb_2O_5 com uso de luz violeta e avaliar a estabilidade química, potencial clareador e efeitos na microdureza, rugosidade de superfície, concentração de Ca e P e morfologia do esmalte dental.

2 ARTIGO: EFFECTS OF EXPERIMENTAL BLEACHING GELS CONTAINING CO-DOPED TITANIUM DIOXIDE AND NIOBIUM PENTOXIDE COMBINED WITH VIOLET LIGHT

Submitted to the Clinical Oral Investigation (Anexo 2)

Effects of experimental bleaching gels containing co-doped titanium dioxide and niobium pentoxide combined with violet light

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Abstract

This study evaluated the bleaching potential of 6% hydrogen peroxide (6% HP) gels containing NF_TiO_2 or Nb_2O_5 irradiated with a violet LED light, and the effects on enamel mineral content and surface morphology. First, particles were synthesized and experimental gels were chemically analyzed by preliminary and accelerated stability tests, pH, and HP decomposition rate. Enamel blocks were treated with 6% HP gels containing (n=10): 5% NF_TiO_2, 5% Nb_2O_5, 2.5% NF_TiO_2 + 2.5% Nb_2O_5 or without particles (6% HP), irradiated or not with LED, and the positive control was treated with 35% HP. Color (ΔE_{00}) and whitening index (ΔW_{ID}) variations, surface microhardness (SH), average roughness (ΔRa), Ca and P concentration (EDS), and enamel morphology (SEM) were assessed. Bleaching was performed in 3 sessions of 30 minutes and 7-day intervals. Data were submitted to two-(pH, decomposition rate, $\otimes E_{00}$, and W_{ID}) and three-way (SH) ANOVA, Kruskal-Wallis (ΔRa), with Tukey and Dunnet (control) post-hoc tests ($\alpha = 0.05$). No changes in the gel's color, odor, or translucency were observed, pH (6 to 6.5) remained stable over time, and light irradiation boosted the H_2O_2 decomposition rate. NF_TiO_2 and Nb_2O_5-containing gels displayed higher $\otimes E_{00}$ and $\otimes W_{ID}$ when light-irradiated ($p<0.05$). Nb_2O_5 and Nb_2O_5 + TiO_2 decreased enamel SH ($p<0.05$), but no discrepancies were found among the groups ($p>0.05$). The research did not observe changes in ΔRa, Ca-P content, and enamel morphology after treatments ($p>0.05$). In conclusion, experimental and light-irradiated 6% HP gels containing NF_TiO_2 or Nb_2O_5 were chemically stable, exhibiting bleaching potential comparable with 35% HP without causing enamel adverse effects.

Keywords: nanoparticles, titanium, niobium, tooth whitening

INTRODUCTION

Alternative protocols have been proposed to improve safety and minimize bleaching adverse effects [1]. The incorporation of catalytic particles into HP gels allegedly increases and fastens the dissociation of hydrogen peroxide into ROS, thereby optimizing the breakdown of staining molecules in enamel and outer dentin. Because of ROS's short lifetime, ROS generated in the outer dental surface would not be able to diffuse and reach the pulp chamber [2], thus decreasing the capacity of the HP decomposition products to cause an inflammatory response.

Over the years, light sources with different wavelengths have been indicated for in-office bleaching to accelerate HP decomposition. Recently, a novel generation of violet LED light (~405 nm) has been developed specifically for tooth-bleaching applications [3]. According to reports, the violet LED light will deliver a bleaching effect, regardless of the application of hydrogen or carbamide peroxide, because the emission peak of the violet LED is compatible with the absorbance band of certain organic stains in the dental structure. Therefore, the organic stains will react and decompose because of the wavelength emitted by the light source [4,5]. In this context, even though the violet light could stand as a peroxide-free tooth-whitening approach, a recent clinical trial concluded that the violet irradiation alone rendered poor aesthetic outcomes [6]. However, the combination of violet LED with 37% carbamide peroxide (CP), which presents a concentration three times lower than 35% HP, increased the clinical efficacy for 37% CP with reduced risk and intensity of tooth sensitivity [6].

Metallic oxides, such as titanium oxide (TiO_2), were incorporated into experimental bleaching gels as a tactic to enhance peroxide redox and promote safer bleaching [1]. Studies have shown that TiO_2 nanoparticles (NPs) co-doped with nitrogen (N) and fluorine (F), incorporated into low concentration HP gels (6% and 15%) and irradiated with visible light (wavelengths ranging from 400 to 460 nm), behave as semiconductors. They enhance the HP decomposition, promoting optimal aesthetic results, comparable to high concentration HP gels [1,7,8]. Also, reports of the clinical application of NPs combined with 6% and 15% HP indicate lower dentin sensitivity than standard bleaching agents (35-40% HP) [7,8].

Niobium (Nb), a semiconducting metal, has been explored in several research fields. In dentistry, reports indicate that Nb promotes the remineralization of dental structures [9,10]. Besides, in combination with oxygen (niobium pentoxide, Nb_2O_5), the molecule exhibits bioactivity potential when incorporated into dental materials [11, 12]. Some reports indicate that Nb could enhance the bleaching efficacy of low concentration bleaching gels [13], but literature is still scarce on this matter. Moreover, studies have observed that Nb doped with TiO_2 increases the catalytic activity of this molecule in comparison to pure TiO_2 [14]. In addition to these characteristics, TiO_2 and Nb_2O_5 are sensitive to the optical absorption of light at visible wavelengths, which highlights the capacity of both compounds to incite photocatalytic reactions [15]. Therefore, using light at the ideal wavelength could increase the reactivity of these molecules.

Bleaching agents containing NF_TiO_2 nanoparticles associated with Nb_2O_5 could operate synergically and increase the bleaching potential of H_2O_2 when irradiated with a violet LED light source. We believe that this combination could minimize the adverse effects resulting from the application of high concentration bleaching agents (35% HP) on the enamel. It does this by increasing the reactivity of H_2O_2 and enabling the decrease in the concentration required to maintain the same optimal aesthetic outcomes attained by 35% HP. Therefore, this study developed experimental bleaching gels containing 6% HP and NPs of NF_TiO_2 associated with Nb_2O_5 combined with violet light in order to assess the chemical stability, bleaching potential, and its effects on enamel surface microhardness, surface roughness, Ca and P concentration, and morphology.

Materials and Methods

Experimental Design

This in vitro study was divided into three methodological phases: i) experimental gel synthesis, incorporation with NF_TiO_2 and Nb_2O_5, and characterization; ii) assessment of the experimental 6% HP bleaching potential, and iii) evaluation of enamel mineral content, roughness, and surface morphology. After synthesizing the experimental gels selected specimens of the enamel of bovine incisors (n=10/group) were treated with 6% HP incorporated with (n=20): 5% Nb_2O_5, 5% NF_TiO_2, 2.5% Nb_2O_5 + 2.5% NF_TiO_2 or 6% HP without particles. All groups were subdivided and irradiated with violet LED light (LED). The control group (35% HP) was treated with a commercial bleaching gel (Whiteness HP, FGM) and was not light-irradiated.

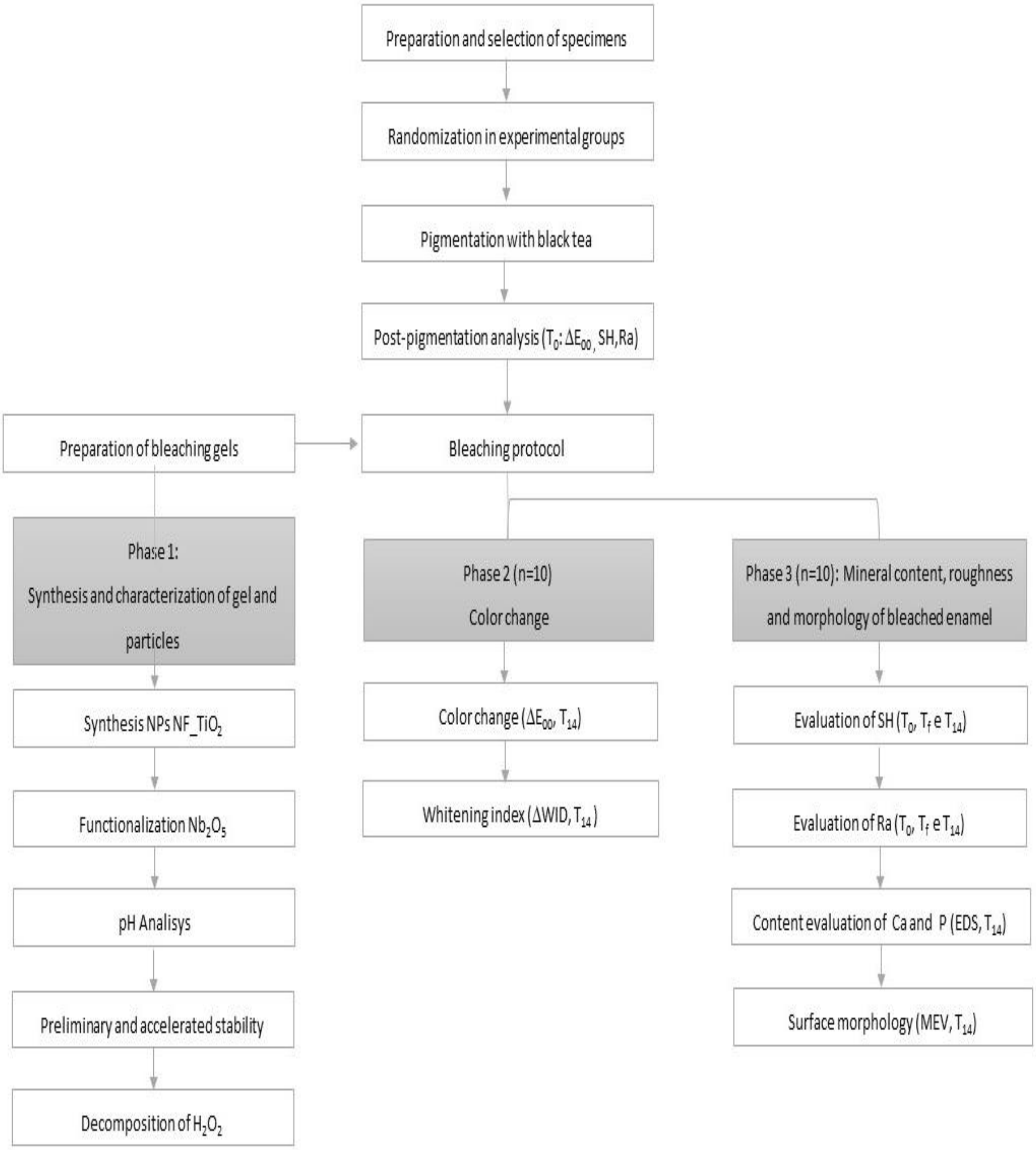

Figure 1. Flowchart representing the phases of the study.

The dependent variables of phase 1 (preliminary and accelerated stability and pH) were descriptive, and the titration analysis was statistically analyzed. A previous pilot study determined the number of specimens for phases 2 and 3, with color change (E_{00}) and surface microhardness (SH) as the dependent variables. In this pilot study, five specimens were tested (n=5) and the sample size was calculated (G-Power) with a significance level of 5% (〈) and test power at 80% (1-ß). The results indicated n=10 as the number of specimens required for phases 2 and 3, in line with previous studies with similar methodologies [1].

Phase 1. Characterization of the developed nanoparticles and experimental bleaching gels

Synthesis of NF_TiO_2 nanoparticles

NF_TiO_2 nanoparticles were synthesized by solvothermal processes at the Biomaterials Laboratory at the University of Oklahoma. They were manufactured according to the protocol previously described by Esteban Florez et al. [16]. A solution composed of 1.7g of Ti (IV-Butoxide, Sigma Aldrich, 97%), 4.6g of ethanol (Decon Labs), 6.8g of oleylamine (Sigma Aldrich, 70%), and 7.1g of oleic acid (Sigma Aldrich, 90%) was prepared and mixed with 20 ml of 4% hydrated alcohol (18-MΩ Milli-Q, Decon Labs) [17]. The solution was inserted into a high-pressure reaction vessel (Paar Series 5000 Multiple Reactor System) at 180°C for 24h. Containers were shaken in an external magnetic field with stir bars. After cooling, the solutions were decanted and rinsed three times with anhydrous ethanol to remove surfactants. Pure TiO_2 NPs were immediately stored in 20mL of ethanol and centrifuged for 15min at 8000 rpm.

Functionalization of niobium pentoxide

Table 1 displays the specifications of the Nb_2O_5 (Sigma-Aldrich®) used. The particles were immersed in an anhydrous ethanol solution and centrifuged for 5min at 10,000 rpm for disaggregation. Afterward, Nb_2O_5 was immersed in a 2M HCl solution in a water bath for 60min (50ºC) under constant agitation. Particles were then rinsed with ethanol, centrifuged three times, and stored in ethanol.

Table 1. Niobium pentoxide particle characteristics (Nb_2O_5)

Component	**Caracterísitcs of Niobium Pentoxide** (Nb_2O_5)		
Niobium Pentoxide (Nb_2O_5)	**Molecular formula**	**Molecular weight**	**PubChem CID**
	O=[Nb](=O)O[Nb](=O)=O	265.81 g/mol	2485207

1.1 Synthesis of experimental bleaching agents.

Table 2 describes the components of the experimental bleaching gel. After manufacturing the gel, the NF_TiO_2 and Nb_2O_5 particles were weighed on a precision analytical scale and incorporated into the thickening agent at the reported concentrations (wt%). The thickening agent containing the particles was homogenized in a specific mixer (Speed Mixer, Dac Iso 1. FVZ, Flack Teck, Inc.) and preparation occurred 12h before bleaching. Immediately before bleaching, HP (6%) was added and homogenized with the thickening agent containing the particles in a 3:2 proportion.

Table 2. Composition of the experimental bleaching gel

Components	Molecular formula	Molecular Weight (g/mol)
Carbomer 940	[-CH 2-CH(COOH)-]n	104.400
6% HP	H_2O_2	34.014

pH determination

The pH of the gels was measured in triplicate in a pH-meter (Equilam, Diadema, SP, Brazil) coupled to a potentiometer (Orion Research Incorporated, Boston, MA) previously calibrated with pH 4.0 and 7.0 standards, mixing 1 g of bleaching gel to 10 mL of deionized water in a magnetic stirrer for 10 min at 20º C. The pH was evaluated at times 0min, 15min, and 30 min, denoting the contact time of the bleaching gel on the dental surface

Preliminary stability test

Brazil's National Health Regulatory - Agency (ANVISA) [18] defines the preliminary stability tests as the initial screening of the experimental formulations [19]. Samples in triplicate, stored in transparent sealed glass vials, were submitted to cycles of 24 h in an oven at 37 ºC (± 2 ºC) and 24 h in a refrigerator at 4 ºC (± 2ºC) during 4 weeks. Then, the color, odor, and pH values of the gels were determined and described

Accelerated stability test

The accelerated stability test determines the stability of the formulation over 60 days and predicts the estimated shelf life [18]. Samples in triplicate were stored in sealed transparent glass bottles and divided into two groups: G1 - stored in an oven at 37 ºC (± 2 ºC) and G2 - stored in a refrigerator at 4 ºC (± 2 ºC). Groups were evaluated immediately (0), 24 h, and 30 and 60 days later. Then, color, odor, and pH values were determined and described.

Decomposition of bleaching agents

An automatic titrator (HI902C1-02, Hanna Instruments, Carrolton, Texas, USA) evaluated the decomposition using 0.1 N potassium permanganate ($KMnO_4$), according to the methodology described by Ono & Torres [19]. Previous to the decomposition test the $KMnO_4$ solution was standardized using sodium oxalate ($Na_2C_2O_4$) at 0.67% (w/v). For standardization, 25 mL of the oxalate solution and 25 mL of sulfuric acid were added to the titrator flask, up to the equivalence point, to obtain the correction factor.

The experimental bleaching gel was prepared and the decomposition rate of the peroxide was determined at 0 and 30min, in triplicate. An aliquot of the gel (0.01g) was weighed and diluted in 1M sulfuric acid (20 mL) with continuous stirring until homogenization was complete. Thirty minutes after mixing the bleaching gels a new aliquot was collected to determine the peroxide concentration.

Phase 2. Bleaching potential of the experimental bleaching gels

Preparation and selection of specimens

Bovine teeth free of defects were selected, cleaned, and disinfected in 0.1% thymol solution (Labsynth, Diadema, SP, Brazil). The crowns were sectioned from the root with a diamond disc (KG Sorensen, São Paulo, SP, Brazil) and a high-precision diamond saw mounted in a high-precision cutter (Isomet 1000, Buheler, Illinois, USA). Under water irrigation, the crowns were cut obtaining enamel blocks measuring 5 x 5 x 3mm. The dentin surface of the blocks was flattened (#320) in a polishing machine (Arotec, São Paulo, SP, Brazil) to allow parallelism with the outer enamel surface. Subsequently, enamel was abraded with silicon carbide sandpaper (# 600, 1200, and 2000) and polished with a felt disk and a diamond suspension (with abrasive particles of 6, 3, 1, and ¼ µm) for 1 min. The initial surface microhardness (SH) was obtained by averaging three indentations, 100 µm-distant from each other, in the central region of the specimen, with a Knoop-type indenter (Future Tech-FM-1e, Tokyo, Japan, 50 g/5 s). The SH average was obtained (319.6 kg/cm2), and the selected specimens exhibited mean values up to 10% (+/-) of the general average.

Enamel artificial staining

After selection, a thin layer of nail polish covered the specimens except for the buccal enamel, which remained exposed. The exposed enamel surface was immersed for 24h under agitation at room temperature in a buffered black tea solution (Dr.Oetker, São Paulo, SP, Brazil, pH = 7.0), prepared with 2g of black tea diluted in 100ml of distilled water for 5min [20]. Then, specimens were brushed with pumice stone powder to remove the non-adherent particles and then kept in artificial saliva (1.5 mM Ca, 0.9 mM P, 150 mM KCl, and 0.1 M Tris, pH 7.0) [20] for seven days (replaced every two days) at 37°C for color stabilization. Specimens were randomly allocated into the groups previously described (n=10).

Bleaching protocol

To allow comparisons among groups, the same protocols were adopted for the commercial and experimental bleaching gels [1]. The 35% HP and 6% HP gels were weighed (0.1g) and applied to the exposed enamel. Bleaching was performed in three sessions, each with a single bleaching gel application for 30 min and a 7-day interval between applications. Due to the photocatalytic characteristic of the particles, the designated groups were light-irradiated with a violet LED device (Bright Max Whitening, MMOptics, São Carlos, SP, Brazil, 405 +/- 10|m, 12 W [6]). The light was irradiated for 1min followed by a 30s pause and this cycle was repeated 20 times [6]. During the intervals, the specimens remained in the artificial saliva [21].

Colorimetric evaluation

A digital spectrophotometer (EasyShade 4.0, Vita Zahnfabrik, Bad Säckingen, Germany) determined the color parameters L* (black-white axis), a* (red-green axis), and b* (yellow-blue axis) immediately after staining (T_0), 24 h after the last bleaching session (T_f), and 14 days after the last bleaching session (T_{14}). Color change was evaluated using the CIEDE2000 formula: $\Delta E_{00}\ (T_f - T_0) = [(\Delta L'/K_L S_L)^2 + (\Delta C'/K_C S_C)^2 +$

$(\Delta H'/K_H S_H)^2 + R_T*(\Delta C'/K_C S_C)*(\Delta H'/K_H S_H)]^{1/2}$. The whitening index for dentistry (W_{ID}) was calculated according to the equation: $W_{ID} = 0.511L^* - 2.324a^* - 1.100b^*$ and the index difference (ΔWI_D) was determined by T_{14} - T_0. Color change values (ΔE_{00}) adopted for perception (PT) and acceptance (AT) limits (50:50%) were 0.81 (PT) and 1.8 (AT) units. The whitening index (ΔW_{ID}) adopted for PT and AT limits (50:50%) were 0.7 (PT) and 2.6 (AT) units [22,23].

Phase 3. Evaluation of enamel mineral content, surface roughness and surface morphology after the bleaching treatment

3.1 Surface Microhardness (SH)

SH was obtained by averaging 3 indentations in the central region with a Knoop indenter (Future Tech-FM-1e, Tokyo, Japan, 50g/5s) and 100µm-distant from each indentation. The procedure was conducted at baseline (T_0), 24 h after the last bleaching session (T_f), and 14 days after the last bleaching session (T_{14}). The %SHL was determined according to the equation:

$$\%SHL = \frac{(SH_{14} - SH_0)\ 100}{SH_0}$$

3.2 Surface roughness (Ra)

A roughness meter (Surfcorder SE 1700, Kosalab) determined the enamel surface average roughness (Ra, in µm) at T_0, T_f, and T_{14}. The measuring tip of the equipment remained perpendicular to the surface and three measurements were performed by rotating the specimen 45º, obtaining the mean Ra value per specimen. The equipment operated with a cut-off at 0.25mm and a speed of 0.2mm/s. The average surface roughness change (∆Ra) was determined by T_f -T_0 and T_{14} -T_0.

3.3 Scanning Electron Microscopy (SEM) and Energy Dispersive X-ray Spectroscopy (EDS).

Three representative specimens from each group were selected and analyzed for mineral content (EDS) and morphology (SEM) at T_f and T_{14}. Specimens were washed in an ultrasonic bath (Ultra Cleaner, Unique, Indaiatuba, SP, Brazil) for 10 min and dried overnight in an oven at 37ºC. After drying, specimens were sputter-coated with a thin carbon layer and observed under SEM (JEOL-JSM, 6460LV, Tokyo, Japan), operating at 15kV in vacuum mode (45 Pa) [24]. Images were recorded at 3,000· magnification. Alongside the SEM images acquisition, the software of the energy dispersive X-ray spectroscopy (EDS, VANTAGE System - Easymicro Noran Instruments, Middleton, Wisconsin USA) provided semi-qualitative data on the percentage of chemical elements (atomic percentage) in three standard areas (600 ⌠m^2) of the specimens [24].

5. Statistical analysis

Shapiro-Wilk and Levene tested data normality and homoscedasticity ($\alpha > 0.05$). Two-way ANOVA and Tukey's post hoc tests analyzed the decomposition rate, ΔE_{00}, and ΔW_{ID}, while three-way ANOVA for repeated measures and Bonferroni tests analyzed the SH values. The Dunnet test compared the control (35% HP) with the other experimental groups, and Kruskal-Wallis compared ΔRa values. The software SPSS was used for all the analyses (Version 15.0, SPASS, IBM SPSS Inc., Armonk, NY, USA) with the alpha set at 0.05.

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RESULTS

Phase 1

pH analysis. Figure 2 displays the pH analysis. In general, the pH of the experimental gels at baseline was 6.5 (immediately after the incorporation of 6% HP, or NF_TiO_2, Nb_2O_5). After 30 minutes, the pH decreased for all groups ($p<0.001$) regardless of irradiation with LED light ($p=0.508$), exhibiting mean values of ~6.0. The gels containing NF_TiO_2 (Fig. 2B) and Nb_5O_2 + NF_TiO_2 (Fig. 2C) showed the lowest pH values (pH = 5.9) after 30 minutes, regardless of LED light irradiation.

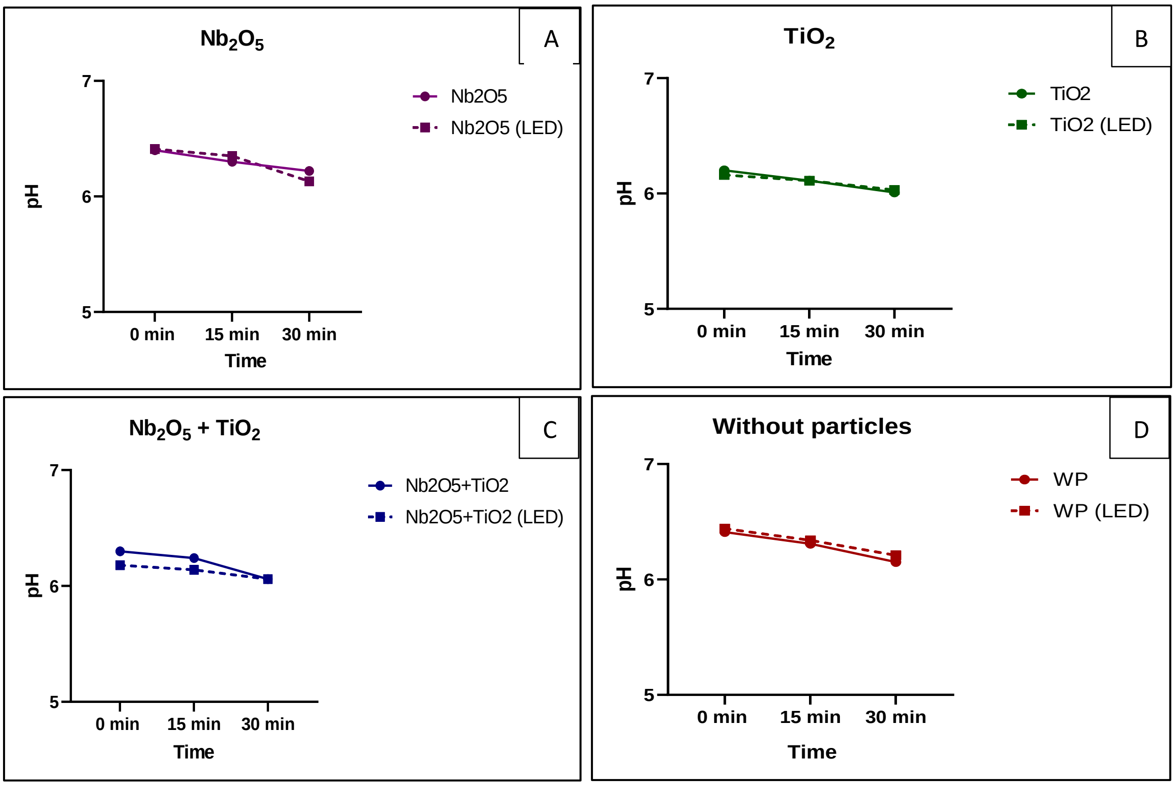


Figure 2. Graph showing mean pH values of experimental bleaching gels for time.

Preliminary and accelerated stability test. No qualitative differences in the preliminary and accelerated analyses were noticed since no color, odor or translucency changes occurred in the experimental bleaching gels over time. The results of the preliminary stability analysis (Fig. 3) indicate that the pH values of the experimental gels increased after 30 days in comparison with the baseline values ($p<0.001$). The baseline values of the experimental gels were ~6.4 and ~6.5 after 30 days. In the accelerated stability test (Fig. 4) the pH of the experimental gels at baseline ranged between ~6.2 and 6.4 and remained so after 24h. After 30 days of evaluation, the groups kept at 4ºC exhibited a slight drop in pH value (~6.1), but after 60 days, the measurements of all groups were close to 6.5.

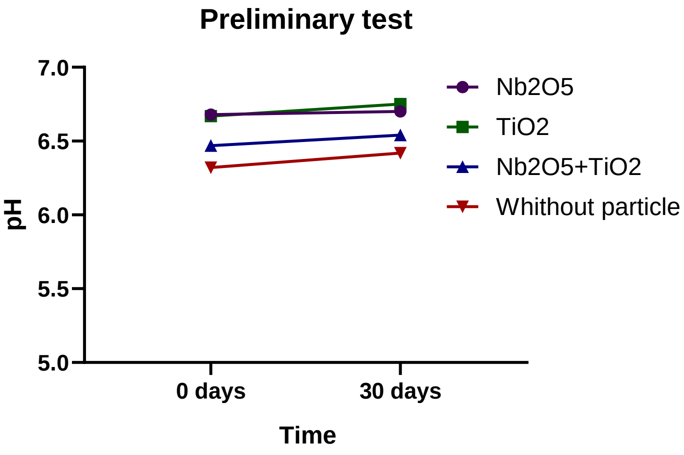


Figure 3. Graph showing mean pH values of the preliminary stability test for time.

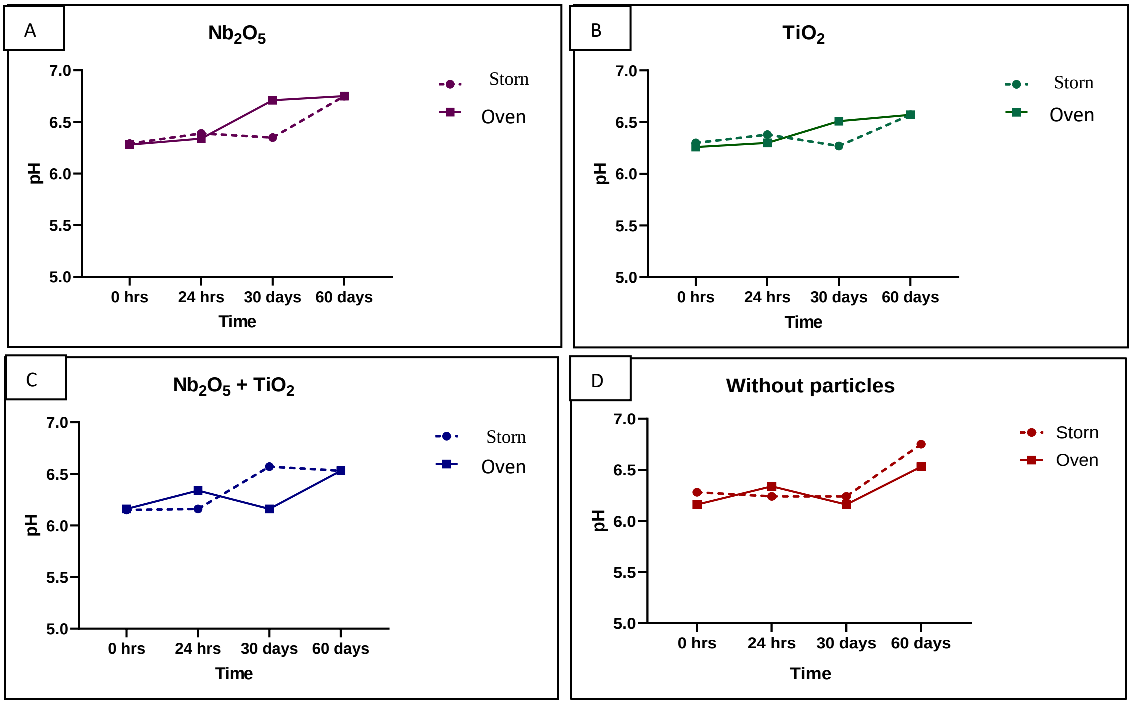


Figure 4. Graph showing mean pH values of the accelerated stability test for time.

Decomposition rate of H_2O_2. Table 4 display the mean percentage of decomposition rate of H_2O_2 in the bleaching gel 0 and 30 minutes after the mixture of the gel with the thickener. Significant differences were found for the factor “time” ($p<0.001$) and the interaction “time and light” ($p=0.026$). No differences were found among groups without violet LED irradiation ($p>0.05$). After 30 minutes of decomposition, the Nb_2O_5, NF_TiO_2, and Nb_2O_5 + NF_TiO_2 groups irradiated with violet light increased the hydrogen peroxide concentration in the solution ($p<0.05$). All experimental groups (PH 6%) exhibited significantly lower concentrations than the control group (PH 35%, $p<0.05$).

Table 4. Mean and standard deviation of the mean decomposition rate (%) of H_2O_2 in the bleaching gels.

Bleaching Treatments	Without LED irradiation		With LED irradiation	
	0 min	30 min	0 min	30 min
6% HP + Nb_2O_5	3,56% (0,29%) **Aa***	3,73% (0,29%) **Aa***	3,75% (0,30%) **Aa***	4,23% (0,35%) **Ba***
6% HP + NF_TiO_2	3,78% (0,16%) **Aa***	3,73% (0,34%) **Aa***	3,77% (011%) **Aa***	4,12% (0,11%) **Ba***
6% HP + Nb_2O_5 + NF_TiO_2	3,88% (0,07%) **Aa***	3,90% (0,37%) **Aa***	3,70% (0,10%) **Aa***	4,00 % (0,02%) **Ba***
6% HP	3,83% (0,43%) **Aa***	3,97% (0,40%) **Aa***	3,69% (0,13%) **Aa***	3,67% (0,26%) **Ab***
35% HP	*0 min* = 25,72% (1,16%)* *30 min* = 26,23% (2,51%)*			

Means followed by different letters indicate statistical differences, with a significance level of 5%. Uppercase letters compare bleaching treatments (vertical) for the same time, and lowercase letters compare LED irradiation (horizontal) for the same bleaching treatments and irradiation. The asterisk indicates the difference between the experimental groups and the control (PH 35%) at 2 times (0 and 30 min).

Phase 2

Color change (ΔE_{00}). Table 5 displays the color change (ΔE_{00}) having elapsed 14 days from bleaching. The factor "LED irradiation" was statistically significant ($p<0.0001$), and LED increased the ΔE_{00} for the groups containing NF_TiO_2 and NB_2O_5 + TiO_2 ($p<0.05$). No changes in ΔE_{00} were observed among groups, regardless of the light irradiation ($p>0.05$). The non-irradiated groups, NF_TiO_2 and Nb_2O_5 + NF_TiO_2, showed lower color change than the positive control (35% HP), while Nb_2O_5 and 6% HP showed no differences compared with the control (35% HP, $p>0.05$). All groups irradiated with LED were statistically the same from the control ($p>0.05$).

Table 5. Mean and standard deviation of color change (ΔE_{00}) at T_{14}.

Bleaching Treatments	**ΔE_{00}**	
	Without LED irradiation	**With LED irradiation**
6% HP + Nb_2O_5	5.38 (2.13) **Aa**	7.11 (3.15) **Aa**
6% HP + NF_TiO_2	4.37 (1.40) **Ab**$^{\#}$	7.25 (1.90) **Aa**
6% HP + Nb_2O_5 + NF_TiO_2	4.39 (1.21) **Ab**$^{\#}$	7.37 (2.35) **Aa**
6% HP	5.18 (1.79) **Aa**	6.48 (1.72) **Aa**
35% HP	7.66 (2.07)	

Means followed by different letters indicate statistical differences, with a significance level of 5%. Uppercase letters compare bleaching treatments (vertical) for the same time, and lowercase letters compare LED irradiation (horizontal) for the same bleaching treatments and irradiation. The hashtag indicates the difference between the experimental groups and the control (PH 35%) at 2 times (0 and 30 min).

Whitening index (ΔWI_D). Table 6 displays the whitening index variations (ΔWI_D) at T_{14}. The factors “treatment” ($p=0.034$) and “LED irradiation” ($p<0.0001$) were significant and LED light irradiation increased the ΔWI_D regardless of the particle’s presence ($p<0.05$). Among the irradiated groups, NF_TiO_2 exhibited a higher ΔWI_D than 6% HP ($p=0.027$), while groups Nb_2O_5 and Nb_2O_5 + NF_TiO_2 showed intermediate values and were not different from NF_TiO_2 or 6% HP.

No differences were detected between groups not exposed to violet light ($p>0.05$). The non-irradiated NF_TiO_2 was the only group with no differences from the control (35% HP, $p>0.05$).

Table 6. Mean and standard deviation of the whitening index change (ΔW_{ID}) 14 days after bleaching.

Bleaching Treatments	ΔWI_D	
	Without LED irradiation	**With LED irradiation**
6% HP + Nb_2O_5	13.9 (10.2) **Ab**$^{\#}$	24.0 (10.4) **Aba**
6% HP + NF_TiO_2	15.1 (6.9) **Ab**	26.7 (9.6) **Aa**
6% HP + Nb_2O_5 + NF_TiO_2	12.6 (6.6) **Ab**$^{\#}$	24.1 (11.1) **Aba**
6% HP	6.4 (9.4) **Ab**$^{\#}$	17.2 (11.6) **Ba**
35% HP	27.7 (11.0)	

Means followed by different letters indicate statistical differences, with a significance level of 5%. Uppercase letters compare bleaching treatments (vertical) for the same time, and lowercase letters compare LED irradiation (horizontal) for the same bleaching treatments and irradiation. The hashtag indicates the difference between the experimental groups and the control (PH 35%) at 2 times (0 and 30 min).

Phase 3

Surface Microhardness (SH). Table 7 shows the surface microhardness values and %SHL values. The “time” factor was statistically significant ($p=0.01$). In general, none of the analyzed groups showed variation in SH over time, regardless of violet light irradiation, with an overall mean hardness reduction of 0.96% ($p>0.05$).

The non-irradiated Nb_2O_5 and Nb_2O_5 + NF_TiO_2 groups and the light irradiated Nb_2O_5 treatments decreased their SH at T_{14} in comparison with the baseline (T_0) ($p<0.05$), but with an average reduction of 1.62%. No statistical difference in SH was observed among enamel bleached with the experimental gels, regardless of the time when the measurement was conducted ($p>0.05$).

Table 7. Mean and standard deviation of surface microhardness (SH) at times T_0, T_f e T_{14}.

Bleaching Treatments	**Surface microhardness (SH)**							
	Without LED irradiation				**With LED irradiation**			
	T_0	**Tf**	**T_{14}**	**%SHL**	**T_0**	**Tf**	**T_{14}**	**% SHL**
6% HP + Nb_2O_5	324.2(16.5) **Aa**	316.5 (11.5) **Aab**	319.8(13.4) **Ab**	1.36%	322.4 (16.3) **Aa**	319.4 (8.1) **Aab**	316.5 (11.9) **Ab**	1.83%
6% HP + NF_TiO_2	323.3(16.4) **Aa**	320.9 (9.3) **Aa**	323.8 (15.2) **Aa**	0.15%	321.1 (15.7) **Aa**	314.2 (13.1) **Aa**	320 (11.9) **Aa**	0.34%
6% HP + Nb_2O_5 + NF_TiO_2	323.9(16.4) **Aa**	322.3 (19.4) **Aab**	318.4 (10.9) **Ab**	1.67%	321.4 (15.8) **Aa**	315.2 (15.3) **Aa**	318.7(14.4) **Aa**	0.84%
6% HP	320 (15.2) **Aa**	317.0 (14.8) **Aa**	316.2 (13.1) **Aa**	1.19%	319.8 (14.9) **Aa**	313.7 (11.1) **Aa**	316 (10.9) **Aa**	1.19%
35% HP	**T_0**		**Tf**		**T_{14}**		**% SHL**	
	325.1 (16.4)		321.8 (13.8)		322.1 (14.7)		0.92%	

Means followed by different letters indicate statistical differences, with a significance level of 5%. Uppercase letters compare bleaching treatments (vertical) for the same time, and lowercase letters compare LED irradiation (horizontal) for the same bleaching treatments and irradiation. The hashtag indicates the difference between the experimental groups and the control (PH 35%) at 2 times (0 and 30 min). %SHL: loss of surface hardness in comparison with T_0.

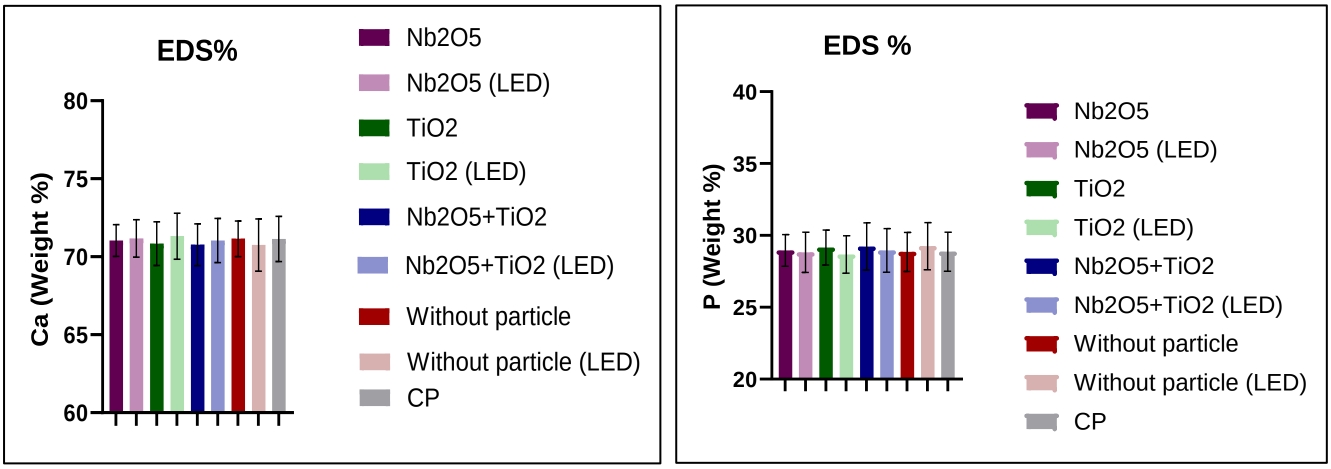
Surface roughness (ΔRa). Table 8 describes the average surface roughness changes (ΔRa). No statistical difference was observed at the end of the bleaching treatment (ΔR_f, p=0.484), not even 14 days after treatment (ΔRa_{14}, p=0.476), regardless of irradiation with light. Comparisons made with the control group showed no statistical difference, regardless of the time point evaluated (p>0.05).

Table 8. Mean and standard deviation (SD) of surface roughness results (ΔRa).

Bleaching Treatments	**ΔRa_f**		**ΔRa_{14}**	
	Sem LED	**Com LED**	**Sem LED**	**Com LED**
6% HP + Nb_2O_5	0,003 (0,01)	0,004 (0,006)	0,000 (0,009)	0,007 (0,008)
6% HP + NF_TiO_2	0,006 (0,01)	0,006 (0,01)	0,004 (0,01)	0,002 (0,008)
6% HP + Nb_2O_5 + NF_TiO_2	0,001 (0,01)	0,008 (0,01)	0,003 (0,02)	0,004 (0,009)
6% HP	-0,001 (0,01)	0,003 (0,01)	-0,001 (0,01)	0,003 (0,01)
	35% HP			
	ΔRa_f		ΔRa_{14}	
	0,013 (0,009)		0,006 (0,007)	

SEM and EDS. Figure 5 shows the mean percentagem (%) of atomic weight for calcium (Ca) and phosphorus (P) content on enamel determined by EDS. No variations in Ca or P rates were detected among the groups (p<0.05). Representative SEM images and EDS graphs (Fig. 6) indicate that 35% HP treatment did not cause enamel surface alterations, despite of light irradiation. The enamel surface remained unaffected after the treatments with no porosity or demineralized areas (Fig. 6), independently of the bleached treatments.

Figure 6. Graph showing mean percentage (%) Ca and P atomic weight on treated enamel, determined by EDS.



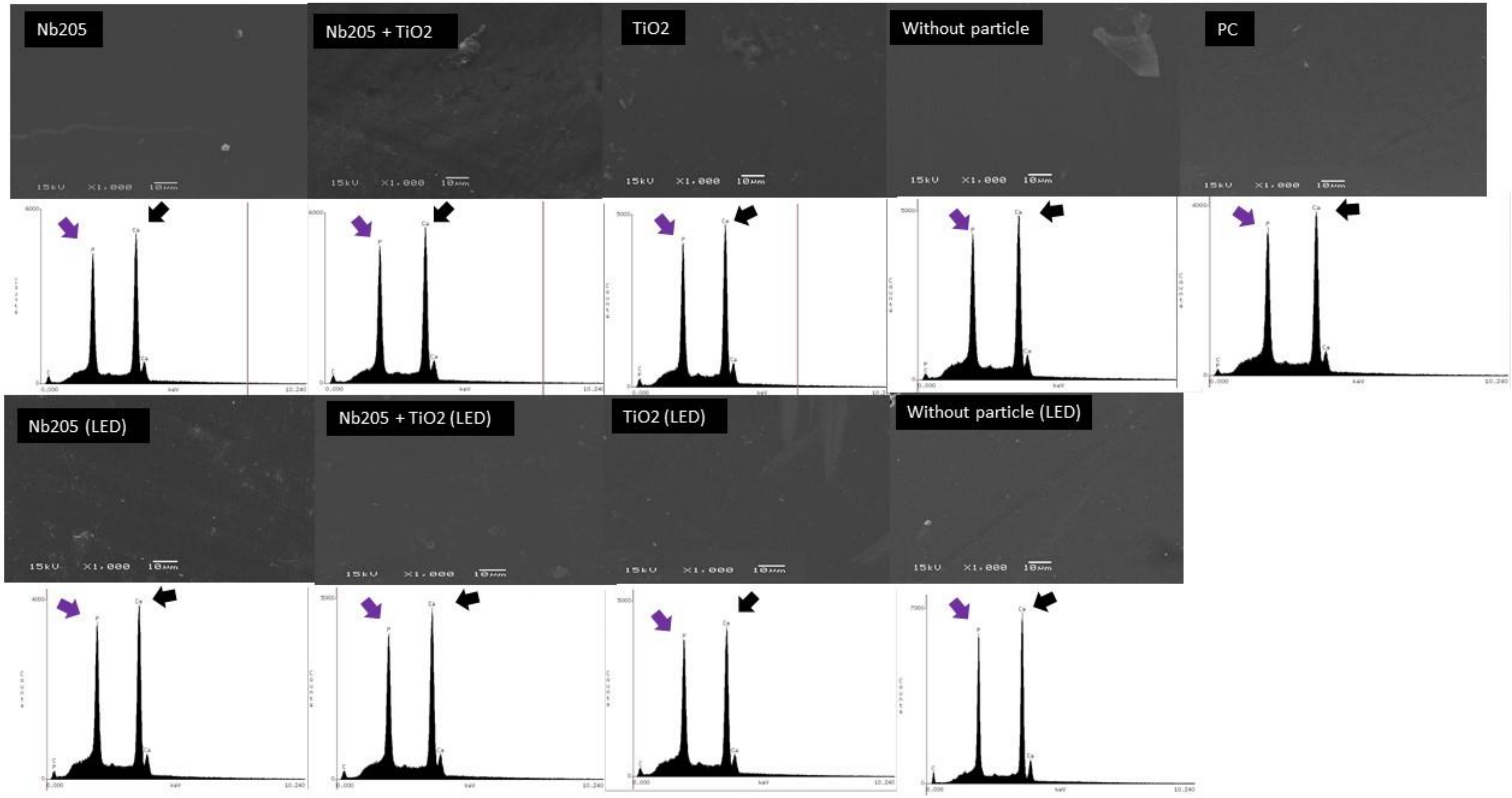


Figure 7. Representative SEM and EDS images. No enamel surface changes, porosities, or irregularities are observed on the enamel surface, and no evidence of demineralizing areas representing enamel mineral loss is observed. Light did not change the surface pattern. In the EDS plots, the black arrows represent Ca (calcium) peaks, and the purple arrows represent P (phosphorus) peaks.

DISCUSSION

The main purpose of this research was to reduce or eliminate the adverse effects of 35% HP gels, improving the bioactive and biocompatible features while maintaining the bleaching efficacy by adding catalyst particles to accelerate the H_2O_2 reaction. The preliminary and accelerated stability tests and the pH of the experimental gels indicated that 6% HP remained adequate for the 30-minute application period and for 30 and 60 days of storage at 37ºC (± 2ºC) and 4ºC (± 2ºC), regardless of the presence of the catalyst particles.

Immediately after production the gel's pH was 6.5, but the pH of the groups slightly decreased after 30min (pH = 6.0), including the NF_TiO_2 (Fig. 2B) and Nb_2O_5 + NF_TiO_2 (Fig. 2C) groups, with a pH of approximately 5.9. Although a pH reduction was observed, it is worth mentioning that these figures are still above the critical values by when the enamel demineralization process starts (pH<5.5) [25]. Carlos et al. [26] analyzed low and high concentration HP gels containing TiO_2 nanotubes (TiO_{2_NT}) and reported a significant increase in the pH values of TiO_{2_NT} -containing gels, with pH close to 6. Although distinctions in the crystalline structure of the TiO_2 nanotubes and TiO_2 nanoparticles may induce different behavior, it should be noted that the mean pH values for both remained similar (pH ± 6). Manzoli et al. [27] evaluated the pH of high concentration HP gels combined or not with light and reported that although pH decreased over time, it remained comparable to the initial values.

H_2O_2 is stable in acidic mediums, which explains the increase in the gel's shelf life [27]. The experimental gels tested in this study exhibit a pH value close to the commercial gel's pH and those manipulated by other authors (pH ± 6). Besides, we consider the pH values identified as safe for enamel surface application because the pH remained faintly acidic, and the bleaching protocol was restricted to three sessions of 30 minutes with 7-days intervals. Furthermore, enamel blocks remained stored in artificial saliva during the intervals allowing remineralization of the enamel surface [28].

In turn, the preliminary (30 days) and accelerated analysis (24h, 30, and 60 days) showed an increase in pH values for all groups, with a pH close to 6.5 at the end of the evaluations, corresponding to the commercial pH value (pH = 6.83) [29]. The addition of catalysts can interfere with the stability of the gels during its storage, for instance, with agglomeration or change in the crystalline structure of the particles [30]. Contrary to this assumption, the gels showed stability in long-term storage (preliminary and accelerated stability tests) reinforcing the soundness of the experimental gels in all evaluated groups. In both analyses, pH increased over time despite the storage protocol, but without statistical differences.

The experimental gels displayed no color, odor, translucency or viscosity changes. Monteiro et al. [31] demonstrated, through polydispersion and zeta potential analysis, that TiO_2_NT did not alter the physicochemical properties of bleaching gels. Previous findings confirmed that TiO_{2_NT} incorporation [26] and violet LED light did not change the rheological features of the gels. Evaluations of the stability of experimental gels containing catalysts are required as few studies evaluated those particles separately, and no study assessed the combination of NF_TiO_2 with Nb_2O_5 in a hydrogen peroxide gel.

Studies addressing decomposition rate noted an inverse performance. Cavalli et al. [32] observed that the H_2O_2 concentration of in-office gels irradiated with LED (450 nm), LED/Laser, and halogen light decreased over the 40min evaluation. Marson et al. [33] reported the same behavior [33]. Differently from those reports, the violet LED used in the current study possibly accelerated the decomposition of HP gels favoring the increased concentration of H_2O_2 detected [25].

The increased production of ROS by violet light exposure can be explained by the thermocatalytic theory of pH decomposition [34], which states that increasing temperature accelerates the production of hydroxyl radicals. Thus, part of the light's energy is converted into energy (heat) in the bleaching gel, which would in turn explain the increased production of ROS. Besides, the photocatalytic potential of the NF_TiO_2 and Nb_2O_5 might have contributed to this outcome [15] because in experimental gels without the NF_TiO_2 and Nb_2O_5 no H_2O_2 increase occurred even when exposed to light. Therefore, the NF_TiO_2 and Nb_2O_5 combined with the violet LED accelerated the free radical release process, increasing the hydroxyl concentrations [1].

Even though the tests performed in Phase 1 indicated the stability of the experimental gels and confirmed that the catalysts can chemically fasten the decomposition of hydrogen peroxide, the primary evidence of the action of these catalysts was observed in Phase 2, with outcomes of color change and whiteness index (ΔE_{00} and ΔW_{ID}). The experimental gels combined with light promoted the ΔE_{00} of the control group (35% HP). However, all groups irradiated with the violet LED light exhibited higher ΔW_{ID} than those without light, while only the groups submitted to treatment with NF_TiO$_2$ and Nb_2O_5 + NF_TiO$_2$ and light-irradiated showed higher ΔE_{00} compared with non-irradiated groups.

A relevant result was that, for both variables (ΔE_{00} and ΔW_{ID}), all light-irradiated groups containing catalysts had an outcome comparable to the control (HP 35%). Although the light irradiated 6% HP group without catalysts was statistically similar to 35% HP, it could be noted that numerically it presented a lower average than the groups with catalysts.

These results reinforce the photocatalytic aspect of NF_TiO$_2$ and Nb_2O_5 and the ability of these molecules to absorb light in the violet wavelength (405-415nm) [15]. Another study validated the effectiveness of 6% HP containing 5% NF_TiO$_2$ subjected to violet LED light and the capacity of NPs to potentiate the H_2O_2 reaction when light is irradiated, promoting the same color change efficacy as 35% HP [1]. To confirm these findings, Caneschi et al. [35] observed that low concentration bleaching gels (3% HP) containing Nb but without light exposure promoted color change akin to 35% HP. This positive Nb performance is explained by the modulation of Nb particles in association with H+, leading to an increase in the oxidizing sites, intensifying the oxidative capacity of the bleaching gels, and contributing to the cleavage of chromophores.

Contrary to these findings, some authors observed the physicochemical properties of HP gels (35% and 7%) combined with 1% TiO_{2_NT} with or without violet LED irradiation and showed that the nanotubes did not potentialize their effects [26]. Such discrepancies could be related to the crystalline structure of the TiO_2 nanotube, as different molecule shapes changes the catalysis potential of the TiO_2 particle [36]. Additionally, the authors utilized 1% of particles, while the present study used 5% NF_TiO$_2$ by weight.

No differences in ΔE_{00} and ΔW_{ID} were noted among light-irradiated groups containing NF_TiO$_2$ combined or not with Nb_2O_5. Because of the reports on the photocatalysis potential of TiO_2 [1,26,37,38], we first believed that NF_TiO$_2$ could be more efficient than Nb_2O_5 due to the higher stability of the hydrocolloids of the TiO_2 particle. However, Prado et al. [15] showed that Nb_2O_5 generates oxide deposits, decreasing the Nb_2O_5 catalytic activity. In that investigation, authors determined the photodegradation potential of TiO_2, ZnO, and Nb_2O_5 and graded from highest to lowest catalytic activity as follows: TiO_2 > ZnO > Nb_2O_5 [15].

On the other hand, reports indicate that Nb_2O_5 exhibits the ability to activate H_2O_2 for the formation of ROS [39]. The pH of the solution influences the type and amount of ROS formed in the $Nb_2O_5-H_2O_2$ association [39]. This combination produces hydroxyl radicals (•OH) and superoxide radical anions (O^{2-}•) through electroprotic reactions, meaning reactions involving the transfer of electrons and protons [40]. The first step in the activation of H_2O_2 over Nb_2O_5 is the formation of HO^{2-} through the dissociation reaction: **$H_2O_2 + S-OH \rightarrow HO_2^- + S-OH^+$** *(where S represents a surface location)*.

The formed HO_2^- reacts in the liquid phase with H_2O_2 through the electroprotic reaction $H_2O_2 + HO_2^- \rightarrow HO^\bullet + O_2^{\bullet-} + H_2O$, generating hydroxyl and superoxide radicals. Since the greatest efficiency of this reaction is observed under acidic conditions (pH ~3) [41], the potential of the Nb_2O_5 incorporated into the 6% HP gel with an average pH of 6.0-6.5 may not have been fully observed.

Additionally, the association of NF_TiO_2 with Nb_2O_5 did not potentiate tooth whitening compared to gels containing the catalysts alone. The lack of synergy between these particles may have occurred due to the difference in the size of the molecules used. While Nb_2O_5 measures 100 to 2500nm, NF_TiO_2, a nanoparticle, has 6 to 10nm [42]. Such discrepancy in size may have impeded the interaction and oxidative performance. Therefore, new strategies should be considered such as solvothermal treatments that produce Nb on a nanometric scale or the co-doping of NF_TiO_2 with $Nb2O_5$ [43].

The ΔE_{00} and ΔW_{ID} results demonstrated that all light-irradiated groups had higher color and whitening index differences than groups not exposed to violet LED. Numerous reports indicate the ability of violet LED light to promote color change, especially when combined with low concentration peroxide gels [1, 15, 26, 27, 44]. Although the catalysts have oxidative potential, irradiation with a violet LED light was the key factor for color-changing indexes.

There was no significant decline in microhardness in most groups, except for Nb_2O_5 (with and without LED) and Nb_2O_5 + TiO_2 (without LED). However, these groups were not different from the others and the percentage surface hardness loss (%SHL,

Table 7) was lower than 2% of the initial value. Therefore, the SH figures remained compatible with values of sound enamel [31]. Kolsuz et al. [45] demonstrated that bleaching gel containing TiO_2 and chitosan did not affect microhardness, corroborating our outcomes. On the other hand, others showed that enamel surface microhardness decreased following bleaching [46,47], but most of these reports use high concentration HP gels with a low pH. The positive control group used (35% HP) presents a pH close to neutrality (pH = 6.8) [29], justifying the lack of hardness loss. Besides, the low concentration tested (6% HP) and the reduced contact time of the gel on the enamel surface, combined with the remineralization capacity of saliva in controlling the inorganic content [28], minimize the %SHL (< 2%).

None of the bleaching protocols tested modified enamel roughness (ΔRa) after treatment, confirming previously reported results. That demonstrated low peroxide concentrations (6% HP) do not change surface roughness [29,45,48]. Although the roughness meter detects slight modifications in the surface pattern of peaks and valleys, the reported values are minimal and will not cause consequences to the optical properties of the enamel nor will it increase the risk of biofilm formation – which could happen on surfaces with roughness values higher than 0.2µm [49]. These results were ratified by the unaltered enamel morphology under SEM (Figure 7) and the absence of demineralizing areas or porosities.

Ca and P enamel concentration following treatment remained unchanged, regardless of the presence of light. Opposed to these results, some authors demonstrate mineral content decrease after using different application modes and HP concentrations [1, 32]. Kobayashi et al. [50] evaluated the effect of bleaching protocols with a violet LED light on bovine enamel, observing no changes in Ca and P enamel concentrations, reinforcing the hypothesis that the use of whitening protocols with a violet LED light did not change bleached enamel properties. However, semi-quantitative analysis as EDS must be interpreted with caution since mechanical or chemical tests are required to validate the results.

The experimental bleaching gels exhibited short- and long-term chemical stability, and the addition of NF_TiO_2 or Nb_2O_5 (combined or not) potentialized the decomposition rate of the bleaching gel. Nonetheless, the bleaching efficacy is significantly higher with violet LED light irradiation. Furthermore, low concentration bleaching gels did not promote adverse effects on tooth structure, regardless of the addition of catalysts or light irradiation. Adjustments in Nb_2O_5 concentrations and modifications in the molecule's crystalline structure (doped or not with TiO_2) could increase the photocatalytic behavior, reactivity, and potential to generate ROS on the outer enamel surface. Although increasing the oxidative potential of these experimental gels may increase bleaching efficacy, cytotoxic evaluation and cell viability studies are still necessary.

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CONCLUSION

Within the limitations of this in vitro study, the following conclusions were drawn

- The experimental bleaching gels containing 6% HP showed adequate preliminary and accelerated stability and pH close to neutrality, regardless of the addition of NF_TiO_2, Nb_2O_5, or violet LED light irradiation. The incorporation of these catalysts enhanced the decomposition of 6% HP.
- Experimental bleaching gels containing 6% HP and NF_TiO_2 or Nb_2O_5 that were light-irradiated exhibited a similar whitening potential to 35% HP.
- The experimental gels did not significantly change bleached enamel surface microhardness, roughness, Ca and P concentration, or morphology, indifferent to the catalysts or light irradiation.

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3.CONCLUSÃO

Diante dos resultados deste estudo *in vitro*, podemos concluir que os géis clareadores experimentais contendo 6% HP e partículas de NF_TiO_2 ou Nb_2O_5, apresentam estabilidade adequada, e a adição de partículas ou a irradiação com luz LED violeta não alterou as propriedades do gel. A decomposição do 6% HP é maior no gel com incorporação de partículas. Ainda, quando irradiados pela luz LED violeta, o 6% HP com partículas apresenta potencial clareador semelhante ao PH 35%. Ainda, os géis experimentais não promoveram alterações significantes na microdureza, rugosidade, concentração de Ca e P e morfologia do esmalte clareado.

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[1*] De acordo com as normas da UNICAMP/FOP, baseadas na padronização do International Committee of Medical Journal Editors - Vancouver Group. Abreviatura dos periódicos em conformidade com o PubMed.

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Anexo 1 – Verificação de originalidade e prevenção de plágio

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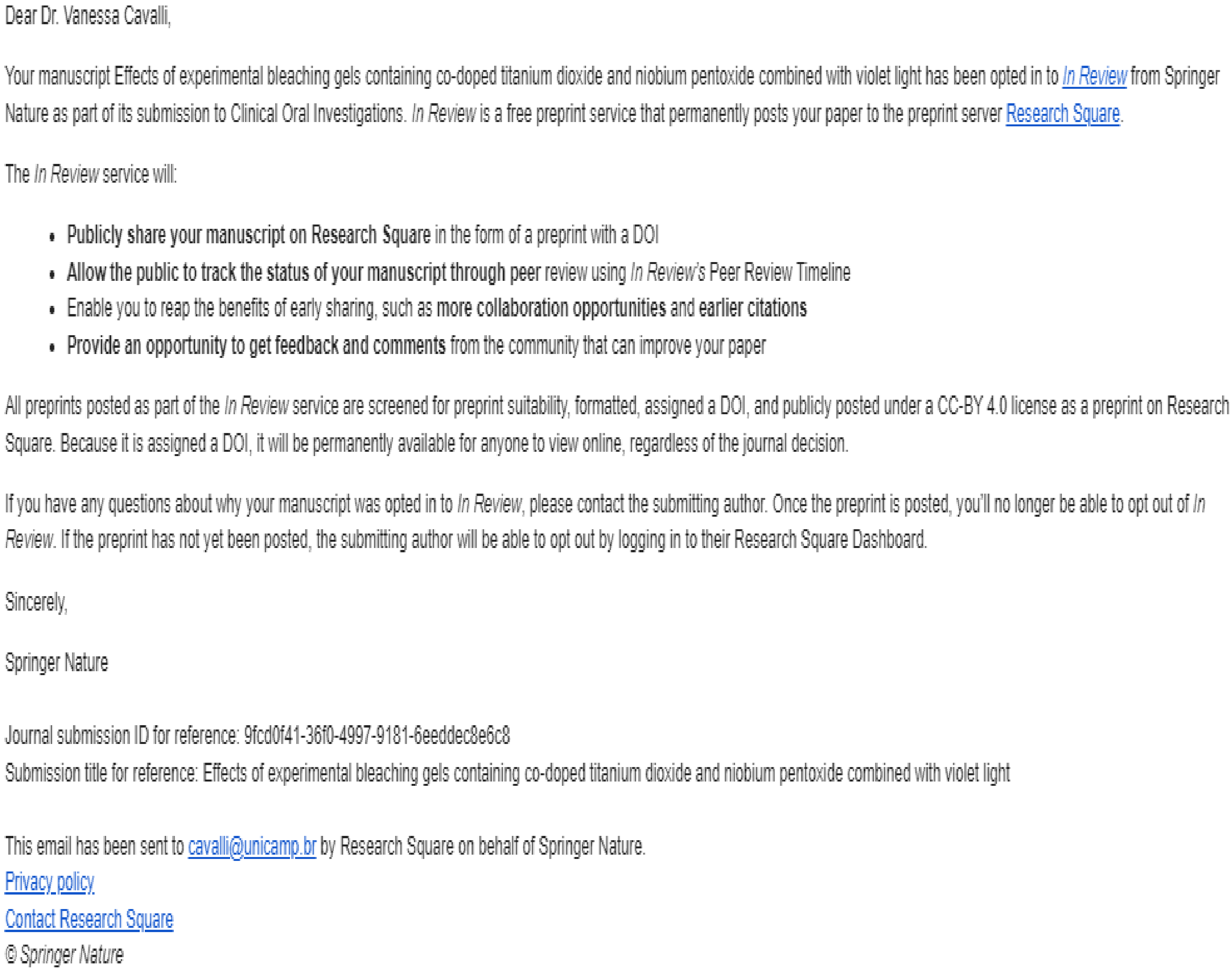

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